UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS INSTITUTE OF SOUND AND VIBRATION RESEARCH

BY

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ABSTRACT

FACULTY OF FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS
INSTITUTE OF SOUND AND VIBRATION RESEARCH

Doctor of Clinical Practice

Neural refractory properties and behavioural measures of temporal resolution and speech perception in cochlear implant users.

by Sharmila Patel

Temporal processing is of increased importance in cochlear implant users due to the degraded spectral information provided by cochlear implant devices in comparison to what is heard by normal hearing individuals. Studies have shown that speech perception through a cochlear implant is limited when the transmission of temporal information is impeded and there is considerable individual variability in performance. The health of the underlying neural population is thought to be a key predictor of temporal processing efficiency and speech perception outcomes. The central aim of the work reported here was to attempt to delineate the relative contribution of peripheral and central temporal processing on speech perception. This was achieved by comparing objectively measured temporal properties of the auditory nerve with behavioral measures of temporal processing, and analysis was completed to determine if these measures predicted speech perception in cochlear implant users.

An experiment was conducted with 18 unilaterally implanted adults who were stratified by deafness onset, which was used an indicator for neural survival and by stimulation rate. The electrically evoked compound action potential (eCAP) recovery function was used as an objective measure of recovery from refractoriness and the Random Gap Detection Test (RGDT) was used as a behavioral measure of temporal processing. Arthur Boothroyd (AB) word phoneme scores were measured for each subject across a range of presentation levels. The results of this study showed the eCAP recovery function was not affected by deafness onset and stimulation rate and was not a predictor speech performance; but RGDT thresholds were strongly correlated with deafness onset and stimulation rate, and were a very strong predictor of speech performance in the same individuals across presentation level.

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Academic Thesis: Declaration of Authorship

I, Sharmila Patel, declare that the thesis entitled “Neural refractory properties and behavioural measures of temporal resolution and speech perception in cochlear implant users” and the work presented in it are my own has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
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5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. None of this work has been published before submission

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Date: 23/10/2020 .....

