

# Development and Significance of the Spatial Auditory Change Complex in Adult Cochlear Implant Users

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# Declaration

I, Rajeev Mathew, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

# Acknowledgements

Although this thesis starts with a declaration that it is my own work, I have been far from alone during the last three years. For that, I shall be eternally grateful. I had two wonderful academic supervisors in Debbie Vickers and Jaime Undurraga. Debbie has guided, supported and encouraged me over the years. She has always been a source of positive energy and I admire her as a great problem solver. Despite her numerous commitments, she has been incredibly generous with her time. Jaime's kindness and intelligence have been truly inspiring, and he has become a great friend. Despite being on the other side of the world, he has been an ever present help, particularly for Python and R related queries. Jaime was responsible for introducing me to the world of open source and I must confess that I am a full convert!

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# Abstract

Despite their great success, cochlear implants (CIs) are associated with a wide range in speech perception outcomes. Interactions of electrode contacts on the CI array, resulting in impaired transmission of the auditory signal, may contribute to poor outcome in certain individuals. The aim of this thesis was to determine whether the spatial auditory change complex (ACC), an electrophysiological measure of electrode discrimination, could be used to objectively assess electrode independence, with a view to using this as a clinical tool for patient assessment.

In a series of experiments, the spatial ACC and behavioural electrode discrimination were measured in adult CI users. It was found that it is feasible to measure the spatial ACC in CI devices from different manufacturers and during the early period after switch-on. There was a strong relationship between objective and behavioural measures of electrode discrimination and in several cases, the development of the spatial ACC preceded accurate behavioural discrimination. Longitudinal measurements revealed that the amplitude of the spatial ACC and behavioural discrimination scores increased significantly over the first 6 to 12 months of CI use, providing evidence for auditory plasticity. The time course of adaptation varied substantially, and was slower and more limited in certain individuals. Speech perception was found to be more consistently related to behavioural measures of electrode discrimination than to the spatial ACC. Increasing stimulus intensity led to a significant increase in the spatial ACC amplitude and behavioural discrimination scores. By altering the recording setup and stimulus characteristics, the efficiency and sensitivity of spatial ACC measurements could be improved.

These findings show that the spatial ACC provides a useful measure of electrode independence. It is proposed that these measurements could be used to guide clinical interventions that lead to improved hearing outcome in CI users.

# Impact Statement

In this thesis, the methodology for recording and assessing cortical responses in cochlear implant (CI) users was developed. Furthermore, the findings show that cortical response measurements provide meaningful information that could be used for decision making in a clinical setting. It is therefore expected that this research will have significant impact on research in the field of CI electrophysiology, on industry that is developing CI technology and on clinical practice.

One of the traditional challenges with measuring cortical responses in CI users is the presence of electrical artefact from the device. A technique for effectively removing artefact was developed (Chapter 2). In addition, a technique for objectively assessing cortical responses based on statistical criteria was developed to determine whether a significant brain response was present or not (Chapter 2). Use of such a technique makes interpretation of brain responses simpler, quicker and less prone to bias. The technique for recording cortical responses in CI users was developed to improve the efficiency of recordings (Chapter 6). The above developments in methodology will make it easier to measure cortical responses in CI users in the research and clinical settings.

It was found that cortical response measurements provide meaningful information about how signals from an implant are encoded in the brain. In some cases, they provide information over and above that gained by behavioural testing. This information could be used to guide the rehabilitation strategy, including implant programming and auditory training. Future research must focus on whether the use of cortical response measurements lead to actual gains in hearing outcomes. It is hoped that the findings of this research will encourage industry to develop CI hardware and software, in order to facilitate cortical response measurements. A potential future development of particular interest is remote measurement of cortical responses. This would allow clinicians to gain a wealth of information about auditory processing with a CI and would also save a wealth of time for patients and clinicians alike.

The impact of this thesis will be delivered through publication in peer reviewed journals, presentation at international conferences and through future projects. There are already 2 peer reviewed journal publications and 13 conference presentations from this thesis. Further projects involving collaboration from industry and clinicians are already under way.

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# List of Abbreviations

AB	Advanced Bionics
ACC	acoustic change complex / auditory change complex
ACE	advanced combination encoder
AFC	alternative forced choice
ANSD	auditory neuropathy spectrum disorder
BKB	Bamford-Kowal-Bench
CAEP	cortical auditory evoked potential
CAPT	CHEAR auditory perception test
CI	cochlear implant
CIF	channel interaction function
CIS	continuous interleaved sampling
CSI	channel separation index
CT	computed tomography
DC	direct current
DR	dynamic range
EABR	electrically evoked brainstem response
eACC	electrically evoked auditory change complex
ECAP	electrically evoked compound action potential
EDL	electrode discrimination limen
EEG	electroencephalography
FS4	fine structure 4
HDCIS	high definition continuous interleaved sampling
Hotelling-T2	Hotelling's t-squared
ISI	inter-stimulus interval
LDL	loudness discomfort level
LME	linear mixed-effects
MC	most comfortable
MDS	multi-dimensional scaling
MIC	monaural interaction component
MMN	mismatch negativity
NH	normal hearing

PCA	principal component analysis
PSP	platinum sound processor
PTC	psychophysical tuning curve
PPS	pulses per second
RMS	root mean squared
RN	residual noise
SMRT	spectral-temporally modulated ripple test
SNR	signal-to-noise ratio
SOA	stimulus onset asynchrony



# Publications and Presentations

## Publications

1. **Mathew R**, Undurraga J, Li G, Meerton L, Boyle P, Shaida A, Selvadurai D, Jiang D, Vickers D. Objective assessment of electrode discrimination with the auditory change complex in adult cochlear implant users. *Hearing Research*, 2017, 354:86-101.
2. **Mathew R**, Vickers D, Boyle P, Shaida A, Selvadurai D, Jiang D, Undurraga J. Development of electrophysiological and behavioural measures of electrode discrimination in adult cochlear implant users. *Hearing Research*, 2018, 367:74-87.

## Oral Presentations

1. **Mathew R**, Undurraga J, Boyle P, Shaida A, Selvadurai D, Jiang D, Vickers D. Squiggles on the brain – objective assessment of auditory processing in cochlear implant users. Royal Society of Medicine, February 2018.
2. **Mathew R**, Undurraga J, Boyle P, Shaida A, Selvadurai D, Jiang D, Vickers D. Brain waves and electrode Interactions. ENT Masterclass, Doncaster, January 2018.
3. **Mathew R**, Undurraga J, Vickers D. Advanced Objective Measures. Advances in Auditory Implants, UCL Ear Institute, London, July 2017.
4. **Mathew R**, Undurraga J, Li G, Shaida A, Selvadurai D, Jiang D, Vickers D. Measurement of cortical auditory responses for the pre-operative assessment and post-operative rehabilitation of cochlear implant patients.' Joint British-Scandinavian Otology Meeting, Uppsala, September 2016.
5. **Mathew R**, Undurraga J, Li G, Boyle P, Shaida A, Selvadurai D, Jiang D, Vickers D. Objective measurement of auditory discrimination development after cochlear implantation. Improving Cochlear Implant Performance Conference, UCL, July 2016.
6. **Mathew R**, Undurraga J, Li G, Boyle P, Vickers D. The acoustic change complex as an objective measure of electrode discrimination in adult cochlear implant users. Objectives Measures in Auditory Implants, Szeged, Hungary, June 2016.

## Poster Presentations

1. **Mathew R**, Undurraga J, Boyle P, Shaida A, Selvadurai D, Jiang D, Vickers D. 'Measuring Central Auditory Plasticity in Adult Cochlear Implant Users with the Auditory Change Complex'. Conference on Implantable Auditory Prostheses, California, USA, July 2017.
2. **Mathew R**, Nimat R, Undurraga J, Meerton L, Selvadurai D, Jiang D, Vickers D. 'The effect of stimulus intensity on auditory evoked cortical responses in individuals with normal hearing and cochlear implants'. British Cochlear Implant Group Meeting, Birmingham, March 2017.
3. **Mathew R**, Undurraga J, Boyle P, Shaida A, Selvadurai D, Jiang D, Vickers D. 'Development of the auditory change complex after cochlear implant switch-on.' Basic auditory science conference, Cambridge, September 2016.
4. **Mathew R**, Undurraga J, Li G, Meerton L, Boyle P, Shaida A, Selvadurai D, Jiang D, Vickers D. 'Brain plasticity after cochlear implantation – an auditory evoked potential study.' Improving Cochlear Implant Performance Conference, UCL, July 2016.
5. **Mathew R**, Undurraga J, Li G, Boyle P, Vickers D. 'Pre-operative measurement of auditory evoked cortical responses in adult cochlear implant candidates.' Objectives Measures in Auditory Implants, Szeged, Hungary, June 2016.
6. **Mathew R**, Undurraga J, Li G, Boyle P, Selvadurai D, Shaida A, Vickers D. 'Objective measurement of electrode discrimination with the acoustic change complex.' British Cochlear Implant Group Meeting, London, April 2016.
7. **Mathew R**, Undurraga J, Li G, Meerton L, Selvadurai D, Shaida A, Vickers D. 'Pre-operative assessment of cochlear implant candidates with auditory evoked cortical responses.' British Cochlear Implant Group Meeting, London, April 2016.

## Chapter 1 Introduction

The first auditory implant in a human was performed by Djourno and Eyries in Paris in 1957 (Wilson and Dorman, 2008). This device consisted of an induction coil with one end placed at the auditory nerve and the other within the temporalis muscle. With this device, the patient could hear environmental sounds but not speech. Over the next 30 years the modern day cochlear implant (CI) was developed. This consists of a multi-channel electrode array inserted in the cochlea with each electrode contact theoretically stimulating distinct populations of auditory neurons. This device has entered mainstream clinical practice and there are approximately 600,000 implant users worldwide with more than 1200 individuals undergoing implantation in the UK every year (The Ear Foundation, 2016). Although, this technology has proven revolutionary in restoring hearing to individuals with profound deafness, there is significant variability in hearing outcomes in paediatric and adult populations (Blamey et al., 1996, 2013; Niparko et al., 2010; Wooi Teoh et al., 2004). While there are many potential causes for this variability, one important factor that may contribute to poor outcomes is the non-independence of electrode contacts on the CI array resulting in distortion of the transmitted sound signal. Broadly, the goal of this research was to determine whether an electrophysiological response from the brain called the spatial auditory change complex (ACC), could be used to assess electrode independence with a view to using this as a clinical tool for patient assessment.

This chapter reviews the literature that is relevant to the rationale and methodology of this study. The following sections will provide details of (1) how a CI works (2) hearing outcomes with a CI (3) evidence that channel interactions limit hearing outcome and (4) techniques for assessing channel interactions including cortical auditory evoked potentials (CAEPs).

### 1.1 How a CI works

#### 1.1.1 Components of the CI system

The three main manufacturers of CI devices are Advanced Bionics (AB), MED-EL and Cochlear Limited. The main components of CI devices consist of the following 1) the

microphone which picks up the acoustic signal 2) the sound processor, which converts the microphone output to electrical signals 3) a head piece with a transmitting coil, which is held in place by a magnet and uses radio frequency to transmit the signal transcutaneously 4) the implant receiver/stimulator, which decodes information from the transmitter and generates electrical stimuli and 5) the electrode array, which is used to stimulate auditory neurons innervating the cochlea.

The electrode array consists of multiple electrode contacts, each of which is intended to stimulate a distinct population of auditory neurons. CIs attempt to mimic natural tonotopic encoding by representing high frequencies at the basal end and low frequencies at the apical end of the array. The array is ideally placed in the lower compartment of the cochlea, the scala tympani, where it lies closer to target auditory neurons. The intra-cochlear length varies from 6 to 31mm for different arrays designs (Brant and Ruckenstein, 2016) but none of the current arrays cover the whole cochlear length. Electrode arrays can vary in their intended position relative to the modiolus, where auditory neurons are located. Peri-modiolar electrodes are pre-curved and should lie close to the modiolus, allowing more focused neural stimulation. In contrast, lateral wall electrodes lie further from the modiolus, resulting in greater current spread but are associated with less traumatic insertions (Brant and Ruckenstein, 2016).

A CI stimulation channel consists of an active and one or several reference electrodes (Zhu et al., 2012). For example, in monopolar mode, the reference electrode is located outside the cochlea and the active electrode is located within the cochlea. In bipolar mode, the reference electrode is a neighbouring intra-cochlear electrode, whilst in tripolar mode the return electrodes are 2 intra-cochlear electrodes on either side of the active electrode. There is evidence that bipolar and tripolar stimulation modes produce more focused excitation patterns (Bierer and Middlebrooks, 2002) as current flows between neighbouring electrodes but this comes at the cost of greater current requirements and shorter battery life for the device. The partial tripolar mode (Bierer and Faulkner, 2010) has been developed as a compromise to improve current focusing whilst reducing current requirements – in this mode the current returns from the active electrode to 2 neighbouring electrodes as well as an extra-cochlear reference electrode. Most current CI devices however utilize monopolar stimulation as this mode

requires less current and is associated with similar levels of performance to other stimulation modes (Mens and Berenstein, 2005; Zwolan et al., 1996).

### 1.1.2 Electrical stimulation of the auditory nerve

#### *1.1.2.1 Site of stimulation*

CIs bypass the damaged cochlea and directly stimulate auditory neurons. Electrical stimulation can lead to activation of the auditory nerve at several sites including the peripheral processes, the central process or through either mechanical or electrical stimulation of inner hair cells (Javel and Shepherd, 2000; Moxon, 1971). Van den Honert and Stypulkowski (1984), recorded single auditory nerve fibre responses to pulsatile electrical stimulation in cats. Low stimulus intensities led to long latency responses (500 to 800  $\mu$ s) associated with significant latency variability. In contrast, high stimulus intensities led to short-latency (300 to 500  $\mu$ s) highly synchronous responses. It was postulated that as stimulus intensity increased, the site of activation shifted from peripheral processes to the central process of the auditory neurons. This was supported by the findings that short-latency low-jitter responses were also obtained in animals that underwent surgical removal of the peripheral processes and spiral ganglion cell bodies. Given that deafness is associated with significant degeneration of the inner hair cells and peripheral processes (Hinojosa and Marion, 1983; Nadol et al., 2001), it is likely that that in CI patients, activation of the auditory nerve occurs in the central processes.

#### *1.1.2.2 Phase locking of auditory neurons*

Moxon (1967) showed that the absolute refractory period of auditory neurons in cats was as short as 500  $\mu$ s. However, nerve fibres could not fire at the maximum possible rate. It was found that for bursts of electrical stimuli, the maximum rate of stimulation was 900 pulses per second (pps) but this fell to 500 pps after around 2 minutes. In comparison to acoustic stimulation, electrical stimulation leads to a greater level of phase locking of auditory neurons. Javel et al. (1987), showed that there was one to one correspondence of the discharge of auditory neurons with electrical pulses up to rates of 800 pps. Their study also showed that the dynamic range of auditory neurons

was small (1 to 6 dB, reference to  $1\mu\text{A}$ ) and increased with stimulation rate. Similar to Javel et al. (1987), Hartmann et al. (1984), showed that electrical stimulation led to more synchronous firing of the auditory nerve compared to acoustics stimulation, though for higher stimulation rates, larger stimulus intensities were required to maintain phase locking. Electrical stimulation, however, leads to much more deterministic firing of auditory neurons compared to acoustic stimulation. Clark (1998), measured interspike interval histograms of units in the cat anteroventral cochlear (AVCN) nucleus. At low stimulation rates, electrical stimulation led to few peaks in the interval histogram and very little jitter. However, at higher rates of around 800 pps, the firing became more stochastic with a greater number of peaks and latency jitter, similar to acoustic stimulation. Paolini and Clark (1997) showed that at stimulation rates of 1800 pps, for which the period of the stimulus approaches the absolute refractory period of auditory neurons, the response of the AVCN neurons is not related to the stimulus rate.

Shepherd and Javel (1997), compared response characteristics of auditory neurons in hearing and deaf animals. They showed that auditory neurons from deaf animals displayed little or no spontaneous activity. Furthermore, neurons from deaf animals displayed less jitter and poorer phase locking to electrical stimuli. Whilst auditory neurons from deaf animals could fire in response to every pulse at stimulation rates up to 800 pps, fibres from deaf animals were not capable of this at rates above 400 pps. Auditory neurons from deaf animals also displayed abnormal discharge patterns alternating between periods of synchronous firing and complete inactivity.

Although electrical stimulation leads to strong phase locking of the auditory neurons in animal experiments, temporal processing in higher auditory centres appears to be much poorer. Clark (1969) measured the response of cells in the superior olivary complex of cats and found that electrical stimulation above 200 to 500 pps did not produce the same firing rate or pattern as an acoustic tone with the same frequency. Merzenich et al. (1973), measured interspike interval histograms in the inferior colliculus of cats and found that sinusoidal electrical stimuli were encoded in the discharge pattern of neurons up to rates of 400 to 600 pps. The poorer phase locking of higher auditory centres may be due to the fact that electrical stimulation results in

strong inhibition in the brainstem. Furthermore, these data suggested that speech information, which includes frequencies up to 4000Hz, could not be conveyed by temporal coding alone.

#### *1.1.2.3 Effect of stimulation mode*

Van den Honert (1987), examined how response threshold of auditory nerve fibres varied with stimulation mode. The electrical threshold of auditory neurons with different acoustic characteristic frequencies was measured for a large population of neurons. For monopolar stimulation, the electrical thresholds were similar across the cochlea indicating poor spatial selectivity. In contrast, with bipolar stimulation, auditory nerve fibres adjacent to stimulated electrode had much lower thresholds, implying better spatial selectivity. These findings are supported by compound action potential responses with monopolar stimulation in human CI users, which are broader when compared to responses obtained with bipolar or tripolar stimulation, indicating a broader area of neural activation (Miller et al., 2003). Electrophysiological studies in the inferior colliculus (Merzenich and White, 1977) and auditory cortex (Bierer and Middlebrooks, 2002) show that the greater spatial selectivity associated with bipolar and tripolar stimulation modes is maintained further up the auditory pathway. One potential disadvantage of bipolar stimulation is that it may lead to bimodal patterns of stimulation, where two peaks of stimulation are produced at the active and return electrodes (Kral et al., 1998; Undurraga et al., 2012). There is evidence in humans that the anodic phase of an electrical pulse is more effective at stimulating auditory neurons than the cathodic phase (Macherey et al., 2008; Undurraga et al., 2012) and recent studies have attempted to manipulate the pulse shape in order to avoid multiple peaks of excitation that may be associated with focused stimulation modes (Undurraga et al., 2012).

#### *1.1.2.4 Effect of electrode position*

There is evidence that the position of the electrode array in the cochlea has an important influence on activation of the auditory pathway by the CI. Shepherd et al. (1993) found that the threshold of the auditory brainstem response in cats was reduced by moving the position of the electrode a) from the outer part of the cochlea

towards the modiolus and b) towards the osseous spiral lamina closer to the peripheral processes of auditory neurons. This finding is in line with evidence from compound action potential measurements in human CI users, in whom it has been found that peri-modiolar electrodes have less spread of electrical excitation and possibly lower thresholds, compared to more laterally placed electrodes (Tsuji et al., 2009; van Weert et al., 2005; Xi et al., 2009).

### 1.1.3 Sound processing strategies

Sound processing refers to how the acoustic signal is encoded into an electrical stimulus. Present day sound processing strategies are generally based on temporal envelope extraction and are variants of the Continuous Interleaved Sampling (CIS) strategy (Wilson et al., 1991). First, a series of bandpass filters are used to decompose the acoustic signal into frequency components. The temporal envelope of each of these waveforms is extracted and compressed into the narrow dynamic range (DR) of electrical hearing. The compressed envelope output is then used to modulate fixed rate electrical pulses at individual electrodes, with the output of each band pass filter mapped to a single electrode along the array. A requirement for safe electrical stimulation is that pulses must be charge balanced – this is typically achieved by using symmetric biphasic pulses, which consist of two phases with equal amplitude and duration but opposite polarities. Pulse trains across different channels are temporally interleaved in order to reduce channel interactions.

Each of the implant companies has its own speech processing strategy with features aimed at improving spectral or temporal encoding of the acoustic signal. The HighRes strategy used in the AB device is a variation of CIS which uses high stimulation rates to provide better temporal envelope information and a relatively high cut off frequency for the envelope detector (Wilson and Dorman, 2008). The HiRes120 strategy uses a technique called current steering to improve spectral resolution by increasing the number of stimulation sites. This is achieved with the creation of ‘virtual channels’ between electrode contacts, by varying the proportion of current delivered at two neighbouring simultaneously activated electrodes. Whilst there is evidence that this can lead to an increased number of pitch percepts (Firszt et al., 2007), evidence for a



consistent gain in speech perception with this strategy is lacking (Brendel et al., 2008; Donaldson et al., 2011).

High Definition CIS (HDCIS) is used in the MED-EL device and is similar to CIS, but utilizes overlapping bell shaped filters which enable delivery of current at virtual channels. More recently, the manufacturers of the MED-EL device have implemented Fine Structure strategies such as Fine Structure 4 (FS4) in order to improve temporal cues in the low frequencies. In FS4, the apical 4 electrodes do not use fixed rate envelope based coding; rather stimulation pulses are triggered by zero-crossings in a channel's band-pass filter output, thereby providing a temporal code. Most Cochlear devices use an n-of-m strategy, where 'n' electrode with the highest energy in their associated analysis filters are stimulated out of a total of 'm' electrodes. By limiting the number of active electrodes, interactions are theoretically reduced whilst preserving the most important aspects of the auditory signal. This approach is utilized in Cochlear's Advanced Combination Encoder (ACE) strategy, which also uses high stimulation rates.

#### 1.1.4 Fitting a CI

The CI must be programmed for each individual to ensure that it can be used safely and effectively – this procedure is usually referred to as fitting or programming (Wolfe and Schafer, 2014). The integrity of electrodes can be checked with impedance measurements, which identify electrodes contacts with an open circuit (high impedance) or a short circuit (very low impedance). These malfunctional electrodes are typically switched off. Extra-cochlear electrodes, identified on X-ray or cone beam computed tomography (CT) imaging, are also switched off. A key aspect of the fitting procedure consists of determining the lower and upper limits of stimulation. This involves estimating the threshold level and most comfortable (MC) level of stimulation for individual electrodes. Typically, these estimates are based on behavioural responses or verbal feedback. This may not be possible in young children and in these situations, electrophysiological measurements, such as the electrically evoked compound action potential (ECAP) (Alvarez et al., 2010; Franck and Norton, 2001; Seyle and Brown, 2002), the electrically evoked stapedius reflex (Hodges et al., 1997;

Stephan and Welzl-Müller, 2000), or the electrically evoked auditory brainstem response (EABR) (Brown et al., 2000), may be used to determine stimulation levels.

Threshold and MC level measurements are usually performed for a subset of electrodes and interpolation is used to determine stimulation levels for the rest. Electrodes are then loudness balanced by stimulating a number of electrodes in sequence at the MC level and adjusting their levels until they produce similar loudness percepts. The implant is then activated in 'live speech' mode with all channels activated and the overall volume can be adjusted as necessary. The above fitting procedure is repeated several times during the first 6 months after switch-on, as DR increases during this period (Hughes et al., 2001; Vargas et al., 2012) due to the development of loudness tolerance.

There is some flexibility with fitting parameters which varies between manufacturers. For example, selection of the sound processing strategy, stimulation rate, number of maxima (i.e. number of 'n' channels) for n-of-m strategies, pulse width, sensitivity (adjusts automatic gain control parameters) and the input DR of the microphone. Patients can be provided with specialized programmes, which can be selected depending on the listening situation. For example, programmes are available to aid speech perception in noisy conditions, to allow the use of wireless external listening accessories and to reduce noise due to wind. Depending on the device and audiologist recommendation, patients may be able to control the volume and sensitivity settings of their device. In contrast to adults, flexibility is seldom provided for children.

## 1.2 Outcomes with CI – success and variability

CIs have proven to be one of the greatest technological innovations in medicine in the 20<sup>th</sup> century. The restoration of hearing to profoundly deaf individuals has far reaching personal and socio-economic consequences. For example, hearing restoration with a CI is associated with higher educational attainment for children, improved vocational outcomes and better quality of life (Crowson et al., 2017; Emmett and Francis, 2015; Semenov et al., 2013). Nonetheless, studies in adults and children have shown that cochlear implantation is associated with considerable variability in hearing outcomes. Niparko et al. (2010) assessed language development in children implanted before the

age of 18 months using the Reynell Developmental Language Scale. It was found that after 3 years of CI use, comprehension scores ranged from approximately 2 to 65 points, with a mean score of approximately 42 points. Holden et al. (2013), measured word recognition scores in post-lingually deafened adults and found that after 2 years of CI use, scores ranged from 3 to 90 % with a median score 65 %. Even in individuals with good speech perception in quiet, outcomes are generally poor for more challenging auditory tasks. This include speech perception in noise (Zeng, 2004), speaker recognition (Vongphoe and Zeng, 2005) and music appreciation (Kong et al., 2004).

Some of the factors that contribute to the variation in hearing outcomes after cochlear implantation are well understood. For pre-lingually deafened children and adults, age at implantation is a critical determinant of hearing outcome. Specifically, outcomes are poorer with increasing age (Kirk et al., 2002; Nikolopoulos et al., 1999). If implantation is performed after the age of 7, then open-set speech perception is particularly poor (Fryauf-Bertschy et al., 1997; Manrique et al., 1999). This is because there is a sensitive period for auditory development, beyond which auditory plasticity is reduced and auditory deprivation leads to abnormal patterns of brain connectivity (Kral et al., 2016; Kral and Sharma, 2012; Sharma et al., 2005a; Teoh et al., 2004). For post-lingually deafened individuals, duration of profound hearing loss is a key predictor of hearing outcome (Blamey et al., 2013; Holden et al., 2013). Longer duration of deafness is associated with degeneration of elements in the peripheral auditory system as well as cortical reorganization (Nadol et al., 1989; Sandmann et al., 2012). In both pre- and post-lingually deafened CI users, speech perception is affected by the duration of CI use (Blamey et al., 2013). Outcomes in young children continue to improve for many years as they acquire language (Wooi Teoh et al., 2004). In adults, speech perception usually plateaus after around 6 – 12 months of CI use (Lenarz et al., 2012; Wooi Teoh et al., 2004) though in certain individuals, improvement may continue for several years (Heywood et al., 2016; Tyler et al., 1997).

Other patient/disease related factors that have been correlated with speech perception include the amount of pre-operative residual hearing (Holden et al., 2013; Lazard et al., 2012), mode of communication (Holt and Svirsky, 2008; Osberger and

Fisher, 2000), socio economic status (Holt and Svirsky, 2008; Osberger and Fisher, 2000), level of family support (Holt et al., 2013), aetiology of hearing loss (Blamey et al., 1996; Green et al., 2007; Matsushiro et al., 2002) and cognitive function (Holden et al., 2013). Device related factors which have been correlated with speech perception include the percentage of active electrodes in the cochlea (Geers et al., 2003; Lazard et al., 2012), depth of electrode array insertion (Holden et al., 2013; Skinner et al., 2002) and scalar position of CI electrode contacts (Holden et al., 2013; Skinner et al., 2007).

Despite an understanding of these predictive factors, large scales studies have shown that much of the variance in CI outcomes still remains unexplained (Blamey et al., 1996; Lazard et al., 2012). For example, Lazard et al. (2012), assessed the influence of 15 pre, peri and post-operative factors on speech perception in 2251 patients. Using a general linear model, it was found that only 22% of the variance for speech perception in quiet as well as speech perception in noise could be explained.

### 1.3 Channel interactions as a factor limiting CI outcome

Given the large unexplained variance in speech perception as well as the relatively poor outcomes in challenging listening situations, there is a need to identify and address factors that reduce performance in individual CI users. One such factor may be the presence of electrical interactions between electrode contacts on the CI array. These types of interactions would be expected to lead to distortion of the transmitted sound signal and poorer speech perception

CIs transmit the auditory signal by means of a limited number of stimulation channels. Researchers have attempted to investigate the importance of the number, as well as independence of stimulation channels, using simulations in NH individuals with vocoded speech. Vocoders utilize a signal processing technique analogous to that in a CI – the sound signal is processed through a series of band pass filters, and the temporal envelope within each filter is extracted and used to modulate band limited white noise or a tone carrier (Rosen et al., 2015; Shannon et al., 1995). These studies have shown that more complex listening tasks require a greater number of spectral channels to achieve a given level of performance (Shannon et al., 2004). Thus while good levels of speech-in-quiet comprehension can be achieved with as little as 4

spectral channels (Friesen et al., 2001; Shannon et al., 1995), performance continues to improve with up to 20 spectral channels for speech-in-noise perception (Friesen et al., 2001) and 64 channels for melodic contour recognition (Smith et al., 2002) in NH listeners. In addition to the number of spectral channels, the independence of these channels is an important consideration. Spectral smearing can be introduced by altering the slope of the cut-off frequencies of the band pass filters, and increased overlap of the filter outputs is associated with significantly reduced speech perception in noise in NH listeners (Fu and Nogaki, 2005).

In present day CI systems, the number of band pass filters, corresponding to the number of electrode contacts, is between 12 and 22. However, the number of 'effective' channels are often far fewer. This has been revealed in studies of CI users with experimental maps, where the number of channels can be manipulated. These studies have shown that speech perception improves with the number of channels but plateaus beyond 4 to 10 channels depending on the individual and the task (Dorman and Loizou, 1998; Fishman et al., 1997; Friesen et al., 2001). This appears to be the case irrespective of stimulation mode, speech processing strategy and device. Of note, CI users with poor speech perception have no more than 4 effective channels (Friesen et al., 2001).

The presence of channel interactions would also be expected to contribute to poor spectral resolution in CI users. Spectral ripple tests have been used in research settings to provide a broad measure of spectral resolution in CI users. In these tests, a stimulus which has been amplitude modulated in the frequency domain must be discriminated from a stimulus with a different ripple density, an inverted phase or from an unmodulated stimulus (Aronoff and Landsberger, 2013; Henry and Turner, 2003; Saoji et al., 2009; Won et al., 2007). Spectral ripple discrimination scores are substantially poorer in CI users compared to NH individuals (Henry et al., 2005; Henry and Turner, 2003). Spectral ripple discrimination scores are highly variable between CI users (Henry et al., 2005; Henry and Turner, 2003) and these measures have been correlated with vowel detection, consonant detection, speech perception in quiet and speech perception in noise (Henry et al., 2005; Henry and Turner, 2003; Lawler et al., 2017; Won et al., 2007). Henry and Turner (2003), examined the effect of the number of

stimulation channels on spectral ripple discrimination ability. It was found that for CI simulations with NH individuals, spectral ripple scores improved as the number of channels increased from 1 to 16. In contrast, CI users had a performance plateau at 4 to 6 channels. This provides further evidence that CI users are unable to use the spectral information provided by the number of electrodes in their implant.

In summary, the stimulation channels in CI users are not independent and poorer performers appear to have fewer 'effective' channels. The level of interactions between channels may therefore be an important predictor of hearing outcome

#### 1.4 Reasons for channel interactions

A number of factors contribute to interactions of CI stimulation channels. The CI array sits in a fluid filled chamber and is separated from target auditory neurons by porous bone. As a result, current flows longitudinally along the cochlea causing a wide field of electrical excitation. The spread of current will also be affected by the array-to-modiolus distance, which in turn is affected by surgical placement of the array and electrode design (Cohen et al., 2006). Furthermore, the presence of post-surgical fibrosis and ossification (Pfungst B. et al., 1985; Somdas et al., 2007) will influence current pathways. Current spread can also lead to a phenomenon called cross turn stimulation - this occurs when an electrode stimulates neural elements from a more apical turn of the cochlea, rather than the target auditory neurons in the same turn (Frijns et al., 2001). Profound deafness in adults, is associated with 'holes in hearing' due to neural dead regions (Incesulu and Nadol, 1998; Moore, 2001; Shannon et al., 2002) and in these cases, the corresponding CI electrode will only produce an audible percept if neighbouring 'non-target' neurons are stimulated. Reduced spectral resolution due to channel interactions is further compounded by misalignment between the frequency allocation of electrode contacts and the characteristic frequencies of the corresponding auditory neurons, due to the short length of the electrode array relative to the cochlea (Grasmeder et al., 2014; Zeng et al., 2014). Reiss et al. (2007), however, showed that the amount of mismatch between allocated and perceived frequencies reduced over time, suggesting that CI users can at least partially adapt to spectral mismatch.

## 1.5 Assessment of channel interactions in CI users

Identification of the extent and location of channel interactions could provide prognostic information and help guide interventions that lead to improved hearing. For example, there is evidence that auditory training and re-programming of the CI, in individuals with channel interactions, leads to improved hearing outcome (Fu and Galvin, 2008; Saleh et al., 2013). Whilst spectral ripple tests provide a broad measure of spectral resolution, localized assessments of interactions for individual electrodes would be more informative, from a clinical point of view. This can be achieved with either behavioural or electrophysiological measurements. In this section, the main techniques for assessing channel interactions are summarized.

### 1.5.1 Behavioural measures of channel interactions

#### *1.5.1.1 Behavioural electrode discrimination*

Electrode discrimination offers a simple assessment of channel independence. It is measured by asking CI users to identify whether the sound percepts associated with two sequentially stimulated electrodes are different. Electrode discrimination is typically measured with a 2-alternative forced choice (AFC) task. This technique can be used to define the smallest separation between electrodes required for accurate discrimination, which is termed the electrode discrimination limen (EDL). EDLs can be measured with a method of constant stimuli or with an adaptive procedure, both of which produce equivalent results (Busby and Clark, 1996). It is, however, important to accurately loudness balance electrodes in order to reduce the effect of intensity cues on discrimination. Random level variations can be used in addition to loudness balancing in order to reduce intensity cues (Busby et al., 2000; Busby and Clark, 1996). It has been argued that such variations in intensity allow a more functionally relevant assessment of discrimination (Henry et al., 2000). On the other hand, changes in stimulus level can produce perceived changes in pitch (Townshend et al., 1987) which can make the results of the task difficult to interpret.

McKay et al. (1999), examined the effect of stimulus intensity on electrode discrimination ability. Higher stimulus intensities are associated with broader patterns

of excitation within the cochlea causing a greater amount of overlap in the electrical fields of electrodes. It was expected then that increasing stimulus intensity would lead to poorer electrode discrimination. On the contrary, it was found that increasing stimulus intensity actually led to a significant improvement in discrimination scores. The authors concluded that successful electrode discrimination depends on differences in the peaks and edges of the pattern of excitation rather than the amount of non-overlap in excitation fields.

EDLs in CI users are highly variable (Busby and Clark, 1996; Dawson et al., 2000; Zwolan et al., 1997) and there is evidence that electrode discrimination ability, particularly in the apical and mid regions of the array, is related to speech perception (Busby et al., 2000; Dawson et al., 2000; Henry et al., 2000). Busby et al. (2000), showed that in 16 early deafened participants, apical EDL was negatively correlated with closed-set speech perception, with larger EDL predicting poorer speech scores. Dawson et al. (2000), measured apical and mid array EDL in 17 children. They showed that electrode discrimination ability was the strongest predictor of closed-set speech perception, and that factors such as implant experience and duration of deafness did not account for further variance in speech recognition scores in their participants. Henry et al. (2000), found that electrode discrimination in the presence of random level variation was correlated with the amount of speech information perceived in the low and mid frequency bands. Throckmorton and Collins (1999) found that the number of indiscriminable electrodes on the CI array was correlated with average masking level measured with psychophysical tuning curves (PTCs, see section 1.4.1.4). In addition, the number of indiscriminable electrodes was negatively correlated with performance on vowel, consonant, and sentence recognition tasks. Zwolan et al. (1997), found no correlation between electrode discrimination and speech perception. However, in their study, a number of participants only had partial electrode insertions which may have accounted for the difference in findings.

There is limited evidence that the results of electrode discrimination testing can be used to guide interventions to improve speech perception in CI users. Zwolan et al. (1997), provided adult CI users with an experimental map in which indiscriminable electrodes were deactivated, and showed that 7 out of 9 participants had an



improvement in at least one measure of speech perception. Interestingly there was no improvement in vowel or consonant recognition and it was hypothesized that the improvement associated with electrode deactivation might have been due to better speech envelope information. It must be noted that in 2 participants, speech perception deteriorated markedly – one of these participants only had 3 electrodes after deactivation, which may account for the poorer performance in this case.

An alternative approach to deactivating indiscriminable electrodes is to provide electrode discrimination training. This assumes that indiscriminable electrode actually do stimulate different populations of neurons, but that the difference in the stimulation pattern is too small to be perceived. Fu and Galvin (2008) reported a single case study in which electrode discrimination training in an early deafened late implanted individual, resulted in large improvements in electrode discrimination  $d'$  scores. Of note, the improvements in discrimination scores generalized to untrained electrode contrasts. Furthermore, better electrode discrimination was associated with improved vowel and consonant recognition.

The advantage of electrode discrimination testing is that it is quick and easy to perform. Dawson et al. (2000) developed a technique for measuring electrode discrimination based on play audiometry and showed that it could be measured in children as young as 4 years old. In addition, the results of electrode discrimination testing are simple to interpret and can be used to create pass-fail rules in order to define areas of poor discriminability (Throckmorton and Collins, 1999; Zwolan et al., 1997). A limitation of electrode discrimination testing is that the ability to accurately discriminate electrodes does not imply a healthy electrode-neural interface. For example, even if cross turn stimulation or a dead region is present, accurate electrode discrimination may still be possible.

#### *1.5.1.2 Pitch ranking*

Due to the tonotopic arrangement of the CI array, it is expected that the pitch percept will increase in an orderly fashion from the apical to basal end of the electrode array. Pitch ranking is typically assessed by stimulating two CI electrodes and asking

participants to identify which electrode is associated with a higher pitch. Nelson et al. (1995), found that in general, place pitch was ordered from apex to base in CI users, but in certain individuals pitch reversals occurred whereby a more basal electrode produced a lower pitch percept. Whilst some individuals had near perfect pitch ranking ability for adjacent electrodes separated by 0.75 mm, others only achieved perfect performance when the spatial separation between electrodes was 13 mm, which was more than three quarters of the array length. Pitch ranking ability has also been correlated with speech perception (Collins et al., 1997; Nelson et al., 1995).

A number of studies have used the results of pitch ranking tasks to re-programme the CI. Collins et al. (1997), used pitch ranking data to re-order the frequency allocation of electrodes on an experimental programme, in order to produce an orderly pitch percept. In general, the experimental programme was associated with worse speech perception – a number of participants displayed worse vowel, word and sentence recognition scores with only a few participants showing improvements in sentence perception. This may have been because participants were tested acutely i.e. they did not have time to adapt to their experimental programme. Saleh et al. (2013) measured pitch ranking for adjacent electrode pairs in CI users of AB, MED-EL and Cochlear devices. Binomial significance was used to create pass-fail rules for pitch ranking of electrode pairs. These data were used to deactivate electrodes associated with poor pitch ranking. Participants were given 1 month to adapt to their research programme. It was found that 20 out of 25 participants reported an improvement in sound quality. Furthermore, there was a significant improvement in speech-in-quiet and speech-in-noise scores.

Vickers et al. (2016) used a similar approach in CI users but only for those with a Cochlear device using the ACE processing strategy (n-of-m). In contrast to Saleh et al. (2013), direct electrical stimulation rather than acoustic stimulation was used to measure pitch ranking. They found that deactivation of electrodes with poor pitch ranking, resulted in no significant improvement in speech perception score when compared to the clinical programme, and in fact led to worse spectral resolution as measured with the spectral-temporally modulated ripple test (SMRT). Interestingly, deactivation of electrodes with good pitch ranking resulted in similar speech

perception scores to that when electrodes with poor pitch ranking were deactivated. The authors hypothesized that the lack of benefit was due to the fact that only a small number of electrodes were deactivated. Furthermore, the benefits of deactivation may not have been apparent with the n-of-m strategy utilized in ACE, in which only a proportion of the available electrodes are active at a single point in time.

Pitch ranking provides more functional information than electrode discrimination. However, it is a more challenging task to perform, particularly for young children and early-deafened late-implanted individuals. As described above, optimisation of the CI programme based on the pitch ranking has led to mixed results.

#### *1.5.1.3 Multidimensional scaling*

Multidimensional scaling (MDS) is a technique which is used to rate the perceptual difference between electrode pairs and takes into account the possibility that multiple percepts, rather than pitch alone, may change with electrode location (McKay et al., 1996). With MDS, loudness balanced electrode pairs are stimulated in sequence and participants rate the difference between them on a continuous scale. This procedure is performed for all possible electrode pairs and can be used to calculate a stimulus space in which the distances between electrodes is related to the relative perceptual dissimilarity between them. The results of MDS can be used to guide electrode selection. For example, Henshall and McKay (2001), deactivated electrodes that according to the MDS stimulus space were not tonotopically ordered, but this did not result in improved speech perception. McKay et al. (2002), created an experimental programme by selecting the 10 electrodes with the best discrimination based on MDS measurements. However, the experimental programme resulted in equivalent or worse outcome on various measures of speech perception compared to the clinical map.

MDS measurements require testing of all electrode pairs, which is time consuming and limits its clinical applicability. Fitting based on MDS also assumes that percepts across all dimensions should change in an orderly fashion along the electrode array. Whilst this is true for pitch, it is not known how the percept associated with other dimensions

should change. This too may underlie the lack of benefit of re-programming based on MDS in the above studies.

#### *1.5.1.4 Psychophysical tuning curves*

Channel interactions can be measured using PTCs. These assessments are based on the principle of forward masking, whereby the threshold of a probe stimulus can be increased by a prior masker stimulus depending on the level of interaction between the probe and masker electrodes. If probe and masker electrodes stimulate similar populations of auditory neurons, then the probe threshold is expected to increase by a greater amount. PTCs can be measured by measuring the threshold of a fixed probe electrode whilst varying the masker electrode location. The PTC for a single electrode therefore, provides an assessment of how that electrode interacts with every other electrode on the array. The shape of the PTCs can vary substantially across the electrode array within CI users (Chatterjee et al., 2006; Nelson et al., 2008). PTCs have a number of informative features. For example, there may be broadening or flattening of the PTC peak, which implies greater interaction between adjacent electrodes (Chatterjee et al., 2006; Chatterjee and Shannon, 1998; Nelson et al., 2008). PTCs can display tip shifts, whereby, the greatest level of masking is not produced when the masker electrode is the same as the probe electrode. It has been hypothesized that this indicates the presence of a neural dead region at the site of the probe electrode. PTCs may also display secondary peaks - in these cases, an additional area remote from the site of the probe electrode causes significant masking. It is thought that this effect may be due to the presence of cross turn stimulation (Nelson et al., 2008).

Previous studies have not shown a consistent relationship between PTC measures of spatial tuning and speech perception (Anderson et al., 2011; Boëx et al., 2003; Hughes and Stille, 2008; Throckmorton and Collins, 1999). Furthermore, these measurements are very time consuming, which make them impractical for clinical application.

## 1.5.2 Objectives measures of channel interactions

Behavioural measurements of channel interactions are dependent on attention, cognition and linguistic ability. This can reduce their reliability and makes them unfeasible in very young children. This limitation can be overcome with the use of objective electrophysiological measurements that not require active participation in an auditory task. These techniques involve measuring the neural response to sound stimuli at various levels of the auditory pathway. The objectives measures of channel interactions are summarized in the following sections.

### *1.5.2.1 ECAP channel interaction functions*

ECAPs can be measured by stimulating individual electrodes and measuring the response of the auditory nerve from neighbouring intra-cochlear electrodes. Similar to PTCs, ECAP channel interaction function (CIFs) (Cohen et al., 2003) are based on the principle of forward-masking. The reduction in the ECAP response amplitude of the probe electrode, due to a preceding masker, is assumed to reflect the amount of overlap in their stimulation fields. CIFs are typically obtained by measuring the ECAP response amplitude to a fixed probe, whilst varying the location of the masker across the array. Electrophysiological recordings in CI users are affected by artefacts associated with electrical stimulation from the device. The artefact can be measured by recording the response to the masker and probe presented in isolation, and using a subtraction technique to isolate the neural response. The spread of excitation with ECAP CIFs is usually quantified by measuring the function width. In general, the excitation profile obtained with ECAP CIFs shows good agreement with PTCs, though there is some inter-individual variability (Cohen et al., 2003; Hughes and Stille, 2008).

The ECAP CIF can also be used to calculate a metric called the channel separation index (CSI) which provides a measure of the non-overlap in excitation fields of two electrodes (Scheperle and Abbas, 2015a). The CSI is calculated from the difference between the CIF functions of two electrodes across the whole array, with a greater CSI value implying less overlap. Hughes and Abbas (2006), showed that the CSI, but not

the CIF width, was correlated with pitch ranking ability, suggesting that the CSI is a better parameter for quantifying spread of excitation from CIFs.

Most studies have not revealed a correlation between ECAP CIF measures and speech perception (Cohen et al., 2003; Hughes and Abbas, 2006; Hughes and Stille, 2008; van der Beek et al., 2012). More recently, Scheperle and Abbas (2015a), examined the relationship between the CSI and speech perception. Three experimental programmes with 7 active electrode were created in order to vary the likelihood of channel interactions. This was done by selecting either adjacent electrodes, every second electrode or every third electrode from the CI array for each of the programmes. The within-subject analysis in this study showed a significant positive relationship between the CSI and speech perception. However, the programme with the largest electrode separation, which also had the largest CSI, was the most similar to the user's clinical programme and this may have confounded the analysis. No relationship between the CSI and speech perception was found in the between-subject analysis. Due to the within and between subject variability in CIFs, there is no clear definition of what constitutes a significant interaction and re-programming interventions based on ECAP CIFs, have not yet been performed.

#### *1.5.2.2 EABR monaural interaction component*

Channel interactions have also been assessed with the EABR. Guevera et al. (2016) measured the EABR to simultaneous stimulation of 4 electrodes on the array. In addition, the EABR for each of the electrodes was measured individually. A monaural interaction component (MIC) was calculated as the ratio of the sum of the individual responses to the simultaneous response – a large MIC was hypothesized to indicate greater levels of channel interactions. It was found that the size of the MIC was negatively correlated with performance on a vowel-consonant-vowel test. Whilst this technique appears promising, it requires further validation. It would also be useful to measure the MIC for electrode pairs, to provide a more spatially specific measure of channel interactions. Furthermore, if these measurements are to be used to guide clinical interventions in CI users, it will be necessary to define what constitutes a significant interaction based on the MIC.

### *1.5.2.3 Cortical measures of channel interactions*

CAEPs can be used to objectively assess electrode discrimination, which as described earlier, provides a measure of channel interactions. CAEPs take into account central as well as peripheral auditory processing and therefore may provide a more functionally relevant assessment of channel interactions compared to the ECAP or EABR measurements. The CAEPs that can be used to assess discrimination include the mismatch negativity response (MMN), the P300 and the ACC. The focus of this thesis is the ACC as a measure of electrode discrimination. Therefore, the background to CAEPs and their measurement will be provided in the following section.