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List of Abbreviations

ACE - Advanced Combination Encoder

ADRO - Automatic Dynamic Range Optimisation

AGC- Automatic gain control

AM - Amplitude modulation

AN - Auditory neuron

ANF - Auditory nerve fibre

ANOVA- Analysis of variance

ARP - Absolute Refractory Period

AZBio - Arizona Biomedical Sentence Recognition Test

BKB - Bamford-Kowal-Bench

BKB-SIN - Bamford-Kowal-Bench Speech-in-Noise Test

BM - Basilar membrane

BP - Bipolar

C- level - Comfort level

CF- Characteristic frequency

CI - Cochlear implant

CIS - Continuous interleaved sampling

CN - Cochlear Nucleus

CNC - Consonant-Nucleus-Consonant

dB - Decibel

DR - Dynamic range

eCAP - Electrically evoked action potential

GDT - Gap Detection Threshold

FFT - Fast Fourier transform

HI - Hearing impaired

HL - Hearing level

Hz - Hertz

IC - Inferior colliculus

IDR - Input dynamic range

IHC - Inner Hair Cell

HSRF - High spontaneous rate fibres

K+ - Potassium

LL - Lateral lemniscus

LLC - Lateral lemniscus complex

LSRF - Low spontaneous rate fibres

MAP - Measurable Auditory Percept

MCL - Most Comfortable Loudness

MDT - Modulation detection threshold

MP - Monopolar

MPI - Masker Probe Interval

Na+ - Sodium

NH - Normal hearing

NICE - National Institute for Clinical Excellence

n-*of*-m - number-of-maxima

OC - Organ of Corti

OHC- Outer Hair Cell

pps/ch - Pulses per second per channel

RF - Radio Frequency

RGDT - Randomised Gap Detection Test

RGDT-EXP - Expanded Randomized Gap Detection Test

RM - Reissner's Membrane

RRF - Refractory Recovery Function

RRP - Refractory Recovery Period

SD - Standard deviation

SGC - Spiral Ganglion Cell

SGN - Spiral Ganglion Neuron

SM - Scala media

SNR - Signal-to-noise ratio

SOC - Superior olivary complex

SPEAK - Spectral Peak

SPL - Sound pressure level

SR - Spontaneous discharge rate

SRT - Speech reception threshold

ST - Scala tympani

SV - Scala vestibuli

T-level - Threshold level

TM - Tectorial membrane

TMTF - Temporal modulation transfer function

VCV- vowel-consonant-vowel

Chapter 1: Introduction

Cochlear Implants (CIs) are hugely successful in restoring hearing for people with severe to profound hearing loss however, there is significant individual variability in speech recognition performance among CI users. For example, the median recognition of disyllabic words is 70% 1-year post implantation with a range 0-100% (Lazard et al., 2010). This variability is observed in both post-lingually deaf adults and congenitally deaf children (Lee et al., 2005). The proportion of recipients with word recognition scores less than 10% is approximately 10% (Bodmer et al., 2007). This marked variance has not been fully explained and researchers have suggested that patient related factors such age, deafness onset and cognitive function are likely contributors (Blamey et al., 1996; Holden et al., 2013; Lazard et al., 2012; Kaandorp et al., 2017; James et al., 2019). Furthermore, peripheral predictors such as the health of the underlying neural population (Nadol et al., 2016); and the duration of auditory deprivation which impacts both the peripheral and central auditory systems (O'Donoghue et al., 2000) may account for some of the variance in speech recognition. Other factors that may influence speech recognition outcomes are device related, such as the electrode array position, insertion depth and the number of active channels (Skinner et al., 2002; Yukawa et al., 2004; Finley et al., 2008; Lazard et al., 2012; Esquia Medina et al., 2013; Holden et al., 2013; James et al., 2019). It is therefore reasonable to assume that CI users who have the fewest limiting factors are likely to achieve the highest speech recognition scores (Holden et al., 2013).

Blamey et al. (1996) examined data from 808 CI recipients retrospectively and found that duration of deafness had a strong significant negative effect on speech perception. The data was obtained from several different centres which created some limitations as different programming methods, speech recognition tests and rehabilitation techniques were used across centres. More recent studies also support the findings in the Blamey et al., (1996); Rubinstein et al., (1999) found a strong negative correlation between duration of deafness and post-operative monosyllabic word recognition. Green et al. (2007) reported duration of deafness to be an independent predictor of performance, accounting for 9% of the variability in a retrospective study examining 117 post-lingually deaf patients implanted between 1988 and 2002. Leung et al., (2005) examined a large group of CI recipients who were divided into a younger group (<65 years of age, n = 491) and an older group (≥65 years of age, n = 258); and found monosyllabic word scores significantly declined with longer duration of deafness.

Holden et al., (2013) conducted a study with 114 post-lingually deaf adults from a single centre; to identify sources of variability in CI outcomes by evaluating monosyllabic word recognition scores at numerous test intervals over a 2-year period post device activation. Participants were divided into six outcome groups based on the percentile ranking of their final word score. Figure 1 shows each participant's final word score in rank order from lowest to highest, along with the outcome groupings and demonstrates the high levels of inherent variability in CI performance between individual subjects. Overall the study found that the higher performing outcome groups consisted of subjects who had a shorter duration of severe to profound deafness, as shown in figure 2.