## 1.6 Cortical response measurements in CI users

### 1.6.1 The P1-N1-P2 complex

CAEPs can be evoked by a range of stimuli including clicks, tone-complexes and speech. CAEP measurements require that participants are awake, though not necessarily attending to the auditory stimulus. Broadly, there are two type of CAEPs i) obligatory responses (also termed exogenous responses), which can be recorded during passive listening and ii) endogenous responses, which are recorded during active listening and whose characteristics vary with the cognitive demand of the task (Cone-Wesson and Wunderlich, 2003).

The most commonly studied CAEP is the cortical onset response, an obligatory CAEP that occurs when there is a transition from silence to sound. This response typically occurs at a latency of 50 to 300ms after sound onset and is characterized by the P1-N1-P2 complex. The P1, N1 and P2 waves have been shown to have a number of generators in the brain – the measured wave therefore represents the summation of brain activity from multiple sources (Crowley and Colrain, 2004; Huotilainen et al., 1998; Liégeois-Chauvel et al., 1994; Näätänen and Picton, 1987). Whilst in young children, the P1 response dominates the CAEP, N1 and P2 waves are more prominent in adults and are usually used to evaluate auditory processing. The onset response is sensitive to stimulus features such as frequency, duration, intensity and interstimulus

interval (ISI) as well as subject factors such as age, wakefulness and attention (Picton, 2010). Furthermore, the onset response is affected by the integrity of the auditory pathway – it has therefore been used to assess hearing thresholds and has gained widespread clinical use for this purpose (Lightfoot and Kennedy, 2006).

The onset response has been widely used to study the hearing pathway in CI users. A number of well-known studies have used CAEP measurements to assess maturation of the auditory system in children (Ponton et al., 1996; Ponton and Eggermont, 2001; Sharma et al., 2005a). Sharma et al. (2005), showed that in children implanted before the age of 3.5 years, there was rapid development of the CAEP characterized by a reduction in P1 latency to within normal limits. In contrast, implantation after the age of 7 was characterized by abnormal CAEP morphology and prolonged P1 latencies. This study provided evidence for a sensitive period of auditory development in children. Cortical onset response characteristics have been correlated with speech perception in CI users (Kelly et al., 2005; Makhdoum et al., 1998), suggesting that these measurements could be used to objectively assess hearing benefit with a CI. More recently, Visram et al. (2015) showed that the cortical onset response thresholds were highly correlated with behavioural thresholds. This raises the possibility of using CAEPs to determine stimulation levels during CI fitting.

### 1.6.2 Recording CAEPs

When a sound is presented to the auditory system an electrical signal is transmitted through the nervous system to the auditory cortex. It is possible to record these electrical signals from the scalp non-invasively using electro-encephalography (EEG) (Luck, 2005). The electrical potential of individual neurons is too small to be recorded from the scalp. Rather, EEG records voltage due to the synchronous activity of thousands or millions of neurons which have a similar spatial orientation. It is thought that EEG signals predominantly represent post-synaptic potentials from pyramidal cells - these cells lie perpendicular to the surface of the auditory cortex and are well aligned with each other. As current flows from the brain, through the cerebrospinal fluid, skull and scalp tissue, it becomes more dispersed and attenuated, and therefore activity from deep brain regions are more difficult to record.



In addition to electrical activity from the brain, EEG systems pick up biological and environmental sources of electrical noise. EEG systems utilize differential amplifiers that amplify the difference between an active and reference electrode relative to a ground electrode. This process also removes sources of noise which are common to the active and reference electrodes. An analog-to-digital converter then samples the EEG signal and converts the voltage fluctuations into numerical representations. The EEG signal is then usually filtered digitally in order to reduce noise. High pass filtering removes low frequency noise due to movement or changes in the conductance of the skin whilst low pass filtering removes higher frequency noise due to muscle contraction or electrical line noise (typically 50-60 Hz). In addition, specialized, artefact reduction techniques can be used to remove artefacts, due to eye movements or the heartbeat, for example.

CAEPs are time locked to the auditory stimulus whilst most sources of noise occur randomly. Therefore, by measuring the evoked response potential over many trials and averaging the EEG signal, the brain response is consolidated whilst the noise is attenuated. Whilst CAEPs can be recorded with as little as 3 electrodes (active, reference and ground), the use of high density recording (eg 64-128 scalp channels) allows the EEG signal to be measured at a greater number of locations. This can be particularly useful for noise reduction algorithms as well as for source localization in order to investigate the EEG signal generator sites within the brain (Jatoi et al., 2014).

### 1.6.3 The problems of CI artefact

CAEP recordings in CI users represent a special case, due to the presence of large electrical artefacts which can be several hundred times the amplitude of the cortical response (Mc Laughlin et al., 2013). The characteristics of the CI artefact vary between devices and stimulation strategy (Martin, 2007; Viola et al., 2011) and consist of a number of components i) The radio frequency coil artefact, which is in the Megahertz range and is typically removed by the low-pass filter in the hardware of EEG recording systems ii) A high frequency artefact related to the pulse trains delivered through the CI array - this can be removed by using a digital low pass filter of around 30-40Hz as CI

stimulation rates are usually much higher ii) Direct current (DC) artefact which has a similar onset and offset to the electrical stimulus. This is thought to be related to a capacitance effect at the EEG channel - scalp interface or the CI electrode-neuron interface. The DC artefact can be particularly problematic to remove.

A number of methods have been used to reduce CI artefact (Hofmann and Wouters, 2010; Martin, 2007). These include the use of very short duration stimuli which do not overlap with the CAEP, choosing a reference electrode location that minimizes artefact pick up and using alternating polarity stimuli, which reduces the effect of polarity dependent artefacts. The DC artefact can also be minimized by ensuring similar low levels of impedance on the recording scalp channels (Mc Laughlin et al., 2013). Despite using these methods, substantial CI artefact may still be present and effective techniques are then required to remove these. Mc Laughlin et al. (2013), have shown that it is possible to remove the DC artefact by modelling it from the pulse amplitude of the stimulus. This technique appears to be feasible even when using a limited number of recording channels. An alternative approach is to use high density EEG scalp recordings. The cortical response and artefacts are measured across the whole scalp and this allows removal of the artefact using techniques such as beamforming, spatial filtering, principal component analysis and independent component analysis (Campos Viola et al., 2009; Martin, 2007; Wong and Gordon, 2009). Using high density recordings is more time consuming both in terms of data collection and data processing. However, these techniques have been widely used in CI users and may be more reliable for modelling and removing artefacts from different devices and individuals.

#### 1.6.4 Cortical measures of discrimination

In addition to assessing sound detection, CAEPs can be used to assess auditory discrimination. This forms the basis of their use for measuring channel interactions. A summary of the discriminatory CAEPs follows.

#### *1.6.4.1 The MMN*

The MMN is an obligatory response, which can be recorded in a passive listening condition. It is recorded with an oddball paradigm consisting of frequent standard stimuli and rare deviant stimuli (for a review see Näätänen et al., 2017). The MMN is usually seen as a late negativity in the difference wave between the responses to the standard and deviant stimuli. The MMN can be used as a measure of discrimination of stimulus duration, frequency and loudness. In addition, MMN characteristics such as latency and amplitude are well correlated with psychophysical measurements of auditory discrimination (Näätänen et al., 2017). Typically, the ratio of standard to deviant stimuli is 4:1. This means that the deviant stimulus is only presented 20% of the time and as a result, a large number of trials are usually needed to record the MMN, which makes it a time consuming measurement. More efficient 'multi-feature' MMN recording paradigms have been developed but there are limited numbers of studies using these techniques in CI users (Näätänen et al., 2017; Sandmann et al., 2010).

The MMN response is usually small and a lack of sensitivity at the individual level has been reported by a number of investigators (Bishop and Hardiman, 2010; Picton, 1995; Singh et al., 2004). The MMN has been used as a measure of electrode discrimination in CI users in a single study (Wable et al., 2000) in which the standard and deviant stimuli were presented by stimulating different electrodes. In the study by Wable et al. (2000), it was found that the MMN could be measured for various electrode contrasts at the group level but data for individual CI users was not presented. No correlation between speech perception scores and the MMN was found. The lack of recording efficiency as well as the poor sensitivity at the individual level, limits the use of the MMN as a measure of channel interactions in CI users.

#### *1.6.4.2 P300*

The P300 is an endogenous CAEP that provides an objective assessment of auditory attention and discrimination. Like the MMN, it is recorded with an oddball paradigm but the participant is required to attend and respond to the deviant stimulus, for example by pressing a button. The P300 is seen as a positive wave occurring at a

latency of around 300 ms to the deviant stimulus. The characteristics of the P300 response are affected by the probability of occurrence of the deviant stimulus, the difficulty of the auditory task as well as the amount of effort that a participant devotes to the task (Luck, 2005). A number of studies have found a relationship between P300 amplitudes/latencies and speech perception in CI users (Groenen et al., 1996; Kileny et al., 1997; Kubo et al., 2001). To date, the P300 has not been used to assess electrode discrimination in CI users. As these measurements require active participation in an auditory task, they offer limited benefit compared to behavioural measures of electrode discrimination.

#### *1.6.4.3 The acoustic change complex*

Another discriminatory CAEP, which has gained much interest in recent years, is the acoustic change complex (also referred to as the auditory change complex or ACC). This is an obligatory CAEP that occurs in response to a change in an ongoing stimulus. The response to the initial part of the stimulus is a cortical onset response, which occurs due to a change from silence to sound. The subsequent response, which occurs due to a change in the ongoing stimulus, is the ACC. Both the onset and ACC responses have similar morphologies and it is thought that similar processes underlie these CAEPs. In order to record the ACC, it is necessary to use long duration stimuli of several hundred milliseconds duration, so that it is not masked by the cortical onset response.

A major advantage of the ACC over the MMN is that it can be recorded with greater efficiency. With oddball paradigms, the deviant stimulus is typically presented on 20% of trials, whilst for ACC paradigms there is an acoustic change on every trial. Martin and Boothroyd (1999), reported that the average amplitude of the ACC was 2.5 times larger than that of the MMN and concluded that the ACC provides a more sensitive index of discrimination capacity. Furthermore, the ACC has a high test-retest reliability (Friesen and Tremblay, 2006; Tremblay et al., 2003) and there is a close relationship between behavioural discrimination thresholds and ACC thresholds (Atcherson et al., 2009; He et al., 2012; Michalewski et al., 2005). For example, He et al. (2012) measured behavioural discrimination and ACC thresholds in 26 NH adults. The mean

intensity discrimination threshold was 1.77 dB for behavioural measurements and 2 dB for ACC measurements. The mean frequency discrimination threshold was 3.55 Hz for behavioural measurements and 5.81 Hz for the ACC. It was found that increasing the magnitude of change across different acoustic dimensions, led to consistent changes in the ACC amplitude but not the ACC latency, indicating that the former is a better measure of auditory discrimination.

A number of investigators have measured the electrically evoked ACC (eACC) in CI users. Friesen et al. (2006), first measured the eACC to natural speech tokens. Similar to NH listeners, it was found that the ACC had good test-retest reliability and that different speech tokens resulted in distinct ACC responses. In subsequent studies, the eACC has been measured to changes in spectrum, intensity and temporal gaps (He et al., 2013; Kim et al., 2009; Martin, 2007). The eACC to a change in place of stimulating electrode has been termed the spatial auditory change complex (spatial ACC) (Scheperle and Abbas, 2015b). This provides an objective measure of electrode discrimination. Studies relating to the spatial ACC shall be reviewed in the following section.

### 1.7 The spatial ACC

Brown et al. (2008), first measured the spatial ACC in 9 post-lingually deaf adults with a Cochlear device. All of the participants in their study had been using their CI for at least 1 year. In general, it was found that there was a monotonic relationship between electrode separation and ACC amplitude i.e. as separation increased, spatial ACC amplitude also increased. However, in this study, electrode pairs were not explicitly loudness balanced and therefore it is possible that cortical responses occurred due to perceived changes in loudness. The relationship to behavioural electrode discrimination was not examined in the above study. Subsequently, Hoppe et al. (2010), measured the spatial ACC in 16 post-lingually deafened adult users of the Cochlear device who had been using their implant for at least 6 months. The spatial ACC was measured at apical, mid and basal electrode locations in each CI user after loudness balancing. A 3-AFC task was used to measure behavioural discrimination and calculate a  $d'$  score at the same location. The spatial ACC could be recorded in 88% of

cases. Furthermore, a significant but relatively weak correlation was found between the  $d'$  score and ACC amplitude and latency.

He et al. (2014), measured the relationship between the spatial ACC and behavioural discrimination in 15 children with auditory neuropathy spectrum disorder (ANSD). The children in their study all had a Cochlear device and had been using their CI for at least 9 months. Loudness balancing was performed and EDLs were measured around a single electrode in the middle of the array, using both spatial ACC and behavioural measures of electrode discrimination. A spatial ACC 'pass' was defined on two criteria: i) mutual agreement based on visual inspection by 2 raters ii) root mean squared (RMS) amplitude of the ACC at least 50% greater than that of the noise floor. Behavioural electrode discrimination was measured with a 2-AFC task and a pass was defined as a correct response for at least 4 out of 6 trials. He et al. (2014), showed that there is a strong relationship between spatial ACC and behavioural measures of electrode discrimination. Unlike Brown et al. (2008), a non-monotonic relationship between electrode separation and spatial ACC amplitude was found. Of note, spatial ACC EDLs and ACC amplitudes were significantly different between groups of children with good and poor open-set speech perception.

Scheperle and Abbas (2015b), examined the relationship between peripheral and central measures of channel interactions by measuring ECAP CIFs and the spatial ACC in 11 post-lingually deafened adults. All of the participants had at least 15 months of experience with a Cochlear device. A peripheral measure of channel interactions for electrode pairs was calculated using the CSI. The relationship between the CSI and spatial ACC amplitudes was modelled using a saturating exponential function. Although a significant relationship was found, there was substantial variation in the nature of this relationship between participants. The fact that ACC amplitude was partially independent of the peripheral measures of spatial selectivity, was interpreted as providing evidence of variation in central processing between CI users. It was hypothesized that the difference in central processing might account for the failure to find a relationship between ECAP CIFs and speech perception in previous studies (as described in section 1.4.2.1).

In a follow-up study, Scheperle and Abbas (2015a), examined the relationship between speech perception and central as well as peripheral measures of spatial selectivity in the same participants. As described in section 1.5.2.1, three experimental maps which varied in their likelihood of channel interaction were created. ECAP CIFs were measured and the CSI was calculated for all adjacent pairs of electrodes. In addition, the individual exponential function from the first study was used to predict the spatial ACC amplitude for adjacent electrode pairs from the CSI. The within-subject analysis showed that CSI and spatial ACC amplitude were significant predictors of speech perception, with the CSI being the stronger predictor. In the across subject analysis, it was found that spatial ACC amplitude but not ECAP CSI was significantly correlated with speech perception.

### 1.8 Summary and rationale for this study

Multiple lines of evidence show that the channels on a CI array are non-independent. The presence of substantial channel interactions and the associated loss of spectral resolution, may contribute to poor outcomes in certain CI users. Although electrode discrimination provides a fairly coarse measure of channel interactions compared to other techniques, it is easy and quick to measure. Furthermore, the finding of poor electrode discrimination is significant as it implies that the sound signal from the CI is not being preserved in the auditory pathway. Previous studies have shown that poor electrode discrimination in CI users is not uncommon and that this is related to poor speech perception. Furthermore, there is evidence to suggest that identification of areas of poor discrimination on the CI array, may allow interventions that improve hearing outcome such as auditory training or re-programming of the CI.

Behavioural assessments of electrode discrimination are dependent on cognition, attention and language, which limits their use in difficult to test patient groups such as young children. This limitation may be surmounted by the use of the spatial ACC, which is an obligatory CAEP that provides an objective assessment of electrode discrimination. Previous studies of the spatial ACC have shown that it is related to behavioural measures of electrode discrimination as well as speech perception. This raises the possibility of using this objective measure to guide clinical interventions that lead to improved hearing outcome. However, further characterization of the spatial

ACC is required if it is to be used as a clinical tool. Furthermore, the aforementioned studies of the spatial ACC suffer from a number of limitations which shall be outlined below.

To date, the spatial ACC has only been measured in relatively experienced CI users and its development over time is yet to be determined. Previous studies in children and adults, have shown that cortical responses undergo significant morphological changes during the first 6 months after switch-on (Burdo et al., 2006; Jordan et al., 1997; Pantev, 2005; Ponton and Eggermont, 2001; Sharma et al., 2005a). Cortical responses in CI users are typically small immediately after switch-on and amplitude increases with hearing experience (Burdo et al., 2006; Sandmann et al., 2015). It therefore may not be feasible to measure the ACC in the early period after switch-on. Early assessment of electrode discrimination could help to guide management during the sensitive period of auditory development in children. Even in adults, it would be beneficial to use such assessments to optimize hearing performance as soon as possible. It will also be important to understand how the spatial ACC develops over time in relation to behavioural discrimination. If, for example, the spatial ACC develops over a long period of time with CI listening experience, then prematurely altering clinical management on the basis of these measurements may be detrimental to outcome.

Previous studies of the spatial ACC have only included participants with a Cochlear device. As discussed earlier, one of the challenges with measuring CAEPs is the presence of CI artefact which varies between devices (Viola et al., 2011). When using long duration stimuli, as the for the ACC, the electrophysiological response necessarily overlaps with the CI artefact. Martin et al. (2007), measured the eACC to a change in second formant frequency in an adult with the MED-EL device. A large device related scalp artefact was present but the eACC could be teased apart using signal processing techniques. Hoppe et al. (2010), also reported significant scalp artefact when measuring the spatial ACC with the Cochlear device. For the spatial ACC to be clinically useful it must be measurable in different CI devices and techniques for dealing with artefact in different devices and individuals are necessary.



Further investigation into the relationship between the spatial ACC and behavioural electrode discrimination is warranted. As discussed earlier, Hoppe et al. (2010), showed a significant but weak relationship between spatial ACC amplitude and behavioural  $d'$  score. However, this study included repeated measurements from individuals which may have artificially increased correlation coefficients. In the study by He et al. (2014), behavioural electrode discrimination was assessed with a 2-AFC task and a pass required at least 4 correct responses on 6 trials. With these criteria, the binomial probability of achieving a behavioural pass by chance is 34% and a high false hit rate would be expected. Stricter criteria should be used to validate the spatial ACC as a measure of electrode discrimination. Furthermore, in the study by He et al. (2014), the criteria for defining an ACC pass included visual assessment of the response by 2 non-independent raters. This may have resulted in bias when evaluating the responses. From a clinical point of view, using pass-fail criteria is relevant as this could help to determine management decisions such as electrode selection for deactivation. However, it would be fairer and quicker to use statistical criteria to compare the ACC response to the noise floor to determine the presence or absence of a response, rather than using visual criteria.

The relationship between the spatial ACC and speech perception also needs further examination. Although He et al. (2014), showed that the EDLs measured with the spatial ACC were significantly different between good and poor performers, their results may not be generalizable. Firstly, the participants were children with ANSD and secondly, EDLs in their study population ranged from 1 to 2 electrodes. Studies in non-ANSD children and adults, have shown that EDLs are much more variable and can be as large as 9 electrodes (Busby and Clark, 1996; Dawson et al., 2000; Kopelovich et al., 2010; Zwolan et al., 1997). Scheperele and Abbas (2015a), found that spatial ACC amplitude was correlated with speech perception scores on a continuous scale, but the spatial ACC amplitude was not measured, but rather was predicted from ECAP CIP functions. The relationship between the CSI and spatial ACC varied substantially between individuals (Scheperele and Abbas, 2015b) and therefore, the accuracy of the predicted spatial ACC values is questionable.

It will also be important to gain an understanding of how the characteristics of the spatial ACC are affected by factors such as stimulus intensity, duration and ISI. This would allow a sensitive and efficient recording paradigm to be developed for clinical application.

## 1.9 Aims

The overall aim of this thesis was to determine whether the spatial ACC can be used to assess electrode discrimination objectively in CI users with a view to using this as a clinical tool for patient assessment. The specific objectives were to:

- 1) determine whether the spatial ACC can be measured in CI devices from different manufacturers (Chapter 3)
- 2) determine whether the spatial ACC can be measured in the early period after CI switch-on and whether it relates to behavioural electrode discrimination at this stage (Chapter 3)
- 3) assess how behavioural and objective measures of electrode discrimination develops with CI experience (Chapter 4)
- 4) determine the relationship between the spatial ACC and behavioural electrode discrimination during the first year after switch-on (Chapter 4)
- 5) examine the effect of stimulus intensity on the spatial ACC and behavioural electrode discrimination (Chapter 5)
- 6) examine the relationship between speech perception and electrode discrimination, as measured with the spatial ACC and a behavioural task (Chapters 3, 4 and 5)
- 7) determine whether the recording of the spatial ACC can be made more efficient and sensitive for clinical application (pilot study, Chapter 6)

Appendix A consists of an analysis of test-retest reliability. This analysis was performed retrospectively with data that was collected > 6 months post CI activation as part of the above experiments.

## Chapter 2 General Methods

This section describes common methodology used for data collection in Chapters 3 to 5. Further details for each experiment are provided in the relevant section. In Chapter 6, the methodology for recording ACC measurements was developed to improve efficiency and will be described separately.

Only adult CI participants were recruited to this study. All participants had full electrode array insertions and normal electrode impedances. Demographic details of participants in each experiment are provided in the relevant chapter. The studies were approved by the UK National Health Service Research Ethics Committee (14/LO/2076) and the University College London Research Ethics Committee (7161/002). All participants provided written informed consent prior to testing and received a small payment for taking part in the study.

### 2.1 Stimuli for ACC measurement

Stimuli were adapted from Brown et al. (2008). The participants own sound processor was bypassed and electrodes were stimulated directly with a monopolar configuration through a research interface specific to each CI manufacturer (RIB2 for MED-EL and BEDCS for AB devices). A schematic of stimuli that were typically used is shown in figure 2.1. Stimuli were 800 ms in duration and consisted of biphasic pulses presented at a rate of 1000 pps and phase duration of  $\sim 50 \mu\text{s}$ . The first and last 12 ms of the stimulus consisted of zero amplitude pulses, during which the processor still communicates with the internal receiver. This period was included to reduce potential overlap between CI artefact and the cortical response. Stimuli were presented at a rate of 0.51 Hz which resulted in an ISI of 1161 ms. When measuring the spatial ACC there was a change in stimulating electrode at 400 ms which is the midpoint of the stimulus. The first electrode will be referred to as the 'reference electrode' and the second electrode will be referred to as the 'test electrode'. The cortical responses elicited by the reference and test electrodes will be referred to as the 'onset response' and the 'ACC' respectively.

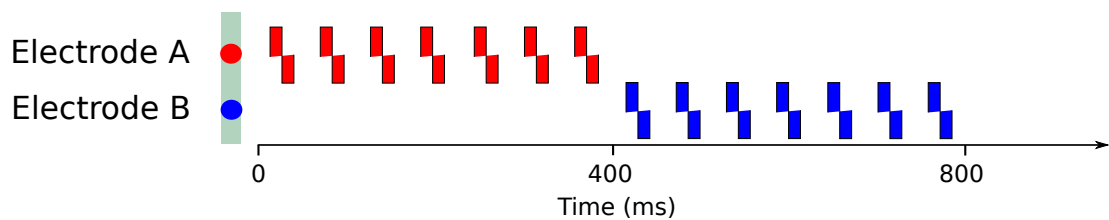


Figure 2.1 Schematic of the stimuli used for measuring the spatial ACC. Stimuli consisted of 800ms biphasic electrical pulses at 1000 pulses per second with a change in stimulating electrode at the midpoint of the stimulus. The ISI was 1161 ms. The reference electrode is shown in red and the test electrode is shown in blue.

## 2.2 Stimulus intensity and loudness balancing

For each electrode, the threshold level was measured with an ascending method of adjustment. Stimulation began at a level which was inaudible and increased in 5  $\mu\text{A}$  steps until participants reported that they could just hear a sound. The threshold level was determined by repeating this procedure until the same value was obtained twice in a row. The most comfortable level for the reference electrode was determined by gradually increasing the stimulation level until participants indicated that the loudness was at point 6 on a 10-point AB loudness chart. This procedure was repeated twice and the average of the two estimates was taken as the MC level of the reference electrode.

It is known that the ACC amplitude is affected by changes in loudness as well as spectrum (Kim et al., 2009; Martin and Boothroyd, 2000). In order to minimize loudness cues when switching the active electrode, electrode pairs were carefully loudness balanced. A loudness balancing procedure was adapted from He et al. (2014). The stimulation level of the test electrode was initially set at the MC level of the reference electrode. The reference and test electrode were then stimulated in sequence separated by a gap of 600ms. Based on feedback from the participant, the experimenter adjusted the level of the test electrode until both stimuli were perceived to have the same loudness. This procedure was repeated a total of three times and the average was used as the loudness balanced MC level for the test electrode.



session, participants sat in a comfortable chair in an acoustically isolated sound booth and watched a subtitled film of their choice. Participants were encouraged to sit as still as possible.

## 2.4 EEG Processing

Recordings were processed off-line using a custom analysis module in Python 2.7 written by Dr Jaime Undurraga. Unconnected and poor EEG electrode contacts were automatically detected and removed from the analysis. Data were down sampled (1000 Hz), band-pass filtered between 2-30 Hz (zero-phase, third-order Butterworth filter) and referenced to the contralateral mastoid. Eye movement and eye blink artefact were removed by means of a standard correlation subtraction. EEG responses were de-noised using spatial filtering (Cheveigné and Simon, 2008; Undurraga et al., 2016) as follows:

- 1) Epochs from each EEG channel were normalized and submitted to principal component analysis (PCA), where components with negligible power were discarded. The remaining components were normalized to obtain a set of orthonormal vectors.
- 2) Epochs were submitted to a bias function. The definition of the bias function determined the rotation matrix obtained on a second PCA, and so its definition depends on the particular problem. Since the primary goal was to remove the DC component of the CI artefact, which is larger than the neural response, the bias function was defined as the mean.
- 3) A second PCA was applied to data resulting from the bias function. This resulted in a rotation matrix biased towards the evoked response instead of unrelated events such as residual eye blinks, heart activity, and other ongoing brain activity.
- 4) The rotation matrix resulting from step 3 was applied to the rotation matrix obtained in step 1. The resulting components were ordered by decreasing bias score so that they could be divided into artefact components (which were discarded), signal components (which were kept), and noise components (which were also discarded).

CI artefact was identified from individual components obtained in step 4. Each of the components were projected back to the sensor space. A component was considered a CI artefact when the scalp map showed a centroid on the side of the implanted device, the amplitude was large, and component activations matched the onset/offset of stimulation (Debener et al., 2008). This was typically the first component (the one with largest power) and in a few cases the second or third component also contained DC artefacts.

Per-channel time averages were obtained by applying a weighted averaging method (Don and Elberling, 1994). This method estimates the variance of the noise by tracking one or several fixed points over time from a given subset of consecutive epochs. In this study, the power of the residual noise (RN) was estimated by tracking 256 isochronal points (7.5 ms), from a subset of at least five epochs. The final size was determined adaptively by comparing the variance of successive subsets (Silva, 2009). As the variance of each subset is known, the final average is obtained by weighting each subset by the inverse of its variance.

The presence or absence of the ACC was determined objectively by means of a Hotelling's t-squared (Hotelling-T2) test (Golding et al., 2009) which is a multi-dimensional equivalent of the (squared) univariate t-statistic. In this context, the EEG data can be considered as a multivariate measure, i.e. several samples along a time window of interest which encompasses the waveform region where the response is expected. The samples submitted to the Hotelling-T2 were chosen as in Golding et al. (2009). That is, within a given response window and for each epoch, several sample bins were determined by averaging samples every 40 ms. A typical response window had a length of 200 ms, between 450 – 650 ms after stimulus onset for the ACC response. This time window was chosen as it typically encompasses the P1, N1 and P2 peaks of the ACC. This led to a total of about 5 bins per epoch - equivalent to having 5 variables per epoch. These 5 variables - sampled 300 times each - were submitted to the Hotelling-T2 test which tested the probability that any linear combination of the 5 variables had a mean value significantly different from zero. In certain cases, the response window was adjusted to 450 – 700 ms to account for a late P2, or shortened to 450 – 600 ms to account for an absent P2. An objective ACC pass for an electrode



pair was defined as a Hotelling-T2 p value < 0.05 in at least 5 out of 9 frontal and central scalp channels, where the ACC is usually most prominent (Cz , C1, C2, Fz, F1, F2, FCz, FC1 and FC2; C = central, F = frontal, FC = fronto-central; suffix z represents midline location, 1 represents location to the left of midline and 2 represents location to the right of midline).

An automatic peak detection algorithm was used to identify evoked response peak amplitude and latency. P1 was defined as the maximum peak voltage between 30-90ms for the onset response and between 430 and 490 ms for the ACC. N1 was defined as the minimum peak voltage between 70 and 150 ms for the onset response and between 470 and 550 ms for the ACC. P2 was defined as the maximum positive peak voltage occurring between 150 and 290ms for the onset response and 550 and 690 ms for the ACC. Responses were inspected visually and the time windows were adjusted as necessary. Although the Hotelling-T2 was used to determine whether the ACC was present or absent, the magnitude of the response was quantified by measuring peak amplitude. Data are presented at the scalp location FCz unless otherwise stated as the magnitude of the ACC is typically largest at this site.

## 2.5 Behavioural electrode discrimination

Behavioural electrode discrimination was determined using a 3-interval 2-AFC paradigm. The first interval always contained the reference electrode stimulus and the test electrode stimulus occurred with equal probability in either the second or third interval. Participants were instructed to choose the interval that was different and feedback was not provided. Stimuli consisted of alternating polarity biphasic pulse trains from a single electrode, with pulse rate of 1000 pps, phase width of 50  $\mu$ s and duration of 400 ms. Each interval was 1.4 s long. There were a total of 20 trials per electrode pair. The order of electrode pairs tested in each participants was randomized when testing behavioural discrimination. A behavioural pass was defined as a score of at least 80%. This cut-off was chosen as it has a binomial probability of < 0.01 and reduces the likelihood of a false positive pass. In addition, from a clinical point of view, a high cut off might be more relevant as performance could potentially be improved by addressing electrodes with lower discrimination scores. The behavioural score was

converted to a  $d'$  score. The maximum  $d'$  score was 2.77 based on a correction factor for a score of 100% (Stanislaw and Todorov, 1999).

## 2.6 Speech perception testing

Speech perception testing was conducted in a sound treated booth using the AB-York Crescent of Sound (Kitterick et al., 2011). The crescent of sound is a speaker array, which has been developed for clinical and research speech testing. For the purposes of this study a single speaker from the centre of the array was sufficient. Open-set sentence and closed-set vowel perception were tested, with no feedback provided. A single presentation of the test material was allowed during each trial. Participants used their own sound processor with their preferred CI map and the non-CI ear was unaided.

Open-set sentence perception was tested with the Bamford-Kowal-Bench (BKB) test. Listeners were asked to repeat each sentence and were given a score based on the number of key words correct. Two lists of 16 sentences (100 words) were chosen randomly for testing. Presentation level was 70 dBA in quiet. Closed-set vowel perception was tested with the CHEAR Auditory Perception Test (CAPT) vowel sub-test (Vickers et al., 2018). The CAPT was used because it is sensitive to spectral differences in hearing aid fitting algorithms (Marriage et al., 2018). The CAPT is a 4-AFC monosyllabic word-discrimination test spoken by a female British English speaker. It contains five sets of four minimally-contrastive real words e.g. cat, cot, cut, cart. Listeners were asked to respond by choosing from four pictures on a computer screen. Stimuli were presented at 60 dBA in quiet. This level was intended to be lower than comfortable in order to challenge the auditory system and understand how well an individual can understand speech in non-ideal conditions. The test was repeated to give a total score out of 40. This was converted to a  $d'$  score with a maximum of 3.69 (Stanislaw and Todorov, 1999).

None of the participants had significant residual hearing in the contralateral ear except for participant S10 (see table 3.2). It is unlikely that hearing from the contralateral ear affected this participant's speech scores as his unaided (i.e. no CI or hearing aid) BKB sentence score was 0%.

## 2.7 Statistical analysis

All statistical analyses were performed using the R software package (R Development Core Team, 2015). Parametric correlation analysis was performed with Pearson's correlation coefficient and confidence intervals were calculated based on the standard error. Non-parametric correlation analysis was performed with Spearman's rank correlation coefficient and confidence intervals were calculated using bootstrapping with 1000 repetitions. Linear mixed-effects (LME) models were used to analyze datasets with repeated measurements as they allow complex modelling of random effects and can deal with unbalanced data (Baayen et al., 2008; Bates et al., 2015). The factor 'subject' was set as a random effect in these models. Backward stepwise reduction was used to optimize the model. Visual inspection of residuals and Cook's distance calculation were used to identify outliers and influential data points. The effect size of factors was based on an estimate of the semi-partial  $R^2$ , which was estimated with the R software package 'r2glmm' (Jaeger et al., 2017). An  $R^2$  value of 0.02 – 0.13 is considered small, 0.13 – 0.26 medium and  $> 0.26$  large (Bakeman, 2005).

## Chapter 3 Validation of the spatial ACC in adult CI users

This chapter is based on the following published journal article:

Mathew R, Undurraga J, Li G et al. Objective assessment of electrode discrimination with the auditory change complex in adult cochlear implant users. *Hear Res.* 2017 ;354:86-101. doi: 10.1016/j.heares.2017.07.008.

### 3.1 Abstract

The spatial auditory change complex (ACC) is a cortical response elicited by a change in place of stimulation. To date, the spatial ACC has only been measured in relatively experienced cochlear implant (CI) users with one type of device. Early assessment of electrode discrimination could allow auditory stimulation to be optimized during a potentially sensitive period of auditory rehabilitation. In this study, a direct stimulation paradigm was used to measure the spatial ACC in both pre- and post-lingually deafened adults. It is shown that it is feasible to measure the spatial ACC in CIs from different manufacturers and as early as 1 week after CI switch-on. The spatial ACC has a strong relationship with performance on a behavioural discrimination task and in some cases provides information over and above behavioural testing. These data show that the spatial ACC is a feasible and valid measure of electrode discrimination in CI users.

### 3.2 Introduction

Sound processing strategies with CIs assume that electrodes stimulate distinct populations of neurons in the cochlea in a tonotopic fashion. If electrodes within the CI array are indiscriminable, speech cues will be lost and speech perception may suffer. This has been confirmed by a number of studies which have shown that poor electrode discrimination, particularly in the apical and mid array, is associated with poor speech perception (Busby et al., 2000; Dawson et al., 2000; Henry et al., 2000). Assessment of electrode discrimination ability may be of particular importance, as there is evidence that speech perception in individuals with impaired electrode discrimination, can be improved by deactivating indiscriminable electrodes (Saleh et al., 2013; Zwolan et al., 1997) or by providing auditory training (Fu and Galvin, 2008). Given that there is a

sensitive period for auditory development (Holt and Svirsky, 2008; Kral et al., 2006; Nikolopoulos et al., 1999; Sharma et al., 2005a), and that auditory experience during this period has large-scale and long-term effects (de Villiers-Sidani et al., 2007; Zhang et al., 2001), it follows that interventions to optimize auditory stimulation through the CI should occur as early as possible.

There has been growing interest in measuring discrimination ability in CI users with the ACC. This is an auditory cortical potential which occurs in response to a change in an ongoing stimulus. The advantage of electrophysiological measurements is that they do not require active participation and can be performed in young children including infants (Chen and Small, 2015; Martinez et al., 2013). In addition, there is evidence that changes in electrophysiological measurements precede changes in behavioural performance (Tremblay et al., 1998). The ACC may therefore provide information over and above behavioural testing and be particularly suited to assessing whether stimulus change is encoded in the auditory pathway in the early period after CI switch-on.

The ACC to a change in place of the stimulating electrode has been termed the 'spatial ACC' (Scheperle and Abbas, 2015b). There is evidence that the spatial ACC provides a useful measure of behavioural discrimination (He et al., 2014b; Hoppe et al., 2010). Hoppe et al. (2010) found a significant but weak correlation between behavioural discrimination  $d'$  score and spatial ACC amplitude. He et al. (2014b) measured the relationship between the spatial ACC and behavioural discrimination in children with auditory neuropathy spectrum disorder (ANSD). Using pass-fail rules, a strong relationship between objective and behavioural measures was found.

To date, the spatial ACC has only been measured in relatively experienced CI users and also, only in users of the Cochlear device. For the spatial ACC to be clinically useful it must be measurable in different devices. One of the challenges with measuring auditory cortical responses to long stimuli is the presence of CI artefact, which overlaps the electrophysiological response, and varies between devices and stimulation strategies (Martin, 2007; Viola et al., 2011). In addition, it would be useful to measure the spatial ACC in the early period after CI switch-on. An early assessment of electrode discrimination could help to guide management during a sensitive period

of auditory development in children. Even in adults, it would be beneficial to use such assessments to optimize hearing performance as soon as possible. Previous studies have shown that cortical responses undergo significant morphological changes during the first 6 months after CI switch-on (Pantev, 2005; Ponton and Eggermont, 2001; Sharma et al., 2005a). Pantev (2005), measured cortical responses to frequency shifts with MEG in two adults with magnet-free CIs. Cortical responses could not be detected in these participants for the first 2-3 months after switch-on. To date, the spatial ACC has not been successfully measured in the early period after CI switch-on and its relationship to behavioural discrimination during this period is therefore unknown.

The objectives of this study were to determine:

- 1) whether the spatial ACC can be measured in individuals with different CI manufacturer's devices
- 2) whether it is feasible to measure the spatial ACC in pre and post-lingually deafened adults as early as 1 week after CI switch-on
- 3) how the spatial ACC is related to behavioural discrimination during this period
- 4) if there is a relationship between measures of electrode discrimination and speech perception.

The study consists of two experiments. In the first experiment, the spatial ACC was measured in experienced CI users with two different CI manufacturer's devices. In the second experiment, the spatial ACC was measured in newly implanted CI users.

### 3.3 Experiment 1: Pilot phase – assessment and removal of CI artefact

#### 3.3.1 Design and Methods

##### *3.3.1.1 Participants*

There were four participants, ranging in age from 18 to 68 years. All of them had been using their CI for at least 2 years at the time of testing, and had a unilateral implant except for participant P2, who was bilaterally implanted. In this participant, the ear which was subjectively reported as being the better hearing ear was chosen for

testing. Two participants had MED-EL devices and the other two had an AB device. Demographic details of study participants are provided in table 3.1.

### *3.3.1.2 Test procedures*

The aim of this experiment was to determine the feasibility of measuring the spatial ACC in AB and MED-EL devices. For experiment 1, the reference electrode was chosen from the middle of the array. The reference electrode was paired with an adjacent test electrode, which was described by the participant as clearly having a different pitch. Electrode pairings are shown in table 3.1.

EEG recordings were performed in 3 conditions as shown in figure 3.1. In the 'suprathreshold change' condition (figure 3.1A), the reference electrode was stimulated for 400ms followed by the test electrode for another 400 ms with no gap. Stimulation level was at the most comfortable level as determined by the loudness balancing procedure described in the General Methods (Chapter 2). In addition, there were two control conditions. The first control consisted of a 'suprathreshold no change' condition (figure 3.1B) in which the reference electrode was stimulated for 800 ms at the most comfortable level. This condition was included to evaluate the effect of radio frequency or switch artefacts on the recordings, as the processors were still programmed to "switch" to the same electrode at 400 ms. The second control was the 'subthreshold change' condition (figure 3.1C), in which stimulation level was at 10  $\mu$ A below the threshold level for both test and reference electrodes. By measuring the ACC in a subthreshold stimulation condition, the CI artefact can be measured accurately and compared to artefact isolated with signal processing techniques in suprathreshold stimulation conditions. The order of presentation of conditions was randomized. EEG data were processed as described in the General Methods and are presented at fronto-central channels. In addition, for experiment 1, data for the average scalp response are presented as this allows assessment of whether artefact has been removed across the whole scalp, as opposed to a single scalp location. The total experimental time was 1.5 hours for each participant.

Table 3.1 Demographic details of participants in experiment 1. F= female, M= male, R = right, L= left, AB HR 90K = Advanced Bionics HiRes 90K, FS4 = Fine structure 4, HDCIS = High definition continuous interleaved sampling

Participant ID	Age	Sex	Ear	Risk factor for hearing loss	Communication	Duration profound hearing loss (years)	Duration implant use (years)	Electrode pair tested	Device	Electrode	Processing strategy
P1	41	F	R	Unknown	oral	39.5	6	9 and 7	AB HR 90K	1J	HiRes
P2	18	M	R	X linked inheritance	oral + sign	10	2	6 and 8	MED-EL CONCERTO	Flex 28	FS4
P3	66	M	L	Unknown	oral	16	9	9 and 11	AB HR 90K	1J	HiRes
P4	68	M	L	Guillian Barre Syndrome	oral	5	5	6 and 10	MED-EL SONATA	Flex 28	HDCIS



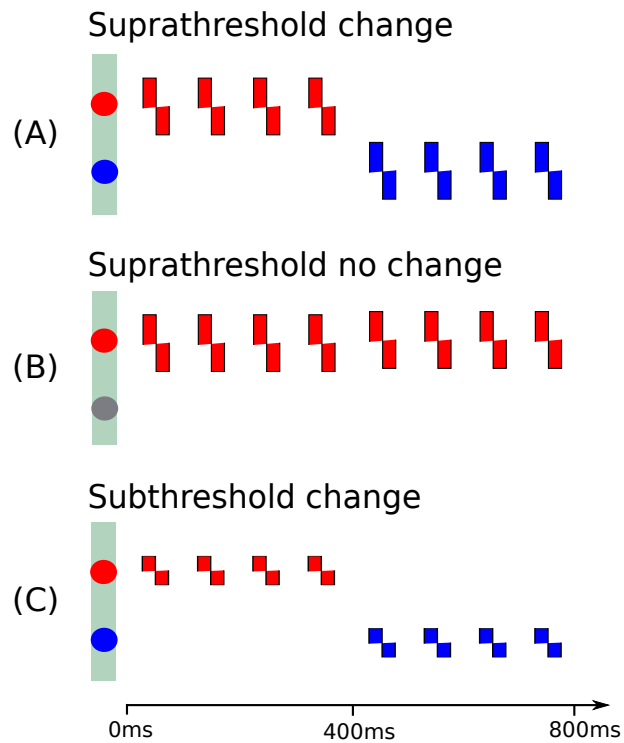


Figure 3.1. Schematic of the stimuli used in experiment 1. Stimuli consisted of 800ms biphasic electrical pulses at 1000 pulses per second. The test electrode is shown in blue and the reference electrode is shown in red. (A) In the suprathreshold change condition, there was a change in stimulating electrode at 400ms. Stimulation was at the loudness balanced most comfortable level. (B) In the suprathreshold no change condition, the reference electrode was stimulated continuously for 800ms at the most comfortable level. (C) In the subthreshold change condition, there was a change in stimulating electrode at 400ms but stimulation was at  $10 \mu\text{A}$  below threshold for the reference and test electrodes. This condition was included to measure CI artefact in the absence of a cortical response.

### 3.3.2 Results

#### 3.3.2.1 Assessment of CI artefact

The CI related artefact varied between participants. Participants P1 and P3 had large CI related artefacts which could be isolated with spatial filtering. The first components of spatial filtering for the 'subthreshold change' condition and 'suprathreshold change' condition are shown in figure 3.2. This component has an onset and offset which corresponds to the duration of electrical stimulation and represents CI DC artefact. Scalp voltage maps show the location of CI artefact on the side of the CI device. The scalp artefact was predominantly in the midline in participant P1 but also extended to the side of the CI. In participant P3, artefact was predominantly at lateral scalp channels on the side of the CI. In neither case was there visible artefact on the contralateral scalp channels in any of the stimulation conditions. A switch artefact, associated with changing the stimulating electrode was present in the 'suprathreshold change' and 'subthreshold change' conditions, but not the 'no change' condition. In participants P2 and P4, who both had MED-EL devices, CI artefact was comparatively much smaller and did not affect the ACC.

As can be seen in figure 3.2, the CI artefact isolated in the 'subthreshold change' condition and 'suprathreshold change' condition are similar in morphology. In participant P1, the artefact was actually larger in the subthreshold change condition compared to suprathreshold change condition. The size of the DC artefact can occasionally change during a recording session and this may be due to a change in the impedance mismatch of recording electrodes (Mc Laughlin et al., 2013). Figure 3.3 shows that spatial filtering can be used to effectively remove CI artefact in the suprathreshold change condition. The average scalp response is shown before CI artefact removal in figure 3.3 A. After removing the first component of spatial filtering (shown in figure 3.2 B), the onset response and ACC can be clearly identified.

### 3.3.2.2 ACC in the test and control conditions

In all four participants, Hotelling-T2 indicated that the ACC was present in the suprathreshold change condition but absent in the two control conditions. An example of responses from the three stimulation condition in participant P4 is shown in figure 3.4. Figure 3.5 shows the N1-P2 peak amplitude of the onset and ACC response for the three stimulation condition in all 4 participants. A linear mixed-effects analysis of the relationship between N1-P2 amplitude and stimulation condition across scalp channels was performed. The dependent variable was the N1-P2 amplitude. Fixed effects included 'condition' (suprathreshold change, subthreshold change and no change), 'scalp channel' (Cz, C1, C2, FCz, FC1, FC2, Fz, F1, and F2) and 'peak type' (onset response or ACC). The interaction term for 'condition' and 'peak type' was included in the model as well. The factor 'scalp channel' was removed from the model as it was not significant ( $F(8, 199) = 0.91, p = 0.512$ ). Analysis of variance of the reduced model showed that there was a significant effect of 'condition' ( $F(2,207) = 443, p < 0.001$ ), 'peak type' ( $F(1,207) = 308, p < 0.001$ ) and the interaction between 'condition' and 'peak type' ( $F(2,207) = 75, p < 0.001$ ). The output of the model is shown in table 3.2.

Post-hoc pairwise comparisons were performed with Tukey correction. This showed that for the ACC, there was a significant difference between the N1-P2 amplitude in the suprathreshold change condition and both control conditions ( $p < 0.001$ ) but no significant difference between the two control conditions ( $p = 0.118$ ). For the onset response, N1-P2 amplitude was significantly different between all 3 conditions ( $p < 0.001$ ). In the no change condition, the same population of neurons are stimulated for twice as long as in the suprathreshold change condition in each trial and neural refractoriness may account for the smaller onset response in this condition.