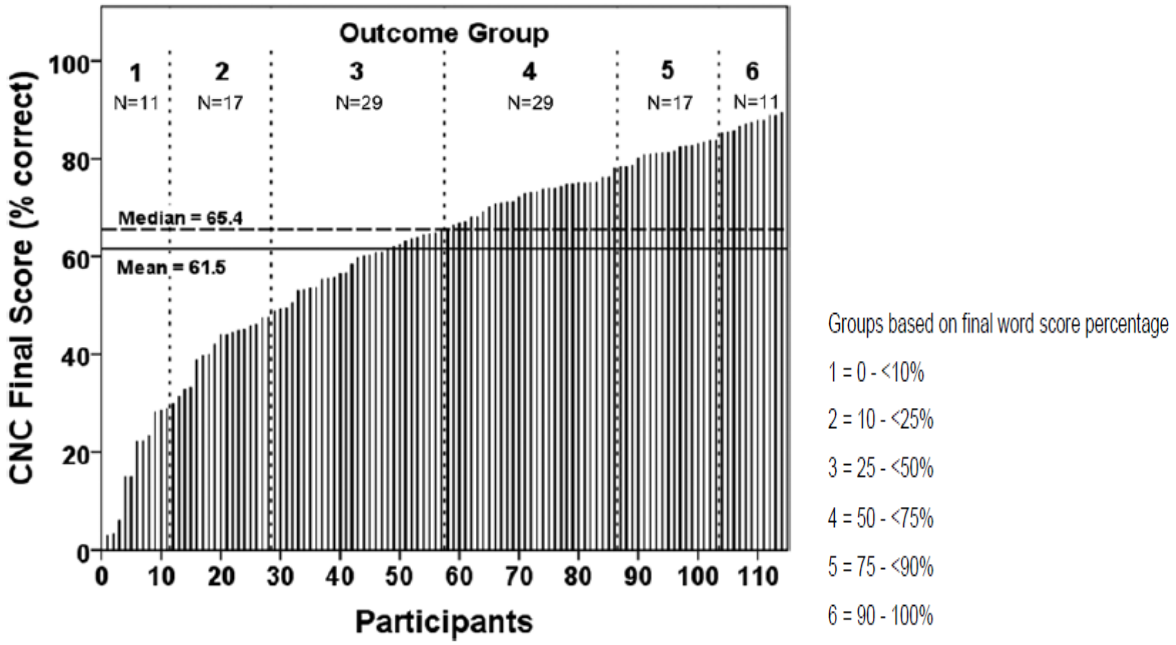

Figure 1: Final word score for each participant ranked in order from lowest to highest score and each participants corresponding outcome group. From Holden et al., (2013). Reproduced with permission, copyright Lippincott Williams & Wilkins.

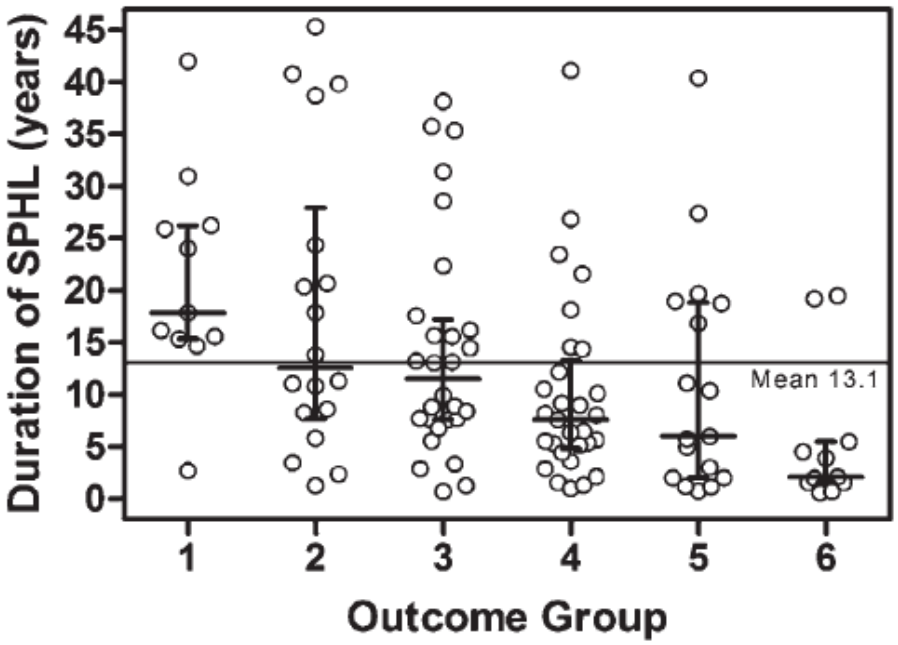

Figure 2: Scatterplot of duration of severe to profound hearing loss in relation to the six outcome groups. Group 1 (poorest performers) and group 6 (highest performers). From Holden et al., (2013). Reproduced with permission, copyright Lippincott Williams & Wilkins.