Table 3.2 Output of mixed model analysis of factors affecting cortical response N1-P2 amplitude

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Initial model					
Scalp channel	(8, 199)	0.91	0.512	0.035	0.023 – 0.137
Condition	(2,199)	442	<0.001	0.816	0.779 – 0.850
Peak type	(1,199)	307	<0.001	0.607	0.533 – 0.675
Peak type * Condition	(2,199)	75	<0.001	0.429	0.338 – 0.521
Reduced model					
Condition	(2,207)	443	<0.001	0.811	0.773 – 0.845
Peak type	(1,207)	308	<0.001	0.598	0.525 – 0.666
Peak type * Condition	(2,207)	75	<0.001	0.429	0.331 – 0.512

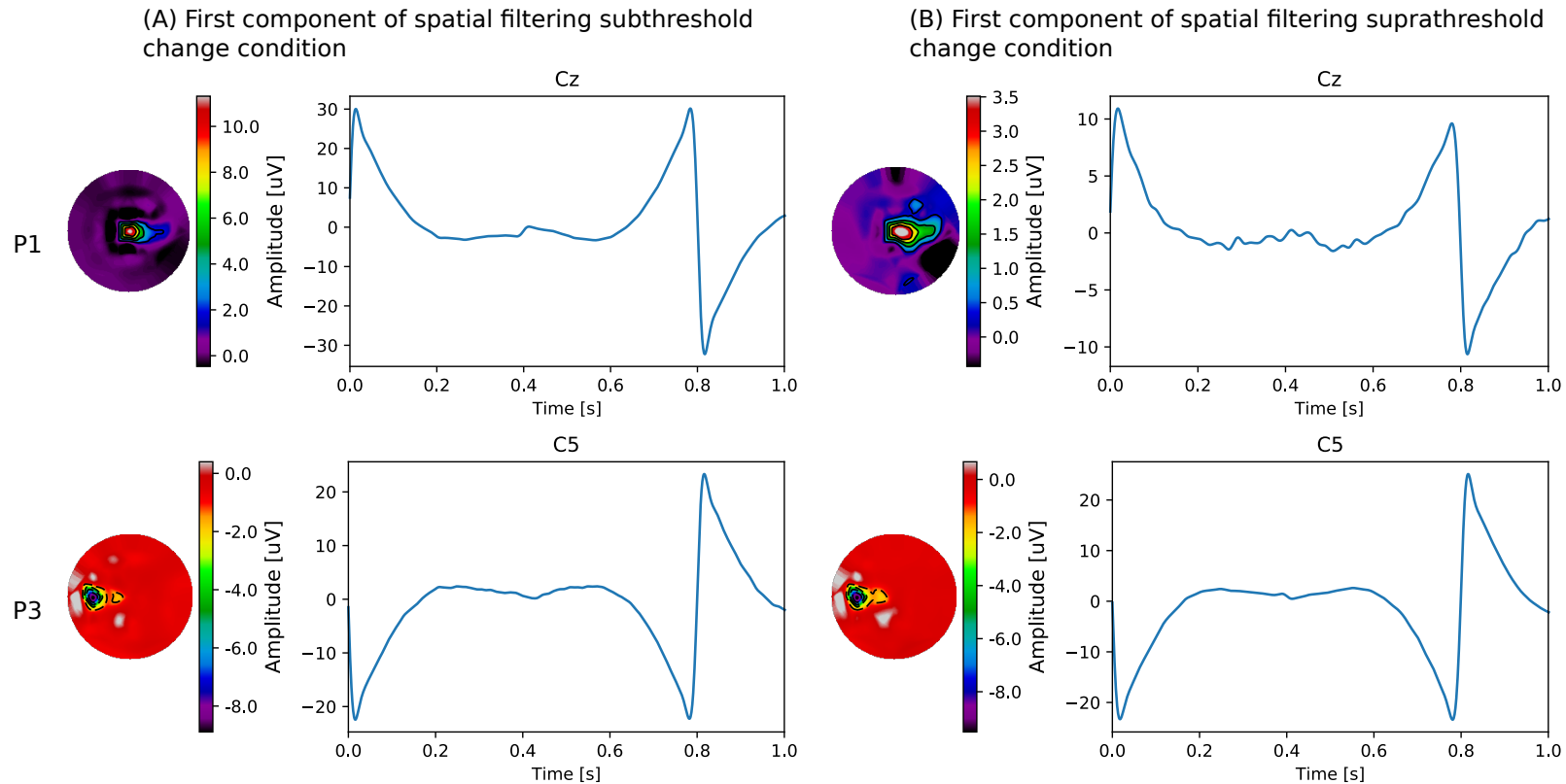


Figure 3.2 Scalp voltage maps and time waveform for the first component of spatial filtering. Data are shown for participants P1 and P3 in the subthreshold change condition (A) and suprathreshold change condition (B). Time waveforms shows that this component has an onset and offset which matches the duration of electrical stimulation. This component represents the CI DC artefact. Time waveforms are shown at the scalp location where amplitude was largest - Cz is located at the vertex and C5 is located laterally on the left side of Cz. Note the similar morphology of the artefact in the subthreshold and suprathreshold change condition. Mean scalp voltage maps between 50 and 120 ms after stimulus onset show that the distribution of CI artefact is biased towards the side of the implant. Isopotential contour lines are shown on scalp voltage maps with black lines.

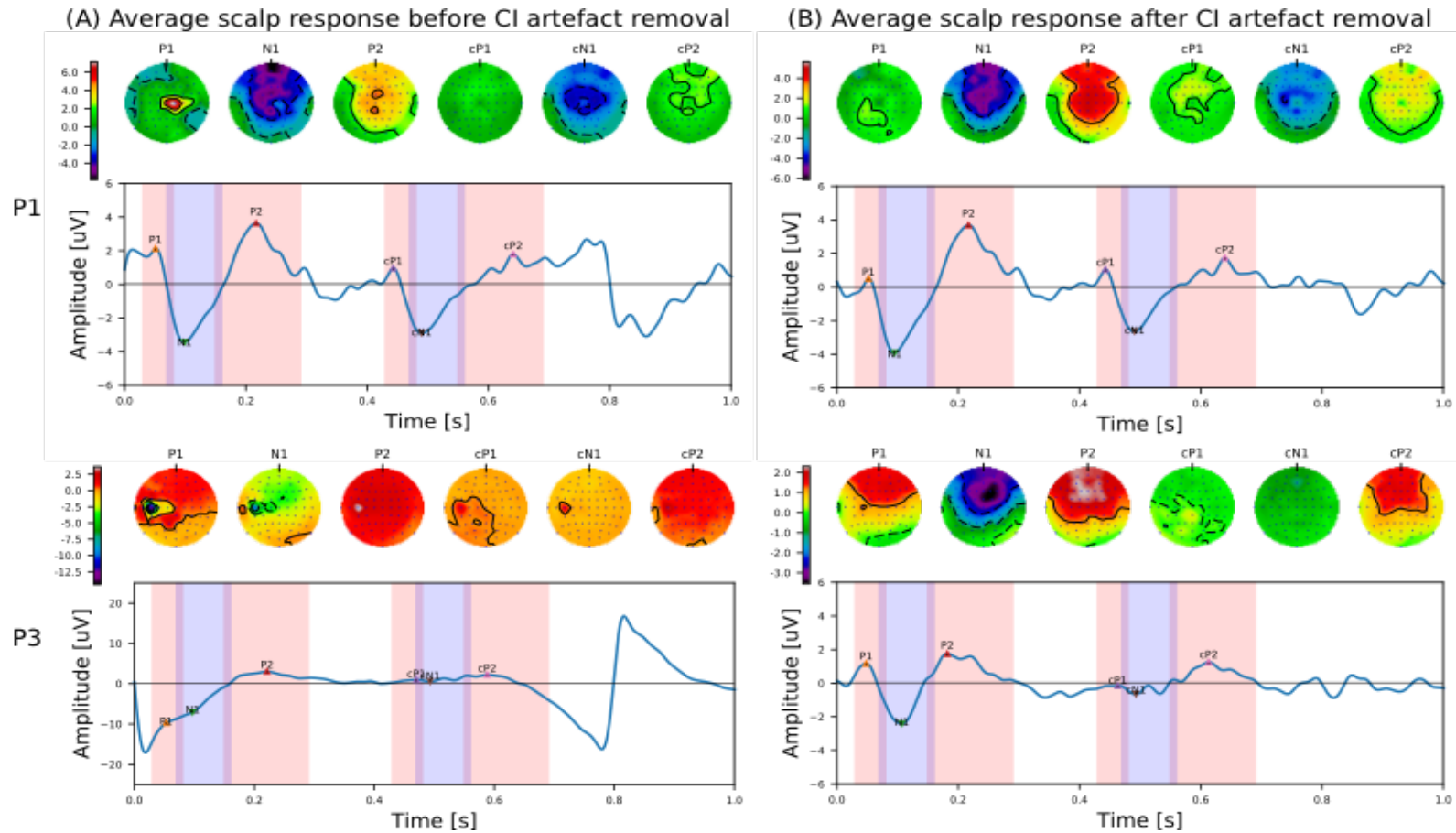


Figure 3.3 Cortical responses during the suprathreshold change condition. Data are shown for participants P1 and P3 (A) Average scalp response referenced to the contralateral mastoid, before CI artefact removal. Onset and offset artefacts can be seen in both cases and a cortical response cannot be identified in participant P3. Scalp voltage maps at peak time points show evidence of CI artefact. (B) Average scalp response after CI artefact removal. Clear onset and ACC responses are now seen and scalp voltage maps appear normal. Time windows used to detect positive and negative peaks for the onset response (P1, N1, and P2) and ACC (cP1, cN1, and cP2) are shown in pink and blue, respectively. The horizontal lines correspond to the level of residual noise.

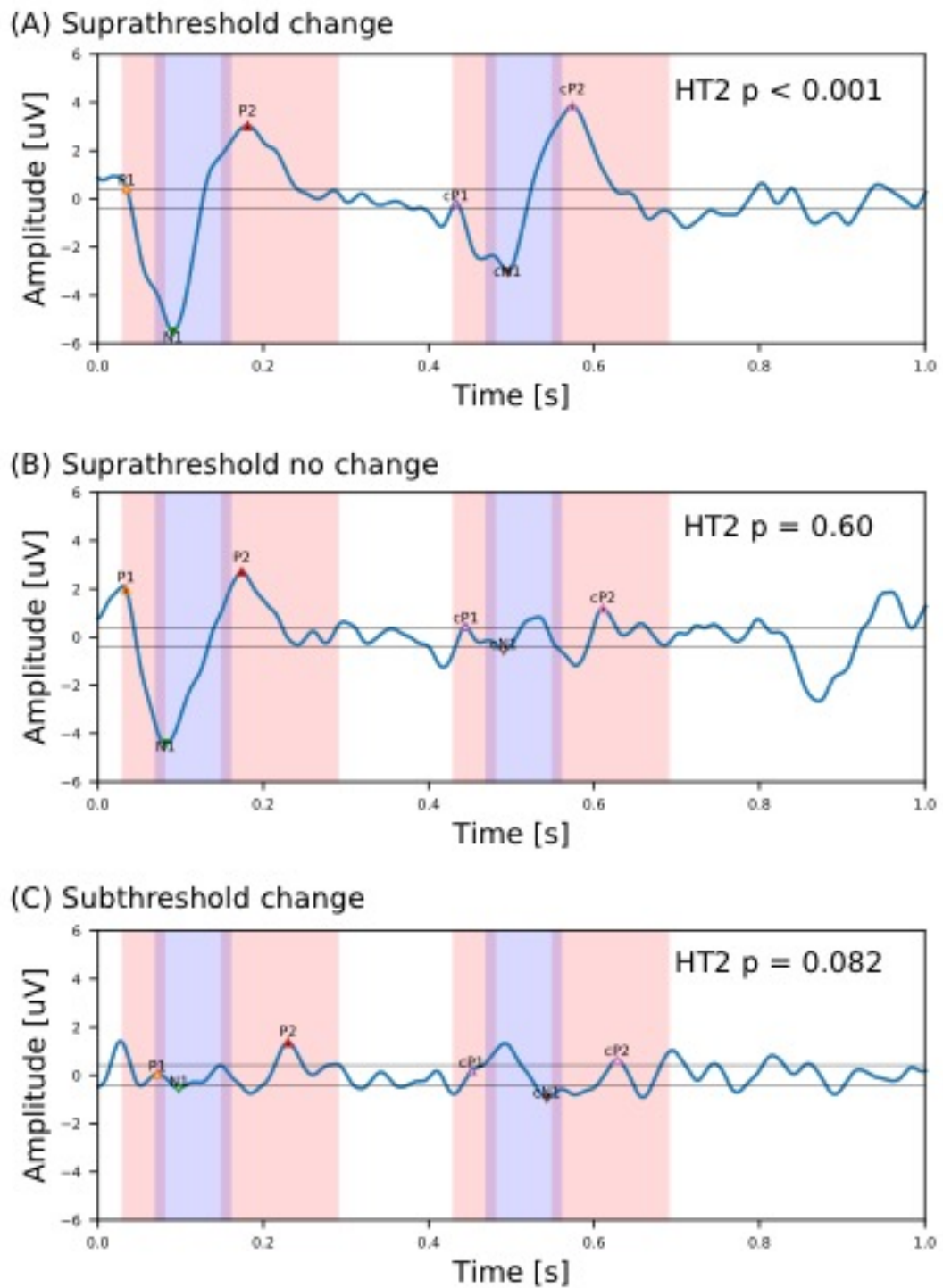


Figure 3.4 Cortical responses for three stimulus conditions. Data are shown at channel Fcz for participant P4. The ACC is seen in the suprathreshold change condition (A) but not the no change condition (B) or subthreshold change condition (C). Hotelling-T2 (HT2) p values are shown on each panel. The shaded areas and horizontal lines are as described in figure 3.3.

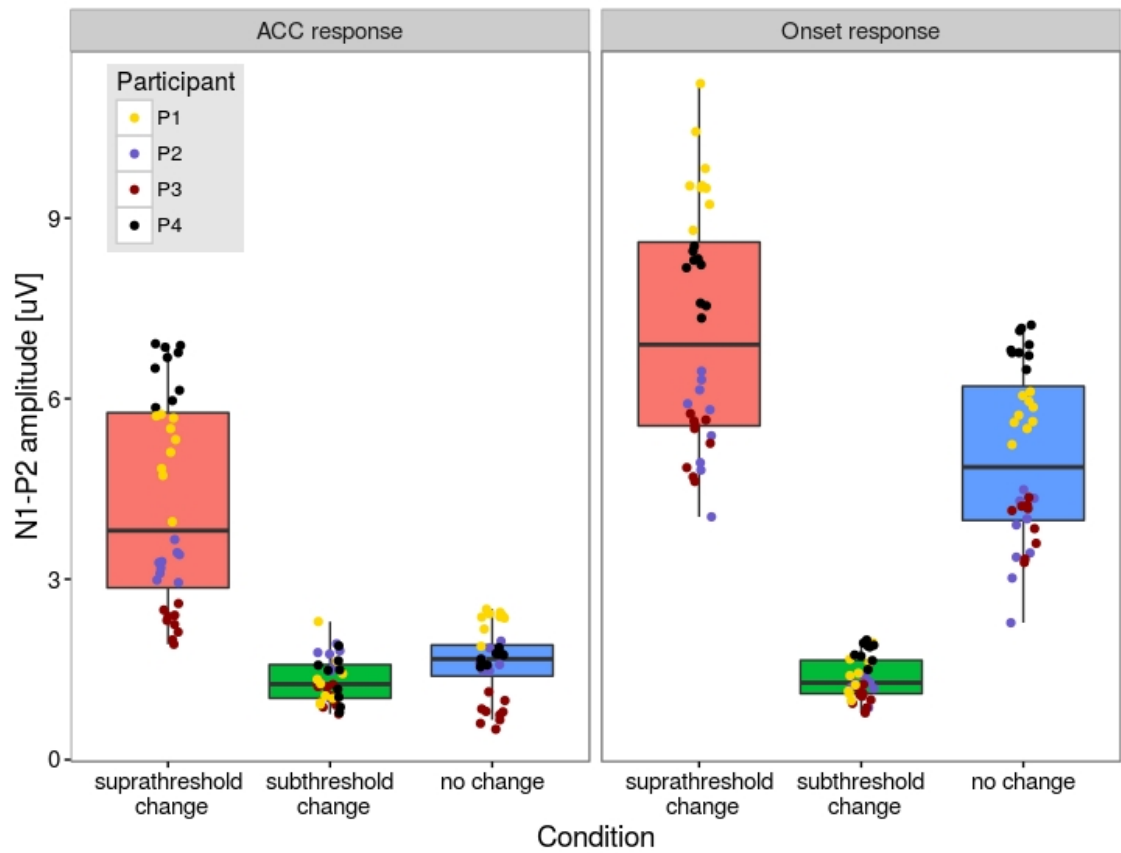


Figure 3.5. Boxplot of N1-P2 amplitude of the onset and ACC response for the three stimulus conditions. Each point represents a different scalp location (Cz, C1, C2, FCz, FC1, FC2, Fz, F1, and F2) and a different colour is used for each participant. The upper and lower hinges of the box plots correspond to the first and third quartiles, whilst the median is indicated by the horizontal line within each box.



### 3.4 Experiment 2: Measurement of ACC at 1 week after switch-on

#### 3.4.1 Design and Methods

##### *3.4.1.1 Participants*

For experiment 2, ten participants (different to those in experiment 1) were recruited and ranged in age from 42 to 80 years. Three participants had pre-lingual onset of deafness and all the others had post-lingual onset of profound deafness. Since one of the objectives of this study was to examine the relationship between electrode discrimination and speech perception, participants with the same device were chosen to reduce the potential variability in outcomes that might be caused by differences in the implant and electrode array design such as inter-electrode distance and array length. All participants were unilaterally implanted with an AB device and tested at approximately 1 week after CI switch-on (range 7-14 days). The AB Hifocus Mid-Scala electrode was used in all participants, except for S4 who had a Hifocus 1J electrode. Both arrays have 16 electrode contacts but the Mid-Scala electrode has an active length of 15mm with electrode spacings of 1 mm, whilst the 1J electrode is a lateral wall electrode and has an active length of 17 mm with electrode spacings of ~1.1 mm. Demographic details of participants in experiment 2 are shown in table 3.3.

##### *3.4.1.2 Test Procedures*

The main objectives of this experiment were to determine whether it is possible to measure the spatial ACC soon after CI switch-on and how this measurement relates to behavioural electrode discrimination. A subsidiary objective was to determine whether objective electrode discrimination (measured with the ACC) and behavioural electrode discrimination are related to speech perception at this early stage.

Only the suprathreshold change condition was used in this experiment and the electrode pairs 1-2, 2-3, 3-4 and 4-5 were tested. These are the apical most electrodes in the AB device and typically encode frequencies of 250-828 Hz. These electrodes encode the first formant of vowels and previous studies have shown that the apical

electrodes are important for speech perception (Busby et al., 2000; Geier and Norton, 1992; Henry et al., 2000). Loudness balancing was performed as described in the General Methods. Electrode 3 was chosen as the initial reference electrode as it lies in the centre of the five electrodes chosen for testing. The MC level of electrode 3 was determined and adjacent electrode pairs were loudness balanced in the following order: electrode 4 with electrode 3, electrode 5 with electrode 4, electrode 2 with electrode 3 and electrode 1 with electrode 2. Loudness balancing was performed three times and the average was used as the final loudness balanced MC level. The standard deviation of the three measurements was on average 4.77  $\mu\text{A}$  (range 0-13  $\mu\text{A}$ ).

For experiment 2, a total of 40 electrode pairs were tested (4 electrode pairs tested in 10 participants). EEG measurements and processing were performed as described in the General Methods. The response window for Hotelling-T2 analysis was adjusted in 4/40 cases, to 450 – 700 ms after stimulus onset, due to a late P2 component. Behavioural electrode discrimination was tested for all 4 electrode pairs. Speech perception testing included open-set sentences with BKB sentences-in-quiet, and closed-set vowel perception with the CAPT vowel test. Details of behavioural electrode discrimination and speech testing are provided in the General Methods. EEG and behavioural testing was completed in a single session, which lasted approximately 2.5 hours including breaks.

Table 3.3 Demographic details of participants in experiment 2. F= female, M= male, R = right, L= left, 4F-PTA = four frequency pure tone average, CI = cochlear implant, HR 90K = HiRes 9

Participant	Age	Sex	Ear	Risk factor for hearing loss	Communication	Duration profound hearing loss (years)	4F-PTA non CI ear (dB HL)	Device	Electrode	Processing strategy
S1	51	M	R	Unknown	oral	10	116	HR 90K	Mid Scala	HiRes Optima-S
S2	50	F	R	Unknown	oral + sign	50	115	HR 90K	Mid Scala	HiRes Optima-S
S3	42	F	L	Unknown	oral	18	118	HR 90K	Mid Scala	HiRes Optima-S
S4	48	M	L	Maternal rubella	oral	46	115	HR 90K	1J	HiRes Optima-S
S5	47	F	L	Unknown	oral	42	103	HR 90K	Mid Scala	HiRes Optima-S
S6	68	F	L	Unknown	oral	10	100	HR 90K	Mid Scala	HiRes Optima-S
S7	57	F	L	Unknown	oral + sign	57	120	HR 90K	Mid Scala	HiRes-S
S8	51	F	R	Unknown	oral	5	96	HR 90K	Mid Scala	HiRes Optima-S
S9	48	M	L	Unknown	oral	1	113	HR 90K	Mid Scala	HiRes Optima-S
S10	80	M	L	Unknown	oral	10	78	HR 90K	Mid Scala	HiRes Optima-S

### 3.4.2 Results

#### 3.4.2.1 Characteristics of the ACC

The presence or absence of the spatial ACC was defined based on Hotelling-T2 criteria as described in the General Methods. The number of electrode pairs that elicited an ACC ranged from 0-4 in each participant as shown in table 3.4. The ACC response morphology was similar to that of the onset response and typically consisted of the P1-N1-P2 complex. Table 3.5 shows the peak latencies and amplitudes of the onset and ACC responses, for recordings where there was an objective ACC pass. The peak latencies of P1, N1 and P2 components of the ACC response were significantly longer than that of the onset response (two-tailed paired t-test  $p < 0.001$ ). In addition, N1-P2 amplitude of the ACC was significantly smaller than that of the onset response (paired t-test,  $p < 0.001$ ).

Table 3.4 The number of discriminable electrode pairs as determined with objective ACC and behavioural criteria as well as speech perception scores. Data are shown for individual participants.

Participant	ACC Discrimination Score	Behavioural Discrimination Score	Sentence score (BKB) (%)	Vowel score (CAPT) (%)
S1	2	2	80	65
S2	2	1	0	25
S3	4	4	61	40
S4	1	2	73	42.5
S5	0	0	2	65
S6	1	1	0	20
S7	1	0	0	25
S8	4	4	43	80
S9	4	4	70	82.5
S10	4	4	75	82.5

Table 3.5 Mean, standard deviation and range for peak latencies and peak-to-peak amplitudes at channel FCz. The first column shows the response type (onset or ACC) and peak label (P1, N1 and P2).

	Peak latency measurements (ms)		
Waveform component	Mean	Standard deviation	Range
Onset P1	43	8	32-59
ACC P1	58	11	38-78
Onset N1	101	8	86-121
ACC N1	118	15	97-143
Onset P2	200	27	159-257
ACC P2	232	36	179-288
	Peak to peak N1-P2 amplitude ( $\mu$ V)		
Onset response	6.71	1.76	3.27-9.56
ACC	2.96	0.92	1.26-4.60

### 3.4.2.2 Relationship between behavioural discrimination and the ACC

#### 3.4.2.2.1 Relationship using pass-fail criteria

The relationship between behavioural discrimination and the spatial ACC was assessed using pass-fail rules. Briefly, a behavioural pass was defined as a score of  $\geq 80\%$  on behavioural testing, and an objective pass required a significant response (Hotelling-T2  $p$  value  $< 0.05$ ) at  $> 4/9$  frontal and central scalp channels. There was agreement between objective and behavioural measures in 35/40 cases: there were 15 electrode pairs with a behavioural fail and objective fail, 20 electrodes pairs with a behavioural pass and objective pass, 3 electrode pairs with a behavioural fail and objective pass and 2 electrode pairs with a behavioural pass and objective fail. Figure 3.6 shows an example of cortical responses in participant S1. This shows that in the same

participant, the ACC is absent for an electrode pair with a behavioural fail (figure 3.6A) but is clearly present for an electrode pair with a behavioural pass (figure 3.6B).

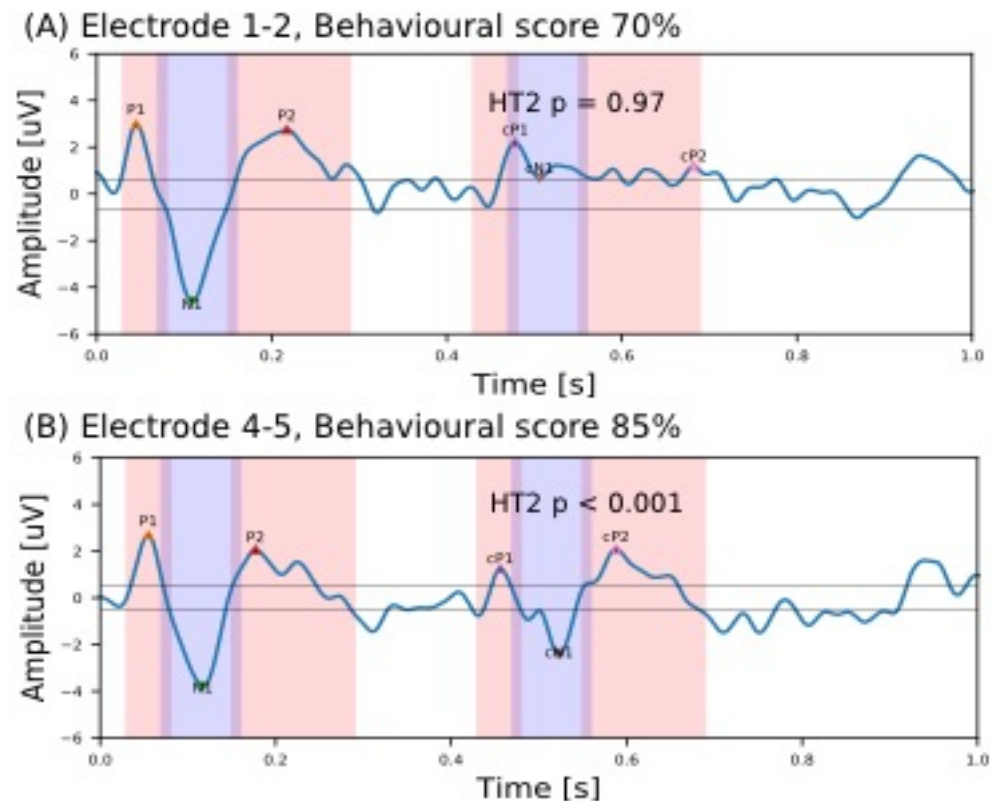
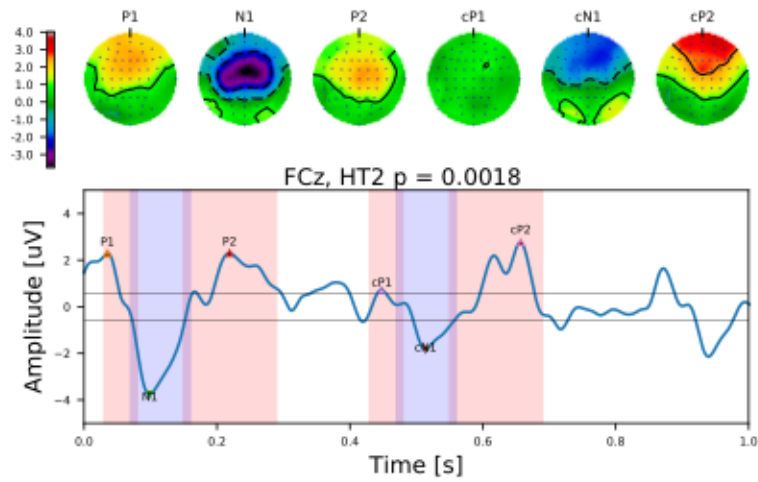


Figure 3.6 Cortical responses showing agreement between the ACC and behavioural measurements. Response at FCz in participant S1 are shown. A behavioural fail is associated with an absent ACC (A) whilst a behavioural pass is associated with a clear ACC response (B). The electrode pair, behavioural score and Hotelling-T2 (HT2) p value are indicated on each panel. The shaded areas and horizontal lines are as described in figure 3.3.

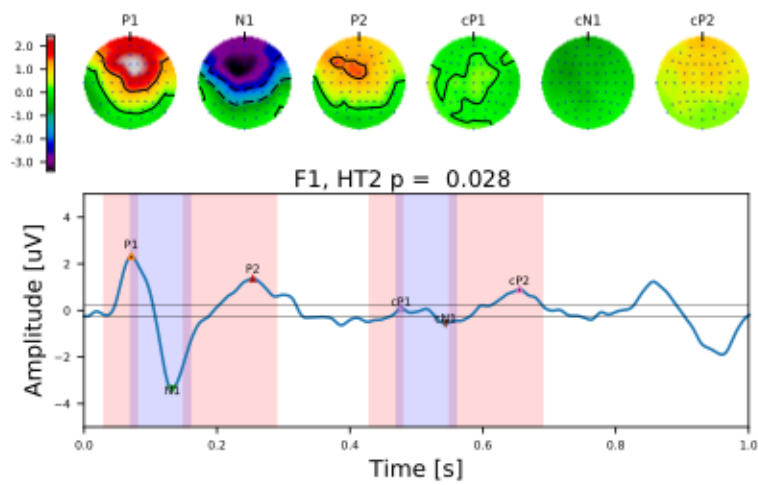
The relationship between the ACC and behavioural measurements can be further examined according to deafness onset. For the seven post-lingually deafened adults, there was agreement between objective and behavioural electrode discrimination for all 28 electrode pairs. For the pre-lingually deafened adults, there was agreement between objective and behavioural discrimination, for 7 out of 12 electrode pairs. There were only two cases from the same participant (S4) with a behavioural pass but objective fail. This participant had small ACC responses across all four electrode pairs (range 0.08 - 1.26  $\mu\text{V}$ ). The 3 electrode pairs with an objective pass but behavioural fail were from the 3 pre-lingually deafened adults (participants S2, S4 and S7) and are shown in figure 3.7. Of note, electrode pair 2-3 in participant S2 (figure 3.7A) had a discrimination score of only 45% but a large ACC amplitude (4.60  $\mu\text{V}$ ). These data show

that an ACC response may be present in the absence of accurate behavioural discrimination.

(A) S2 electrode 2-3, behavioural score 45%



(B) S4 electrode 4-5, behavioural score 70%



(C) S7 electrode 3-4, behavioural score 65%

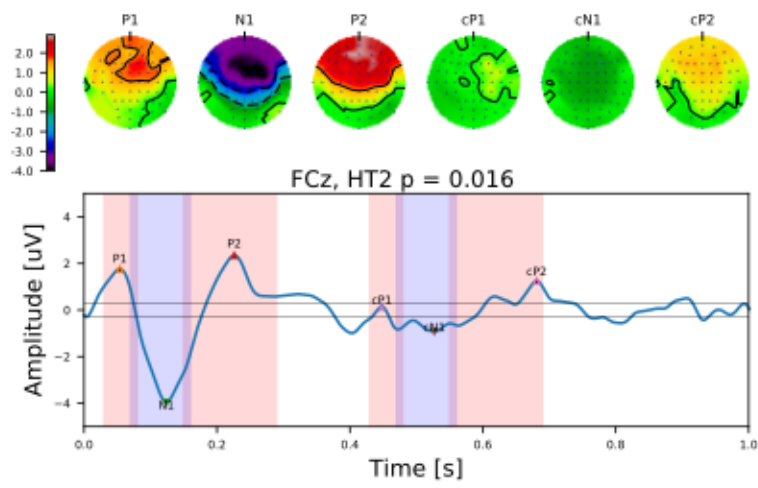


Figure 3.7 Cortical responses from electrode pairs that failed on behavioural testing but passed on objective ACC criteria. Data are presented at a representative scalp channel which is shown on each panel with the corresponding Hotelling-T2 (HT2)  $p$  value. Scalp voltage maps at peak time points are shown above evoked response potentials, and show a similar pattern for the onset and ACC responses. The participant ID, electrode pair and behavioural discrimination score are shown above each panel. The shaded areas, horizontal lines and scalp voltage maps are as described in figure 3.3.



#### 3.4.2.2.2 Mixed model analysis of relationship between N1-P2 peak amplitude and behavioural discrimination

There appears to be a strong relationship between the ACC and electrode discrimination when using pass-fail rules, especially in post-lingually deafened adults. The relationship between the ACC amplitude and behavioural discrimination was examined next. A behavioural pass was set at a score of 80% a priori, but it is possible that the ACC is encoded at lower levels of behavioural discrimination. The aim of this analysis therefore, was to determine whether electrode-pairs with intermediate discrimination scores (e.g. 70%) had larger ACC amplitudes than those with discrimination scores around chance (e.g. 50%). Electrode pairs were divided into three categories based on behavioural discrimination score: 'poor' (score < 60%), 'intermediate' (score 60 - 79%) and 'good' (score  $\geq$  80%). Categories of behavioural discrimination were used due to the small number of participants in this study. Figure 3.8 shows the ACC N1-P2 amplitude according to behavioural discrimination category.

A linear mixed-effects model was used to examine the relationship between N1-P2 amplitude and behavioural discrimination category. The N1-P2 peak amplitude was modelled with fixed factors 'behavioural category' (poor, intermediate or good), 'deafness onset' (pre-lingual or post-lingual) and 'electrode pair' (1-2, 2-3, 3-4 or 4-5). The interaction term for 'deafness onset' and 'behavioural category' was also included in the model. The factor 'electrode pair' was eliminated from the model as it was not significant ( $F(3, 24) = 1.28, p = 0.303$ ). Analysis of variance of the reduced model revealed a significant effect of 'behavioural category' ( $F(2, 31) = 5.01, p = 0.013$ ) and the interaction between 'deafness onset' and 'behavioural category' ( $F(2, 31) = 3.39, p = 0.047$ ). The output of the model is shown in table 3.6.

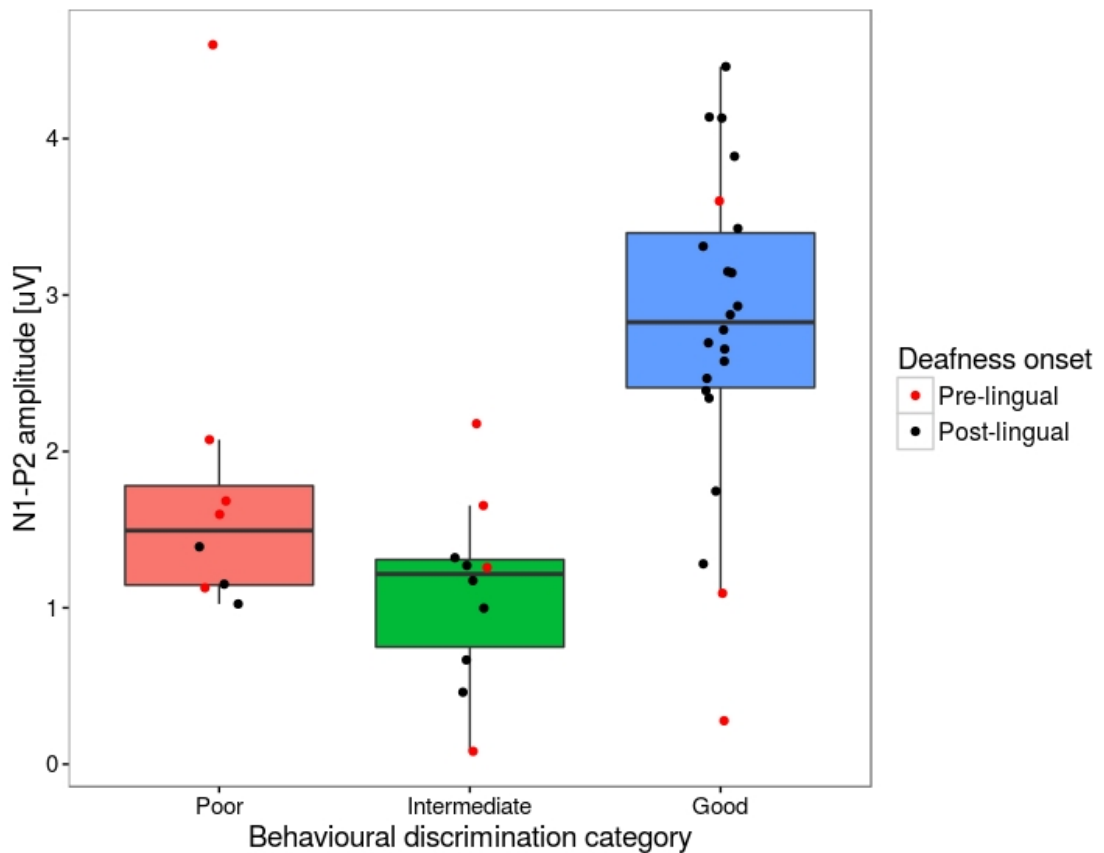


Figure 3.8 Relationship between ACC N1-P2 amplitude and behavioural discrimination category. Depending on behavioural discrimination score, electrode pairs were categorized as being 'good' (score  $\geq 80\%$ ), 'intermediate' (60-79%) or 'poor' ( $<60\%$ ). Data are shown for channel FCz. Each point represents an individual electrode pair. Red and black points are from adults with pre-lingual and post-lingual onset deafness respectively. The upper and lower hinges of the box plots correspond to the first and third quartiles, whilst the median is indicated by the horizontal line within each box.

Post-hoc pairwise comparison of the three behavioural categories, was performed with Tukey correction. This showed that in post-lingually deafened individuals, there was a significant difference in amplitude between the good and poor groups ( $p = 0.020$ ) and the good and intermediate groups ( $p < 0.001$ ). However, there was no significant amplitude difference between the poor and intermediate groups ( $p = 0.921$ ). For the pre-lingually deafened individuals the number of data points is small and there was no significant difference in amplitude between the poor, intermediate or good groups ( $p > 0.600$  for all comparisons).

These data show that in post-lingually deafened adults, only high levels of behavioural discrimination performance are associated with a spatial ACC response. In pre-lingually deafened adults, there does not appear to be a strong relationship between ACC amplitude and behavioural discrimination.

Table 3.6 Output of mixed model analysis of factors affecting ACC N1-P2 amplitude

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Initial model					
Behavioural category	(2,28)	4.39	0.022	0.221	0.045 – 0.506
Deafness onset	(1,8)	0.05	0.830	0.006	0.000 – 0.506
Electrode pair	(3,24)	1.28	0.303	0.137	0.028 – 0.481
Behavioural category * deafness onset	(2,28)	4.33	0.023	0.209	0.040 – 0.495
Reduced model					
Behavioural category	(2,31)	5.01	0.013	0.227	0.053 – 0.497
Deafness onset	(1,8)	0.02	0.888	0.003	0.000 – 0.498
Behavioural category * deafness onset	(2,31)	3.39	0.047	0.159	0.023 – 0.434

#### 3.4.2.2.3 Non-monotonic relationship between N1-P2 amplitude and behavioural discrimination in post-lingually deafened adults

In post-lingually deafened adults, there appears to be a strong relationship between the ACC N1-P2 amplitude and behavioural discrimination. If there was a monotonic relationship between behavioural discrimination and ACC amplitude, then within a participant, larger behavioural discrimination score would be associated with larger amplitude ACC responses for ‘good’ electrode pairs. There were only two participants

who had more than 1 electrode pair in the ‘good category’ which were not all at the ceiling level of behavioural discrimination. As seen in table 3.7, even for electrode pairs in the ‘good category’, higher discrimination scores within a participant are not necessarily associated with larger ACC amplitudes. This suggests that there is a non-monotonic relationship between ACC amplitude and behavioural discrimination.

Table 3.7 ACC amplitude at channel FCz in 2 post-lingually deaf participants. This shows that even in the ‘good category’ (discrimination score  $\geq 80\%$ ) a higher discrimination score is not necessarily associated with a higher ACC amplitude.

Participant	Electrode pair	Behavioural discrimination score (%)	N1-P2 peak amplitude ( $\mu\text{V}$ )
S1	1_2	70	0.66
	2_3	75	1.00
	3_4	100	2.34
	4_5	85	4.46
S9	1_2	100	2.87
	2_3	100	3.14
	3_4	90	2.70
	4_5	100	1.75

### 3.4.2.3 Relationship between electrode discrimination and speech perception

#### 3.4.2.3.1 Behavioural electrode discrimination and speech perception

Electrode discrimination scores for each participant were collapsed to the mean behavioural  $d'$  across the 4 electrode pairs. The mean  $d'$  score was used as this provides a measure of discrimination ability across the apical region of the cochlea. There was a significant correlation between mean behavioural electrode discrimination  $d'$  and vowel  $d'$  ( $r = 0.68$ , 95% confidence interval [0.08, 0.92],  $p = 0.032$ ) and BKB sentence score ( $r = 0.73$ , 95% confidence interval [0.19, 0.93],  $p = 0.016$ ). This relationship is shown graphically in figure 3.9. As the distribution of BKB scores was non-normal, the relationship with the mean  $d'$  score was also examined

with Spearman's rank correlation analysis. This showed a trend towards significant correlation ( $\rho = 0.63$ , 95% confidence interval  $[-0.10, 0.85]$ ,  $p = 0.052$ ).

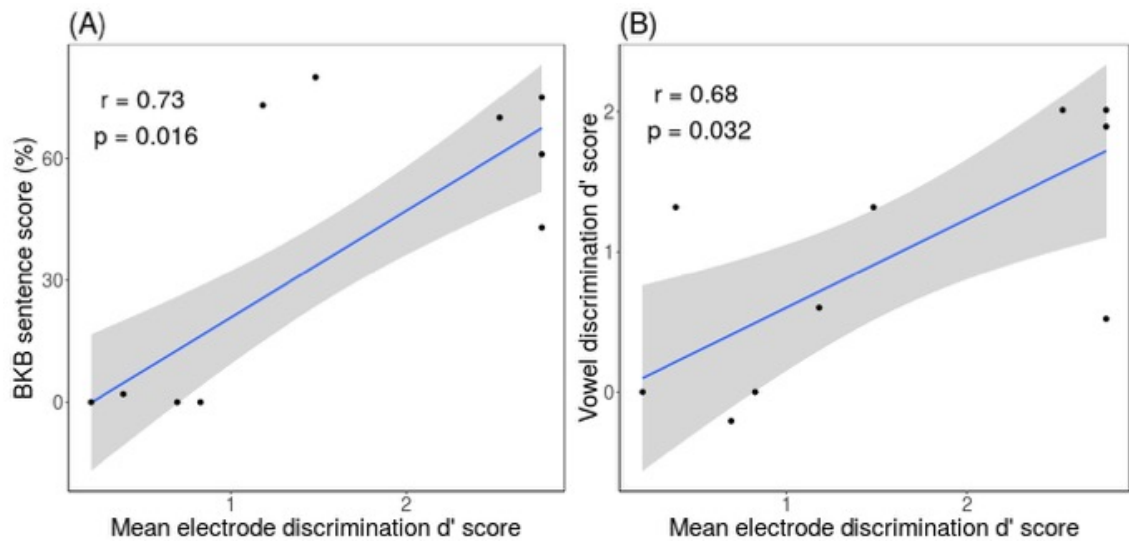


Figure 3.9 The relationship between mean electrode discrimination  $d'$  score and speech perception. Open-set speech perception score, measured with BKB sentences is shown in (A) and closed-set vowel perception measured with CAPT is shown in (B). Each point represents data from a single participant. The 95% confidence interval is shown by the shaded area.

#### 3.4.2.3.2 The spatial ACC and speech perception

An objective discrimination score was calculated for each participant by taking the mean of the ACC N1-P2 peak amplitude across the 4 electrode pairs. There was no significant correlation between the objective discrimination score and vowel perception score ( $r = 0.37$ , 95% confidence interval  $[-0.34, 0.81]$ ,  $p = 0.30$ ) or sentence perception scores ( $r = 0.18$ , 95% confidence interval  $[-0.51, 0.73]$ ,  $p = 0.62$ ). The relationship between the number of discriminable electrode pairs defined using objective pass-fail criteria and speech perception was examined with Spearman's rank correlation coefficient. This also showed no significant correlation with vowel ( $\rho = 0.54$ , 95% confidence interval  $[-0.14, 0.92]$ ,  $p = 0.10$ ) or sentence perception scores ( $\rho = 0.42$ , 95% confidence interval  $[-0.23, 0.82]$ ,  $p = 0.22$ ). Since the relationship between the spatial ACC and behavioural discrimination is not as robust in pre-lingually deafened adults, the analysis was repeated in post-lingually deafened adults alone and this showed a similar pattern of results (table 3.8).

Table 3.8 Correlations between speech perception scores and the spatial ACC measures. Results are shown for the whole group as well as the subgroup of adults with post-lingual onset of deafness.

Variable	Correlation type	Sentence score		Vowel score	
		Correlation coefficient and 95% confidence interval	P value	Correlation coefficient and 95% confidence interval	P value
All participants					
Mean ACC N1-P2 amplitude	Pearson's	0.18 [-0.51, 0.73]	0.62	0.37 [-0.34, 0.81]	0.30
No. discriminable electrodes	Spearman's	0.42 [-0.23, 0.82]	0.22	0.54 [-0.14, 0.92]	0.10
Adults with post-lingual onset deafness only					
Mean ACC N1-P2 amplitude	Pearson's	0.63 [-0.23, 0.94]	0.13	0.48 [-0.43, 0.91]	0.28
No. discriminable electrodes	Spearman's	0.47 [-0.81, 0.87]	0.28	0.56 [-0.24, 1.00]	0.19

### 3.5 Discussion

This study shows that it is possible to measure the spatial ACC in different CI devices and as early as 1 week after switch-on. The sample size in both experiments is small which may limit the statistical analysis. Nonetheless, these data indicate that there is a strong relationship between the spatial ACC and behavioural measures of electrode discrimination. Furthermore, in certain cases the ACC could be recorded in the absence of accurate behavioural discrimination. This suggests that the spatial ACC reflects encoding of stimulus change at the level of the auditory cortex and is not necessarily related to the perception of change itself.

### 3.5.1 Assessment and removal of CI artefact

The size and distribution of artefact varies between individuals and device. In both experiments, it was found that the CI artefact was usually limited to the side of the implant and was never present on the contralateral side. He et al. (2014) and Scheperle and Abbas (2015a) showed that it was feasible to measure the ACC using 1-2 midline scalp channels in the Cochlear device. The data in this study suggest that such an approach, with few scalp channels, could be used in other CI devices provided artefact free locations are selected (explored further in Chapter 6).

The advantage of multi-channel scalp recordings is that CI artefact can be removed allowing assessment of cortical responses at a greater number of locations as well as source localization. A number of techniques have been used to remove CI artefact (Debener et al., 2008; Martin, 2007; Mc Laughlin et al., 2013). Spatial filtering was found to be an effective technique which usually isolates DC artefact in 1-2 components which makes artefact identification relatively simple and quick. In addition, the artefact isolated by spatial filtering in the suprathreshold stimulation condition was similar to that in the subthreshold stimulation condition. This implies that the neural response is unlikely to be significantly affected by artefact removal with this technique.

### 3.5.2 Characteristics of the spatial ACC at 1 week after switch-on

In keeping with other studies (Brown et al., 2008; He et al., 2014; Scheperle and Abbas, 2015b), it was found that the spatial ACC morphology was similar to that of the onset response and was dominated by N1 and P2 components. He et al. (2014), showed that the ACC in children with auditory neuropathy is often characterized by P1 and N2 peaks. This may be a sign of auditory immaturity and this morphology was not observed in any of the participants in this study including pre-lingually deafened adults. Similar to other studies (Brown et al., 2008; He et al., 2014; Martin and Boothroyd, 1999), the amplitude of the ACC was found to be significantly smaller than that of the onset response. In addition, peak latencies of the P1, N1 and P2 components of the spatial ACC were significantly later than that of the onset response.

Other studies have reported ACC peak latency being later (He et al., 2012; Martin and Boothroyd, 1999), no different (Brown et al., 2008; He et al., 2012) or even earlier (Kim et al., 2009) than the onset response peak latency. This may relate to the different stimuli used in these studies.

### 3.5.3 Relationship between the spatial ACC and behavioural discrimination

#### *3.5.3.1 Relationship in post-lingually deafened adults*

There was a strong relationship between the ACC and behavioural discrimination performance in post-lingually deafened adults. The ACC could be used to predict a behavioural pass/fail accurately in 28/28 electrode pairs in 7 adult participants. A number of other studies have reported a strong relationship between objective ACC and behavioural measures of electrode discrimination. He et al. (2014) found a strong relationship between the spatial ACC and behavioural measurements in CI children with auditory neuropathy. Presence of the ACC was determined based on visual identification of a response as well as minimum amplitude criteria. Behavioural discrimination was tested with a 2-AFC task and a pass was defined as a score of  $\geq 4/6$ . According to binomial probability, with these criteria, a pass could have been achieved by chance in 34% of cases. Stricter behavioural pass criteria were used in this study to reduce the false hit rate. Hoppe et al. (2010), reported that the ACC could be measured in 88% of cases in which participants could successfully discriminate electrodes but the criteria for assessing whether the ACC was present or absent were not defined.

The within-subject analysis, showed that only high behavioural discrimination scores are associated with a spatial ACC. Electrode pairs with intermediate discrimination scores, between 60-80%, did not have significantly different amplitudes to electrode pairs with scores at or around chance level (<60%). This finding is in keeping with other studies, which have examined the relationship between the ACC and behavioural performance in NH individuals (He et al., 2012; Michalewski et al., 2005). In the study by He et al. (2012), behavioural threshold for frequency discrimination was determined with an adaptive procedure estimating 70.7% correct detection. It was



found that the ACC threshold was significantly higher than the behavioural threshold suggesting that in general, only behavioural scores greater than 70.7% are associated with an ACC response. Presumably at lower levels of behavioural performance, stimulus change is encoded less reliably in the auditory pathway and there are limits to the sensitivity of recording far-field responses related to the stimulation paradigm and the technique itself.

The data from this study suggests that there is a non-monotonic relationship between ACC amplitude and behavioural discrimination. Within subjects, electrode pairs with the highest behavioural discrimination scores did not necessarily have the largest ACC amplitude. Other studies have found a non-monotonic relationship between spatial ACC amplitude and electrode separation in CI users (He et al., 2014; Scheperle and Abbas, 2015b). The reason for this may be because different electrode locations and therefore, different dipole locations are being compared. It may also be because the ACC is not directly related to the perception of stimulus change. The onset N1 component is associated with encoding and detection of a threshold-level auditory stimulus (Näätänen and Picton, 1987; Parasuraman et al., 1982). The presence of the ACC may therefore signify that a stimulus change above a certain threshold has occurred but the amplitude may not be related to strength of perception.

### *3.5.3.2 Relationship in pre-lingually deafened adults*

This is the first study to examine the relationship between behavioural discrimination and the ACC in pre-lingually deafened adults. The spatial ACC could be used to predict behavioural discrimination accurately in 7/12 electrode pairs in 3 adult participants. In addition, the mixed model analysis, showed that ACC amplitude did not differ significantly between electrode pairs with 'good, 'intermediate' or 'poor' discrimination scores. Given the small sample size, these results must be interpreted with caution and should be considered preliminary in nature. However, the data suggests that the spatial ACC is a less reliable measure of behavioural discrimination in pre-lingually deafened adults compared to those with post-lingual deafness onset. There were two electrode pairs from the same participant which had an objective fail but behavioural pass. All of the responses for this participant were small.

An interesting finding in this study is that in all 3 pre-lingually deafened adults, the spatial ACC could be recorded in the absence of accurate behavioural discrimination. There could be a number of explanations for this. Firstly, it could be argued that the ACC occurred due to a perceived change in loudness if the electrode pairs were not loudness balanced properly. However, this is unlikely, as in the behavioural task, participants were instructed to choose the sound which was different; if there were loudness cues, then higher behavioural scores would be expected in these individuals. Secondly, it could be that the threshold of 80% for a behavioural pass (binomial probability  $< 1\%$ ) was too high. Even if a pass was defined as a score of  $\geq 75\%$  (binomial probability  $< 5\%$ ) these electrodes pairs still would have a behavioural fail. In addition, one participant (S2) had a discrimination score below chance level but had a large ACC amplitude. It is also noteworthy, that in the mixed model analysis of ACC amplitude there was no significant difference between the poor and intermediate behavioural discrimination categories in pre- and post-lingually deafened adults. This suggests that threshold of 80% for a behavioural pass is appropriate for this experimental paradigm.

It therefore appears, that in certain individuals, the change in stimulating electrode is encoded at the level of the auditory cortex but not perceived accurately. After CI switch-on, patients undergo active and passive learning, gained through auditory experience with their CI. There is evidence that learning induces different neurophysiological changes which underlie fast and slow phases of learning (Atienza, 2002). The presence of the ACC in the above participants may therefore indicate that that they have the potential to develop behavioural discrimination at a later stage. This hypothesis is examined and discussed further in Chapter 4. Another possible explanation for the failure to perceive an encoded stimulus is abnormal connectivity of the auditory cortex of congenitally deafened individuals. It has been proposed that congenital deafness can lead to functional decoupling of the primary and secondary auditory cortex (Kral and Sharma, 2012) and imaging studies have provided evidence of abnormal patterns of auditory activation in congenitally deaf individuals (Gilley et al., 2008; Naito et al., 1997).

Taken together, these results suggest that the ACC represents cortical encoding of stimulus change; whilst this encoding is usually associated with change detection, this may not be the case in the early stages of learning or in an auditory cortex which has failed to develop normally due to auditory deprivation.

#### 3.5.4 Reasons for poor electrode discrimination

Apical electrode discrimination ability varied widely, both amongst pre- and post-lingually deafened individuals in this study. In the main, this is likely to be due to peripheral factors including electrode placement, current spread and spiral ganglion survival (Long et al., 2014; Pfingst et al., 1985). Electrode discrimination is affected by stimulus intensity in CI users (McKay et al., 1999). Immediately after switch-on, the MC level is achieved with relatively low stimulation levels and this could have contributed to poor electrode discrimination in certain individuals. Furthermore, the MC level is a fairly imprecise measure and therefore, differences in perceived loudness could have contributed to variation in electrode discrimination ability. As discussed earlier, it was found that in certain individuals, stimulus change was encoded in the auditory cortex but not accurately perceived. This suggests that poor behavioural electrode discrimination can be due to central as well as peripheral factors.

#### 3.5.5 Electrode discrimination and speech perception

Mean electrode discrimination  $d'$  scores were found to be correlated with open-set and closed-set speech perception. Apical electrodes encode low frequencies which provide important cues for speech perception (Li and Loizou, 2008). Although the sample size is small, these results are in keeping with Dawson et al. (2000) and Busby et al. (2000), who found that apical EDLs were negatively correlated with closed-set speech perception. Busby et al. (2000) did not find a relationship between EDL and open-set speech perception. This may be because in the study by Busby et al. (2000), apical EDLs were measured around a single electrode, whereas in this study electrode discrimination ability was measured across multiple electrode pairs. A significant correlation between spatial ACC and speech perception was not found even after excluding pre-lingually deafened individuals. The study was underpowered for this

analysis and the significance levels must be interpreted with caution. The relationship between the spatial ACC and speech perception is examined and discussed further in Chapter 4.

### 3.6 Conclusions

This study shows that the spatial ACC can be measured in different CI devices and at an early stage after CI switch-on. It will be important to understand how the ACC develops in relation to behavioural discrimination and this will be explored further in Chapter 4. The spatial ACC represents encoding of stimulus change at the level of the cortex and can provide information over and above behavioural testing. This raises the possibility of using this objective measure to guide management at an early, and potentially critical period of auditory rehabilitation.

## Chapter 4 Development of the spatial ACC and behavioural electrode discrimination after CI switch-on

This chapter is based on the following published journal article:

Mathew R, Vickers D, Boyle P et al. Development of electrophysiological and behavioural measures of electrode discrimination in adult cochlear implant users. *Hear Res.* 2018 Sep;367:74-87. doi: 10.1016/j.heares.2018.07.002.

### 4.1 Abstract

The plasticity of the auditory system enables it to adapt to electrical stimulation from cochlear implants (CI). Whilst speech perception may develop for many years after implant activation, very little is known about the changes in auditory processing that underpin these improvements. Such an understanding could help guide interventions that improve hearing performance. In this longitudinal study, the change over time in electrode discrimination was examined in newly implanted adult CI users. Electrode discrimination was measured with a behavioural task as well as the spatial auditory change complex (ACC). It was found that there was significant improvement in electrode discrimination ability over time, though in certain individuals the process of adaptation was slower and more limited. There was a strong relationship between objective and behavioural measures of electrode discrimination using pass-fail rules. In several cases, the development of the spatial ACC preceded accurate behavioural discrimination. These data provide evidence for plasticity of auditory processing in adult CI users. Interventions which exploit the plasticity of the auditory system to improve basic auditory processing, could help to optimize performance in CI users.

### 4.2 Introduction

Electrical hearing imposes several limitations compared to acoustic hearing including reduced DR, spectral mismatch between the characteristic frequencies of the auditory neurons and allocated frequencies of the stimulation channels, as well as reduced spectral resolution (Moore, 2003). Learning to hear and communicate effectively with a CI requires significant adaptation on the part of the auditory system. To be able to fully understand speech with a CI, the individual needs to develop perceptual skills

from detection and discrimination through to identification and comprehension (Erber, 1982). Whilst it is well known that a CI user's ability to identify speech can improve over long periods with hearing experience (Tyler et al., 1997), the time course for the emergence of discrimination ability is less well understood.

Understanding the temporal dynamics of discrimination ability could provide insights into basic auditory processing in CI users and help to guide management. In this respect, assessment of electrode discrimination is of particular interest. Electrode discrimination provides a measure of spatial resolution (Collins et al., 1997; Throckmorton and Collins, 1999) and has been correlated with speech perception in paediatric and adult CI users (Busby et al., 2000; Dawson et al., 2000). The results of electrode discrimination tests have been used to guide interventions in CI users, such as deactivation of electrodes and auditory training, in order to improve hearing performance (Saleh et al., 2013; Deborah Vickers et al., 2016; Zwolan et al., 1997). However, if such interventions are to be carried out, then it would be helpful to understand how these psychophysical abilities develop over time. If performance improves for long periods with CI experience, then prematurely intervening, for example by deactivating electrodes, could be detrimental. If on the other hand, performance improves rapidly and then plateaus, remapping interventions are more likely to be appropriate.

Relatively few studies have assessed the emergence of spectral processing in CI users. Sandmann et al. (2015) conducted a longitudinal study in newly implanted post-lingually deaf adult CI users who were given a behavioural task in which they had to identify the direction of pitch change in a frequency modulated tone complex. Participants were followed up for 9 months after switch-on but performance did not increase significantly after 2 months. This study suggests that spectral processing, as measured with a task involving pitch judgements, plateaus very quickly. Landsberger et al. (2018), measured spectral resolution with the SMRT in a cross sectional study of paediatric CI users between the ages of 5 and 13 years. Most children had been using a CI for several years (range 0.8 – 11 years) in their study. It was found that SMRT scores were not correlated with age or CI experience suggesting that the development of

spectral resolution is impaired in early deafened CI users. To date there have not been any longitudinal studies assessing electrode discrimination in CI users.

The spatial ACC is an objective measure of electrode discrimination. In Chapter 3, it was shown that the spatial ACC can be measured in individuals with different CI manufacturers devices and also in newly implanted adult CI users. In addition, a strong relationship between objective and behavioural measures of electrode discrimination was found at 1 week after switch-on. Interestingly, in some pre-lingually deafened late implanted individuals, the spatial ACC could be measured despite relatively poor behavioural discrimination. It was hypothesized that in these cases, the presence of the ACC indicated the potential to develop accurate behavioural discrimination at a later stage.

The aim of this follow up study is to determine how electrode discrimination ability develops over time. The objectives were to:

- 1) determine how the spatial ACC and behavioural electrode discrimination develop over the first 6 to 12 months after switch-on
- 2) examine the relationship between the spatial ACC and behavioural electrode discrimination during this period
- 3) examine the relationship between measures of electrode discrimination and speech perception

## 4.3 Experiment 3: Design and Methods

### 4.3.1 Participants

Eleven participants ranging in age from 42 to 80 years took part in the study. One participant dropped out of the study after the first recording session and was therefore excluded from the analysis. Of the remaining 10 participants, 9 had taken part in the research in Chapter 3. All participants were unilaterally implanted with an AB Hi-Res 90K implant. Demographic details of participants are shown in table 4.1. Of note, deafness onset was pre- or peri-lingual in 3 cases and post-lingual in the remainder of participants.

### 4.3.2 Test procedures

The spatial ACC, behavioural electrode discrimination and speech perception were tested at the following time points after switch-on: 1 week (median 10.5 days, range 7-19 days), 3 months (median 92 days, range 81-108 days) and 6 months (median 180.5 days, range 169-190 days). Additionally, a subset of participants underwent behavioural testing at 12 months after switch-on (see below).

The stimuli for EEG were identical to that in experiment 2 (Chapter 3) - 800 ms alternating polarity biphasic pulse trains presented at a rate of 0.51 Hz. The 4 most apical electrode pairs were tested (1-2, 2-3, 3-4, 4-5) in every participant. Stimuli were presented at the loudness balanced MC level. As stimulation levels required by CI users generally increase over the first 6 months of CI use (Vargas et al., 2012), the procedure for determining stimulation levels was repeated at each visit until 6 months.

There were a total of 120 EEG measurements over 6 months (4 electrode pairs for 10 participants at 3 time points). EEG recording and processing was performed as described in the General Methods (Chapter 2). An objective pass was based on Hotelling-T2 criteria during the response window of 450 – 650 ms. The response window was adjusted, to 450 – 700 ms in 8/120 cases due to a late P2 peak, and to 450 - 600 ms in 2/120 cases, due to an absent P2 peak.



Speech perception and behavioural electrode discrimination (for all 4 electrode pairs) were measured at the 1-week, 3-month and 6-month time points. In addition, behavioural electrode discrimination testing was repeated at 12 months for participants who had not achieved a behavioural pass for all 4 electrode pairs by 6 months. This was motivated by the finding that a number of electrode pairs had an objective pass but behavioural fail at 6 months. Testing at 12 months was therefore performed to determine whether these electrodes would develop a behavioural pass at a later time. For the 12-month time point, the same stimulation levels as at 6 months were used. Loudness balancing was checked and repeated if participants reported a difference in loudness.

Speech perception testing included open-set BKB sentences-in-quiet, and the closed-set CAPT vowel test. EEG, behavioural and speech testing were done in a single session which lasted approximately 2.5 hours including breaks.

Table 4.1 Demographic details of participants in experiment 3. F= female, M= male, R = right, L= left, 4F-PTA = four-frequency pure tone average, CI = cochlear implant.

Participant	Age	Sex	Ear	Communication	Duration profound hearing loss (years)	Deafness onset	4F-PTA non CI ear (dB HL)	Electrode
S1	51	M	R	oral	10	Post-lingual	116	Mid Scala
S2	50	F	R	oral + sign	50	Pre-lingual	115	Mid Scala
S3	42	F	L	oral	18	Post-lingual	118	Mid Scala
S4	48	M	L	oral	46	Pre-lingual	115	1J
S5	47	F	L	oral	42	Peri-lingual	103	Mid Scala
S6	68	F	L	oral	10	Post-lingual	100	Mid Scala
S8	51	F	R	oral	5	Post-lingual	96	Mid Scala
S9	48	M	L	oral	1	Post-lingual	113	Mid Scala
S10	80	M	L	oral	10	Post-lingual	78	Mid Scala
S11	65	F	L	oral	2.5	Post-lingual	98	Mid Scala

## 4.4 Results

### 4.4.1 Changes in behavioural electrode discrimination

Figure 4.1 shows the change over time in mean behavioural discrimination score across the 4 electrode pairs for each participant. As stated in the methods, 12-month data was only collected for participants who had not achieved a behavioural pass for all 4 electrode pairs by 6 months (S1, S2, S5, S6).

Inspection of the individual data shows that there was large variability in discrimination scores as well as the pattern of change over time. Participants S3, S8, S9 and S10 had excellent performance from 1 week, with scores at or near ceiling level for all electrode pairs. Participants S4 and S11 showed a rapid increase in behavioural scores achieving ceiling/near-ceiling level by 3 months. In contrast, participants S2, S5 and S6 had relatively poor discrimination to start with but mean discrimination score increased over 12-months. Only participant S1 showed a decrease in mean behavioural score. This participant had excellent discrimination for electrode pairs 3-4 and 4-5 throughout the study and the decrease in mean score was due to random variation in performance for electrode pairs 1-2 and 2-3, for which the threshold for a behavioural pass was never achieved.

The change in behavioural discrimination score over time was analyzed with a linear mixed-effects model. In order to reduce ceiling effects, only electrode pairs that did not have a discrimination score of 100% at 1 week were included in the analysis. The dependent variable was the 'behavioural  $d'$  score' for each electrode and the independent variables were 'time after switch-on' and 'electrode pair' (1-2, 2-3, 3-4, 4-5). There was no significant effect of 'electrode pair' and this factor was therefore removed from the model. Analysis of the reduced model showed a significant effect of 'time after switch-on' ( $F(3,67) = 5.01, p < 0.001$ ). Post-hoc pairwise comparisons with Tukey correction showed there was a significant difference for the 1 week vs 12 month contrast ( $p = 0.002$ ) and a trend towards significant difference for the 1 week vs 6 month contrast ( $p = 0.054$ ). A summary of the analysis is shown in table 4.2.

Table 4.2 Output of mixed model analysis of factors affecting behavioural discrimination score.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Initial model					
Time after switch-on	(3,65)	5.05	<0.001	0.190	0.072 – 0.386
Electrode pair	(3,66)	1.05	0.375	0.045	0.009 – 0.214
Reduced model					
Time after switch-on	(3,67)	5.01	<0.001	0.182	0.068 – 0.373

Changes in behavioural electrode discrimination were also analyzed in terms of the number of electrodes with a behavioural pass. In this case, the maximum score for an individual at any time point is 4, corresponding to the number of electrode pairs tested. The changes over time in the number of electrodes with a behavioural pass are shown in figure 4.2. This figure shows a similar pattern to figure 4.1 with improvement in electrode discrimination ability for participants S2, S5 and S6 between 6 and 12 months. The total number of electrodes with a behavioural pass increased over time and was 25/40 at 1 week, 29/40 at 3 months and 30/40 at 6 months. At 12 months, 5 additional electrode pairs achieved a behavioural pass.

These data show that apical electrode discrimination ability varies widely amongst CI users but can continue to improve for up to 12 months after switch-on in certain individuals.

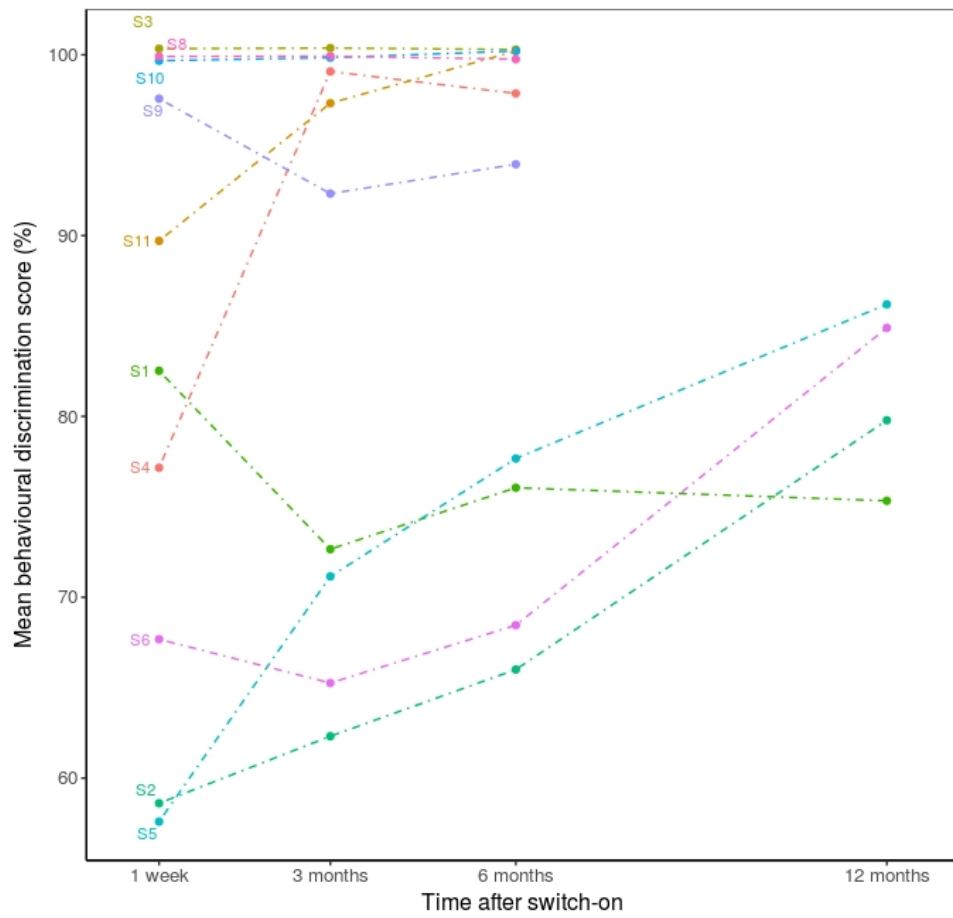


Figure 4.1 Change in mean behavioural electrode discrimination score over time. Data are shown for individual CI users. Note that behavioural scores were only measured at 12 months in individuals who had not achieved a behavioural pass for all 4 electrode pairs by 6 months (S1, S2, S5, S6). Random noise has been added to the discrimination scores in order to improve data visualization.

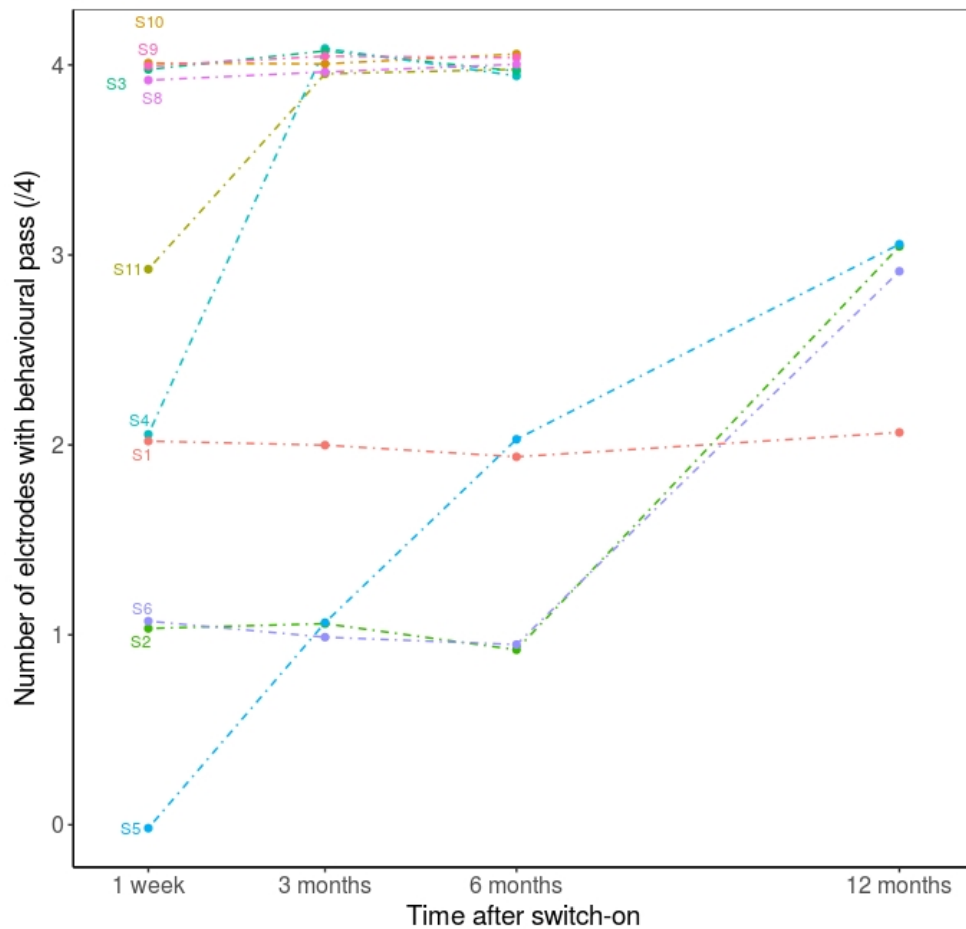


Figure 4.2 Change over time in the number of discriminable electrodes as defined by behavioural pass-fail rules. Data are shown for individual CI users. The maximum score that can be achieved at any time point is 4 corresponding to the number of electrode pairs tested. Behavioural scores were only measured at 12 months in individuals who had not achieved a behavioural pass for all 4 electrode pairs by 6 months (S1, S2, S5, S6). Random noise has been added to the behavioural pass score in order to improve data visualization.

#### 4.4.2 Behavioural discrimination controlling for stimulus intensity

Studies from NH and CI populations have shown that discrimination ability improves with stimulation level (Freyman and Nelson, 1991; McKay et al., 1999). In this study, most participants reported higher MC levels over time and therefore higher stimulation levels were generally used for testing at later time points. The average MC level across participants was 250  $\mu$ A at 1 week, 294  $\mu$ A at 3 months and 313  $\mu$ A at 6 months. Thus, the increase in stimulation levels could potentially account for the improvement in behavioural discrimination scores.

In order to investigate whether improvements in behavioural discrimination were due to the use of higher stimulation levels, electrode pairs were re-tested at later time

point using the original stimulation levels from earlier time points. If discrimination scores at the later time point were higher than that obtained with the same stimulation level as originally used, then this would provide evidence that improvements over time were not just due to the use of a higher stimulation level. Behavioural electrode discrimination was therefore retested for electrode pairs which improved from a behavioural fail to a behavioural pass. This was performed at a median of 16 months after switch-on (range 12 – 20 months) using the 1-month and/or 3-month stimulation levels. For example, if an electrode pair developed a behavioural pass at 12 months, then it was re-tested at the 1-week level. If a behavioural pass was achieved (score  $\geq 80\%$ ), then no further testing was performed but if there was a behavioural fail, re-testing was repeated using the 3-month level. The 6-month level was not used for re-testing as this was the same level used at 12 months. Re-testing of electrode discrimination at earlier levels was done in a separate session to the main experiment in order to reduce within session learning effects. In addition, loudness balancing was checked and repeated if necessary, for all electrode pairs and stimulation levels.

The results of re-testing are shown in table 4.3. There were 10 electrode pairs from 5 participants that developed a behavioural pass from a behavioural fail with CI listening experience. When retested at the original 1-week level, 9 out of 10 electrode pairs had a higher score, with 7 of these achieving a behavioural pass (score  $\geq 80\%$ ). Of the 3 electrode pairs which had not achieved a behavioural pass at the 1 week level, 2 achieved a behavioural pass when tested at the 3-month level. As can be seen from table 4.3, improvements occurred irrespective of whether electrodes were loudness balanced again or not. Only one electrode failed when re-tested at the 1-week and 3-month levels (S6, electrode 3-4). This electrode had a behavioural fail at 6 months (score = 60%) but when tested at 12 months, with the same stimulus level, a behavioural pass was achieved (score = 85%). Therefore, all ten electrode pairs that originally had a behavioural fail, had a behavioural pass when re-tested with the same stimulus level at a later time point.

Table 4.3 Details of electrodes which went from a behavioural fail to a behavioural pass in experiment 3. Original scores when a behavioural fail was achieved as well as retest scores at a later time point with the same levels are shown. MC = most comfortable.

Participant	Electrode	Original score at MC level and date	Retest score at same level	Date of retesting	Re-loudness balanced
S2	2-3	45%, 1 week	85%	16 months	No
	3-4	60%, 1 week	85%		Yes
S4	1-2	60%, 1 week	95%	20 month	No
	4-5	70%, 1 week	95%		No
S5	2-3	40%, 1 week	100%	16 months	No
	3-4	60%, 1 week	100%		No
	4-5	55%, 1 week	75%		Yes
55%, 3 months		80%	Yes		
S6	2-3	75%, 1 week	75%	15 months	No
		50%, 3 months	80%		No
	3-4	50%, 1week	55%		No
65%, 3 months		75%	No		
S11	1-2	70%, 1 week	100%	12 months	No

The effect of time on behavioural discrimination score, with fixed stimulation levels was analyzed with a linear mixed-effects model. The dependent variable was the behavioural  $d'$  score and independent variables included 'electrode pair' (1-2, 2-3, 3-4, 4-5), 'level' (1-week or 3-month level) and 'time' (original or re-test). This analysis showed that there was only a significant main effect of time ( $F(1,20) = 32, p < 0.001$ ). A summary of this analysis is shown in table 4.4. These data demonstrate that electrode discrimination ability can improve with CI experience irrespective of stimulation level.



Table 4.4 Mixed model analysis of change in behavioural discrimination score controlling for stimulus intensity.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Initial model					
Time	(1, 20)	27	<0.001	0.614	0.484 – 0.886
Electrode pair	(3, 20)	0.98	0.422	0.172	0.038 – 0.659
Level	(1, 20)	0.72	0.408	0.028	0.000 – 0.331
Reduced model					
Time	(1, 20)	32	<0.001	0.614	0.373 – 0.805

#### 4.4.3 Development of the spatial ACC

Figure 4.3 shows the change over time in mean spatial ACC amplitude across 4 electrode pairs for each participant. The solid black line represents the grand mean across participants and was 2.16  $\mu\text{V}$  at 1 week, 2.65  $\mu\text{V}$  at 3 months and 2.79  $\mu\text{V}$  at 6 months. Inspection of the individual data reveals large inter-individual variability in spatial ACC amplitude and the changes over time appear to be less consistent in comparison to the behavioural discrimination scores. However, a clear increase in spatial ACC amplitude with time can be observed in 7 out of 10 participants.

The change in spatial ACC amplitude was analyzed with a linear mixed-effects model. The dependent variable was the spatial ACC amplitude for individual electrode pairs and the fixed effects were time after switch-on (1 week, 3 months and 6 months) and electrode pair (1-2, 2-3, 3-4, 4-5). There was no significant effect of electrode pair and this factor was therefore removed from the model. Analysis of the reduced model revealed a significant effect of time after switch-on ( $F(2,108) = 4.93$ ,  $p = 0.009$ ). A summary of the analysis is shown in table 4.5. Post-hoc analysis with Tukey correction showed that there was a significant difference in ACC amplitude for the 1 week vs 6 months contrast ( $p = 0.010$ ) and a trend towards significant difference for the 1 week vs 3 month contrast ( $p=0.056$ ).

Table 4.5 Mixed model analysis of factors affecting change in ACC N1-P2 amplitude over time.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Initial model					
Time after switch-on	(2, 105)	4.88	0.009	0.085	0.018 – 0.214
Electrode pair	(3, 105)	0.67	0.574	0.019	0.004 – 0.126
Reduced model					
Time after switch-on	(2, 108)	4.93	0.009	0.084	0.018 – 0.210

Analysis of the ACC with pass-fail criteria also showed that electrode discrimination ability improved with time. According to Hotelling-T2 criteria, the number of electrodes with an objective pass was 23/40 at 1 week, 28/40 at 3 months and 30/40 at 6 months. Figure 4.4 shows an example of cortical response development for an electrode pair in participant S4 – at 1 week the spatial ACC was absent (4.4 A) but by 3 months a clear response was present (4.4 B).

The change in latency of the ACC was only assessed for electrode pairs for which there was an objective pass, as a meaningful latency cannot be obtained when the ACC is absent. This analysis was limited because a large proportion of the data had to be excluded. The mean latency at 1 week, 3 months and 6 months was 119ms, 123ms and 120ms for the ACC N1 peak and 224ms, 245ms, and 237ms for the ACC P2 peak. Using a mixed model analysis, a significant effect of time on the ACC peak latencies was not observed (table 4.6).

Table 4.6 Mixed model analysis of the effect of time after switch on latency of ACC peaks.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
cN1 peak					
Time after switch-on	(2, 64)	0.34	0.711	0.011	0.001 – 0.137
Electrode pair	(3, 64)	2.09	0.110	0.089	0.020 – 0.276
cP2 peak					
Time after switch-on	(2, 65)	0.30	0.740	0.009	0.001 – 0.134
Electrode pair	(3, 65)	0.88	0.459	0.039	0.008 – 0.209

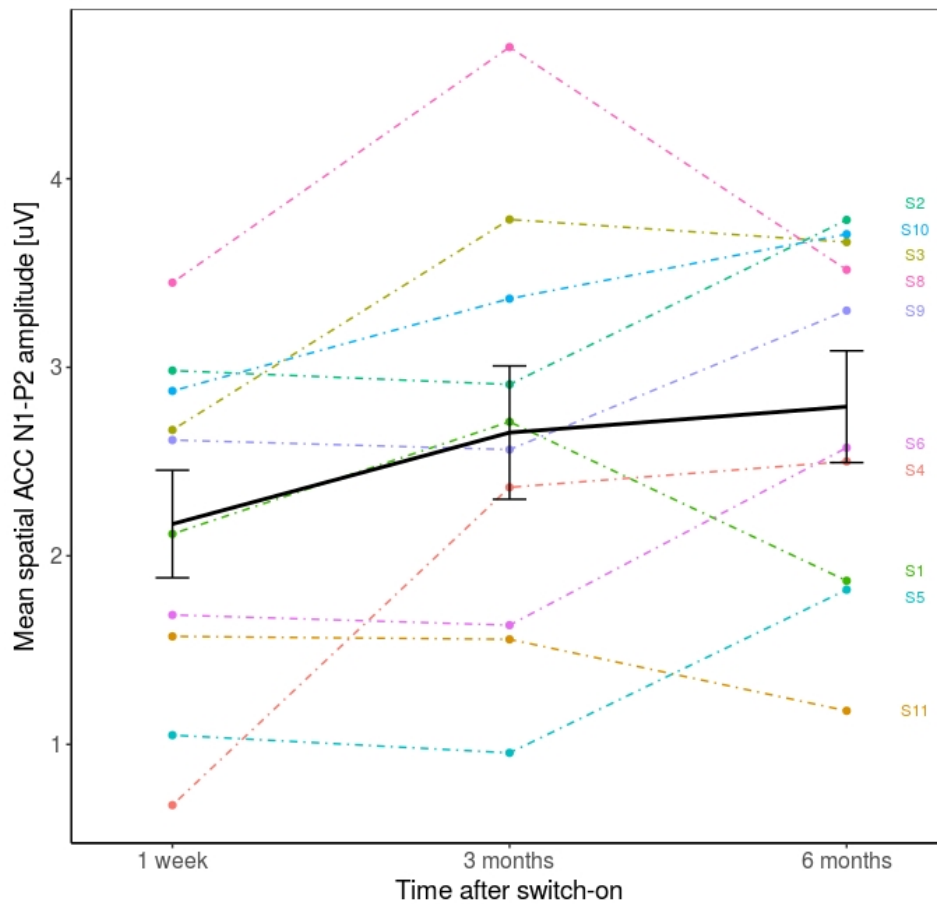


Figure 4.3 Change in the mean spatial ACC amplitude over time. The broken lines show the mean electrode discrimination scores for each individual. The solid line shows that the mean scores across all participants with error bars representing the standard error of the mean. Data at channel FCz are presented.

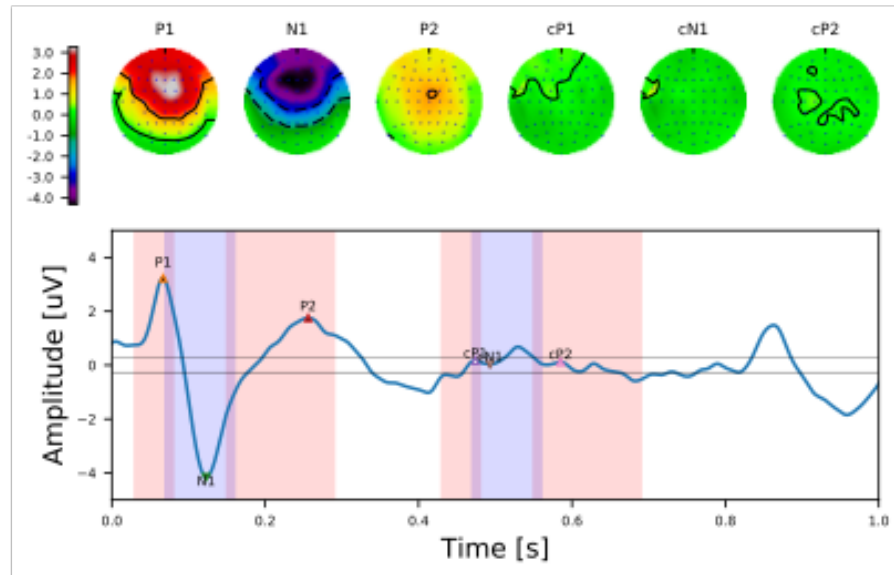
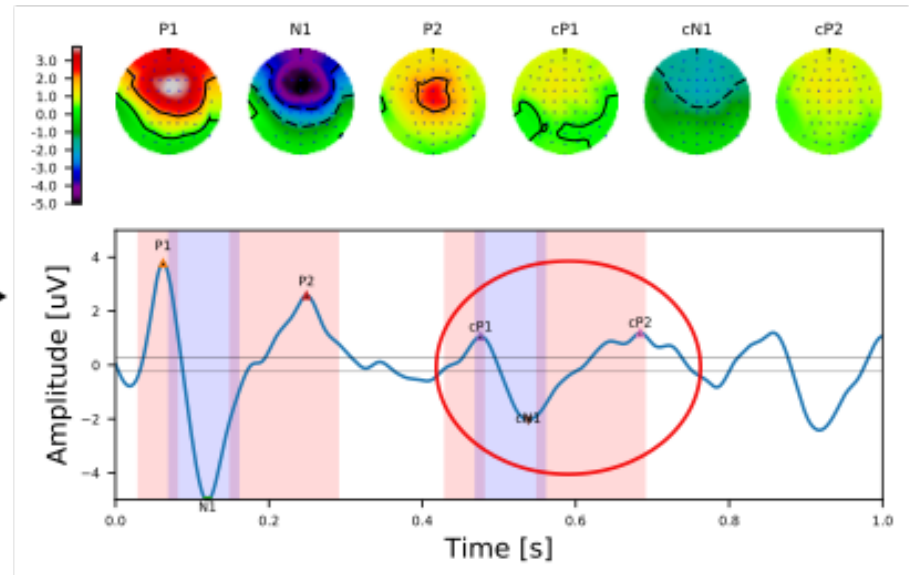
(A) 1 week: behavioural score = 60%, HT2  $p = 0.43$ (B) 3 months: behavioural score = 100%, HT2  $p < 0.001$ 

Figure 4.4 Example of cortical response development. Data are shown for participant S4 electrode pair 1-2 (A) At 1 week after switch-on, the spatial ACC is absent and there is a behavioural fail. (B) At 3 months after switch-on, there is a large spatial ACC response associated with a behavioural pass. The spatial ACC has been highlighted in red. Behavioural scores and the Hotelling-T2 (HT2)  $p$  values are indicated on each panel. The time windows used to detect positive and negative peaks for the onset response (P1, N1, and P2) and ACC (cP1, cN1, and cP2) are shown in pink and blue, respectively. Scalp voltage maps for automatically detected peaks are displayed, with black lines representing isopotential contour lines. The horizontal lines correspond to the level of residual noise. Data at channel FCz are presented.

#### 4.4.4 Relationship between the spatial ACC and behavioural electrode discrimination

The relationship between objective ACC and behavioural measures of electrode discrimination using pass-fail rules is shown in table 4.7. As described in the methods section, an objective ACC pass was based on Hotelling-T2 statistical criteria whilst a behavioural pass required a discrimination score of at least 80%. Out of 120 measurements over 6 months, there was agreement between objective and behavioural measures in 99 cases: 34/40 at 1 week, 35/40 at 3 months and 30/40 at 6 months. There were 12 electrode pairs from 4 participants in which there was a behavioural pass but an objective fail. Of these disagreements, 8 were from participant S11 (disagreements: 2 at 1 week, 2 at 3 months and 4 at 6 months). Aside from this participant, there were only 4 electrode pairs from 3 participants in which there was a behavioural pass but an objective fail.

Interestingly, there were 9 cases where disagreement was due to an objective ACC pass despite a behavioural fail. Figure 4.5 shows examples of ACC recordings that fell into this group. Table 4.8 shows that the disagreements arose from 7 electrode pairs from 4 participants, 3 of whom had pre or peri-lingual onset deafness. In 6 out of these 7 cases, electrode pairs developed accurate behavioural discrimination at a later time point i.e. the ACC preceded accurate behavioural discrimination. As seen in table 4.4, in most cases a behavioural pass was obtained at the test point immediately following the attainment of an objective pass. However, for electrode pair 2-3 in participant S2, a behavioural pass was only obtained at 12 months despite an objective pass being present from 1 week onwards. These data confirm findings from Chapter 3 that a stimulus change may be encoded in the auditory pathway despite poor behavioural discrimination. Furthermore, the longitudinal data shows that the presence of the ACC indicates potential to develop accurate behavioural discrimination later on.

The relationship between objective and behavioural measures of electrode discrimination was also assessed by performing correlation analysis across participants between mean behavioural  $d'$  score and mean ACC N1-P2 amplitude at each time point. Pearson's correlation did not show a significant relationship at any time point (1 week:  $r = 0.59$ , 95% confidence interval  $[-0.06, 0.89]$ ,  $p = 0.072$ ; 3 months:  $r = 0.55$ ,

95% confidence interval [-0.12, 0.88],  $p = 0.098$ ; 6 months:  $r = 0.13$ , 95% confidence interval [-0.54, 0.70],  $p = 0.710$ ;  $N = 10$  for all correlations). The correlation was particularly poor at 6 months which was also reflected in the greater level of disagreement in the pass-fail analysis at this time point, as seen earlier. The study was underpowered for this analysis and the correlation analysis should be interpreted with caution.

Table 4.7 Agreement between objective and behavioural electrode discrimination at different time points.

	1 week		3 months		6 months	
	Behavioural Pass	Behavioural Fail	Behavioural Pass	Behavioural Fail	Behavioural Pass	Behavioural Fail
Objective Pass	21	2	26	2	25	5
Objective Fail	4	13	3	9	5	5
Total agreement	34/40		35/40		30/40	

Table 4.8 Details of electrodes with an objective ACC pass and a behavioural fail. 1W = 1week, 3M = 3 months, 6M = 6 months, 12M = 12 months and NA = not applicable, NT = not tested.