The perception of complex signals such as speech involve the processing of both spectral and temporal information (Rosen, 1992; Shannon et al., 1995; Moore, 2008). The most successful CI users are unable to discriminate speech as well as normal hearing (NH) listeners, especially in adverse listening conditions (Bhargava et al., 2016). This may be because CI speech processing signals do not replicate the sophisticated nonlinear mechanisms involved in the normal peripheral auditory system; therefore, the auditory information delivered by a CI remains coarse and CI users receive impoverished and degraded spectral information about the speech signal when compared to NH listeners (Cohen et al., 2003; Loizou, 1999; Zeng et al., 2004), consequently temporal information plays a critically important role in CI users. Psychophysical studies have found that the large variability in speech perception in CI users is significantly related to the individual differences in temporal processing abilities (Looi et al., 2008; Cazals et al., 1991, 1994; Muchnik et al., 1994; Busby and Clark 1999; Fu et al., 2002). This work examines how peripheral factors of variability (degree of neural survival) that are associated with the duration of auditory deprivation (which influences how central auditory pathways are reorganised) differ between pre- and post-lingually deafened adult CI users. This study investigates how objectively measured temporal properties of the auditory nerve relate to behaviourally measured temporal processing and speech perception. As these measures are underutilised in CI users they may help us better understand if a significant

neural-behavioural relationship exists that can account for the individual differences and variability in speech recognition following cochlear implantation.

Some studies have investigated the speech perception abilities in NH listeners under acoustic conditions that are sufficiently degraded to produce average performance comparable to that observed in CI users. O'Niell et al., (2019) examined the contribution of perceptual and cognitive factors for speech perception in NH listeners and CI users, in order to identify how much more variable speech perception is between CI users than between NH listeners, under similarly degraded conditions. 30 CI users were tested on word intelligibility in sentences with and without semantic context, presented in quiet and in noise. Performance was compared with measures of spectral ripple detection and discrimination, thought to reflect peripheral processing, as well as with cognitive measures of working memory and non-verbal intelligence. 30 age matched and 30 younger NH adults were also included in the study and were presented with materials via a tone excited vocoder, that was adjusted to simulate the effects of loss of spectral resolution and to produce performance for speech perception in noise that was comparable to that found for the CI users. Results showed that CI users performed more poorly on sentences lacking semantic context than either NH group, suggesting CI users rely more heavily on contextual cues to assist with speech understanding similar to the findings of Dingemanse and Goedegebure, (2019) who showed that CI users made more use of contextual information in recognition of words and sentences than NH listeners. The between subject variance was greater for CI users than for either group of NH listeners in speech perception for speech stimuli both with and without context. A strong correlation was found between the speech measures and the measures of spectral resolution in CI users, similar to other studies (Henry et al., 2005; Holden et al., 2016; Jeon et al., 2015; Won et al., 2011; Zhou, 2017), which suggest that the measures of spectral resolution capture more than just peripheral contributions to speech perception. The average performance for CI users was also poorer than both NH groups on measures of both working memory and non-verbal intelligence, which indicates that central factors such as cognition may influence speech understanding and could explain some of the individual differences in CI users.

It is important to consider physiological differences between the normal functioning and impaired auditory system and how these might influence speech recognition. The inner hair cell (IHC) and auditory nerve fibre (ANF) synapse is the primary conduit through which auditory information is transmitted to the auditory nervous system. In the normal ear, 95% of ANFs make synaptic connection only with IHCs (Spoendlin, 1972). Each ANF has a cell body in the spiral ganglion neuron with a peripheral axon that contacts acoustic receptors in the

organ of Corti, with a terminal bouton that forms a synapse with the IHC. The central processes collect together to form the auditory nerve that projects into the brain. In a healthy ear, movement of the stereocilia of IHCs leads to streams of neural impulses in ANFs. This electrical activity has patterns with temporal and spectral characteristics that essentially enable identification and interpretation of speech at higher neural levels (Moore, 2013). Temporal information is carried through the precise timing of neural impulses both within and between nerve fibres, whereas spectral information is represented in the spatial distribution of activity across the neural population (Wouters et al., 2015).