Subject and electrode	Date objective pass first achieved	Date behavioural pass first achieved	Behavioural scores (%)			
			1W	3M	6M	12M
S2 1-2	6M	NA (fail at 12M)	30	55	60	55
S2 2-3	1W (and at 3M and 6M)	12M	45	55	45	85
S2 3-4	6M	12M	60	40	60	80
S4 4-5	1W	3M	70	100	100	NT
S5 2-3	3M	6M	40	70	85	NT
S5 4-5	6M	12M	55	55	50	85
S6 2-3	6M	12M	75	50	55	90

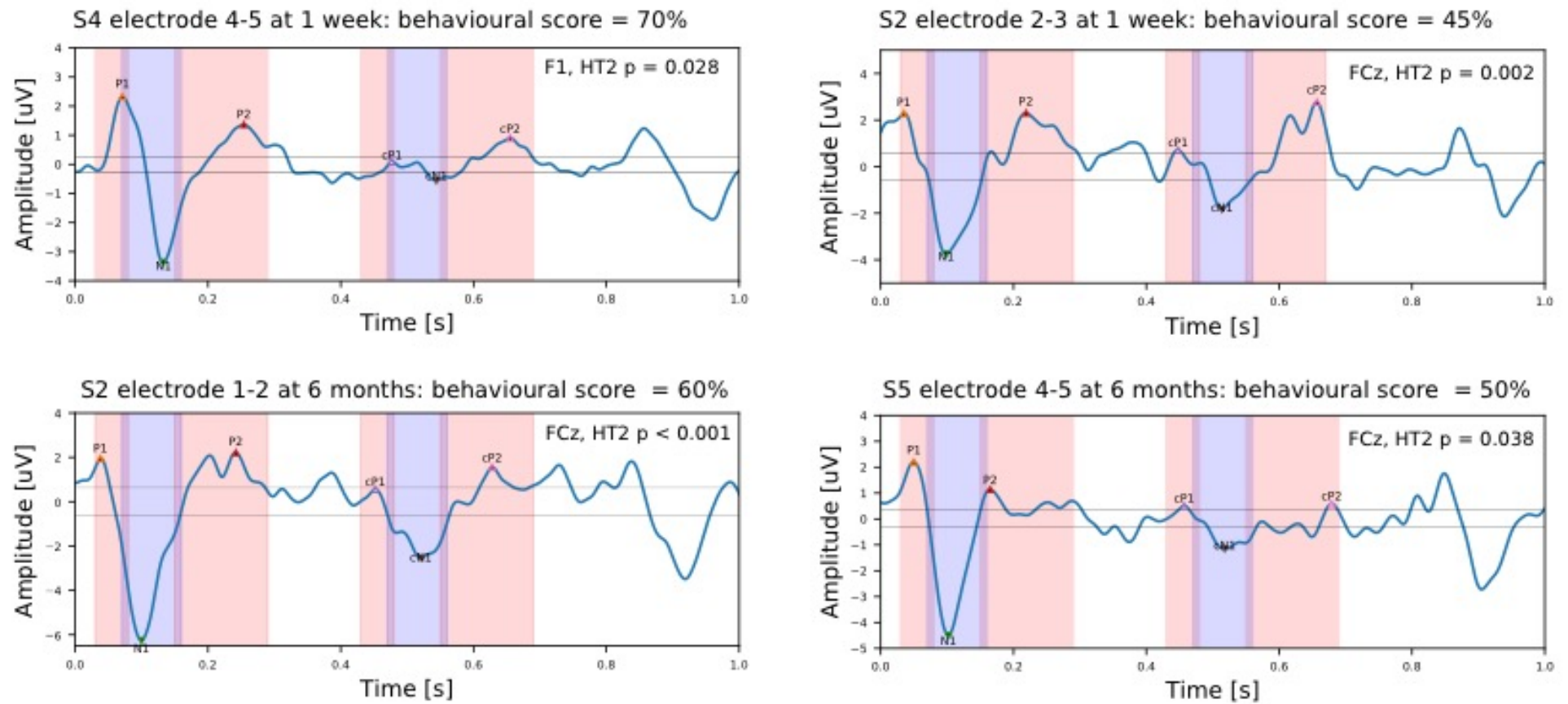


Figure 4.5 Examples of cortical responses with an objective ACC pass despite the presence of a behavioural fail. The participant ID, electrode pair, test time point and corresponding behavioural score are shown above each panel. Data are presented at a representative fronto-central channel which is indicated on each panel along with the Hotelling-T2 (HT2) p value. Shaded areas and horizontal lines are as described in figure 4.4.



#### 4.4.5 Relationship between electrode discrimination and speech perception

Figure 4.6 shows how sentence and vowel perception scores changed over time. The solid black line represents the mean speech perception score across participants. Both vowel perception and speech perception improved in all participants with the exception of S2, in whom sentence perception score remained at 0%. This participant had congenital deafness and used both oral and sign language.

It is interesting to note that participants S2, S5 and S6, who had relatively poor electrode discrimination at 6 months (see figure 4.1), were also three of the poorest performers in terms of speech perception at 6 months. On the other hand, participant S1 could only discriminate 2 out of 4 electrodes accurately throughout the 12-month study period but had consistently excellent speech perception scores. Participant S8 showed the opposite pattern, with excellent electrode discrimination but relatively poor speech perception.

The factors affecting speech perception were investigated with a linear mixed-effects model, with the dependent variable 'speech perception score' (either sentence perception or vowel perception score) and independent variables 'time after switch-on' (1 week, 3 months, 6 months) and 'mean behavioural electrode discrimination  $d'$  score' (averaged across 4 electrodes for each participant). For sentence perception as the dependent variable, there was a significant main effect of time after switch-on ( $F(2,18) = 4.80, p = 0.022$ ) and mean behavioural electrode discrimination  $d'$  score ( $F(1,18) = 6.22, p = 0.021$ ). Similarly for vowel perception score as the dependent variable, there was a significant main effect of time after switch-on  $F(2,19) = 6.84, p = 0.006$  and mean behavioural electrode discrimination  $d'$  score ( $F(1,14) = 5.73, p = 0.032$ ). The summary of this analysis is shown in table 4.9.

Table 4.9 Mixed model analysis of factors affecting speech perception with behavioural electrode discrimination as an independent variable.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Sentence perception					
Time after switch-on	(2, 18)	4.8	0.022	0.339	0.088 – 0.662
Behavioural discrimination d' score	(1, 18)	6.2	0.021	0.198	0.007 – 0.514
Vowel perception					
Time after switch-on	(2, 19)	6.8	0.006	0.424	0.156 – 0.713
Behavioural discrimination d' score	(1, 14)	5.7	0.032	0.039	0.010 – 0.654

In order to investigate whether there is a relationship between the spatial ACC and speech perception, the mixed model analysis was repeated with speech perception score (either sentence perception or vowel perception score) as the dependent variable and 'mean spatial ACC amplitude' (averaged across 4 electrode pairs), 'number of objective discriminable electrode' (ranging from 0 to 4) and 'time after switch-on' on' (1 week, 3 months, 6 months) as the independent variables. The analysis confirmed a significant main effect of time after switch-on for sentence perception ( $F(2,18) = 9.38$ ,  $p = 0.002$ ) and for vowel perception ( $F(2,18) = 9.79$ ,  $p = 0.001$ ). However, there was no significant effect of mean spatial ACC amplitude or number of objective discriminable electrode in either case (table 4.10).

Table 4.10 Mixed model analysis of factors affecting speech perception including spatial ACC measures as an independent variable.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
I	Sentence perception : initial model				
Time after switch-on	(2, 17)	6.0	0.010	0.406	0.311 – 0.787
Mean spatial ACC amplitude	(1, 22)	0.57	0.459	0.023	0.000 – 0.279
Number of objective discriminable electrodes	(1, 18)	2.7	0.118	0.120	0.001 – 0.456
Sentence perception : reduced model					
Time after switch-on	(2, 18)	9.4	0.002	0.510	0.243 – 0.764
II	Vowel perception: initial model				
Time after switch-on	(2, 18)	6.6	0.008	0.412	0.142 – 0.710
Mean spatial ACC amplitude	(1, 25)	0.34	0.564	0.012	0.000 – 0.224
Number of objective discriminable electrodes	(1, 23)	0.021	0.886	0.001	0.000 – 0.205
Vowel perception: reduced model					
Time after switch-on	(2, 18)	9.8	0.001	0.521	0.255 – 0.769

These data show that both sentence and vowel perception improve with hearing experience in CI users. Although behavioural and objective measures of electrode

discrimination are related, the former appears to be the more important predictor of speech perception.

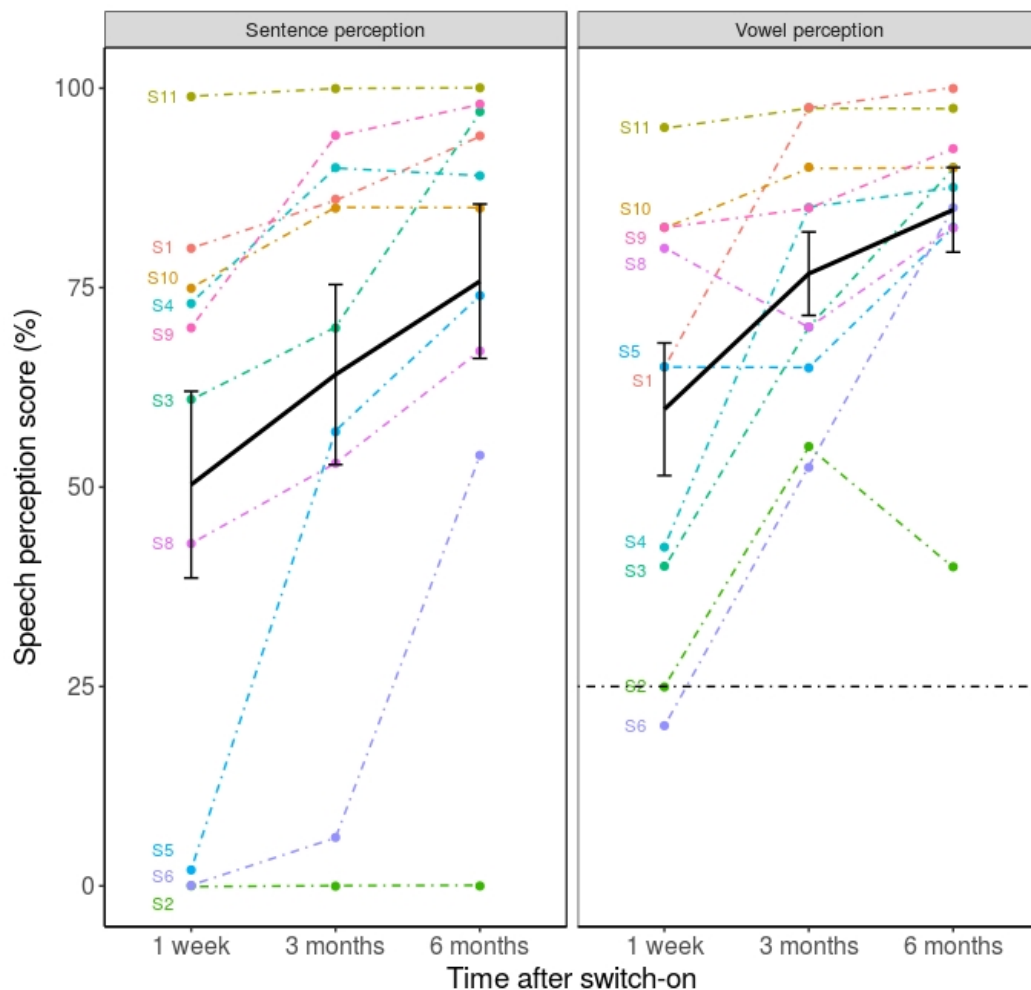


Figure 4.6 Change in speech perception over time. The broken lines show data for individual participants and the solid black lines shows the mean across participants with error bars representing the standard error of the mean. The black broken horizontal line in the vowel perception panel shows chance score in the 4-alternative forced-choice task. Random noise has been added to speech scores in order to improve data visualization.

#### 4.5 Discussion

This study shows that electrode discrimination ability can improve markedly with CI experience and improvements can occur over relatively long periods of time. Changes in behavioural performance were paralleled by an increase in the amplitude of the spatial ACC providing evidence for plasticity of auditory processing in adult CI users. Furthermore, the data provides further evidence that behavioural electrode discrimination is a significant predictor of speech perception. Targeting improvements in spatial resolution could therefore lead to better hearing outcomes in CI users.

#### 4.5.1 Changes in electrode discrimination over time

This is the first study to examine changes in electrode discrimination ability over time in CI users. Electrode discrimination ability continued to improve for up to 12 months after switch-on in certain individuals. While it is known that speech perception in CI users may improve for many years (Heywood et al., 2016; Tyler et al., 1997), it was somewhat surprising that discrimination of, what are in principle, simple stimuli would continue to improve for so long. The relatively long time course of improvement in some individuals suggests that central rather than peripheral factors, are responsible for the change in performance over time. The late improvements occurred in poorer performers, 3 of whom had pre or peri-lingual onset deafness, indicating that the history of hearing loss may account for the different time course of adaptation in different individuals.

The data suggests that the improvements over time were not just due to task related learning for two reasons. Firstly, the improvements in behavioural scores over the first 6 months were paralleled by an increase in the mean spatial ACC amplitude. Secondly, all but one participant could accurately discriminate at least one electrode pair from the first test session. This implies that participants were competent at the behavioural task from an early stage and improvements in discrimination ability over time were more likely due to perceptual rather than task related learning. For example, participants S2 and S6 achieved a behavioural pass for only a single electrode pair from 1 week to 6 months but then showed improved discrimination for other electrode pairs at 12 months.

There is limited evidence from longitudinal studies that spectral resolution improves with CI experience. Sandmann et al. (2015), showed that in post-lingually deaf CI users, the ability to judge the direction of pitch change in a modulated tone complex increased rapidly until 8 weeks after switch-on and thereafter plateaued. The individual behavioural data was not presented in that study but the rapid asymptotic performance is similar to that seen in the good performers who achieved electrode discrimination ceiling levels by 1 week to 3 months in this study. Jeon et al. (2015) provide evidence of more long term improvements in spectral resolution using spectral

ripple discrimination tests. Post-lingually deafened adults who had spectral ripple scores measured in a previous study (Henry et al., 2005) were retested several years later. The mean duration of CI use was 2 years at the original test point and 12.5 years at the time of re-testing. In 3 out of 4 cases, scores increased over time, with considerable improvement in 2 cases. In contrast, Landsberger et al. (2018), found that spectral resolution as measured with the SMRT did not improve with age in paediatric CI users. However, this was a cross-sectional study and most CI users had been using their device for several years so it is possible that the spectral resolution had improved prior to testing. The different findings in these studies are likely due to differences in the behavioural task and study populations. However, taken together, it appears that improvements in spectral/spatial resolution predominantly occur during the first few weeks to months after switch-on but further gains may be possible over long periods of time in certain individuals.

In this study, improvements in behavioural electrode discrimination were accompanied by an increase in spatial ACC amplitude over the first 6 months of CI use. Whilst changes in the spatial ACC over time have not been previously reported, a number of studies have assessed longitudinal changes in discrimination ability in CI users using MMN measurements (Lonka et al., 2004, 2013; Purdy and Kelly, 2016; Vavatzanidis et al., 2015). In general, these studies have shown an increase in MMN amplitude with CI experience, but in most cases the MMN could not be recorded in the early period after switch-on. As most studies do not report concurrent behavioural data, it is not clear whether the early absence of the MMN is due to the inability of CI users to discriminate the relevant stimuli or due to a lack of sensitivity in the recording paradigm.

Purdy et al. (2016), measured the MMN to a change in frequency using pure tone stimuli and showed that MMN amplitude increased and latency decreased during the first 9 months of CI use, though this effect was not statistically significant. Of note, the MMN could not be recorded in the first week after switch-on in 40% of cases, despite the stimuli being behaviourally discriminable, suggesting a lack of recording sensitivity. Similarly, Lonka et al. (2004) and (2013), measured the MMN to vowel contrasts and a change in pure tone frequency respectively. In both studies, the MMN could not be

recorded until 1 year after switch-on due to large CI artefact. Nonetheless, there was a significant increase in MMN amplitude from 1 year to 2.5 years after switch-on. Behavioural discrimination data were not reported in their study although concurrent improvements in speech perception occurred over the same period. Pantev (2005), reported long term changes in acoustic ACC responses, using a continuous pure tone stimulus with a regular 100 Hz change in frequency, in 2 post-lingually deafened adult CI users. The ACC could not be recorded for the first 2-3 months after switch-on in either case. Thereafter the response increased in amplitude until 6 months for one user and for 2 years in the other user. These electrophysiological data provide evidence for long term changes in auditory discrimination, which is consistent with the findings of this study.

The data did not show an effect of CI experience on the latency of the N1 or P2 components of the spatial ACC response. It must be noted that the study was underpowered for this analysis as only measurements with an objective ACC pass could be included in order to obtain a meaningful latency value. Purdy et al. (2016), examined changes in MMN latency for pure tone stimuli in 10 adults with CI who were followed up on 5 occasions over 9 months after switch-on. It was found that there was a decrease in the MMN latency over time but this was not statistically significant. Lonka et al. (2013), did not find an effect of CI experience on the MMN latency. In contrast, a number of studies have reported that with CI experience, there is a shortening of latency of the cortical onset response (Burdo et al., 2006; Sandmann et al., 2015; Sharma et al., 2005b). This difference may be because the ACC and MMN are markers of auditory discrimination rather than detection. In addition, He et al. (2012) showed that increasing the magnitude of change across different acoustic dimensions, such as frequency or intensity, led to consistent changes in the ACC amplitude but not the ACC latency, indicating that the latter is a poorer marker of discrimination.

An important confound to consider with behavioural and electrophysiological measurements over time is the stimulus level. During the first 6 months after CI, stimulation levels required by patients increase (Vargas et al., 2012) due to the development of loudness tolerance. It is known that for the cortical response to sound onset, increasing stimulus level leads to larger amplitude and shorter peak latency in

both NH and CI populations (Firszt et al., 2002; Picton et al., 1976). This effect of stimulus level on evoked response has not been controlled for in the aforementioned MMN studies. In CI users, improved electrode discrimination scores with stimulus level has been reported, though there is much variability between individuals and even between electrode locations within an individual (McKay et al., 1999; Pfingst et al., 1999). When electrode pairs that originally had a behavioural fail, were re-tested at a later time point with the same stimulation levels, significantly higher discrimination scores were obtained. This shows that improvements in behavioural discrimination over time cannot be completely accounted for by the increase in stimulation level. It is still possible that the changes in spatial ACC amplitude over time were due to level effects. Nonetheless, it is an important finding that the spatial ACC amplitude can increase at a relatively constant perceptual level and that this is paralleled by improvements in behavioural electrode discrimination. The effect of stimulus level on electrode discrimination is examined further in Chapter 5.

#### 4.5.2 Reasons for improved electrode discrimination

Reiss et al. (2007), showed that the pitch percept associated with an individual electrode can change by up to 2 octaves over time. This appears to be driven by the spectral mismatch between the allocated frequencies of the CI stimulation channels and the characteristic frequencies of the corresponding auditory neurons. Hence, the absolute percept associated with an electrode may change over time, but this does not imply better spatial resolution. It is therefore interesting to consider two questions.

*Firstly, what was driving the improvement in spatial resolution in CI users given that they did not undergo any discrimination training?*

The improvements could be due to top-down processes - exposure to speech and the feedback that CI users obtain through their daily interactions, are in essence 'passive training', which could drive better spatial resolution. Such a top-down effect was seen in the study by Rosen et al. (1999), who showed that connected discourse tracking training resulted in improved vowel recognition in CI simulations with NH listeners. Improvements in spatial resolution could also occur due to passive exposure to electrical stimulation through the CI. Kurkela et al. (2016) passively exposed rats to



behaviourally irrelevant speech stimuli for 36 hours. They showed that the MMN for small changes in spectrotemporal sounds could be recorded in animals previously exposed to these sounds but not in the animals exposed to different sounds. The authors suggest that passive exposure to sounds can result in a formation of long-term memory representation which aids auditory discrimination.

*Secondly, how and where do improvements in spatial resolution occur in the auditory pathway?*

Animal studies have shown that chronic auditory stimulation with a CI leads to re-organization of cortical and sub-cortical structures (Kral and Tillein, 2006; Moore et al., 2002). Whilst tonotopic representation of sound is absent in the auditory cortex of neonatally deafened cats, there is evidence that chronic stimulation with a CI can lead to partial restoration of tonotopicity (Fallon et al., 2009). Dinse et al. (2003), however, found that a 3-month period of CI stimulation in neonatally deafened adult cats did not lead to normal patterns of auditory cortex activation. Rather, individual electrodes were associated with broad patterns of overlapping cortical activation and reduced cortical tonotopy compared to NH cats. The authors suggest that perceptual improvements are not due to restoration of normal patterns of cortical activation, but rather are due to learning effects mediated by large populations of overlapping neurons. There is evidence that the area of cortical activation is related to behavioural discrimination performance. Recanzone et al. (1993) showed that frequency discrimination training in owl monkeys led to an increase in the area of representation in the auditory cortex, as well as sharper cortical tuning for the trained frequencies. Of note, the area of representation was correlated with behavioural discrimination performance suggesting that the cortical spatial code is important for frequency discrimination. Improved electrode discrimination in CI users, may be due to increased cortical representation of electrodes in association with higher auditory learning. There is, however, evidence for tonotopic organization in the auditory cortex of adult CI users (Guiraud et al., 2007). It is therefore possible that long-term use of a CI leads to restoration of tonotopy in the auditory pathway. At this point in time, the mechanism by which auditory discrimination improves in CI users remains poorly understood and further research into this area is required.

#### 4.5.3 Relationship between the spatial ACC and behavioural electrode discrimination

A high level of agreement between the spatial ACC and behavioural discrimination was found. In 12 out of 120 cases however, the ACC could not be recorded despite accurate behavioural discrimination. Eight of these 'false negative' recordings were from participant S11. The absence of a response was thought to be due to overlap between a prolonged onset response and the ACC. This hypothesis was subsequently tested by measuring the spatial ACC in this participant using a longer duration stimulus. Two conditions were used, each with a change in stimulating electrode at the midpoint of the stimulus. The first condition was the standard stimulus, which consisted of biphasic pulses of 800 ms duration presented at 0.51 Hz. For the test condition, the stimulus had duration of 1400 ms and was presented at a rate of 0.4 Hz. The same stimulation level was used for both conditions. As can be seen in figure 4.7, the ACC is clearly seen in the test condition but not the standard condition. This shows that the sensitivity of the spatial ACC can be improved by altering stimulus characteristics and this is examined further in Chapter 6.

Disagreement between the objective and behavioural measurements also occurred when a significant spatial ACC response was recorded despite poor behavioural discrimination. This was observed for 9 electrode pairs from 4 CI users. Previously, it was hypothesized that the presence of these 'false positive' recordings indicated the potential to develop accurate discrimination. In this longitudinal study, it was shown that this is indeed the case. In 8 out of 9 'false positive' recordings, a behavioural pass was achieved at a later date. Interestingly for participant S2, the ACC for electrode pair 2-3 was consistently present from 1 week onwards but a behavioural pass was only achieved at 12 months after switch-on.

Tremblay et al. (1998), measured MMN and behavioural discrimination after training participants to discriminate stimuli that differed in voice onset time. Four out of ten participants showed significant changes in MMN prior to changes in identification ability. Similarly, Trautwein et al. (1998), measured duration discrimination thresholds with behavioural and MMN measurements in CI users. The MMN threshold was found to be smaller than the behavioural threshold in 6/8 cases suggesting the MMN is a

more sensitive measure of discrimination. The greatest disparity between objective and behavioural measures was seen in pre-lingually deafened adults. In this study, 3 out of 4 of the participants with 'false positive' ACC recordings had pre- or peri-lingual onset deafness. Only one participant had post-lingual onset deafness - although this participant had profound deafness for 10 years, the duration of bilateral hearing loss was 57 years. Early onset and long durations of deafness, are likely associated with a longer time course for auditory learning and could affect an individual's ability to perceive a stimulus change that is encoded in the auditory system. Further confirmation of these findings are required, but these data suggest that the ACC may precede the development of accurate behavioural responses and this may make it particularly useful from a clinical point of view.

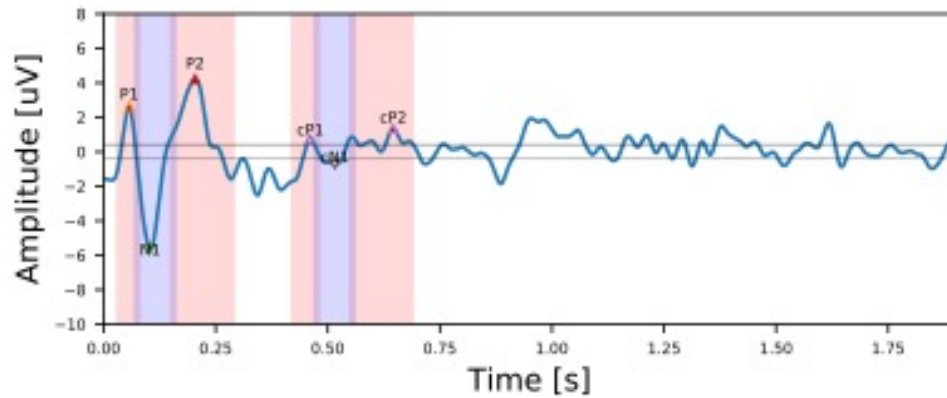
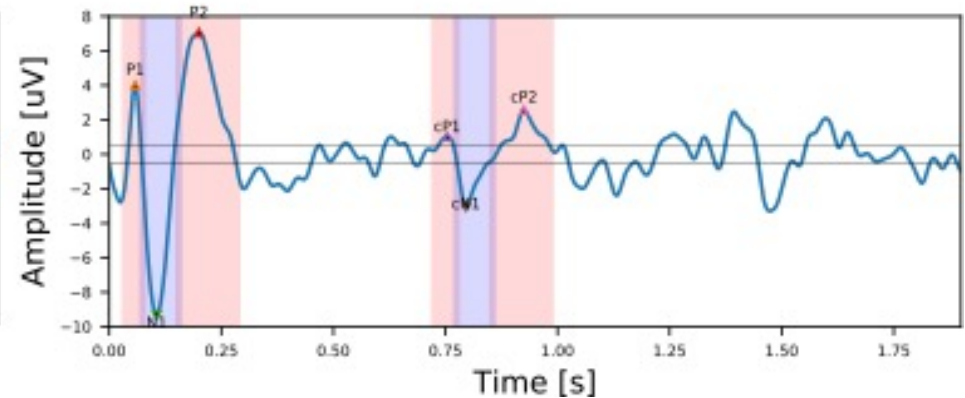
(A) Stimulus duration 800ms, HT2  $p = 0.14$ (B) Stimulus duration 1400ms, HT2  $p < 0.001$ 

Figure 4.7 Spatial ACC recordings using stimuli with different durations. (A) The ACC is absent for the standard stimulus (800 ms duration, presented at 0.51Hz). (B) A clear ACC response is seen for the test stimulus (1400 ms duration, presented at 0.4 Hz). Stimuli consisted of biphasic pulses at 1000 pps with a change in stimulating electrode at the midpoint of the stimulus. Hotelling-T2 (HT2)  $p$  values are shown above each panel. Data are for electrode pair 4-5 in participant S11 and are presented at FCz. Shaded areas and horizontal lines are as described in figure 4.4.

#### 4.5.4 Electrode discrimination and speech perception

In keeping with the results of Chapter 3, it was found that behavioural electrode discrimination score is a significant predictor of speech perception. It must be borne in mind that only a limited range of electrodes were tested in this study and the allocated frequencies would only cover the first formant region of speech. Apical electrode discrimination does not necessarily reflect discrimination ability in the rest of the CI array. This may explain the disparity between electrode discrimination performance and speech perception in certain participants such as S8 who had excellent apical electrode discrimination but relatively poor sentence perception, or S1 who had relatively poor apical discrimination but excellent speech perception.

A significant relationship between the amplitude of the spatial ACC and speech perception was not found in this study. Wable et al. (2000), measured electrode discrimination around a single apical electrode with the MMN and did not find a correlation between speech perception and MMN latency or amplitude. The lack of relationship between the ACC amplitude and speech perception may be due to a number of reasons. Firstly, there is large inter-subject variability in ACC amplitude. This variability has been observed in other studies of NH and CI populations (Brown et al., 2008; He et al., 2012, 2014) and is likely a result of differences in cortical folding and resultant dipole orientations. In the study by He et al. (2012), the ACC amplitude elicited by a change in frequency of 100Hz, varied from 1.51 to 6.85  $\mu\text{V}$  in NH individuals. Secondly, the ACC response did not always reflect behavioural discrimination ability (discussed in section 4.5.3). In a number of cases the spatial ACC could be recorded despite poor behavioural discrimination and appeared to reflect discrimination potential rather than ability. It may be that the spatial ACC is a more strongly correlated with speech perception in experienced CI users in whom the full potential for discrimination has been achieved. Indeed, He et al. 2014 found that the EDL measured around a mid-array electrode with the spatial ACC was associated with speech perception when categorized as 'good' or 'poor'. Of note, most of the participants in their study had several years of CI experience.

These data provide further evidence that behavioural electrode discrimination is related to speech perception. Interventions that enhance spatial resolution may therefore improve hearing performance.

#### 4.6 Conclusions

This study provides behavioural and electrophysiological evidence for improvements in discrimination ability in CI users over time. This is paralleled by improvements in speech perception. The ability of the auditory system to adapt to electrical stimulation through the CI underlies the excellent outcomes that this technology yields. This process of adaptation is slower and more limited in certain individuals and targeted therapies to exploit auditory plasticity may help improve hearing performance further.

## Chapter 5 The effect of stimulus intensity on electrode discrimination

### 5.1 Abstract

In Chapter 4, it was found that the amplitude of the spatial auditory change complex (ACC) increased significantly over the first 6 months of cochlear implant (CI) use. These measurements could have been confounded by changes in loudness perception that CI users experience in the early period after switch-on. The aim of this study was to determine the effect of stimulus intensity on the characteristics of the ACC as well as its sensitivity as a measure of behavioural electrode discrimination. Behavioural electrode discrimination and the spatial ACC were measured in adult CI users at stimulus intensities ranging from 40 to 80% of the electrical dynamic range (DR). Increasing stimulus intensity led to an increase in the spatial ACC amplitude which was accompanied by improvements in behavioural electrode discrimination. The sensitivity of the spatial ACC as a measure of behavioural discrimination decreased at the lower end of the DR. These data show that it is important to consider the effect of stimulus presentation level when measuring the spatial ACC.

### 5.2 Introduction

In Chapter 4 it was found that the spatial ACC amplitude and behavioural electrode discrimination scores increased significantly over the first 6 to 12 months of CI use. As discussed in Chapter 4, these measurements could have been confounded by the effect of stimulus intensity. The spatial ACC and behavioural discrimination were tested at the MC level, which was re-measured at each time point, in order to maintain a relatively constant perceptual level. However, in order to achieve this, higher stimulation levels were required over time in most participants.

Studies of the cortical onset response have shown that increasing stimulus intensity leads to larger peak amplitudes and shorter peak latencies in NH (Picton, 2010) and CI populations (Firszt et al., 2002). Unlike the cortical onset response, the ACC is a measure of auditory discrimination and therefore, may be affected differently by

changes in stimulus intensity. To date, the effect of stimulus intensity on the ACC has not been characterized.

The relationship between stimulus intensity and the spatial ACC might be inferred from studies examining the the relationship between stimulus intensity and behavioural electrode discrimination. McKay et al. (1999) showed that there was a significant improvement in behavioural electrode discrimination with stimulus level, although the exact nature of the relationship varied between and within individuals for different electrode locations. Chatterjee and Yu (2010) similarly found that electrode discrimination improved with stimulus level in most CI users, irrespective of whether a bipolar or monopolar configuration was used. Pfungst et al. (1999), did not find a significant effect of level on electrode discrimination score for adjacent electrode pairs. However, for electrode locations where the EDL was greater than one, there was a significant improvement in discrimination scores with level. Based on these studies, it might be expected that increasing stimulus intensity would lead to a larger magnitude ACC response.

Stimulus intensity may also affect the relationship between the spatial ACC and behavioural electrode discrimination. In the previous studies that found a strong relationship between the spatial ACC and behavioural discrimination (Chapters 3 and 4; He et al., 2014) stimuli were presented at loud but comfortable levels or the MC level i.e. in the upper part of the DR. Since speech is dynamic, the ability to discriminate electrodes across the DR may be correlated with speech perception. If the spatial ACC is to be used to assess electrode discrimination at the lower end of the DR, then it will be important to determine its sensitivity as a measure of behavioural discrimination at lower stimulus levels.

It has been hypothesized that high threshold levels and small DR measurements are associated with an impoverished electrode-neural interface (Bierer, 2010). If this is the case, then it might be expected that electrodes with high thresholds/low DR will also have poor electrode discrimination. Pfungst et al. (1999), used a bipolar configuration and found that behavioural electrode discrimination was correlated with DR but not threshold levels. The relationship between electrode discrimination and threshold/DR



measurements with a monopolar configuration, which leads to broader patterns of excitation, is yet to be examined.

The main objectives of this aims of this study were to:

- 1) determine the effect of stimulus intensity on the spatial ACC amplitude and behavioural electrode discrimination ability
- 2) examine the sensitivity of the spatial ACC as a measure of behavioural discrimination at different stimulus intensity levels

Subsidiary objectives were to:

- 3) examine the relationship between electrode discrimination and threshold/DR measurements
- 4) examine the relationship between electrode discrimination ability across the DR and speech perception

### 5.3 Experiment 4: Design and Methods

#### 5.3.1 Participants

Nine participants ranging in age from 42 to 69 years were included in the study. All participants were unilaterally implanted with an AB HiRes 90K device and had taken part in experiment 3 (Chapter 4). Demographic details are summarized in table 5.1. Of note, 4 of the participants had pre or peri-lingual onset deafness. Whilst most participants had around 1 year of CI experience, P1 had been using her CI for almost 7 years at the time of testing. None of the participants had significant residual hearing in the contra-lateral ear.

#### 5.3.2 Test procedures

The stimuli for EEG were as described in the General Methods (Chapter 2) - 800 ms alternating polarity biphasic pulse trains presented at a rate of 0.51 Hz. A single electrode pair was chosen for testing in each participant. Since the aim of this study was to determine the effect of stimulus level on electrode discrimination, it was

important to avoid choosing an electrode pair which was indiscriminable throughout the DR. Electrode 4, which typically represents frequencies of 587 to 697 Hz in the AB device was chosen as the reference electrode for all participants. This is because, in previous experiments with the same participants, it was found that this electrode was well discriminated from neighbouring electrodes. The DR of the reference electrode was determined using an ascending method of adjustment. Stimulation began at a level which was inaudible and increased in 5  $\mu$ A steps until participants reported that they could just hear a sound. The threshold level was determined by repeating this procedure until the same value was obtained twice in a row. The loudness discomfort level (LDL) was then determined by gradually increasing the stimulation level until participants indicated that the loudness was at point 9 on a 10-point AB loudness chart. The DR for the reference electrode was calculated as  $20 \times \log_{10}(\text{LDL}/\text{Threshold level})$ .

Electrode 4 was then paired with a neighbouring electrode following a short screening procedure for discriminability. Electrode 4 was initially paired with electrode 5 in all participants and its stimulation level was set to 80% of the DR. In order to reduce loudness cues when switching electrodes, a loudness balancing procedure similar to that described in the General Methods (Chapter 2) was used. The stimulation level for the test electrode was set to the same level as the reference electrode. The reference and test electrode were then stimulated in sequence separated by a gap of 600 ms and the level of the test electrode was adjusted until both stimuli were perceived to have the same loudness. This procedure was repeated and if the same value was obtained consecutively then this level was used for the test electrode; if not, then loudness balancing was performed a third time and the average was used as the loudness balanced level.

Participants were then asked whether they perceived a clear difference in pitch between electrode 4 and 5 during sequential stimulation at the loudness balanced level. If they failed to do so, then the same electrode pair was tested at 40% of the DR following loudness balancing. This was done, as previous studies have shown that electrode discrimination can be better at the lower end of the DR in certain individuals/electrode locations (McKay et al., 1999; Pfingst et al., 1999). If participants

still failed to perceive a difference in pitch, then electrode 4 was paired with electrode 6 and the screening procedure was repeated. All of the participants perceived a difference in pitch with either electrode 5 or 6, so no other electrodes were tested. The details of electrodes pairs tested, threshold level and LDL for each participant are shown in table 5.2.

For the main experiment there were 5 conditions which varied in stimulus intensity – these included stimulation levels of 40, 50, 60, 70 and 80% of the linear DR of the reference electrode calculated in  $\mu\text{A}$ . In each case the corresponding loudness balanced level of the test electrode was determined using the procedure described above. The standard deviation of the loudness balancing measurements was  $1.81 \mu\text{A}$  (range 0 –  $8.66 \mu\text{A}$ ).

EEG recording and processing was performed as described in the General Methods. In total there were 45 EEG measurements (5 conditions for 9 participants). The presence or absence of the ACC was determined by means of the Hotelling-T2 test in the ACC response window from 450 – 650 ms after stimulus onset. For 6/45 recordings, the response window was adjusted to 450-700 ms, due to a late P2 component.

Behavioural electrode discrimination was tested at each stimulus level and speech perception was tested using open-set BKB sentences-in-quiet. The procedures for testing behavioural discrimination and speech perception are described in the General Methods. EEG, behavioural and speech testing were done in a single session which lasted approximately 2.5 hours including breaks.

Table 5.1 Demographic details of participants in experiment 4. F= female, M= male, R = right, L= left

Participant	Age	Sex	Ear	Risk factor for hearing loss	Communication	Age at deafness onset (years)	Duration of CI use	Electrode
P1	42	F	R	Unknown	oral	1.5	6 years 10 months	1J
S1	53	M	R	Unknown	oral	41	14 months	Mid Scala
S2	52	F	R	Unknown	oral + sign	0	12 months	Mid Scala
S3	44	F	L	Unknown	oral	24	14 months	Mid Scala
S4	50	M	L	Maternal rubella	oral	2	14 months	1J
S5	48	F	L	Unknown	oral	5	11 months	Mid Scala
S6	69	F	L	Unknown	oral	58	10 months	Mid Scala
S8	52	F	R	Unknown	oral	46	11 months	Mid Scala
S9	49	M	L	Unknown	oral	47	8 months	Mid Scala

Table 5.2 Details of the electrode pair tested in experiment 4. Threshold and loudness discomfort levels for the reference electrode (electrode 4) are shown.

Participant	Electrode pair tested	Threshold level ( $\mu\text{A}$ )	Loudness discomfort level ( $\mu\text{A}$ )
P1	4-6	75	240
S1	4-5	150	450
S2	4-5	140	460
S3	4-5	110	370
S4	4-5	130	630
S5	4-6	110	360
S6	4-6	120	450
S8	4-5	130	360
S9	4-5	110	370

## 5.4 Results

### 5.4.1 Effect of stimulus intensity on behavioural discrimination

Figure 5.1 shows the effect of stimulus intensity on behavioural discrimination according to which electrode was tested (4-5 or 4-6). The broken lines show individual data whilst the solid black line represents the mean score across participants. This figure shows that in both groups, the mean behavioural discrimination score increases with stimulus intensity and this effect is greatest in the lower part of DR. There is however substantial inter-individual variability in the relationship between stimulus intensity and behavioural discrimination. Whilst discrimination ability was excellent throughout the tested DR in most participants, it was highly dependent on presentation level in participants P1, S2, S5 and S6. Of note, three of these participants were in the electrode 4-6 group. Electrode discrimination did not decrease significantly with increasing stimulus level in any of the participants. Although scores for participants S1 and S6 decreased for the 80% DR condition, these were still above the threshold for a behavioural pass (score  $\geq 80\%$ ). The score for participant S2 decreased for the 70% DR condition but then increased again for the 80% of the DR. The number of participants with a behavioural pass was 4/9, 6/9, 8/9, 7/9 and 9/9 for the 5 intensity conditions (in ascending order of stimulus intensity).

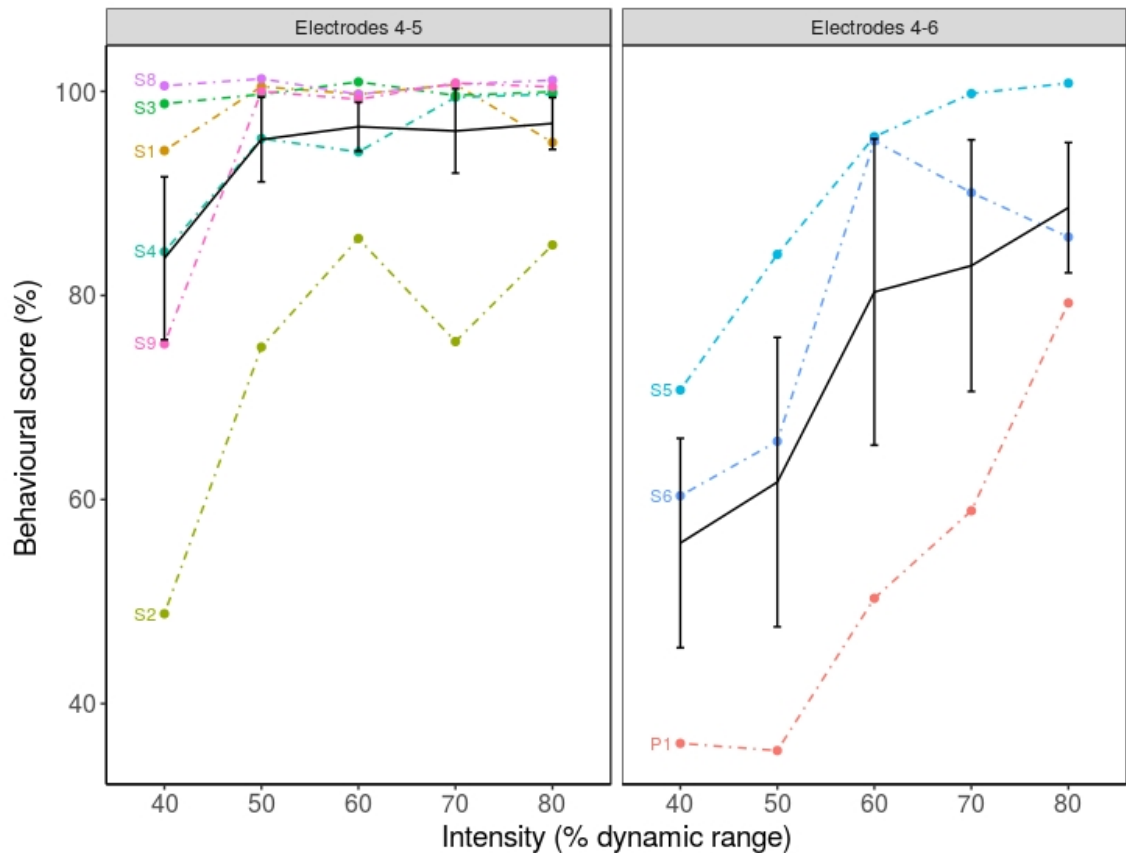


Figure 5.1 Relationship between stimulus intensity and behavioural electrode discrimination score according to which electrode pair was tested. Electrode pair 4-6 was tested in individuals who could not discriminate electrode pair 4-5 as determined by a screening procedure. The broken lines show the data for individual CI users. The solid black line shows the mean scores across participants in each group with error bars representing the standard error of the mean. Random noise has been added to the discrimination scores in order to improve data visualization.

The effect of stimulus intensity on behavioural discrimination was analyzed with a mixed-effects model. The dependent variable was the behavioural discrimination  $d'$  score and the fixed effects included 'stimulus intensity', 'electrode pair' (4-5 or 4-6) and the interaction term. The analysis showed that there was a significant effect of 'stimulus intensity' ( $F(4,28) = 15, p < 0.001$ ) and the interaction term ( $F(4,28) = 4.9, p = 0.0042$ ) whilst the 'electrode pair' was not significant ( $F(1,7) = 4.5, p = 0.072$ ) (see table 5.3). Post-hoc pairwise comparison with Tukey correction showed that for participants in whom electrode 4-5 was tested, there was only a significant difference in discrimination score between contrasts involving the 40% DR condition. The behavioural  $d'$  score for the 40% DR condition was significantly lower than the 60%, 70% and 80% DR conditions ( $p < 0.05$  for all 3 contrasts). There were only 3 participants in whom electrode 4-6 was tested. Post-hoc Tukey test showed that there was a significant difference between contrasts involving the 40% and 50% DR

conditions. The behavioural  $d'$  score for both the 40% and 50% DR conditions were significantly less than the 60%, 70% and 80% DR conditions ( $p < 0.05$  for all contrasts).

Table 5.3 Mixed model analysis of factors affecting behavioural electrode discrimination score.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Intensity	(4, 28)	15	<0.001	0.684	0.527 – 0.828
Electrode pair	(1, 7)	4.5	0.072	0.389	0.012 – 0.821
Electrode pair * intensity	(4, 28)	4.9	0.004	0.410	0.214 – 0.668

This analysis shows that increasing stimulus intensity leads to improved behavioural electrode discrimination, particularly in the lower part of the DR. The effect was less pronounced in participants in whom electrode 4-5 was tested and this is likely due to ceiling effects in this group.

#### 5.4.2 Effect of stimulus intensity on cortical response amplitude

Figure 5.2A shows the relationship between spatial ACC N1-P2 amplitude and stimulus intensity. The solid black line represents the mean amplitude across all participants. There was no obvious difference between participants in whom electrode pair 4-5 or 4-6 was tested and therefore all the data are shown in a single plot. This figure shows that mean spatial ACC amplitude increases with stimulus intensity but plateaus around 70% of the DR. Similar to the behavioural data, the individual data displays much inter-individual variability, both in terms of absolute amplitude values and the relationship with stimulus intensity. The ACC amplitude increased with stimulus intensity in most participants except for S3 in whom the ACC amplitude was high throughout the DR. The number of participants with an objective pass was 1/9, 3/9, 6/9, 7/9 and 9/9 for the 5 intensity conditions (in ascending order of stimulus intensity).

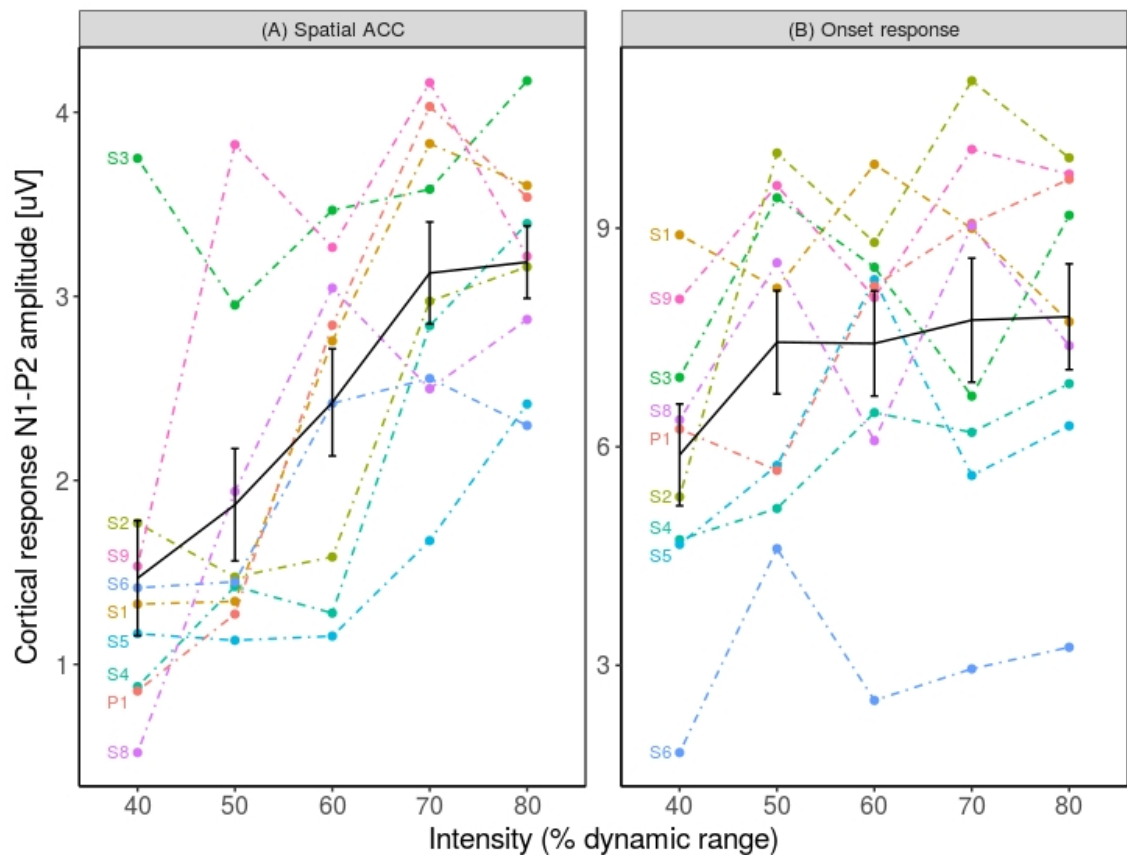


Figure 5.2 Effect of stimulus intensity on the N1-P2 amplitude. Data are shown for the spatial ACC in (A) and for the cortical onset response in (B). The broken lines show the data for individual CI users. The solid black line shows the mean amplitude across participants in each group with error bars representing the standard error of the mean.

A mixed-effects model was used to analyze the factors affecting spatial ACC N1-P2 amplitude. The fixed effects included ‘stimulus intensity’, ‘electrode pair’ and the interaction term. This showed that there was no significant effect of ‘electrode pair’ or the interaction term and these factors were therefore removed from the model (see table 5.4). Analysis of the reduced model showed that there was a significant effect of ‘stimulus intensity’ ( $F(4,32) = 14, p < 0.001$ ). Post-hoc pairwise comparison with Tukey correction showed that there was only a significant difference in contrasts involving the 40% and 50% DR conditions. The amplitude of the 40% condition was significantly less than that of the 60%, 70% and 80% DR conditions ( $p < 0.05$  for all 3 contrasts), whilst the amplitude of the 50% condition was significantly less than that of the 70% and 80% DR conditions ( $p < 0.01$  for both contrasts).



Table 5.4 Mixed model analysis of factors affecting ACC response amplitude.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Initial model					
Intensity	(4, 28)	11	<0.001	0.618	0.441 – 0.791
Electrode pair	(1, 7)	2.0	0.205	0.218	0.001 – 0.741
Electrode pair * intensity	(4, 28)	0.15	0.961	0.021	0.019 – 0.349
Reduced model					
Intensity	(4, 32)	14	<0.001	0.639	0.478 – 0.793

The relationship between stimulus intensity and the cortical onset response amplitude is shown in figure 5.2B. This shows that the mean onset response amplitude also increases with stimulus intensity but effectively plateaus at 50% of the DR. A mixed-effects analysis was conducted with the dependent variable ‘onset response N1-P2 amplitude’. The fixed effects included ‘stimulus intensity’, ‘electrode pair’ and the interaction term. Similar to the spatial ACC analysis, there was no significant effect of ‘electrode pair’ or the interaction term and these were therefore removed from the model (table 5.5). Analysis of the reduced model showed that there was a significant effect of ‘stimulus intensity’ ( $F(4,32) = 4.0, p = 0.010$ ). Post-hoc pairwise comparisons with Tukey correction showed that the amplitude of the 40% DR condition was significantly less than 70% and 80% DR conditions ( $p < 0.05$ ). None of the other contrasts were statistically significant.

Table 5.5 Mixed model analysis of factors affecting cortical onset response amplitude.

Factor	Degrees of freedom (numerator, denominator)	F value	P value	Effect size	95% confidence interval of effect size
Initial model					
Intensity	(4, 28)	3.4	0.022	0.325	0.145 – 0.613
Electrode pair	(1, 7)	4.3	0.077	0.380	0.010 – 0.818
Electrode pair * intensity	(4, 28)	0.48	0.750	0.064	0.026 – 0.401
Reduced model					
Intensity	(4, 32)	4.0	0.010	0.331	0.155 – 0.598

These data show that similar to behavioural discrimination scores, the amplitude of the spatial ACC increases with stimulus intensity and the effect is greater in the lower part of the DR. Stimulus intensity appears to have a greater relative effect on the spatial ACC amplitude compared to the onset response, at least in the DR that was tested in these participants.

#### 5.4.3 Relationship between the spatial ACC and behavioural electrode discrimination

The relationship between behavioural and objective measures of electrode discrimination was examined using the pass fail rules described in the General Methods. The results of this are shown in table 5.6. The agreement between both measures was 6/9, 6/9, 5/9, 7/9 and 9/9 for the 5 intensity conditions (in ascending order). The disagreements were predominantly due to a lack of sensitivity of the spatial ACC in the lower part of the DR. The sensitivity of the spatial ACC was calculated as the proportion of electrode pairs with a behavioural pass (score  $\geq 80\%$ ) which had a significant spatial ACC response according to objective pass criteria. Figure 5.3 shows that the sensitivity of the ACC increases with stimulus intensity. Two disagreements between objective and behavioural measures occurred due to the presence of a spatial ACC despite a behavioural fail in participant P1. Figure 5.4 shows

the cortical responses for these cases. Of note participant P1 had congenital onset deafness and this type of ‘false positive’ spatial ACC was observed in Chapters 3 and 4.

Table 5.6 Agreement between objective and behavioural measures of electrode discrimination at different stimulus intensities.

Outcome of objective and behavioural measures	Stimulus intensity (% DR)				
	40%	50%	60%	70%	80%
Behavioural fail Objective fail	5	3	0	1	0
Behavioural pass Objective pass	1	3	5	6	9
Behavioural fail Objective pass	0	0	1	1	0
Behavioural pass Objective fail	3	3	3	1	0
Total agreement	6/9	6/9	5/9	7/9	9/9

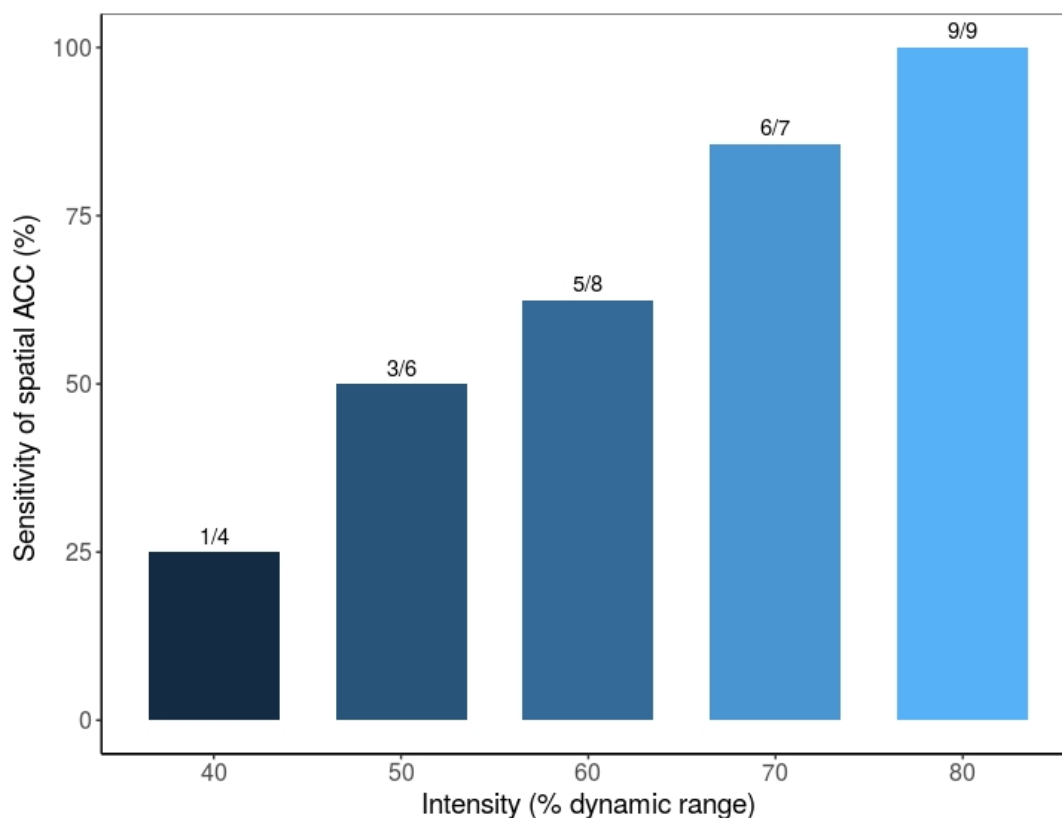


Figure 5.3 Relationship between stimulus intensity and spatial ACC sensitivity. Sensitivity was calculated as the proportion of electrode pairs with a behavioural pass that also had an objective ACC pass. This proportion is shown above each bar.

The relationship between objective and behavioural measures of electrode discrimination can also be examined by correlating the spatial ACC amplitude and behavioural  $d'$  scores across participants. The spatial ACC amplitude and behavioural  $d'$  scores were collapsed to the mean across the 5 intensity conditions for each participant. Pearson's correlation showed that there was no significant relationship between the two measures ( $r = 0.27$ , 95% confidence interval [-0.48, 0.79],  $p = 0.48$ ).

These results show that the spatial ACC is a more reliable measure of electrode discrimination at higher stimulus intensity levels. The amplitude of the spatial ACC appears to be a poor predictor of behavioral discrimination across participants.

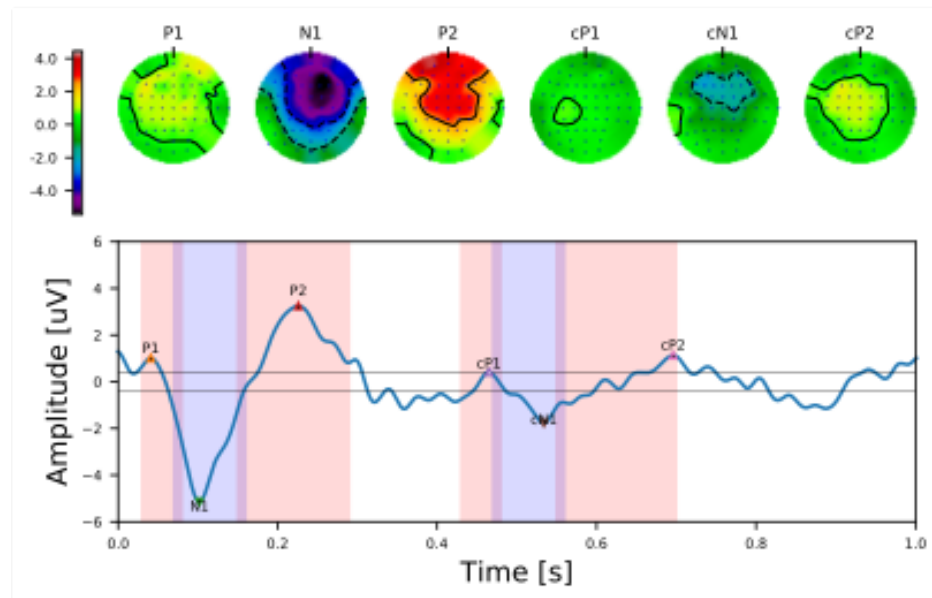
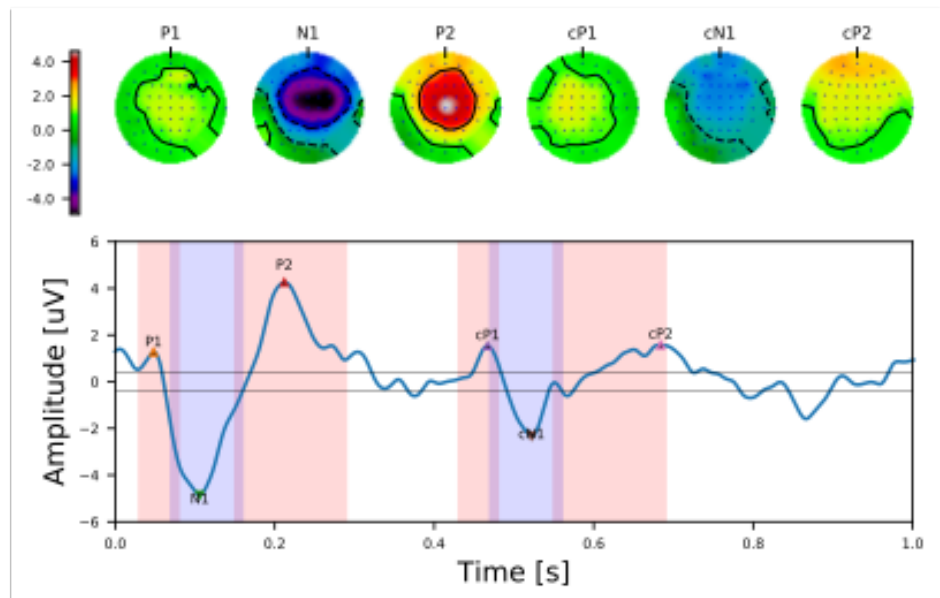
(A) 60% DR, BS = 50%, HT2  $p = 0.032$ (B) 70% DR, BS = 60%, HT2  $p < 0.001$ 

Figure 5.4 Cortical responses with an objective ACC pass despite a behavioural fail in participant P1. The stimulus level, behavioural score and Hotelling-T2 (HT2)  $p$  value is indicated on each panel. The time windows used to detect positive and negative peaks for the onset response (P1, N1, and P2) and ACC (cP1, cN1, and cP2) are shown in pink and blue, respectively. The horizontal lines correspond to the level of residual noise. Scalp voltage maps for automatically detected peaks are displayed, with black lines representing isopotential contour lines. Data at channel FCz are presented.

#### 5.4.4 Relationship between electrode discrimination, threshold level and DR

A measure of discrimination ability across the DR was obtained by calculating 1) the mean behavioural  $d'$  score and 2) the mean spatial ACC amplitude across the 5 intensity conditions for each participant. Figure 5.5 shows that there is no clear relationship between mean behavioural  $d'$  score and threshold level or DR of the reference electrode. Correlation analysis was performed with Pearson's correlation for the threshold level and Spearman's rank correlation coefficient for the DR, since the latter was not normally distributed. This showed that there is no significant relationship between mean behavioural  $d'$  score and threshold level ( $r = 0.22$ , 95% confidence interval  $[-0.52, 0.77]$ ,  $p = 0.57$ ) or DR ( $\rho = -0.13$ , 95% confidence interval  $[-0.76, 0.76]$ ,  $p = 0.75$ ). Using the mean behavioural  $d'$  score is limited by the fact that most participants had reached ceiling levels by 50-60% of the DR. Therefore, the correlation analysis was repeated using the behavioural discrimination score for the 40% DR condition alone. Again, no significant relationship was found (for threshold:  $r = 0.37$ , 95% confidence interval  $[-0.39, 0.83]$ ,  $p = 0.33$  and for DR:  $\rho = -0.14$ , 95% confidence interval  $[-0.81, 0.74]$ ,  $p = 0.72$ ). The relationship between mean spatial ACC amplitude and threshold level/DR is shown in figure 5.6. Again, correlation analysis showed no significant relationship between mean spatial ACC amplitude and threshold level ( $r = -0.42$ , 95% confidence interval  $[-0.85, 0.34]$ ,  $p = 0.26$ ) or DR ( $\rho = 0.05$ , 95% confidence interval  $[-0.74, 0.74]$ ,  $p = 0.91$ ).

The study is underpowered for this type correlation analysis and the  $p$  values must therefore be interpreted with caution. Nonetheless, visualization of the data does not indicate any clear relationship between measures of electrode discrimination and threshold/DR using a monopolar configuration.

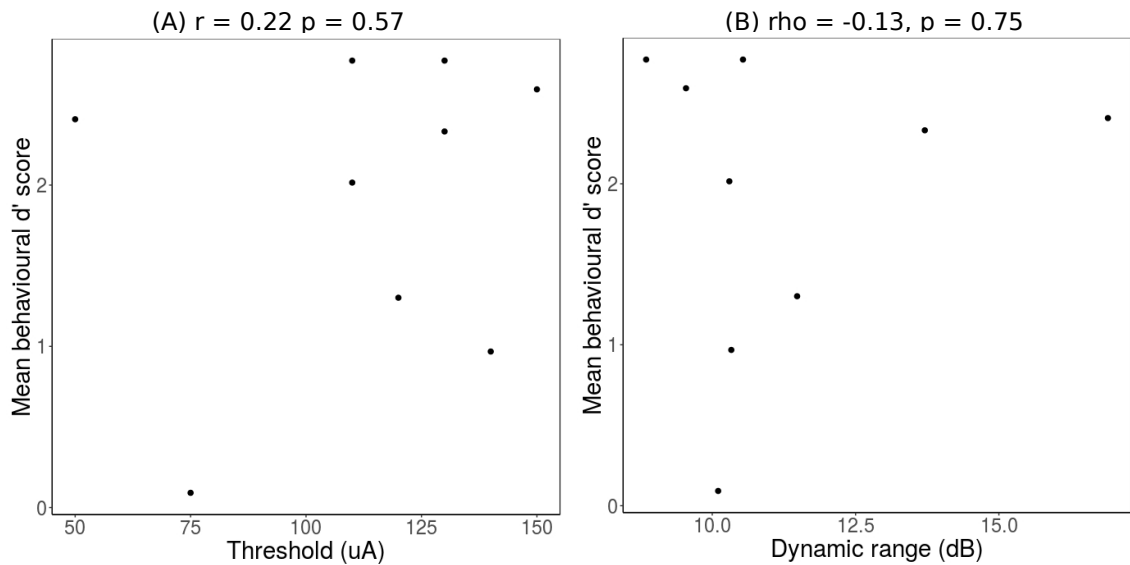


Figure 5.5 Relationship between reference electrode parameters and mean behavioural electrode discrimination score. The abscissa shows reference electrode threshold level (A) or DR (B). The ordinate shows mean behavioural discrimination scores across the 5 intensity conditions for each participant. Correlation coefficients and p values are shown above each panel.

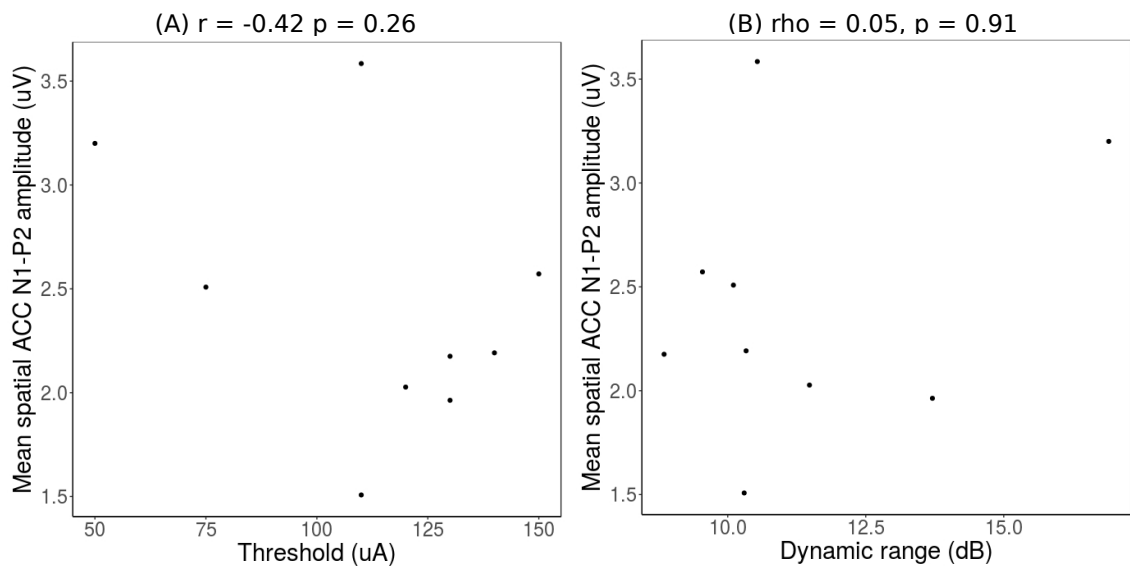


Figure 5.6 Relationship between reference electrode parameters and mean spatial ACC amplitude. The abscissa shows threshold level (A) or DR (B) of the reference electrode. The ordinate shows mean spatial ACC amplitude across the 5 intensity conditions for each participant. Correlation coefficients and p values are shown above each panel.

#### 5.4.5 Relationship between electrode discrimination and speech perception

It was hypothesized that participants who could discriminate electrodes well across the whole DR range would have better speech perception. The relationship between sentence perception and mean electrode discrimination score across the 5 intensity conditions is shown in figure 5.7. Participant S2, who was had congenital deafness and

was a total communicator (oral and sign language), had a speech perception score of 0% and appears to be an outlier. Spearman's rank correlation analysis showed that there was no significant relationship between sentence perception score and mean behavioural  $d'$  score ( $\rho = 0.50$ , 95% confidence interval [-0.26, 0.95],  $p = 0.17$ ). In contrast, a significant relationship between mean spatial ACC amplitude and sentence perception score was found using Spearman's rank correlation analysis ( $\rho = 0.77$ , 95% confidence interval [-0.08, 1.00],  $p = 0.021$ ). Again, due to the small number of participants it is difficult to draw strong conclusions from this data. However, it is possible that electrode discrimination ability across the DR is important for speech perception.

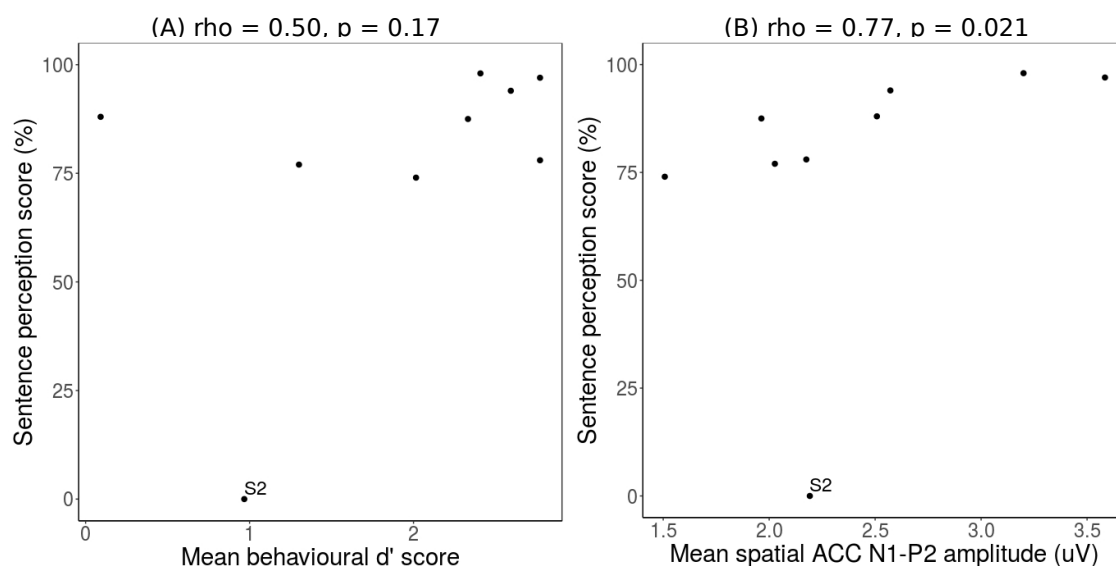


Figure 5.7 Relationship between sentence perception score and measures of electrode discrimination. Open-set sentence perception was assessed with BKB sentences. The mean behavioural discrimination score (A) and mean spatial ACC amplitude (B) were calculated by taking the average of the values across the 5 intensity conditions for each participant. Participant S2, who had pre-lingual onset deafness and used total communication (oral and sign language), is highlighted as an outlier. Correlation coefficients and  $p$  values are shown above each panel.

## 5.5 Discussion

This is the first study to examine the effect of stimulus intensity on the ACC. It was found that increasing stimulus intensity led to a significant increase in the amplitude of the spatial ACC as well as the cortical onset response. This was accompanied by improvements in behavioural electrode discrimination. Furthermore, the sensitivity of



the spatial ACC as a measure of behavioural electrode discrimination, was found to be poorer at lower stimulus presentation levels.

#### 5.5.1 Stimulus intensity and auditory cortical responses

The findings of this study are consistent with previous studies, which have shown that increasing stimulus intensity leads to an increase in the amplitude of the cortical onset response in both NH (Picton, 2010) and CI populations (Firszt et al., 2002). It was found that stimulus intensity had a greater relative effect on the spatial ACC amplitude compared to the onset response amplitude, in the DR tested in this experiment. On average, the spatial ACC amplitude increased with level up to 70% of the DR, while for the onset response amplitude there was little effect of level beyond 50% of the DR. This difference may be due to the fact that the spatial ACC is a discriminatory potential, while the onset response occurs due to a change from silence to sound. The effect of stimulus intensity on the spatial ACC latency was not analyzed. This is because a significant spatial ACC response was absent in a large proportion of measurements, particularly at the lower end of the DR, and a meaningful latency could not be obtained in these cases.

A common approach in longitudinal studies of auditory evoked cortical responses in CI users is to present stimuli at a relatively constant perceptual level. This can be achieved by presenting stimuli at a fixed acoustic level whilst participants wear their own sound processors (Burdo et al., 2006; Sharma et al., 2005a). Alternatively, loudness growth can be measured in order to determine the level which leads to a particular loudness percept, such as the MC level (Purdy and Kelly, 2016). Due to the development of loudness tolerance, increasing stimulus levels are required to achieve the same loudness percept, particularly during the early period after CI switch-on (Hughes et al., 2001; Vargas et al., 2012). In this study, increasing stimulus intensity was associated with an increase in loudness perception - therefore this situation is not directly comparable to the early period after CI switch-on. Nonetheless, these data indicate that stimulus level could contribute to changes in CAEPs over time, and this effect should be considered in longitudinal studies with CI users.

### 5.5.2 Stimulus intensity and behavioural electrode discrimination

The increase in spatial ACC amplitude with stimulus intensity was accompanied by an improvement in behavioural discrimination. This change in behavioural electrode discrimination with presentation level is generally consistent with findings from other studies (Chatterjee and Yu, 2010; McKay et al., 1999; Pfingst et al., 1999). Increasing stimulus intensity results in a broader pattern of excitation in the cochlea. McKay et al. (1999), suggest that the fact that electrode discrimination improves despite this presumed broadening of excitation, implies electrode discrimination depends on difference in the peaks and edges rather than the amount of non-overlap in the pattern of excitation associated with individual electrodes.

On average, behavioural electrode discrimination score and spatial ACC amplitude increased throughout the tested DR in this study. Other studies in CI users have also shown an improvement in discrimination performance throughout the DR. McKay et al. (1999), found that behavioural electrode discrimination score increased with level, when tested at 40%, 70% and 100% of the DR in adult CI users. Similarly, Pfingst and Rai (1990), found that pulse rate discrimination improved with level throughout the DR. This finding contrasts with NH listeners in whom frequency discrimination limits improve with presentation level but then plateau at 20 – 40 dB sensation level (Freyman and Nelson, 1991; Pfingst and Rai, 1990; Wier et al., 1977). Pfingst and Rai (1990), suggest that this difference may be accounted for by neural survival. That is, with greater neural survival, activation of auditory neurons with increasing stimulus level may saturate at lower stimulus intensities.

It was found that electrode discrimination was poor in most individuals at the lower end of the DR. The lowest presentation level used in this study was 40% of the DR, which is still well above threshold. Poor electrode discrimination at lower stimulus intensities may reflect poorer neural survival. As stimulus intensity increases, presumably there is greater neural recruitment, making the percept associated with individual electrodes more distinct. Chatterjee and Yu (2010), found that electrode discrimination at the lower end of the DR was correlated with modulation detection

thresholds. The authors suggest that a similar process, such as neural survival may underlie performance on both tasks. Furthermore, it was found that stimulus intensity had a greater effect for electrode locations with a larger discrimination limen i.e. for electrode pair 4-6 in this study. A larger discrimination limen may also reflect poorer neural survival and a consequent greater level dependence. Pfungst et al. (1999), similarly found that larger EDLs were associated with a greater level dependence for discrimination.

Similar to other studies, substantial inter-individual variability in the relationship between stimulus level and the spatial ACC/behavioral electrode discrimination was found. In contrast to Pfungst et al. (1999) and McKay et al. (1999), electrode discrimination ability did not deteriorate significantly with stimulus level in any of the study participants. The variability between individuals and electrode locations, could be accounted for by differences at the electrode-neural interface. Furthermore, it is known that the loudness growth functions may vary considerably between CI users (Shannon, 1983). Recent evidence from Anzalone and Smith (2017), shows that loudness growth may even vary depending on the history of hearing loss. Specifically, loudness growth functions in early-deafened late-implanted adults were found to be different from post-lingually deafened CI users. The perceived loudness associated with a stimulus at a fixed point in the DR may vary significantly between CI users. This in turn may contribute to variability in electrode discrimination measures.

Middlebrooks and Bierer (2002), assessed the effect of stimulus level on auditory cortical images of anaesthetized guinea pigs. Acutely deafened guinea pigs were implanted with a 6-channel electrode array and the spatiotemporal pattern of neural spike activity was measured across 16 primary auditory cortex locations spanning approximately 2–3 octaves of the tonotopic axis. An artificial neural network was trained to recognize and discriminate stimuli from different electrodes based on the spatiotemporal patterns of cortical activity. Interestingly it was found that increasing stimulus level was associated with a wider cortical image as well as poorer electrode discrimination by the artificial neural network. This is at odds with findings from this and other studies (Chatterjee and Yu, 2010; McKay et al., 1999), which have shown that electrode discrimination improves with stimulus level. In the study by

Middlebrooks and Bierer (2002), responses from only a limited area of the primary auditory cortex were sampled and other areas of the auditory pathway (subcortical as well as cortical) may play an important role in discrimination. Furthermore, the guinea pigs in their study were acutely deafened and presumably had good neural survival, which contrasts with the poor neural survival expected in human CI users; this too may account for the difference in findings.

It is interesting to consider the percept that underlies improved discrimination with increasing stimulus level. The best evidence suggests that electrode discrimination is a multimodal percept (Collins et al., 1997; Collins and Throckmorton, 2000), which includes pitch, timbre and even loudness. Townshend et al. (1987), showed that increasing level on a fixed electrode can lead to changes in pitch perception and the direction of pitch change can vary between individuals/electrode locations. It is possible then that increasing stimulus level, leads not only to a change in the absolute pitch elicited by an electrode but also an increase in the relative difference in pitch between neighbouring electrodes. In addition, at higher stimulus levels, if there is a greater difference in pitch, it is likely that loudness balancing becomes less accurate. Therefore, a relative increase in loudness difference between electrodes may also contribute to improved discrimination at higher presentation levels.

### 5.5.3 Relationship between the spatial ACC and behavioural electrode discrimination

The study by He et al. (2014) and the results of Chapters 3 and 4, showed that there is a strong relationship between the spatial ACC and behavioural electrode discrimination. In those experiments, stimuli were presented at 'loud but comfortable' levels or at the MC level, which represents the upper end of the DR. The results of this study show that the sensitivity of the spatial ACC as a measure of behavioural discrimination is poor at lower stimulus intensities. It is thought that thousands or even millions of cortical pyramidal neurons must be synchronously active in order to measure CAEPs with EEG (Luck, 2005). This imposes limits on the sensitivity of CAEP measurements particularly at the lower end of the DR where less neural recruitment is expected. Nonetheless, it may be of interest to measure the spatial ACC at a range of intensities which reflect conversational speech and in order to do so it will be

necessary to improve the sensitivity of spatial ACC recordings – this is considered in experiment 5, Chapter 6.

Participant P1 was found to have a good behavioural electrode discrimination score for the 80% DR condition. For the 60% and 70% DR conditions, behavioural discrimination scores were poor but spatial ACC responses could still be recorded. The presence of the ACC in these cases therefore, appears to indicate the potential for discrimination, which is in keeping with the findings of Chapter 4.

#### 5.5.4 Relationship between electrode discrimination and CI programme parameters

In this study, no relationship between electrode discrimination and threshold/DR measurements was found. In contrast, Pfungst et al. (1999) used a bipolar configuration and found that behavioural electrode discrimination was correlated with the DR, but not threshold level. In the study by Pfungst et al. (1999), repeated measures from the same participants were used for the correlation analysis and this may have artificially strengthened the correlation. Monopolar stimulation, which was used in this experiment, leads to broad patterns of excitation in the cochlea. Therefore, threshold/DR measurements with a monopolar configuration may less accurately reflect the status of the electrode-neural interface. There is evidence to suggest that threshold measurements with partial tripolar stimulation provide a better assessment of the integrity of the electrode-neural interface (Bierer, 2010). It may therefore, be of interest to examine relationship between electrode discrimination and focused threshold measurements.

#### 5.5.5 Electrode discrimination, level and speech perception

A number of studies have confirmed a relationship between electrode discrimination and speech perception (Busby et al., 2000; Dawson et al., 2000; He et al., 2014; Henry et al., 2000). In all of those studies, electrode discrimination was measured in the upper part of the DR around the MC level. In this study, no significant relationship between mean behavioural discrimination score across the DR and speech perception was found. This may be due to the fact that discrimination was measured at a single

electrode location. In contrast, the mean spatial ACC amplitude across the DR was correlated with speech perception. Given the small number of participants, the findings of this analysis must be viewed with caution. Larger scale studies are required to determine whether electrode discrimination ability across the DR is related to speech perception.

## 5.6 Conclusion

In this study, a significant effect of stimulus intensity on both the amplitude and sensitivity of the spatial ACC was found. If the spatial ACC, or indeed any type of evoked response potential, is to be used as a measure of auditory processing or development in CI users, then the effect of presentation level should be carefully considered.

## Chapter 6 Improving the clinical applicability of spatial ACC measurements – a pilot study

### 6.1 Abstract

In previous chapters, it has been shown that the spatial auditory change complex (ACC) provides a valuable objective measure of auditory discrimination in cochlear implant (CI) users. The aim of this pilot study was to determine whether the efficiency and sensitivity of spatial ACC measurements could be improved by using a limited number of EEG recording channels and by altering stimulus features.

The spatial ACC was recorded in 5 adult CI users. There were 4 measurement conditions:

- (I) 64 channel scalp recording with the standard stimulus (800ms duration, change in stimulating electrode at 400ms, and inter-stimulus interval (ISI) of 1161 ms).
- (II) Single channel scalp recording with the standard stimulus as in (I).
- (III) Single channel scalp recording, with a 2424 ms stimulus, change in stimulating electrode at 1212 ms and ISI of 20 ms.
- (IV) Single channel scalp recording, with a 3100 ms stimulus, change in stimulating electrode at 2424 ms and ISI of 20 ms.

Outcome measures included spatial ACC N1-P2 amplitude, signal-to-noise-ratio (SNR) and time taken to achieve an SNR value of 2. It was found that spatial ACC recordings obtained with a single scalp channel (condition II) were similar to that obtained with 64 scalp channels (condition I). By altering stimulus characteristics (conditions III and IV), it was possible to improve recording efficiency and sensitivity. These findings are promising for the use of the spatial ACC as a clinical tool.

## 6.2 Introduction

Previous experiments in this thesis have shown that the spatial ACC is a useful measure of electrode discrimination, which has great potential as a clinical tool to aid assessment and management in CI users. In order for the spatial ACC to be clinically applicable, it is necessary that these measurements can be performed in a time efficient manner. In this chapter, techniques for improving the efficiency and sensitivity of spatial ACC recordings shall be considered.

For the EEG recordings in previous chapters, the setup time was approximately 20 to 25 minutes for each participant. This includes placement of a 64 channel EEG cap with recording electrodes and optimization of voltage off sets in the EEG system. The rationale for using a 64 channel EEG cap was to aid CI artefact removal with spatial filtering (Cheveigné and Simon, 2008). As the spatial ACC had not been recorded in the AB device previously, a sophisticated and effective artefact reduction technique was required to ensure cortical responses were appropriately identified in case large electrical artefacts were present. In Chapter 3, however, it was observed that CI artefact was usually well localized and artefact free scalp locations could always be identified. This raised the possibility of using a limited number of recording channels for spatial ACC measurements.

Indeed, previous groups have measured the spatial ACC with a single scalp electrode in the Cochlear device (Brown et al., 2008; He et al., 2014; Scheperle and Abbas, 2015b). For example, He et al. (2014), recorded the spatial ACC differentially between Fz and the contralateral mastoid with Fpz serving as the ground electrode. Two ocular electrodes were also used to identify and remove eye movement artefacts. Using this setup, it was found that the spatial ACC could be recorded successfully and that it had a strong relationship with behavioural electrode discrimination. Clearly, using a limited number of recording electrodes has the advantage of reducing the set up time. To date, single channel recordings of the spatial ACC have not been performed in users of the AB or MED-EL device.



The stimulus used to measure the ACC in previous experiments consisted of alternating polarity biphasic pulses of 800 ms duration, with a change in stimulating electrode at 400 ms. The total trial length was 1961 ms (presentation rate 0.51Hz) and there were 300 trials for each stimulus. The recording time for a single electrode pair was approximately 10 minutes. The setup and EEG recording time for 4 electrode pairs exceeded 1 hour. Furthermore, in Chapters 3 to 5, it was found that the spatial ACC lacked sensitivity in several cases i.e. a significant spatial ACC response could not be recorded even though the participant had accurate behavioural discrimination for the same electrode pair. From a clinical point of view, it is vital to improve the sensitivity and efficiency of spatial ACC measurements.

In Chapter 4, a lack of sensitivity of spatial ACC measurements in participant S11 was found. By increasing the stimulus duration from 800 ms to 1400 ms, it was possible to record a clear spatial ACC response (figure 4.7). Using longer duration stimuli, may reduce masking of the ACC by the cortical onset response. Small and Werker (2012), measured the ACC to consonant contrasts in infants using stimuli with a duration of 564 ms. They found that the ACC could not be reliably recorded for non-native Hindi dental-retroflex /daDa/ stimuli, which was not in keeping with findings from a previous behavioural study (Werker and Lalonde, 1988). However, by increasing the stimulus duration to 820 ms, the ACC could be recorded successfully (Chen and Small, 2015). These findings suggest that ACC recording sensitivity may be improved by using longer duration stimuli.

Another important determinant of CAEP response magnitude is the ISI. The ISI is the period between stimulus offset and onset. The period between stimulus onset for two successive trials has been termed the stimulus onset asynchrony (SOA). Therefore, the SOA is the sum of the ISI and stimulus duration. Figure 6.1 shows some of the terminology that will be used in this chapter to describe various time periods relevant to ACC stimuli. Several investigators have shown that the cortical onset response amplitude increases with increasing ISI, but asymptotes somewhere between 10 and 20 s (Davis and Zerlin, 1966; Nelson and Lassman, 1968). Nelson and Lassman (1968), found that cortical response amplitude was a logarithmic function of the ISI. It is thought that a longer ISI, allows greater recovery from the neural refractory period

and therefore a larger neural response to the onset of sound (Budd et al., 1998; Pereira et al., 2014). Hillyard and Picton (1978), showed that for a fixed SOA of 10.24 s, as stimulus duration increased (resulting in a smaller ISI), the amplitude of the cortical onset response decreased. This study showed that the the ISI is a more important determinant of the cortical onset response magnitude than the SOA, and suggests that neural recovery occurs during the non-stimulus period.

Kalaiah et al. (2017), found that the ACC N1-P2 amplitude increased as the ISI was increased from 500 to 2000 ms. This shows that, similar to the cortical onset response, the ISI has an important effect on the ACC magnitude. For the ACC, it is possible that neural recovery from the refractory state occurs during the period of the reference stimulus, as well as the ISI. Therefore, the offset to onset period of the test stimulus (b to c' in figure 6.1) may be a more important determinant of the ACC response magnitude than the ISI. If this is the case, then it should be possible to record the ACC even with a short ISI.

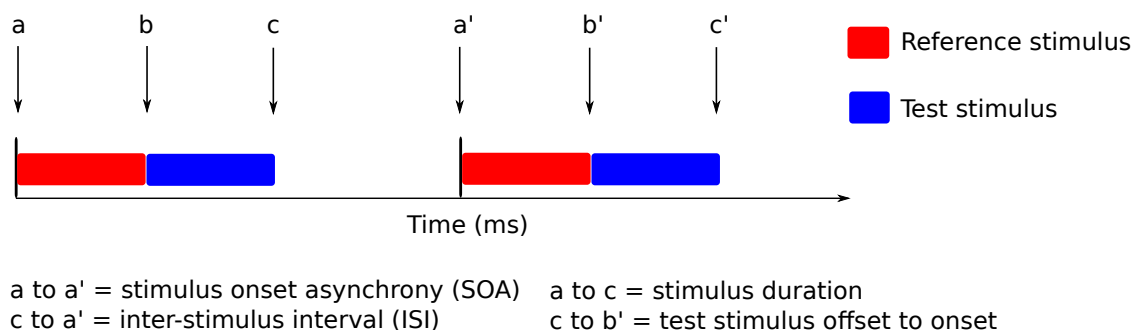


Figure 6.1 Terminology describing various time periods for ACC stimuli. The reference stimulus is shown in red and gives rise to the cortical onset response. The test stimulus is shown in blue and gives rise to the ACC.

Martin et al. (2010), examined whether the efficiency of ACC recordings could be improved by using a shorter ISI. The stimulus used was a synthetic vowel with a 1000 Hz change in second formant frequency. Perceptually, this was associated with a change in vowel from /u/ to /i/. The standard stimulus was 1000 ms in duration with a change at 500 ms and ISI of 1000 ms. The test stimulus was a continuous alternating stimulus, with no silent interval (ISI = 0 ms) i.e. there was a change in 2<sup>nd</sup> formant frequency every 500 ms throughout the recording period. Using this stimulus, the recording time was halved and the number of acoustic changes was doubled, as the

transition from /u/ to /i/ and /i/ to /u/ could be combined. Although reducing the ISI in this way, led to a loss of the component structure of the ACC and smaller ACC RMS amplitude, the signal-to-noise ratio (SNR) and efficiency was improved due to the larger number of trials and reduced recording time.

Whilst using 500 ms continuous alternating stimuli may lead to improved efficiency, it may not lead to improved sensitivity. In the study by Martin et al. (2010), the magnitude of the acoustic change was large, and a significant ACC response could be recorded in most participants irrespective of the stimulus ISI. If, however, the magnitude of the acoustic change is small or cortical responses are generally small in a given participant, then using stimuli as per Martin et al. (2010), may actually lead to a loss of sensitivity due to the short time period for neurons to recover from their refractory state.

It is hypothesized that better recording sensitivity and efficiency can be achieved by using long duration continuous stimuli. The potential advantage of this approach include 1) reduced masking of the ACC by the onset response 2) longer offset to onset period to allow neural recovery and 3) doubling of the number of acoustic changes by combining the response to both directions of change.

The overall aim of this pilot study was to explore whether the efficiency and sensitivity of spatial ACC recordings could be improved. The specific objectives were to

- 1) determine whether it is feasible to measure the spatial ACC with single channel scalp recordings
- 2) examine whether the sensitivity and efficiency of spatial ACC recordings can be improved by using long duration continuous stimuli

## 6.3 Experiment 5: Design and Methods

### 6.3.1 Participants

Five participants ranging in age from 43 to 66 years were included in this experiment.

All participants were AB users and had taken part in previous experiments.

Demographic details are summarized in table 6.1.

Table 6.1. Details of participants and electrode pairs tested in experiment 5. F= female, M= male, R = right, L= left

Participant	Age	Sex	Ear	Age at deafness onset (years)	Duration of CI use	Electrode array	Electrode pair tested
P1	43	F	R	1.5	90 months	1J	4-6
S1	53	M	R	41	21 months	Mid Scala	4-5
S4	50	M	L	2	19 months	1J	4-5
S9	49	M	L	47	14 months	Mid Scala	4-5
S11	66	F	L	62.5	13 months	Mid Scala	4-5

### 6.3.2 Stimuli for ACC measurement

Stimuli consisted of alternating polarity biphasic pulse trains with a rate of 1000 pps and phase duration of  $\sim 50 \mu\text{s}$ . There was a change in stimulating electrode during the stimulus – as in previous experiments, the initial electrode is referred to as the reference electrode and the subsequent electrode is referred to as the test electrode. Either electrode pair 4-5 or 4-6 was tested in each participant (see table 6.1). These electrode pairs were chosen as they were associated with a behavioural pass in previous experiments and it was expected that clear cortical responses would be obtained. The participant’s own sound processor was bypassed and electrodes were stimulated through the BEDCS research interface.

There were 3 stimulus presentation strategies – stimulus A, which was used in previous experiments, is referred to as the standard stimulus, and stimuli B and C are referred to as the experimental stimuli. A schematic of the stimuli is shown in figure 6.2 and the time periods for these stimuli are summarized in table 6.2. Although it was originally intended that the experimental stimuli would produce continuous stimulation without a silent interval, this was not possible. Instead there was a 20 ms silent interval at the end of each trial after the test electrode. This period is required by the AB research interface to load the stimulus parameters for every trial. Importantly, there was no silent interval, during the transition from reference to test electrode.

The three stimuli were as follows

1. Stimulus A (standard stimulus). The stimulus duration was 800 ms with a change in stimulating electrode at 400 ms. The first and last 12 ms of this stimulus consisted of zero amplitude pulses. The ISI was 1161 ms and trial duration was 1961 ms.
2. Stimulus B. This had a duration of 2424 ms, with a change in stimulating electrode at 1212 ms. The ISI was 20ms and trial duration was 2444 ms. By lengthening the stimuli, overlap between the ACC and onset response would theoretically be reduced.
3. Stimulus C. This had a duration of 3100 ms with a change in stimulating electrode at 2424 ms. The ISI was 20 ms and trial duration was 3120 ms. Similar to stimulus B, the reference stimulus was longer in duration than in stimulus A, reducing potential overlap between the ACC and onset response. The offset to onset period for the test electrode was 2444 ms, which was longer than for both stimuli A and B.

Table 6.2 Summary of various time periods for spatial ACC stimuli in experiment 5. ISI = inter-stimulus interval.

Stimulus	Duration (ms)				
	Stimulus duration	Reference electrode	Test electrode	ISI	Test electrode offset to onset period
Stimulus A	800	400	400	1161	1573
Stimulus B	2424	1212	1212	20	1232
Stimulus C	3100	2424	676	20	2444

The loudness balanced MC level was determined for stimulus A using the procedure described in the General Methods (Chapter 2). The same stimulation level was used for stimuli B and C. It was expected that these longer duration stimuli would produce a similar loudness percept to stimulus A, as the temporal integration time is typically less than 100 ms for suprathreshold stimuli in CI users (Shannon et al. 1983). To be certain of this, loudness balancing was checked for stimuli B and C in all cases.