The auditory system uses temporal cues, such as the duration of speech segments and the duration of silent intervals between speech segments, to differentiate various speech sounds (Dorman et al, 1985). In NH subjects, precise perception of spectral and temporal patterns facilitates accurate speech intelligibility, which is dependent on the integrity of neural mechanisms in the auditory periphery and central system (Bregman, 1990; Shannon et al., 1995; Elhilali et al., 2003; Woolley et al., 2005). These processes are compromised in subjects with sensorineural hearing loss (SNHL), which is caused by damage to the inner hair cells (IHCs) of the cochlea; this consequently reduces speech discrimination in these individuals as there are fewer functional channels available to convey auditory information in comparison to NH listeners (Kim et al., 2010; Kirby and Middlebrooks, 2010, 2012; Garadat et al., 2012, 2013; Long et al., 2014).

Spiral ganglion neurons (SGNs) receive synaptic input from IHCs which are responsible for the mechano-electrical transduction of sound; the conversion of mechanical vibrations into action potentials, and provide the sole route to convey speech information from the auditory periphery to the auditory cortex (Myer et al., 2009) (Figure 3). Each human cochlea contains ~15,000 IHCs and ~40,000 auditory nerve fibres (ANFs) and once destroyed, neither of these structures regenerate (Harrison and Howe 1974; Fujioka et al., 2015). SGNs therefore play a crucial role by serving as the initial point at which afferent action potentials are encoded (Boulet et al., 2016). Extensive dysfunction and loss of IHCs following SNHL has been shown to lead to degeneration of the peripheral portion of the SGNs, (Figure 4) (Miura et al., 2002; Nadol et al., 1989; Zimmermann et al.,1995), which decreases the ability of the auditory nerve to transmit spectral and temporal information with high fidelity (Hartmann et al., 1989), and subsequently to significant changes in the central auditory pathways (Webster and Webster, 1977; Kitzes and Semple, 1985; Kral et al., 2005). As it is not possible to directly quantify the

surviving IHCs and SGNs in humans it is difficult to predict how neural degeneration contributes to individual difficulties in speech understanding.

A CI is a neural prosthesis that electrically stimulates the residual SGNs in subjects with severe-profound SNHL. Its efficacy is therefore primarily dependent on the severity of SGN loss as fewer neurons being available for stimulation limits the efficiency of information transmission through a CI system. Neural representations of speech have two vital features, temporal code which is reliant on the SGNs firing in phase with the incoming speech signal, and place code which is tonotopic and determines the perception of pitch depending on the site of stimulation on the basilar membrane (BM) (Robles and Ruggero, 2001). Pitch perception with CIs is poor due to the spread of electrical current in the cochlea which prevents excitation of discrete SGNs and reduces the fine frequency discrimination abilities in CI users. This results in sparser spectral cues being available, making CI users more reliant on temporal information (Xu et al., 2005; Sagi et al., 2009), hence, temporal resolution is of substantial importance in electrical hearing. Temporal resolution plays a critical role in speech comprehension because speech components contain a multitude of temporal cues and allows the identification of small variations that occur in the speech signal over time, which enables the perception of segmental, syllabic, phonetic and word distinctions in continuous speech (Rosen, 1992 and Rupp et al., 2002). We currently have an impoverished understanding of SGN excitability and temporal interactions in response to electrical stimulation and this thesis sheds light on the mechanisms underlying neural temporal processing in CI users and their effects on behavioural measures of temporal resolution and speech perception.