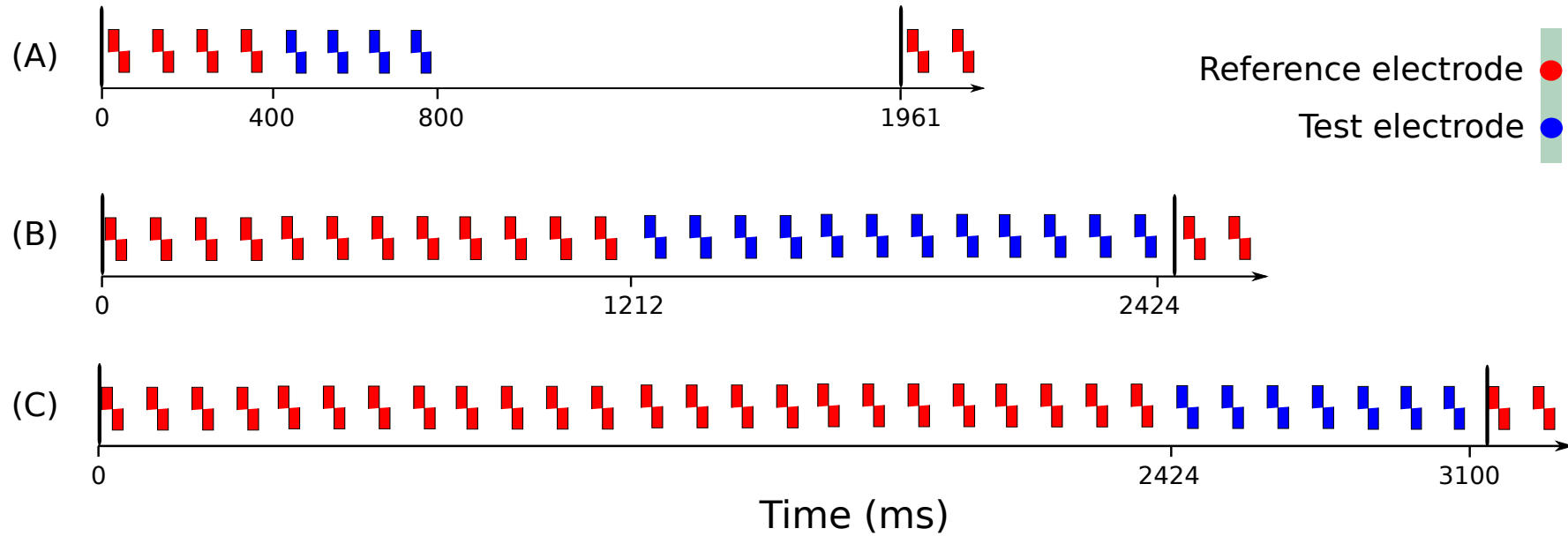


Figure 6.2 Schematic of stimuli used for measuring the spatial ACC in experiment 5. Stimuli consisted of biphasic electrical pulses at 1000 pulses per second with a change in stimulating electrode during the stimulus. The initial electrode is referred to as the reference and is shown in red. The subsequent electrode is referred to as the test electrode and is shown in blue. The solid vertical lines mark the beginning/end of each trial. Stimulus A had a duration of 800ms with a change in stimulating electrode at 400ms. Stimulus B had a duration of 2424 ms with change in stimulating electrode at 1212 ms. Stimulus C had a duration of 3100ms with a change in stimulating electrode at 2424 ms.

### 6.3.3 EEG Recording

A BioSemi Active Two EEG system was used with either one of the following recording configurations:

- 1) Standard recording with 64 channel cap. The technique for EEG recording processing were as described in the General Methods. Data were referenced to the contralateral mastoid and spatial filtering was used to remove CI artefact. Right infra-orbital and right lateral canthus channels were used to measure and remove ocular artefacts.
- 2) Single scalp channel recording. For this configuration, a single EEG recording channel was placed at Cz. This location lies in the midline, midway between the nasion and inion, and is therefore easily identified. Furthermore, a large ACC response can usually be recorded from this site. The forehead and contralateral mastoid were used for ground and reference electrodes respectively. Right infra-orbital and right lateral canthus channels were used to remove ocular artefacts. EEG processing was the same as for the 64 channel recordings, except that spatial filtering was not performed, as this requires high density EEG recordings.

In total there were four measurement conditions:

- I) Stimulus A, 64 channel scalp recording
- II) Stimulus A, single channel scalp recording
- III) Stimulus B, single channel scalp recording
- IV) Stimulus C, single channel scalp recording

Due to time constraints, only measurements conditions I and II were performed in participant S4. The 4 conditions were recorded in separate blocks. The order of the recording conditions was randomized, although the 64 channel recording was always performed either at the beginning or end of the session for practical reasons. The number of trials for EEG recordings was 300 for stimulus A, 250 for stimulus B and 220 for stimulus C. This corresponds to a recording time for a single electrode pair of 9.8 minutes for stimulus A, 10.2 minutes for stimulus B and 11.4 minutes for stimulus C. The number of trials for the longer duration stimuli was reduced to avoid too long a

recording time whilst maintaining a sufficient number of trials for averaging. Participants were given breaks approximately every 10 to 15 minutes. The total experimental time was around 2 hours for each participant.

#### 6.3.4 EEG data analysis

The magnitude of the ACC response was quantified with two methods:

1) ACC N1-P2 amplitude – this was measured using an automatic peak detection algorithm as described in the General Methods. The N1 response was defined as the minimum peak voltage between 70 and 150 ms after electrode change and P2 was defined as the maximum positive peak voltage occurring between 150 and 290 ms after electrode change.

2) ACC SNR – this was calculated using the following equation:

$$\text{SNR} = (\text{RMS}^2 / \text{RN}^2) - 1 \quad (6.1)$$

where RMS is the root mean square amplitude in the ACC response window and RN is the residual noise estimate (Don and Elberling, 1994).

The SNR was calculated as it takes into account the noise floor. At low trials numbers the residual noise is typically high and this may contribute to a large ACC peak amplitude. In contrast, SNR will be small if the noise level is high. Therefore, for smaller trial number this method of quantifying the ACC magnitude may be more appropriate than the N1-P2 amplitude. The ACC response window was defined as the period between 50 – 250 ms after stimulus change as this typically encompasses the P1, N1 and P2 peaks. Only the transition from reference to test electrode was considered a true change response. Although, the initial aim was to combine the transitions from test to reference and reference to test electrode for stimuli B and C, this was not performed due to the presence of a silent interval at the end of the trial as described earlier.

A significant ACC response was defined as having an SNR value of at least 2. A linear SNR of 2 corresponds to approximately 3 dB which has been used as a cut off in other studies of evoked response potentials (Elberling and Don, 1984) The time taken to



achieve an SNR of 2 was calculated with linear interpolation and was used as a measure of recording efficiency.

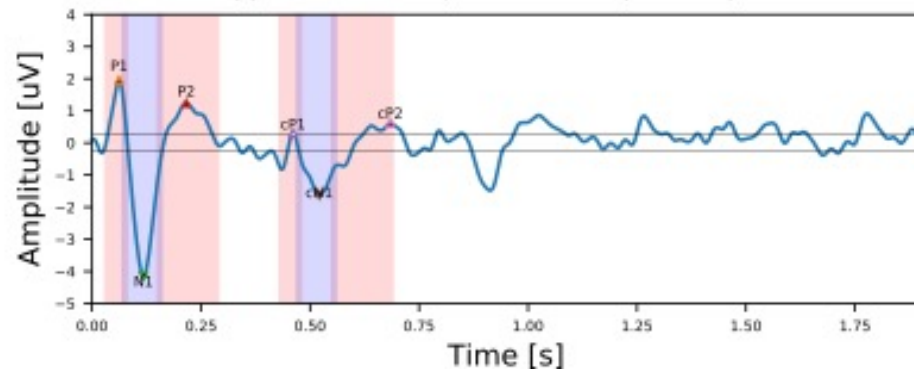
The presence or absence of the ACC response was also determined using the Hotelling-T2 test (Golding et al., 2009). The same ACC response window as for the SNR was used. It was expected that ACC responses which had an SNR value greater than 2 would also have a Hotelling-T2 p value  $< 0.05$ . This would provide additional confirmation that the chosen cut off SNR value was appropriate.

#### 6.4 Results

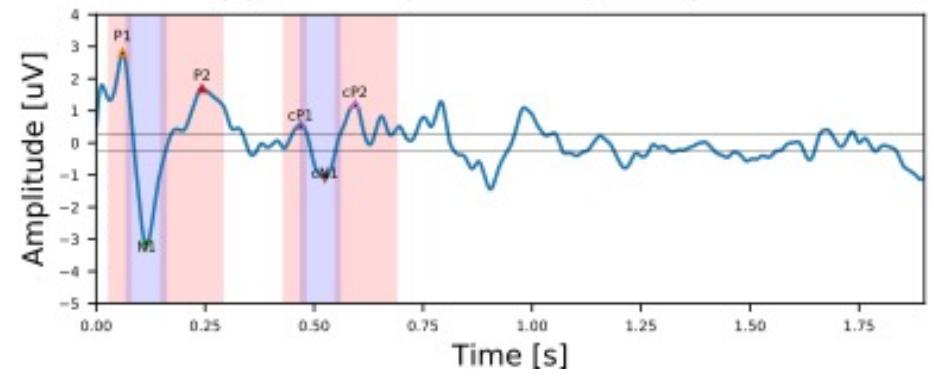
Figures 6.3 shows the cortical response measurements for all participants and measurement conditions. These shall be referred to in the text in more detail in the following sections.

**(A) S4**

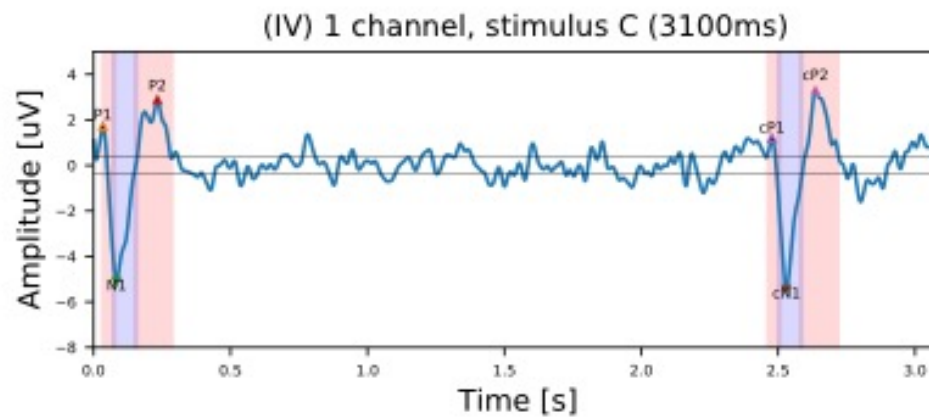
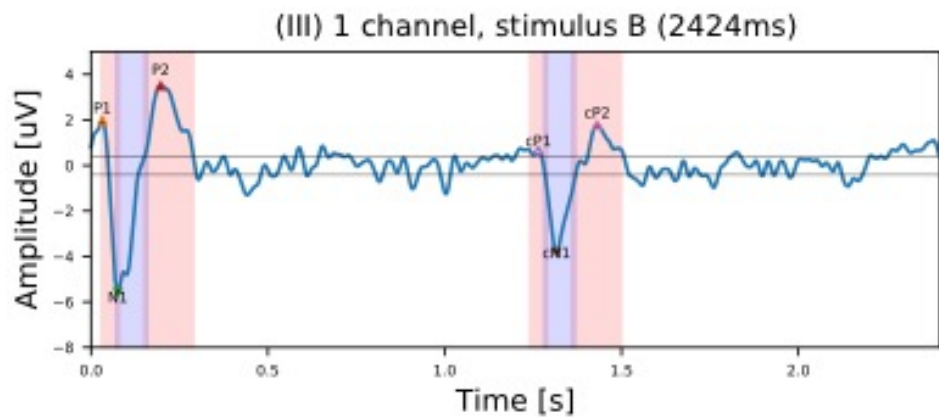
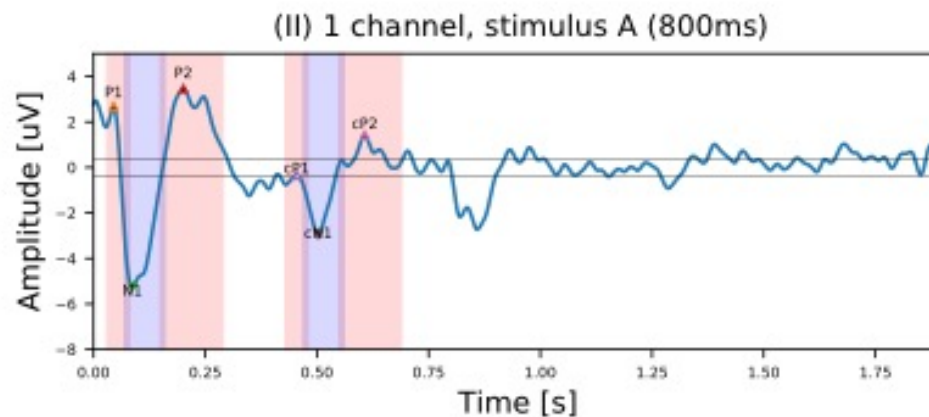
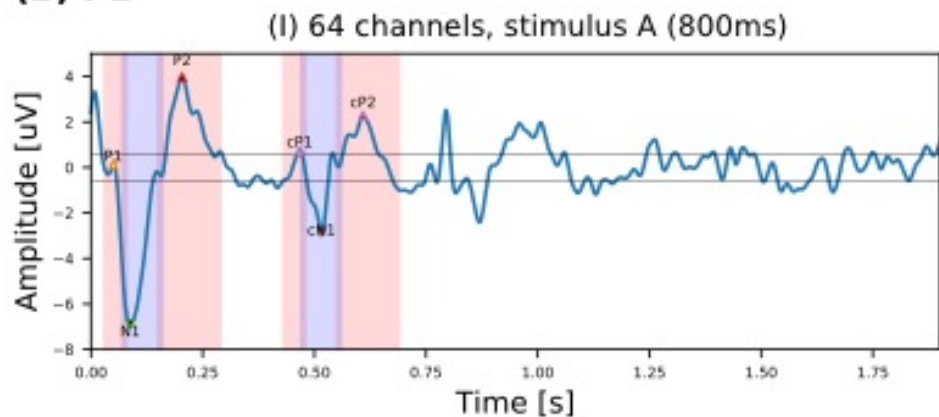
(I) 64 channels, stimulus A (800ms)



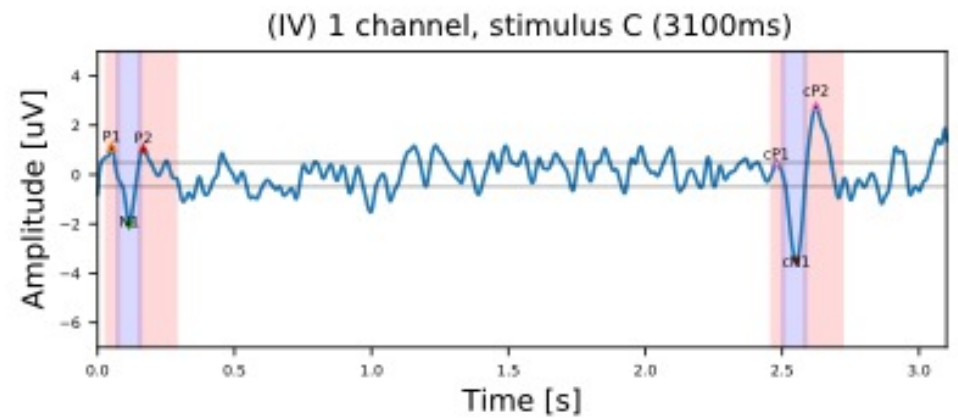
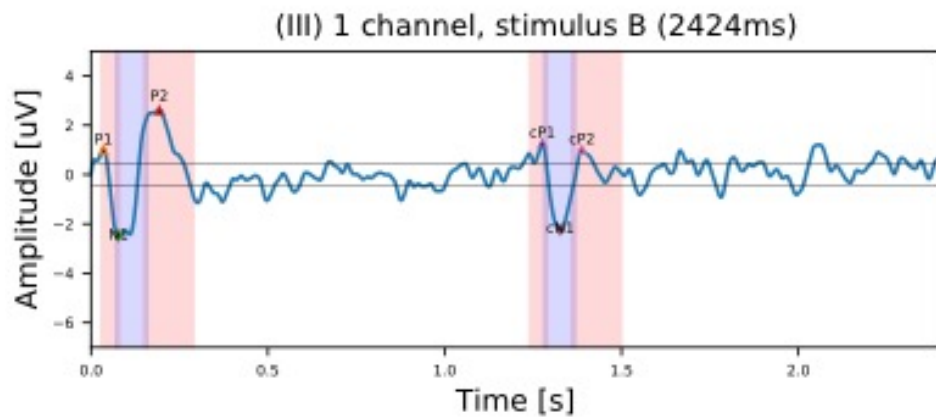
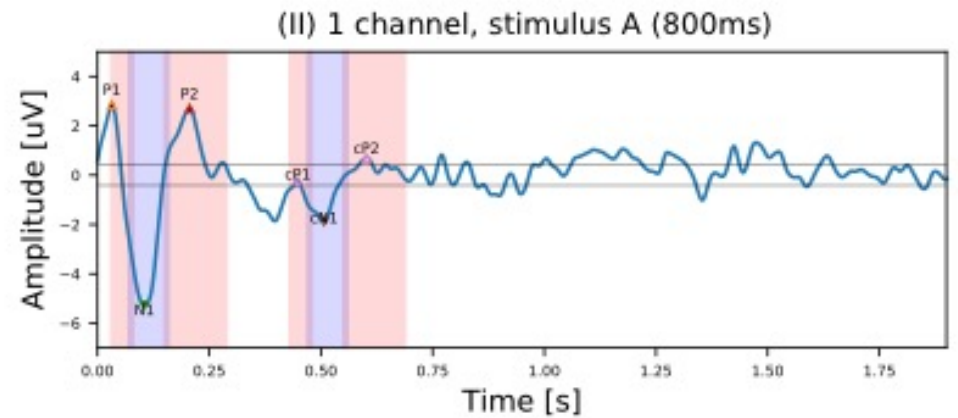
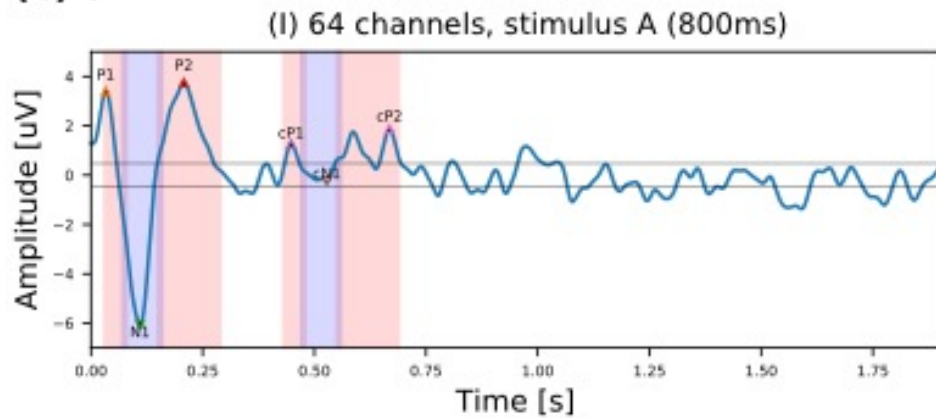
(II) 1 channel, stimulus A (800ms)



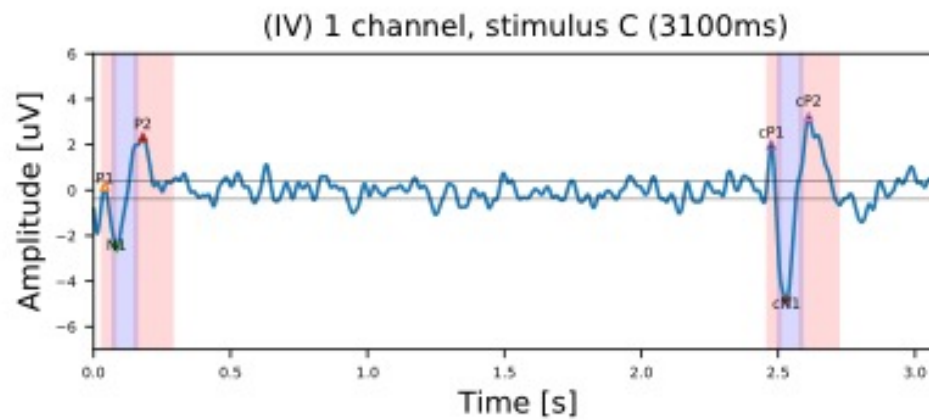
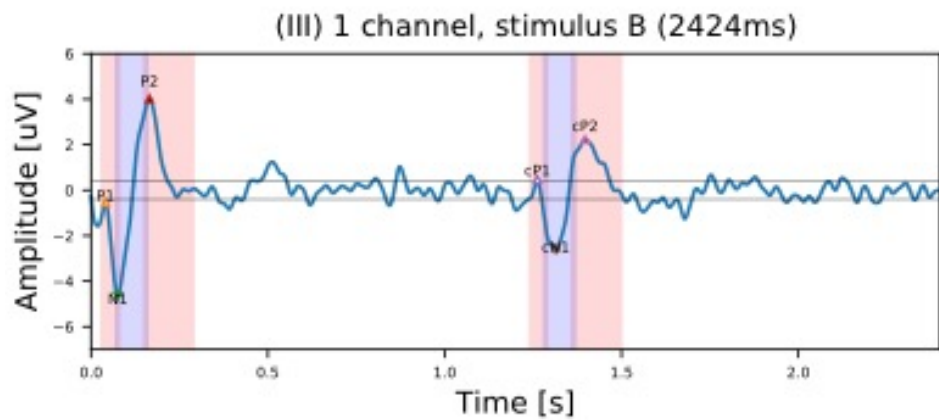
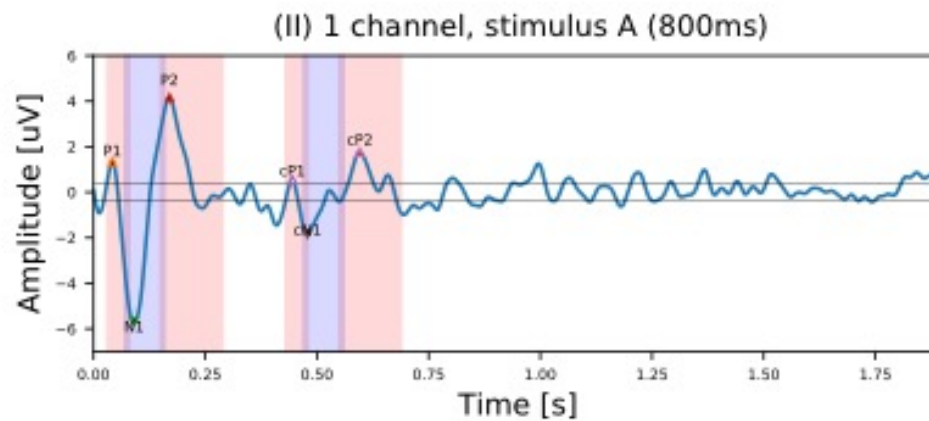
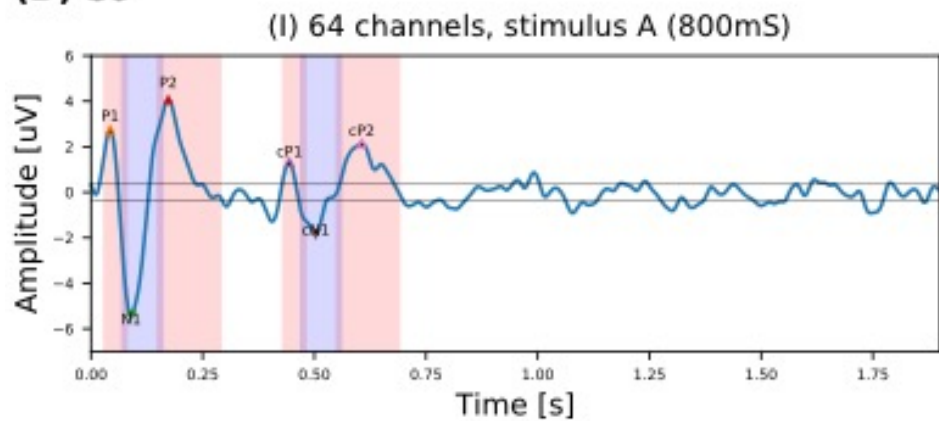
**(B) P1**



**(C) S1**



**(D) S9**



**(E) S11**

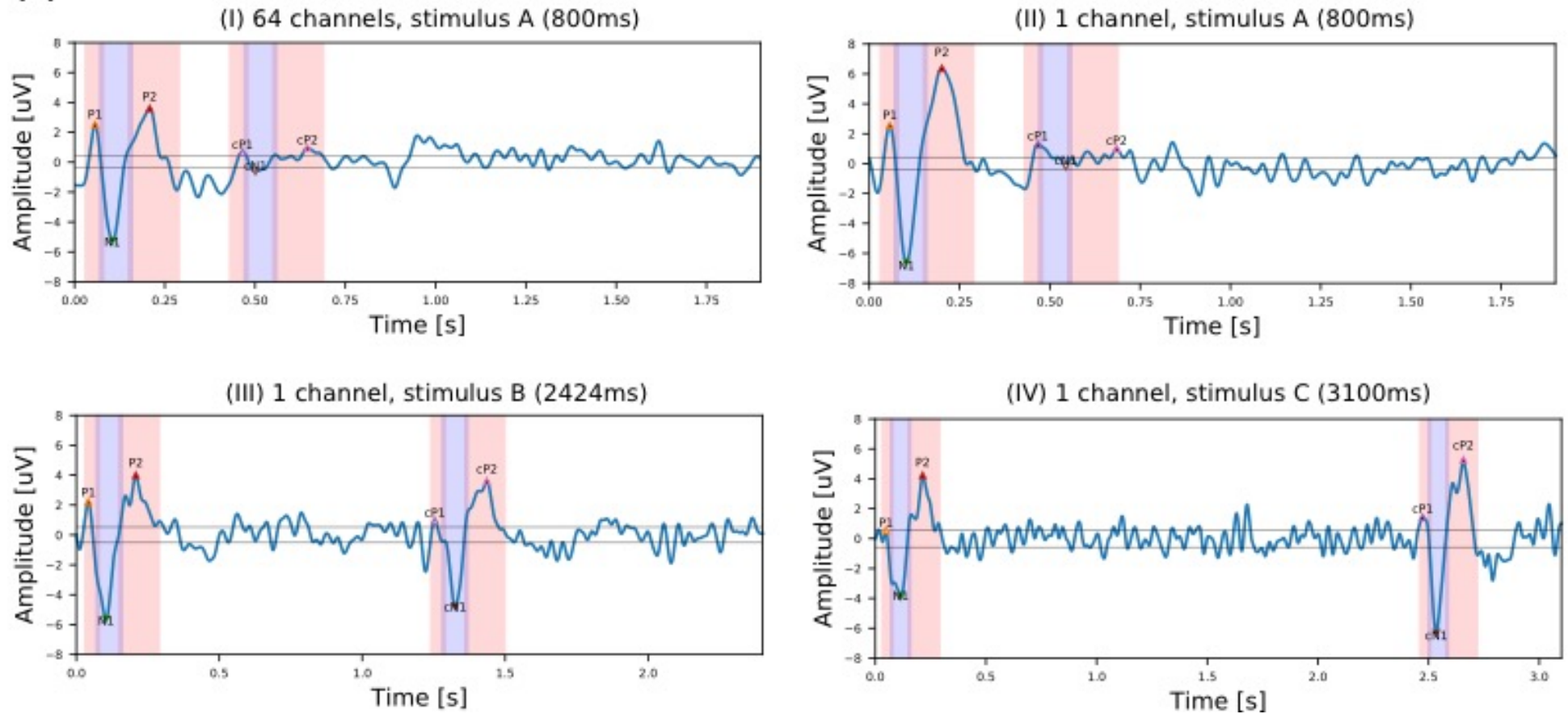


Figure 6.3 Cortical responses for the different measurement conditions. Data are presented at Cz for participants S4 (A), P1 (B), S1 (C), S9 (D) and S11 (E). The measurement condition, number of recording scalp channels and stimulus type are shown above each panel. The time windows used to detect positive and negative peaks for the onset response (P1, N1, and P2) and ACC (cP1, cN1, and cP2) are shown in pink and blue, respectively. The horizontal lines correspond to the level of residual noise.

#### 6.4.1 Comparison of single and 64 channel ACC measurements

The aim of this analysis was to validate single channel recordings for measuring the spatial ACC. In order to do this, the ACC at scalp location Cz for measurement conditions (I) and (II) were compared. Stimulus A, which was of 800 ms duration was used in both of these conditions. Visual inspection of figure 6.3 reveals that single scalp channel EEG recordings were relatively free of CI artefact. Furthermore, the spatial ACC responses for measurement conditions (I) and (II) were similar in most cases. Figure 6.4 shows that the N1-P2 peak amplitude of the spatial ACC for the 2 measurement conditions were broadly similar.

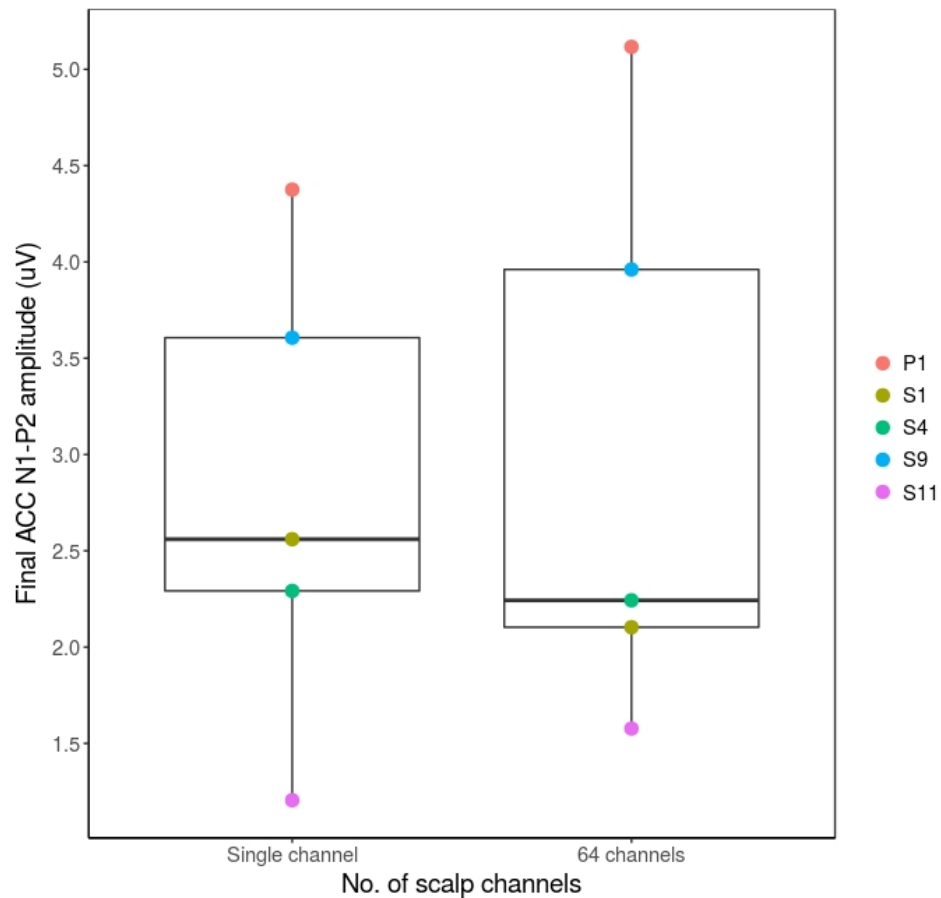


Figure 6.4 Spatial ACC amplitude according to number of scalp recording channels. Identical stimuli (stimulus A) were used for both recordings. Data are presented at channel Cz for individual participants. The upper and lower hinges of the box plots correspond to the first and third quartiles, whilst the median is indicated by the horizontal line within each box.

The change in the SNR over recording time for both measurement conditions was also compared. The individual data are shown in figure 6.5, and the mean data across all participants are shown in figure 6.6. The horizontal dotted line in these figures represents the critical SNR value of 2 for defining a significant ACC response. These figures shows that the single channel scalp recordings have similar efficiency and produce ACC responses with a similar magnitude, compared to 64 channel recordings. For participant S1, the critical SNR value of 2 was reached with the single channel but not the 64 channel recording.

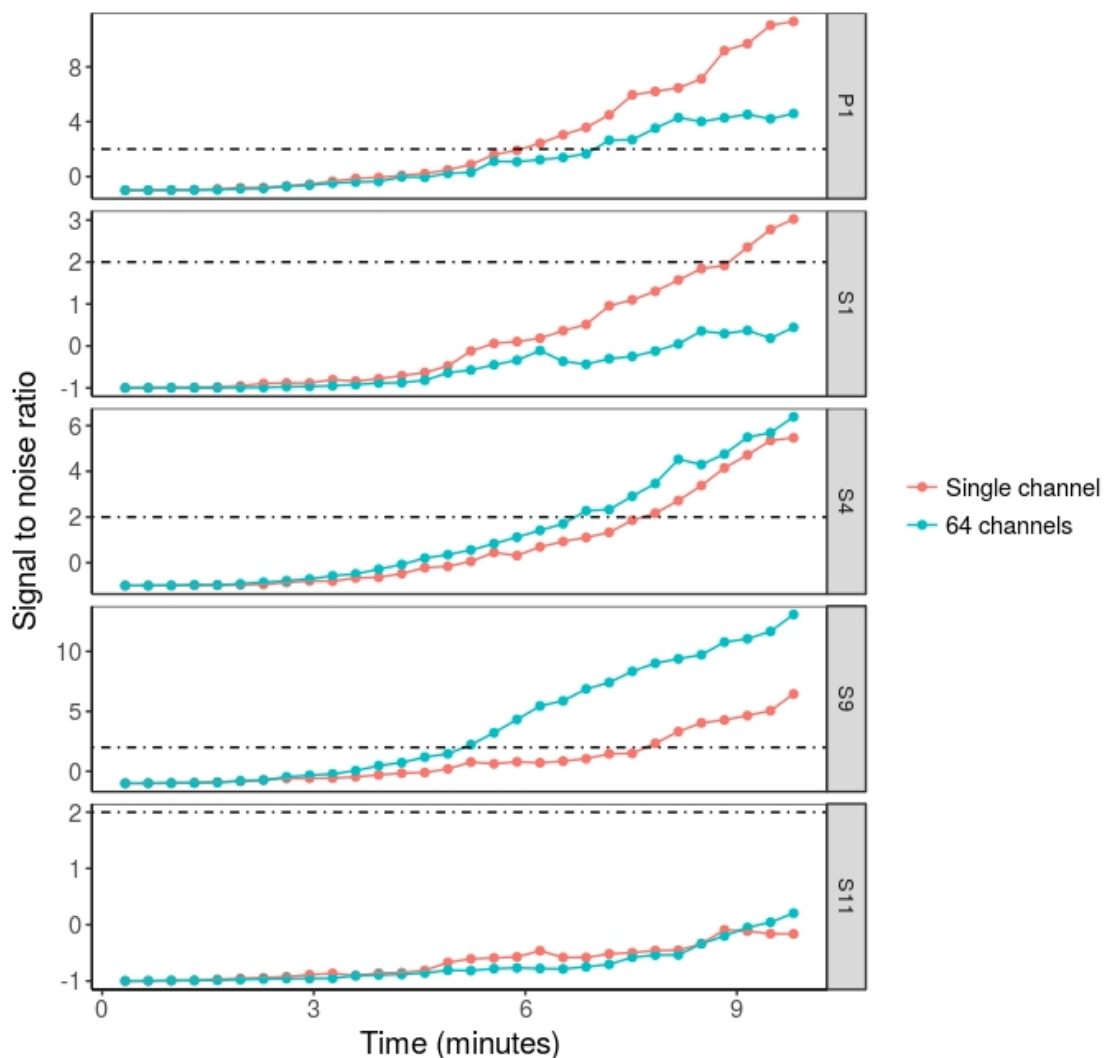


Figure 6.5 Spatial ACC SNR as a function of recording time and number of recording channels for individual participants. SNR was calculated as per equation 6.1 (Don and Elberling, 1994). The horizontal dotted line represents the critical SNR value of 2 at which a significant ACC response was defined. Data are presented at channel Cz.



The setup times (application of conductive gel and recording electrodes) for the single channel and 64 channel scalp recordings were approximately 5 minutes and 20 minutes respectively. These data show that for spatial ACC measurements in users of the AB device, single channel scalp recordings are feasible, valid and time efficient.

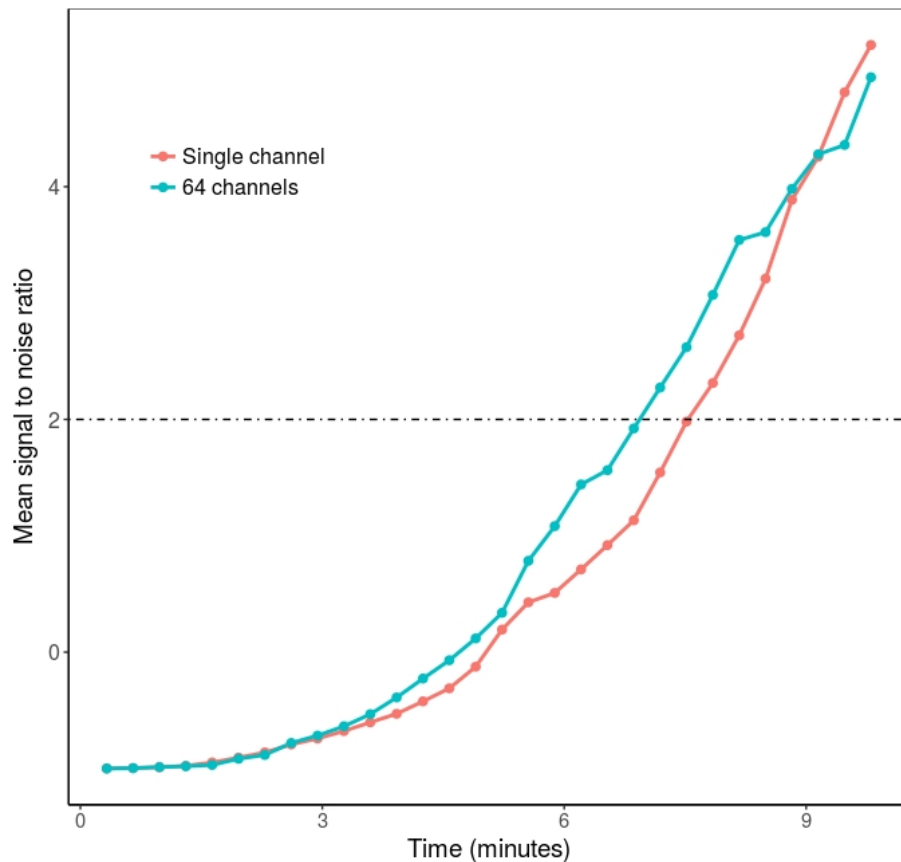


Figure 6.6 Spatial ACC SNR as a function of recording time and number of recording channels for the mean data across participants. The horizontal dotted line represents the critical SNR value of 2 at which a significant ACC response was defined. Data are presented at channel Cz.

#### 6.4.2 Comparison of efficiency and sensitivity of single channel ACC measurements using different stimuli

The aim of this analysis was to determine whether the sensitivity and efficiency of ACC measurements could be improved by altering stimulus characteristics. Spatial ACC recordings from measurement conditions (II), (III) and (IV) are therefore compared – these were all single channel scalp recordings but utilized stimuli A, B and C respectively. Visual inspection of the ACC responses in figure 6.3 shows that larger magnitude responses were generally obtained for the experimental stimuli (B and C) compared to the standard stimulus (A). This is particularly evident for participant S11,

in whom no clear spatial ACC response could be visualized for stimulus A. Figure 6.7 shows that the spatial ACC N1-P2 amplitude is consistently larger for the experimental stimuli compared to the standard stimulus for single channel recordings. However, it must be noted that fewer trials were used for experimental stimuli recordings and therefore higher residual noise levels could have contributed to larger peak amplitude responses.

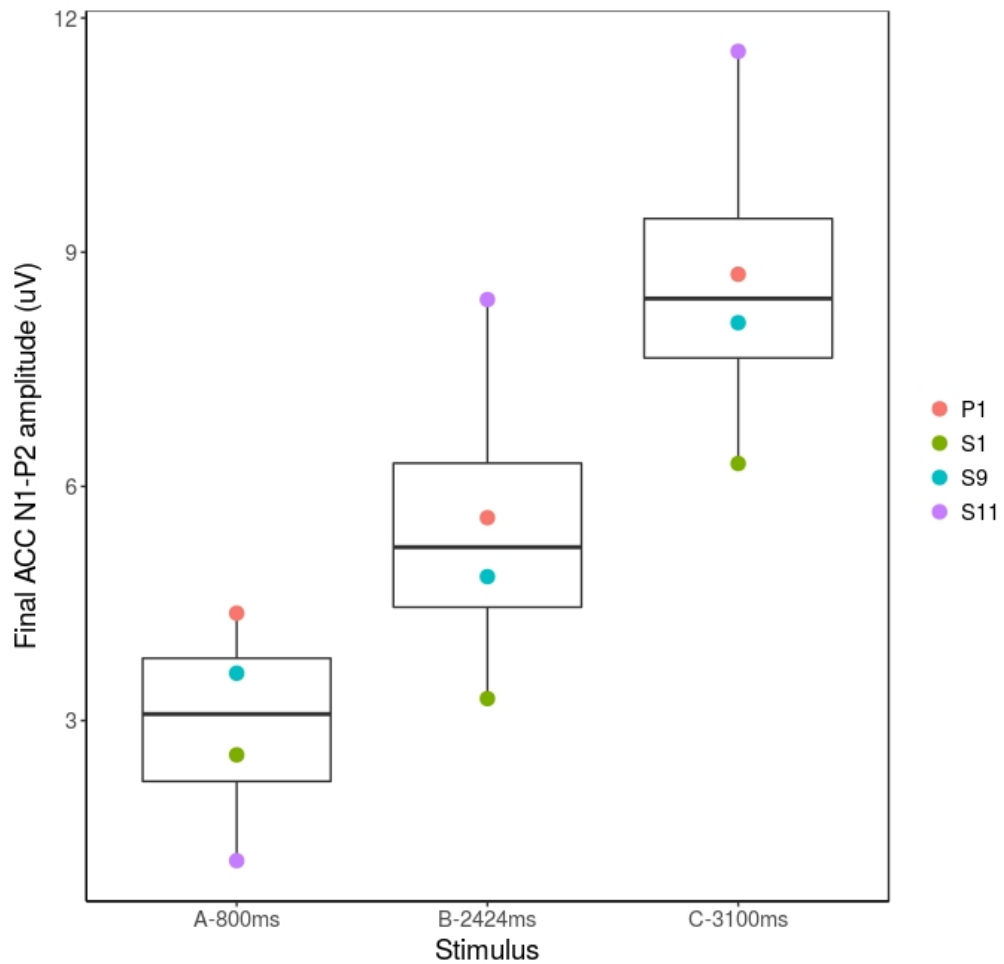


Figure 6.7 Spatial ACC amplitude according to stimulus type. All recordings were performed with a single scalp channel. The upper and lower hinges of the box plots correspond to the first and third quartiles, whilst the median is indicated by the horizontal line within each box.

The SNR provides a fairer comparison of response magnitude when comparing measurement conditions with different numbers of trials since it accounts for the residual noise level. In order to compare response magnitude and recording efficiency for the different measurement conditions, the change in SNR over recording time was analyzed. The individual and mean data are shown in figure 6.8 and 6.9 respectively. The final SNR as well as the time taken to reach an SNR value of 2 are shown in table

6.3. Of note, an SNR value of 2 was achieved with the experimental stimuli but not the standard stimulus for participant S11. Stimulus C produced larger responses and was more efficient compared to stimulus A in 4 out of 4 cases. Stimulus B produced larger responses and was more efficient than the standard stimulus in 3 out of 4 cases. Table 6.4 shows that only ACC measurements which achieved an SNR value of 2, had a statistically significant Hotelling-T2 p value ( $p < 0.05$ ). This suggests that it is reasonable to use a cut-off SNR value of 2 to provide a measure of recording efficiency.

These data show that the efficiency and sensitivity of ACC measurements can be improved by altering stimulus characteristics.

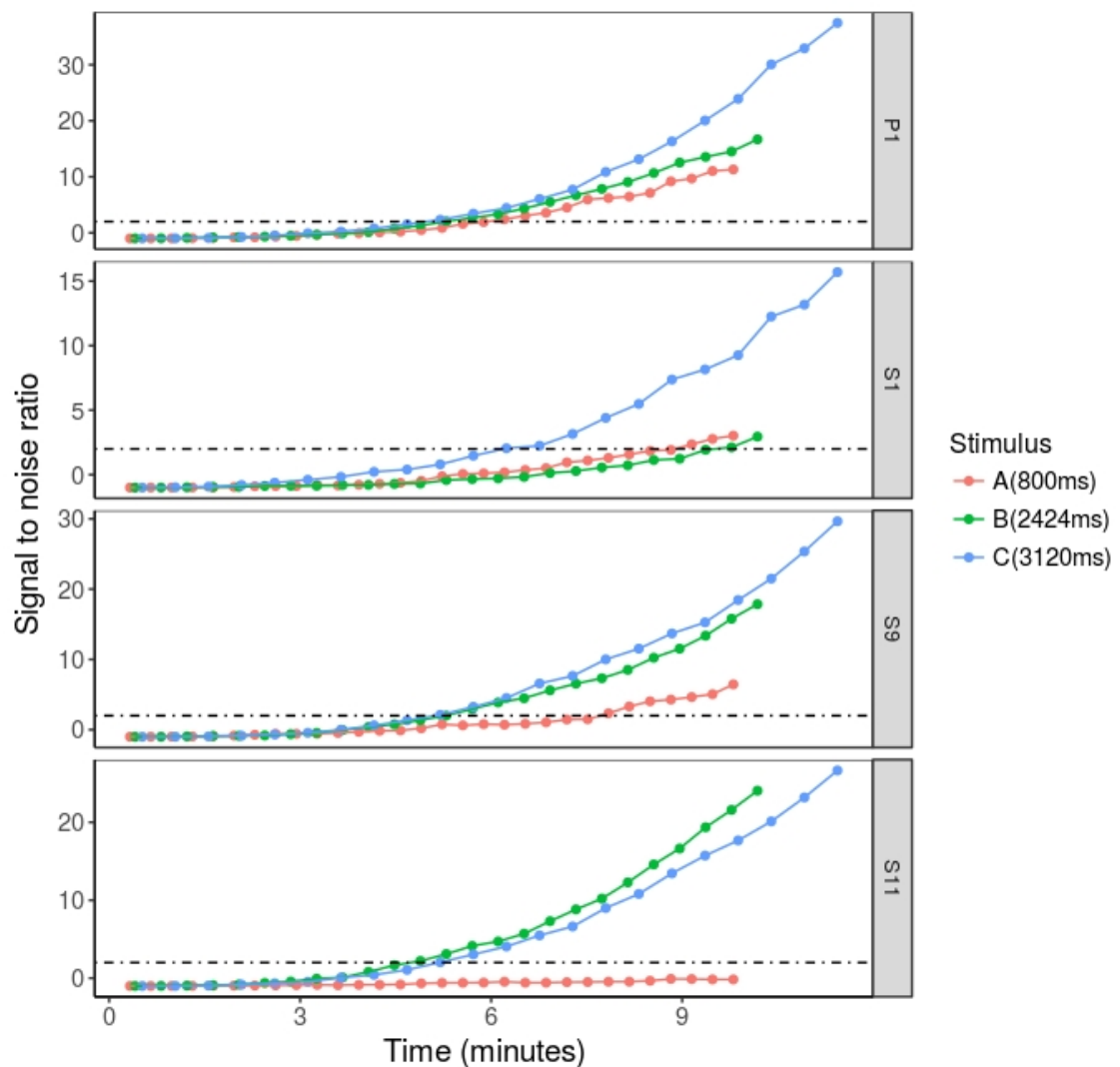


Figure 6.8 Spatial ACC SNR as a function of recording time and stimulus type for individual participants. The horizontal dotted line represents the critical SNR value of 2 at which a significant ACC response was defined.

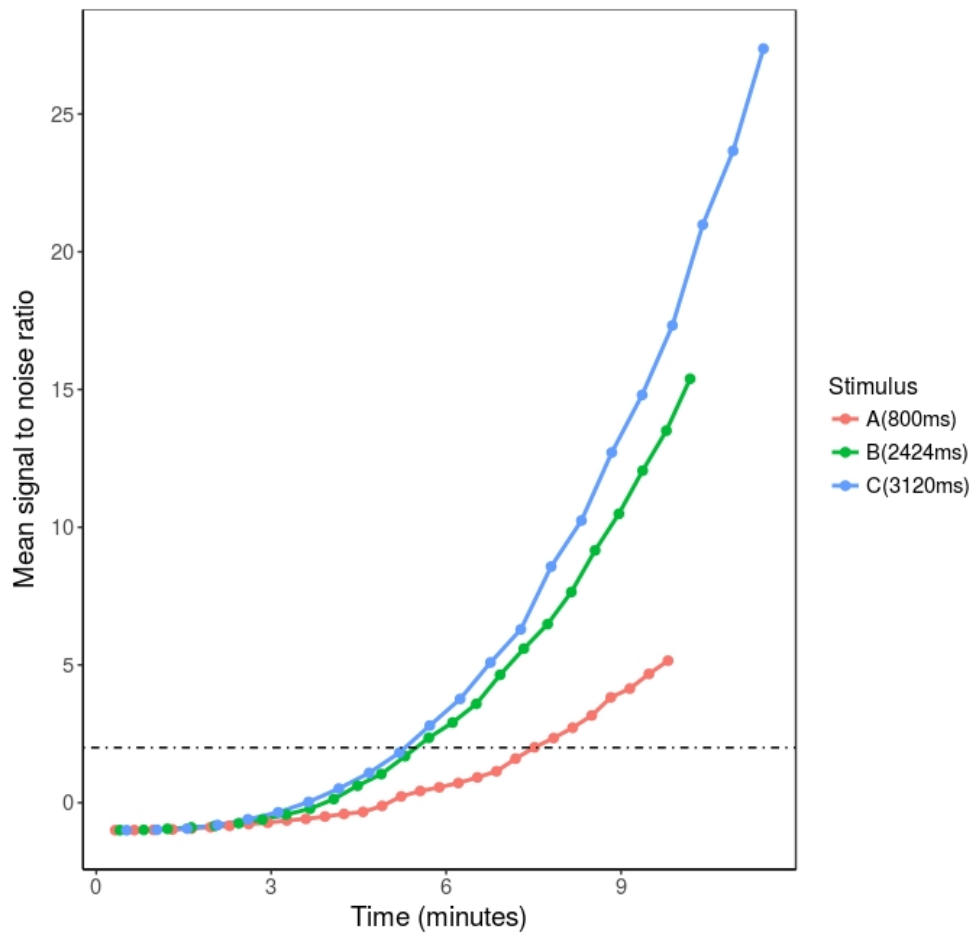


Figure 6.9 ACC SNR as a function of recording time and stimulus type for the mean data across participants. The horizontal dotted line represents the critical SNR value of 2 at which a significant ACC response was defined.

Table 6.3 Time taken to reach an SNR value of 2, peak SNR value and Hotelling-T2 result in the ACC response window. SNR = signal-to-noise ratio, HT2 = Hotelling-T2.

Participant	Outcome measure	Stimulus A (800 ms)	Stimulus B (2424 ms)	Stimulus C (3100 ms)
P1	Time (mins) for critical SNR	5.9	5.3	5.0
	Peak SNR	11.3	16.7	37.5
	HT2 $p < 0.05$	Yes	Yes	Yes
S1	Time (mins) for critical SNR	8.9	9.5	6.2
	Peak SNR	3.0	2.9	15.7
	HT2 $p < 0.05$	Yes	Yes	Yes
S9	Time (mins) for critical SNR	7.7	5.3	5.1
	Peak SNR	6.5	17.9	29.7
	HT2 $p < 0.05$	Yes	Yes	Yes
S11	Time (mins) for critical SNR	NA	4.7	5.2
	Peak SNR	-0.1	24.1	26.7
	HT2 $p < 0.05$	No	Yes	Yes

## 6.5 Discussion

In this pilot study, it was found that spatial ACC measurements could be performed with a limited number of EEG recording channels and that recording efficiency and sensitivity could be improved by altering stimulus characteristics. Despite the small numbers of participants, the results of this experiment are encouraging for the clinical use of spatial ACC measurements.

### 6.5.1 Recording the spatial ACC with a limited number of scalp channels

It was feasible to measure the spatial ACC with a single scalp EEG recording channel in users of the AB device. Despite the absence of a sophisticated artefact removal technique, cortical responses were relatively artefact free, and on average were similar to that obtained with 64 channels. By using this approach, the setup time for EEG recordings was reduced from around 20 to 5 minutes. In addition, the data files obtained with single channel recordings are considerably smaller and are therefore much faster to process. Single channel recordings require application of considerably less conductive gel to the scalp, and this is preferable for participants. The spatial ACC

has been recorded with a limited number of scalp channels in users of the Cochlear device (Brown et al., 2008; He et al., 2014; Scheperle and Abbas, 2015b). Scheperle and Abbas (2015b), recorded the spatial ACC using a single EEG scalp recording channel at Cz. However, two reference electrodes were used with one at the contralateral mastoid and the other at Iz (Inion). For every trial, two differential recordings were averaged in order to reduce the residual noise. This approach could be used to improve recording efficiency further.

#### 6.5.2 Stimulus characteristics and spatial ACC measurements

In this study, the effect of changing stimulus characteristics was examined by altering the stimulus duration, reducing the ISI and varying the offset to onset time of the test electrode. In order to determine the relative importance of these different features a more controlled experiment is required. Nonetheless, it was found that by altering stimulus characteristics, the same magnitude response could be obtained in a shorter period of time for experimental stimuli compared to the standard stimulus i.e. efficiency was improved. Furthermore, in one participant, a significant spatial ACC response (as defined by SNR and Hotelling-T2 criteria) could be obtained with the experimental stimuli, even though this was not possible with the standard stimulus.

The largest spatial ACC responses were obtained with stimulus C. In this case, the duration of the test electrode was 676 ms and its offset to onset period was 2444 ms. The ACC response was larger for stimulus C compared to stimulus B, even though the former had a shorter test electrode duration. It is likely then, that for stimulus C, the larger ACC response was due to the neurons responsible for the ACC having a longer period to recover from their refractory state. Stimulus B generally produced larger magnitude responses compared to stimulus A. This is thought to be due to the longer duration of the reference electrode, since the offset to onset period for stimulus B was shorter compared to stimulus A (stimulus B 1232 ms, stimulus A 1573 ms). The use of longer duration stimuli, reduces the potential overlap between the onset and ACC responses and consequent masking of the latter. In figure 6.3E, for stimulus B, it can be seen that the onset response only returns to baseline at around 500 ms. Further experiments are required to determine the optimum stimulus duration for measuring

the spatial ACC. Chen and Small (2015), showed that ACC reliability could be improved by increasing the stimulus duration from 564 ms to 820 ms. For these stimuli there was a change in formant frequency at the midpoint of the stimulus and a fixed ISI of 2200 ms was used in both cases. Therefore, the larger responses obtained with the 820 ms recording may have been due to a longer offset to onset period for the test stimulus as well as reduced masking effects.

The results of this experiment were limited by the fact that it was not possible to present alternating stimuli continuously for the test stimuli. Similar to the method used in Martin et al. (2010), it was intended, that the response windows for the change from reference to test electrode and from test to reference electrode would be combined for these stimuli. If this was possible, the recording time could potentially be halved, resulting in a substantial improvement in efficiency. Further work with the AB research interface is required in order to achieve this.

## 6.6 Conclusion

This preliminary study shows that setup time for spatial ACC measurement with the AB device can be reduced by using a limited number of EEG recording channels. Furthermore, the efficiency of EEG measurements can be improved by increasing stimulus duration and minimizing the silent period in the stimulus. Further work is required to determine the optimal stimulus characteristics for spatial ACC measurements and other techniques for improving the efficiency/sensitivity are considered in section 7.3 of the General Discussion.

## Chapter 7 General Discussion

In this thesis it has been shown that the spatial ACC provides a useful measure of electrode discrimination in CI users. The spatial ACC represents encoding of stimulus change in the auditory cortex and therefore provides a measure of whether the signal from the CI is actually preserved in the auditory pathway. The advantage of the spatial ACC over behavioural assessments, is that it is an objective measure, which can be performed independent of attention, cognition and language. This makes it feasible to use in difficult to test patient groups including young children. It is proposed that this kind of assessment could be used to guide management of CI users in order to improve hearing outcomes. In the following sections a summary of the main findings, clinical implications of this work and future studies shall be discussed.

### 7.1 Summary and discussion of main findings

In Chapter 3, it was found that it is feasible to measure the spatial ACC in CI devices from different manufacturers and in the early period after CI switch-on. An effective technique for removing CI artefact was implemented and ACC responses with amplitudes and latencies similar to that reported in the literature were obtained. In Chapters 3 to 5, the relationship between the spatial ACC and behavioural measures of electrode discrimination was examined. When using pass-fail criteria, there was generally a strong relationship between the spatial ACC and behavioural electrode discrimination. In certain cases, the spatial ACC did not provide a sensitive measure of behavioural discrimination – that is, a significant spatial ACC response could not be recorded even though the participant could discriminate the electrodes behaviourally. In Chapter 5, it was found that the spatial ACC sensitivity was particularly poor at stimulus intensities in the lower part of the DR. However, the results of Chapter 6 suggest that spatial ACC sensitivity can potentially be improved by altering stimulus characteristics.

In Chapters 3 to 5, it was found that in certain individuals the spatial ACC could be recorded despite relatively poor behavioural discrimination. This indicates that the spatial ACC represents encoding of stimulus change in the auditory pathway and the



potential for discrimination, rather than the actual perception of stimulus change itself. Indeed, in Chapter 4, it was found that most individuals who had a 'false positive' spatial ACC (spatial ACC pass, behavioural fail), developed accurate behavioural discrimination at a later point in time. The 'false positive' spatial ACC was observed in a total of 5 CI users, 4 of whom had pre or peri-lingual onset deafness. While it is expected that the presence of the spatial ACC, would normally be associated with change detection, it was hypothesized that this might not be the case during the early stages of auditory learning after CI switch-on or when there is abnormal cortical connectivity due to auditory deprivation, as might be expected in early-deafened late-implanted individuals.

The relationship between the spatial ACC and behavioural discrimination was also examined by performing correlation analysis between the N1-P2 peak amplitude of the spatial ACC and the behavioural discrimination score in Chapters 4 and 5. This analysis was generally limited by the small number of participants. However, no significant correlation was found in the across subject analysis i.e. a higher spatial ACC N1-P2 amplitude did not imply a better behavioural discrimination score. This is likely due to the substantial inter-individual differences in cortical response magnitude. This is most likely secondary to variations in cortical folding and resulting dipole orientations, which are important in determining the size of the measured EEG response. In Chapter 3, it was seen that even within a participant, an electrode pair with a larger spatial ACC amplitude did not necessarily have a larger behavioural discrimination score. This may be because different electrodes are associated with different cortical dipole locations and orientations. Furthermore, as discussed earlier there may be a dissociation between encoding and perception of stimulus change. These findings suggest, caution must be applied when comparing the magnitude of ACC responses for different electrode locations and individuals.

The longitudinal study in Chapter 4, showed that electrode discrimination improved with CI listening experience after switch-on. During the first 6 months of CI use, the proportion of electrodes with an objective ACC pass as well as the amplitude of the ACC response increased. This was paralleled by improvements in behavioural electrode discrimination as well as speech perception. Notably, in certain individuals,

improvements in electrode discrimination were substantial and could occur over a relatively long period of time. It was found that higher stimulation levels were required over time in order to achieve a relatively constant perceptual level. This could have contributed to the improvements in behavioural and objective measures of electrode discrimination over time. However, when electrode pairs with poor initial behavioural electrode discrimination were re-tested at a later time point using the original stimulation levels, significantly higher discrimination scores were obtained. Therefore, the use of higher stimulation levels, might account for some but not all of the improvements in electrode discrimination that occurred over time. These data provide evidence for auditory plasticity in adult CI users. The mechanisms that underlie this are not well understood, but the possibility of tonotopic re-organization and higher auditory learning were discussed.

The relationship between electrode discrimination and speech perception was examined in Chapters 3 to 5. A significant relationship between behavioural electrode discrimination and speech perception was found in Chapters 3 and 4. This is consistent with findings from other studies (Busby et al., 2000; Dawson et al., 2000; He et al., 2014; Henry et al., 2000). In contrast, a significant relationship between the spatial ACC amplitude and speech perception was not found. The inter-individual variability in cortical response magnitude may have contributed to this finding. The results of Chapter 5 were not in keeping with the Chapters 3 and 4 – it was found that the spatial ACC amplitude, but not behavioural electrode discrimination, was correlated with sentence perception. This results of Chapter 5 are viewed with caution, as there were fewer participants and electrode discrimination was measured for a single electrode pair. An appropriately powered study with a larger cohort of participants and spatial ACC measurements at a greater number of electrode locations is needed to determine the relationship between the spatial ACC and speech perception. It is likely that electrode discrimination will account for a relatively small proportion of the variance in speech perception outcomes. Electrode discrimination provides a relatively low-level assessment of auditory processing. Speech perception, however, is complex and requires the use of spectral, temporal and level cues as well as cognitive ability. While it is expected that CI users with poor electrode discrimination will have poor speech

perception, individuals with good electrode discrimination may not necessarily have good speech perception if there are other limiting factors.

In Chapter 6, techniques for improving the clinical applicability of spatial ACC measurements were explored. A pilot study showed that it is feasible to measure the spatial ACC with a limited number of EEG recording electrodes, which substantially reduced the set up time. Furthermore, by altering stimulus characteristics it was possible to obtain large magnitude responses more quickly, thereby improving recording efficiency. Other challenges and solutions to using spatial ACC measurement in the clinical setting shall be discussed in section 7.3

## 7.2 Clinical implications of the spatial ACC

The findings of this thesis have a number of clinical implications. Firstly, this study provides evidence for auditory plasticity in adult CI users, including individuals with early onset and long durations of deafness. This capacity of the auditory system to adapt may underlie the fact that good results can be achieved in these groups (Lundin et al., 2014; Waltzman et al., 2002). Factors such as deafness onset and duration, in themselves, should therefore not be considered contraindications to implantation.

What is clear from this study is that the time course for adaptation may vary widely between CI users – in certain individuals, electrode discrimination was excellent soon after switch-on, whilst in others performance was initially poor but continued to improve for up to 1 year. This raises the possibility of accelerating auditory adaptation with focused training in poorer performers. Indeed, studies in CI populations have shown that training, over as little as 4 weeks, can result in marked improvements in auditory performance, even after long periods of passive adaptation to the speech processor (Fu and Galvin, 2008). Fu and Galvin (2008), reported an experiment using electrode discrimination training in one pre-lingually deafened adult CI user. Training resulted in improved electrode discrimination for both trained and untrained electrode contrasts. Furthermore, this was associated with improved consonant and vowel recognition. Although the evidence for electrode discrimination training is limited, a number of other studies have shown that ‘bottom-up’ training approaches are beneficial. For example, Fu et al. (2005a) found that phonetic contrast training resulted

in significantly improved vowel, consonant and sentence recognition in adult CI users. In addition, Fu et al. (2005b) showed that vowel contrast training, but not sentence training, in CI simulations with NH listeners led to improved vowel and consonant recognition with spectrally shifted speech. The authors suggest that developing phoneme recognition is particularly important in congenitally deaf late-implanted adults who must develop a 'central speech template'. 'Bottom-up' training approaches, using electrode or phonetic contrasts, may therefore be particularly appropriate for poor performers in order to optimize performance as quickly as possible.

If there are significant interactions in the electrical fields of CI stimulation channels, then it is unlikely that auditory training will yield benefit. CI channel deactivation has been utilized as a strategy to reduce channel interactions and improve performance. The decision to deactivate electrodes has been based on performance on behavioural tasks including electrode discrimination (Zwolan et al., 1997), pitch ranking (Saleh et al., 2013; Vickers et al., 2016) and modulation detection (Garadat et al., 2013). Based on the results of this study, two points are noteworthy. Firstly, it is important to understand the temporal dynamics of performance on psychophysical tasks if they are to be used to guide interventions. If behavioural performance can improve over long periods of time, then re-programming procedures such as electrode deactivation, should not be performed prematurely. Secondly, it may be beneficial to measure auditory processing objectively with measures such as the ACC and MMN, as behavioural performance can lag behind objective measurements. If, for example, an electrode pair cannot be discriminated behaviourally but is encoded in the auditory pathway, as measured with the ACC, providing auditory training is likely to be more appropriate than deactivating electrodes.

One of the limitations of deactivating electrodes is that the frequencies of these channels have to be reallocated, which results in a broadening of the bandwidth at other sites. Zhou and Pfingst (2014), showed that altering stimulation parameters at selected electrode sites can be an effective alternative method to deactivating electrodes in order to improve CI performance. In their study, the minimum stimulation levels of electrodes with the poorest modulation detection thresholds were raised by increasing threshold levels on the clinical programmes by 5%. This

resulted in a significant improvement in speech reception threshold. In contrast, increasing the threshold level for all electrodes did lead to better speech perception. In Chapter 5, it was shown that electrode discrimination scores and spatial ACC amplitude increased with stimulus intensity. Therefore, one approach to improving electrode discrimination and potentially speech perception, would be to increase stimulation levels at electrode sites with poor discrimination. Similar to Zhou and Pfingst (2014), this could be achieved by raising the threshold level on the clinical programme at selected sites. This may be particularly appropriate for electrode pairs that have poor discrimination in the lower part of the DR but good discrimination in the upper part of the DR.

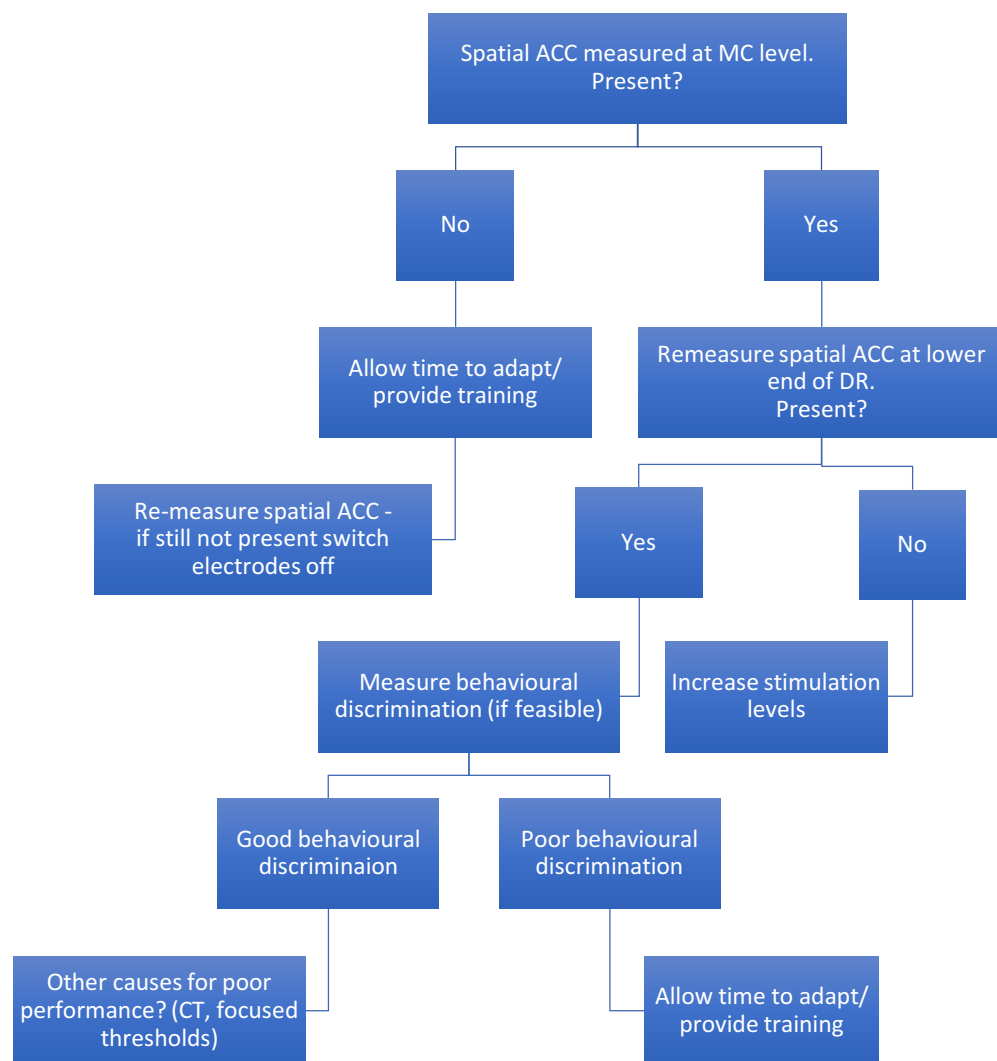


Figure 7.1 Flowchart illustrating clinical decision making with the spatial ACC. DR = dynamic range

In summary, it is proposed that the spatial ACC could be used to guide management in CI users. Figure 7.1 sets out a theoretical framework for how the spatial ACC might be used for clinical decision making. Electrode discrimination assessments are expected to be most useful in poorer performers. The spatial ACC should initially be measured at the upper part of the DR (e.g. the MC level) for apical and mid array electrodes. If ACC responses are absent, the patient should be allowed time to adapt to their CI. If they are already experienced CI users, targeted auditory training should be provided. If training does not result in the development of a spatial ACC response, then re-programming the CI, for example, by deactivating electrodes should be considered. If spatial ACC responses are present, then testing should be repeated in the lower part of the DR. If responses are absent in the lower part of the DR, then threshold levels on the clinical programme should be increased for the problem electrodes. If, spatial ACC responses are present in the upper and lower parts of the DR, but behavioural discrimination is poor, adaptation time/auditory training should be provided. If on the other hand, responses are present throughout the DR and behavioural discrimination is good, then other reasons for poor performance should be considered and further investigations may be required. Clearly, this algorithm is hypothetical. Further research is required to determine the finer details of how the spatial ACC might be used clinically and if interventions based on these measurements lead to improved hearing outcomes.

### 7.3 Limitations and further studies

It would be useful to validate the findings of this study in a larger cohort of CI users including early-deafened late-implanted individuals, as well as children. Previous studies have shown that the ACC measurements can be performed in young children including infants (Chen and Small, 2015; Martinez et al., 2013). Furthermore, the development of the ACC in paediatric populations has recently been characterized (Jeon, 2016). It is therefore expected that spatial ACC recordings in children are feasible. In Chapter 4, it was found that in certain CI users, electrode discrimination ability was continuing to improve at 1 year after switch-on. Therefore, it would be useful to have a longer period of follow-up, to determine how long behavioural and electrophysiological measures of electrode discrimination takes to stabilize.

While the absence of a spatial ACC response indicates the presence of channel interactions either in peripheral or central auditory system, the presence of a spatial ACC response must be interpreted with caution. The ability to discriminate electrodes accurately does not necessarily imply a healthy electrode-neural interface. Indeed, it is expected that electrode discrimination may be accurate despite the presence of a neural dead region or cross turn stimulation. Nonetheless, electrode discrimination is considered to be a useful measure, as it is frequently impaired and has been correlated with speech perception in a number of studies. In poor performers, it offers a simple first line assessment. However, additional evaluation of the electrode neural interface, for example with focused threshold measurements or high resolution imaging, may also be useful in these cases (Bierer, 2010; Long et al., 2014; Noble et al., 2014).

Improving the clinical applicability of spatial ACC measurements was considered in this thesis. An important aspect of this is reducing recording and setup time. Further experiments are required to determine the stimulus characteristics that enable the most efficient recording of spatial ACC responses. If the recording paradigm could be made more efficient, the spatial ACC could be measured for a greater number of electrode pairs. Due to time constraints, the spatial ACC was measured only for adjacent electrode pairs at the apical end of the electrode array. Previous studies have shown that electrode discrimination in the low and mid frequencies is correlated with speech perception (Henry et al., 2000). It would therefore be beneficial to assess the spatial ACC for a greater number of electrode pairs and this would be facilitated by a more efficient recording paradigm.

In this experiment, a single electrode pair was tested in each EEG recording block. It is known that repeated presentation of an auditory stimulus is associated with a decrease in the size of the cortical response (Näätänen and Picton, 1987). One way of overcoming this, whilst measuring the spatial ACC for multiple electrode pairs, would be to use a multi-stimulus recording paradigm. This would involve measuring the ACC for multiple electrode pairs, presented in random order during a single recording block. This type of multi-stimulus paradigm is a highly efficient method for measuring the MMN (Näätänen et al., 2004) and ACC (Iverson et al., 2013). The predictability of the stimuli could be further reduced by randomly varying the stimulus duration. The presence or absence of the spatial ACC was determined objectively with the Hotelling-

T2 test in a defined response window. However, in certain cases, usually due to a very late P2 peak, the response window had to be adjusted. In order, to avoid this type of manual adjustment, an algorithm for determining the response window based on the peak latency and amplitude could be developed.

The dynamic nature of speech means that it will result in multiple transitions of simultaneously active electrodes on the CI array. In contrast, during spatial ACC measurements, electrodes are stimulated in isolation sequentially. The spatial ACC therefore, may not provide a realistic measure of channel interactions. In order to simulate the greater level of across channel interactions that are expected to occur in speech, the paradigm for recording the spatial ACC (as well as behavioural electrode discrimination), could be modified to include continuous suprathreshold stimulation from flanking electrodes. This is illustrated in figure 7.2. In the standard paradigm, discrimination may be possible due to differences in the edge of the excitation fields of the reference and test electrodes. By using flanking electrodes, ‘edge effects’ are likely to be less prominent. The use of such a modified paradigm may provide a more functional measure of channel interactions with a stronger relationship to speech perception.

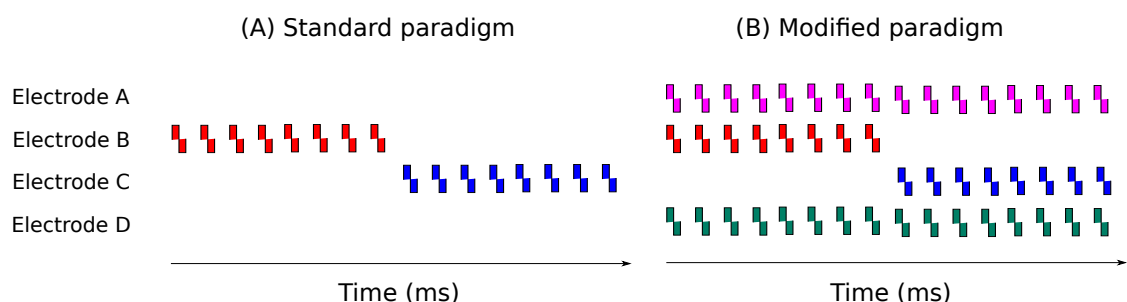


Figure 7.2 Standard and modified paradigms for spatial ACC measurements. In the standard paradigm (A), the ACC is recorded to transitions between the reference and test electrodes which are presented in isolation. In the modified paradigm (B), there is additional continuous suprathreshold stimulation from flanking electrodes.

The use of the CI as an EEG recording device, is further development which may help to improve the clinical applicability of CAEP measurements including the spatial ACC. With this technique, the CI is used to deliver stimuli as well as record cortical responses. This avoids the need to connect external EEG recording electrodes. Whilst the use of the CI to record the ECAP is well established, measurements of longer latency auditory responses have been limited by the short recording window of only a



few milliseconds that the CI device allows. Mc Laughlin et al. (2012), showed that it is possible to use the extra-cochlear electrode in the Cochlear device to record CAEPs. Although the recording window was limited to 1.6 ms, the CAEP was measured by sampling the response to the auditory stimulus every 10 ms at latencies between 10 to 300 ms after stimulus delivery. Although this 'closed loop' technique was extremely time consuming, it was found that the responses obtained were similar to that with a conventional external EEG recording system. Campbell et al. 2012, showed that in the Cochlear device, it was possible to extend the recording window to 10 ms, in order to measure the cochlear microphonic response. Future developments in CI hardware and software may make the use of 'closed-loop' CAEP measurements more practical. If this type of system could be developed, then CAEP measurements could even be performed remotely. This would help to save clinical time and a wealth of information regarding individual auditory processing could be obtained and used to inform clinical management.

#### 7.4 Cochlear implantation – current landscape and future priorities

It is estimated that only 5% of adults who are eligible for CI actually undergo implantation ("The Ear Foundation," 2016). Part of the reason for this is lack of awareness among health professionals about candidacy. Recent work has revealed that following education of community audiologists, there was a 3-fold increase in the CI referral rate (Raine et al., 2016). The UK has relatively stringent criteria for CI candidacy compared to other countries (Vickers et al., 2016). For example, adults must have profound bilateral hearing loss with thresholds worse than 90 dB HL at frequencies  $\geq 2$  kHz. This compared to criteria of bilateral severe hearing loss with thresholds  $\geq 75$  dB HL at frequencies  $\geq 2$  kHz in Australia. It is recognized that many people who are just outside the current UK candidacy criteria would benefit from implantation. Much work is now going on at a national level to relax the candidacy criteria. With greater education of referring clinicians and a change in the candidacy criteria there is potential for a huge increase in the number of CI surgeries over the next few years.

The potential increase in the number of individuals undergoing implantation means that implant programmes will have to expand or new implant programmes will need to

be setup. In addition, the model of care may need to be changed so that more care is provided remotely and is directed by patients themselves (Cullington et al., 2018; Wesarg et al., 2010). As highlighted in the introduction, there is significant variability in CI outcomes and a significant proportion of patients have poor outcomes (Niparko et al., 2010; Wilson and Dorman, 2008). It will therefore become increasingly important to identify and address the factors that are associated with poor hearing outcomes after CI.

Future research must also focus on individualizing patient care. One of the great challenges with cochlear implant research is the heterogeneity of the study population. Patients have different aetiologies, duration of hearing loss, cochlear anatomy and patterns of neural survival. In order for CI users to gain maximum benefit from their implant, individualized device selection, surgery and fitting would seem appropriate. For example, it is possible to individualize the length of cochlear implant electrodes (Mistrík and Jolly, 2016) and insertion technique (Rau et al., 2015) based on pre-operative imaging. Fitting of the implant can be individualized using a combination of imaging, behavioural and electrophysiological measurements including the ACC (Cosentino et al., 2016; Mathew et al., 2017; Noble et al., 2014). This can provide information such as scalar translocation of electrodes, presence of neural dead regions, and higher auditory processing problems. There is growing evidence that auditory deprivation, particularly in early childhood affects not only hearing and language but cognitive function (Kral et al., 2016). Therefore, it has been suggested that auditory rehabilitation could be aided by individualized assessment and treatment of neuro-cognitive deficits.

These types of individualized assessments are likely to be time consuming and may prove to be impractical in the clinical setting. Therefore, it will be necessary to develop a battery of tests and rehabilitation measures which the patient can administer themselves using technology. This is certainly in line with the NHS Five Year Forward View (“NHS England, Harnessing technology and innovation,” 2018) of harnessing technology and innovation to help better their own health. It will also be necessary to determine which assessments and interventions provide the most benefit. The heterogeneity of the CI patients often makes generalizing the findings of small scale studies difficult. Research grants should therefore be geared towards large scale multi-

centre studies. This will require close collaboration between clinicians, scientists and industry. This type of model has been adopted in centres such as the Hearing Hub, Sydney and the Cluster of Excellence Hearing4All, Hannover. In addition, the development of national/international registries of CI patients could help to provide useful epidemiological and outcome data. These types of strategies could enable the provision of truly tailored patient care and allow individuals to gain maximum benefit from their device.

## 7.5 Conclusion

Electrophysiological measurements in CI users allow the objective assessment of how sound is encoded in the auditory pathway. In this thesis, it was shown that the spatial ACC is a feasible and valid measure of electrode discrimination. These measurements can provide information over and above behavioural testing. Furthermore, they provide evidence of plasticity in adult CI users. These types of objective measures could provide prognostic information and help to guide interventions that lead to improved hearing outcome. The widespread use of cortical response measurements in clinical practice could represent the next major development in the field of auditory implants and this area of research holds much promise.

## Appendix A: Test-retest reliability of the ACC

Previous studies have shown that the ACC has good test-retest reliability in both normal hearing and CI users (Friesen and Tremblay, 2006; He et al., 2014). This section consists of a retrospective analysis of test-retest reliability using the methodology of this study. This data was collected during the pilot and experimental phase of experiments 3, 4 and 5 (Chapters 4 to 6). Only data that was collected with the same stimulation parameters was included in the analysis. Since test-retest data was usually several months apart, only data collected at least 6 months post CI switch-on was included in the analysis, as it is likely that plasticity is most pronounced in the early period after activation. Test-retest data was available for electrode pair 4-5 in 7 participants with AB devices (see table A.1). Testing was performed at the loudness balanced MC level. The median time between collection of test-retest data was 3 months (range 2 - 4 months). Test procedures and EEG analysis was performed as described in the General Methods (Chapter 2).

Table A.1. Details of participants with test-retest data.

Participant	Test data: time after switch-on (months)	Re-test data: time after switch-on (months)
P1	82	85
S3	6	8
S4	14	18
S5	6	9
S8	6	10
S9	8	10
S11	6	9

Figure A.1 shows the grand mean response across participants of the test and retest data while figure A.2 shows the individual data. Visual inspection of the waveforms shows good correspondence between the test-retest data. Furthermore, Pearson's correlation coefficient revealed a strong relationship between the grand mean data ( $r = 0.956$  (95% confidence interval 0.952 – 0.960),  $p < 0.001$ ) and individual data ( $r = 0.823$  to  $0.943$ ,  $p < 0.001$ ). The peak-to-peak N1-P2 amplitude of the onset response and spatial ACC for the test and retest data are shown in table A.2. Wilcoxon's signed

ranks test revealed no significant difference in the peak amplitude of the test-retest data for the onset response ( $V = 10$ ,  $p = 0.58$ ) or the ACC ( $V = 17$ ,  $p = 0.69$ ). The agreement between the peak amplitude of the test-retest data was assessed with the intraclass correlation coefficient (ICC). This showed strong agreement for the onset response (ICC = 0.78,  $F(6,7) = 8.44$ ,  $p = 0.006$ ) and the ACC (ICC = 0.84,  $F(6,7) = 11.7$ ,  $p = 0.002$ ).

In conclusion, these data show that spatial ACC measurements in CI users have excellent test-retest reliability.

Table A.2 Amplitudes of N1-P2 response for the onset and ACC response in the test and retest condition.

Participant	Onset response N1-P2 amplitude ( $\mu\text{V}$ )		ACC response N1-P2 amplitude ( $\mu\text{V}$ )	
	Test	Retest	Test	Retest
P1	9.43	9.00	3.56	3.28
S3	8.60	6.64	4.42	3.56
S4	6.07	6.18	2.86	2.74
S5	5.65	7.71	1.73	2.48
S8	7.92	7.39	2.61	2.83
S9	10.10	10.35	4.15	4.70
S11	10.44	9.87	1.41	2.12

Grand mean waveforms,  $r = 0.956$  (0.952 - 0.960),  $p < 0.001$

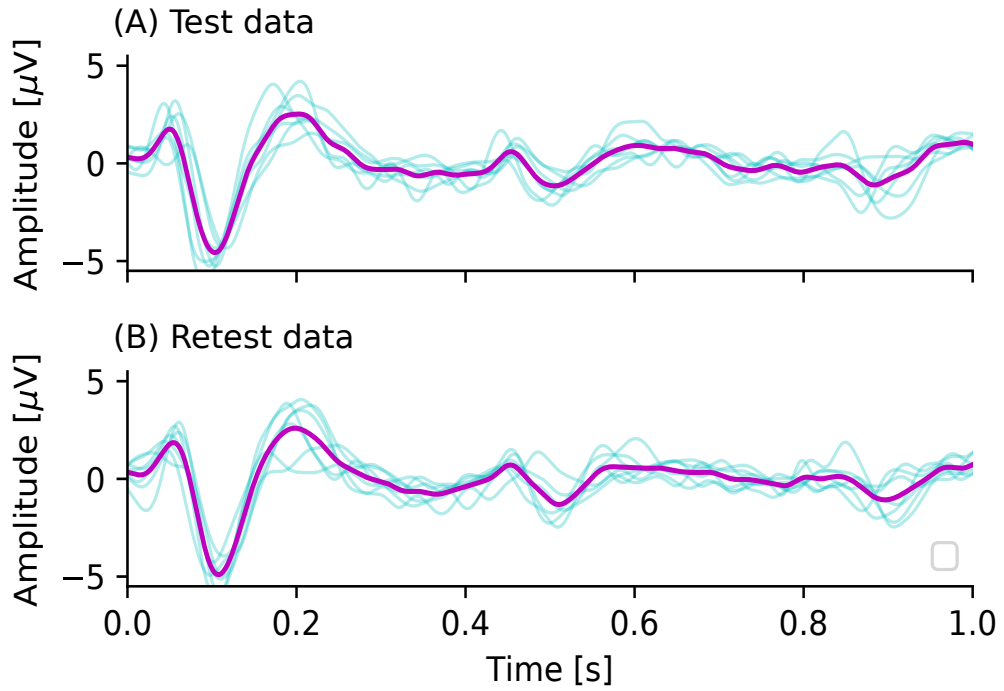
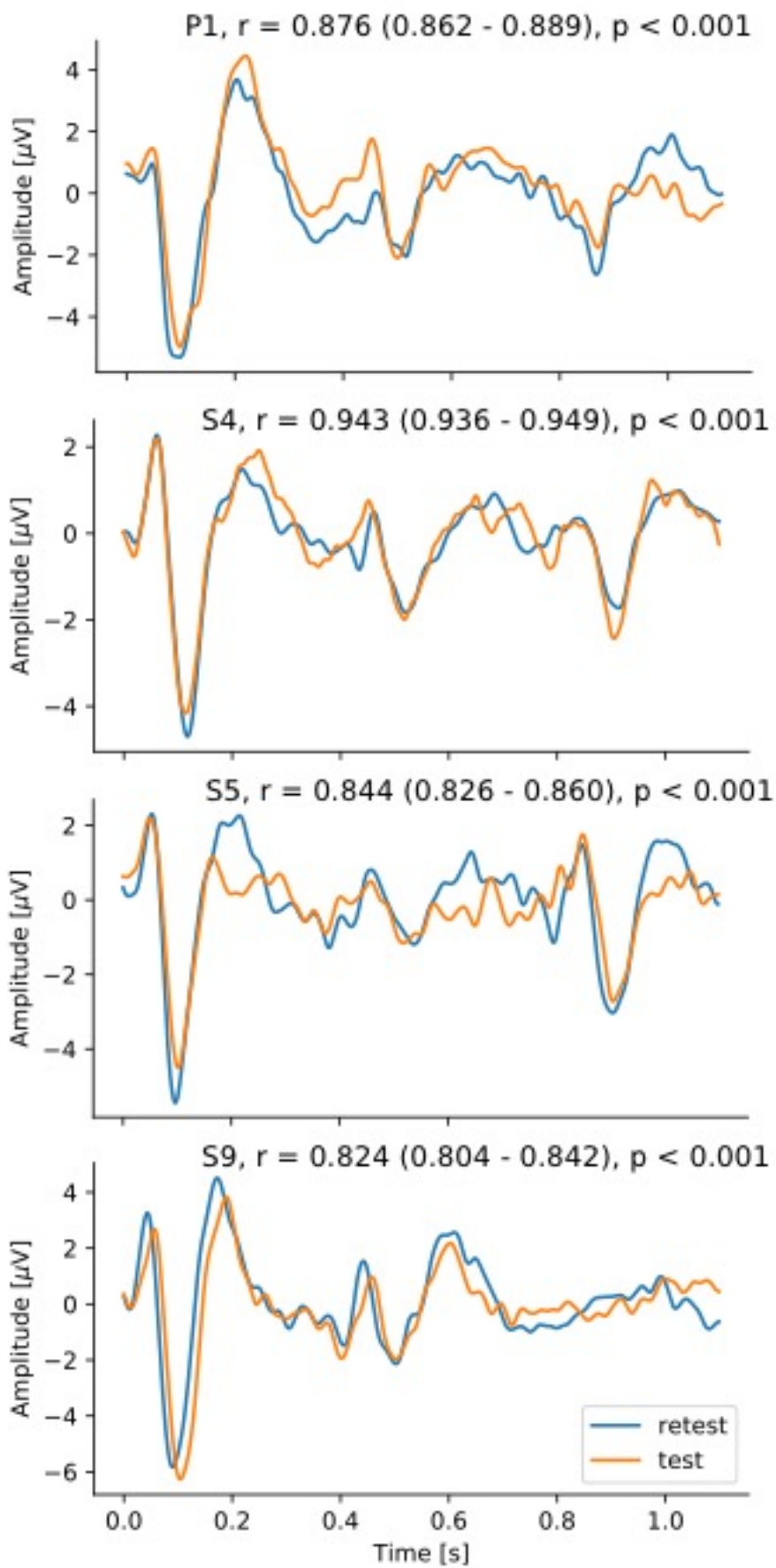


Figure A.1 Auditory evoked cortical responses for (A) test and (B) retest data. The thick purple line shows the grand mean data across participants and the thin blue lines are the individual data. The Pearson's correlation coefficient, 95% confidence intervals and p-value are shown at the top of the panel.



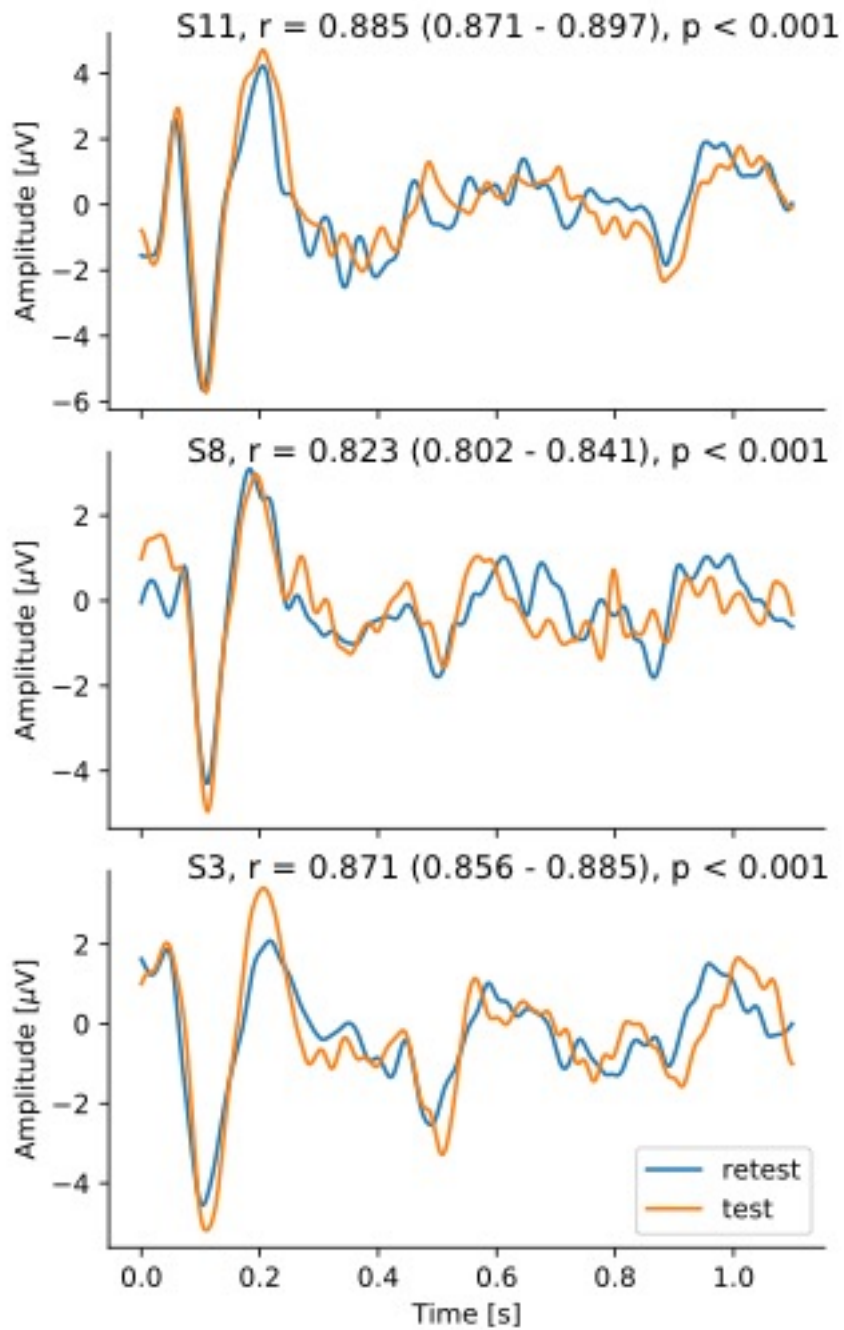


Figure A.2 Individual auditory evoked cortical response test-retest data. The participant ID, Pearson's correlation coefficient, 95% confidence intervals and p-value are shown at the top of each panel.



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