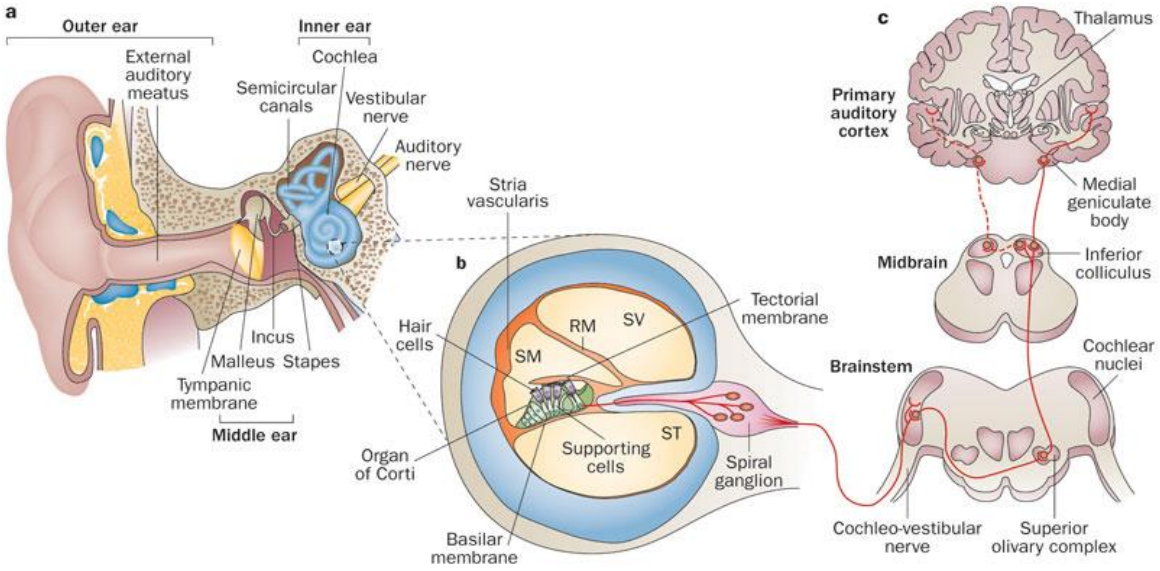

Figure 3: Processing of sound involves the peripheral and central auditory pathways: **a)** Sounds waves are picked up by the outer ear which causes the middle ear bones to vibrate **b)** this produces a traveling wave which causes deflection of IHC bundles in the organ of Corti and this action elicits neural discharge of ANs **c)** these impulses are transmitted to the ascending central auditory pathway. This is the bottom up process for speech perception

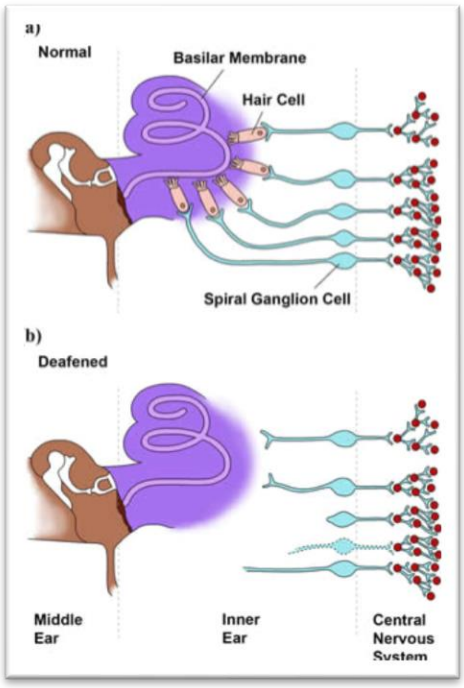

Figure 4: The normal functioning auditory pathway (a) compared to the impaired auditory pathway in profoundly deaf individuals

Although CIs are hugely successful in improving speech perception which is linked to broader outcomes in linguistic, social and educational functioning (Meyer et al., 2003); they do not provide equivalent benefit for all recipients and large individual differences and variability in speech recognition performance is routinely reported in the literature (Niparko et al., 2010; Pisoni et al., 1999); even when factors such as deafness onset, age at implantation, duration of deafness and neural health are taken into account (Pyman et al., 2000; McDermott, 2004; Stickney et al., 2004 and Blamey et al., 2013). The high variability in performance may partly arise due to individual differences in the ability of the central auditory system to adequately resolve and process electric stimuli (Kraus et al., 1993; Micco et al., 1995; Middlebrooks et al., 2005; Moore and Shannon, 2009). Other factors that may explain these differences are the natural variations in the anatomical height, width and length of individual cochlea by as much as 40% (Erixon et al., 2009) between subjects. The electrode array design and proximity of the electrode contact to the target neural region can also result in varied patterns of neuronal stimulation, furthermore differences in speech processing strategies for CIs, which determine the excitation patterns within the cochlea are likely to heavily influence speech recognition (Skinner et al., 1999; Loizou et al., 2000; James et al., 2003; Skinner 2003; Spahr and Dorman 2005; Holden et al., 2011; Van der Beek et al., 2015; Busby and Arora 2016).

In order to convey temporal information to the CI user, the neural discharge pattern in response to electrical stimulation must convey the temporal detail in the input signal. Most CI processors use a temporal code in which the envelopes of speech sounds are extracted and used to amplitude modulate interleaved trains of biphasic pulses. Thus, the ability of CI users to resolve temporal envelope information is crucial for overall speech recognition (Muchnik et al.,1994. Shannon et al., 1995 and Chatterjee and Shannon, 1998) and deficits in temporal resolution can result in reduced phoneme and word identification through the CI (Tyler et al, 1989; Cazals et al., 1991; Muchnik et al., 1994; Sagi et al., 2009). A fundamental property of SGNs that generate action potentials is refractoriness, the period in which SGNs are incapable of generating a subsequent action potential immediately following previous stimulation. Refractory properties are likely to heavily influence the temporal responsiveness of the auditory nerve to trains of pulses that are typical of CI stimulation (Wilson et al., 1997; Tejani et al., 2017). It is reasonable to assume that SGNs that recover from refractoriness more rapidly will be available to generate an action potential to the subsequent stimulus providing a more accurate representation of the temporal code which is vital for encoding speech envelope cues. Results of animal studies support this theory and show that the physiological status of the auditory nerve can influence neural refractoriness which influences how

sequences of electrical pulses presented by the CI are coded by the auditory nerve (Miller et al., 2001; Matsuoka et al., 2000).

It is not possible to directly measure the neural population in human subjects and one method to evaluate the variability in refractoriness in CI users is to objectively measure the electrically evoked compound action potential (eCAP) recovery function. The eCAP is a direct measurement of the summed neural responses generated by an ensemble of SGNs to electrical stimulation (Miller, Brown, Abbas and Chi, 2008) and can therefore be used to evaluate the physiological status (number of neurons recruited) of the peripheral auditory nerve; and the recovery time constants in the responding population of SGNs (Brown et al., 1990). Near field recording of eCAPs is possible using intra-cochlear electrodes utilising the reverse telemetry function implemented in Custom neural response telemetry (NRT) software for Nucleus devices. Neural refractory properties in CI users could provide information on the temporal precision differences in individuals and the functional implications of refractoriness in speech perception. The intent of this thesis is to characterise the effect of refractoriness in the peripheral auditory system and evaluate the eCAP as a location specific measure of the electrode-neuron interface and its likely contribution to temporal acuity and speech perception in CI users.

For the majority of adult CI users, hearing loss has occurred after a substantial period of NH, or following amplification which has allowed adequate auditory function prior to cochlear implantation. One of the strongest predictors of speech perception outcomes following implantation is whether hearing loss and implantation occurred before or after language was acquired (Dawson et al., 1992; Semenov et al., 2012; Zwolan et al., 1996). In post-lingually deaf adults we might expect better speech perception as it is reasonable to assume that in the absence of substantial auditory deprivation, the dysfunction and atrophy in SGNs is less significant in comparison to subjects who are born with severe-profound hearing loss and receive a CI in adulthood. Inadequate stimulation of the auditory system before cochlear implantation causes pathological changes in the cochlea and alters how the central auditory pathways develop (Shepherd and Hardie, 2001); which may impose additional temporal processing limitations in pre-lingually implanted CI users which restricts their speech performance outcomes (Ponton et al.,1996; Ponton and Eggermont, 2001). Hence, even if the auditory nerve was able to respond to electrical stimulation in an efficient manner, the central processing deficits and the ability to adapt to the novel neural stimulation in those with long term deafness may be different compared to those with short durations of deafness. Processing the coarse speech signals provided by a CI requires additional processing beyond

what is necessary for NH listeners and these demands may be greater in subjects with pre-lingual deafness. Thus, an aim of this study is to investigate how temporal processing effects speech perception in CI users based on the duration of auditory deprivation.

To delineate the central contribution to temporal processing from the peripheral influences in CI users, it is possible to measure gap detection thresholds (GDTs), which are commonly used to assess temporal resolution (Garadat and Pfingst, 2011; Lister et al., 2011). Temporal resolution can be defined as the ability of the auditory system to detect gaps between two consecutive sound stimuli which ensures they are detected as separate events. Normal temporal resolution is vital for speech perception which requires rapid separation of speech segments (Swaminathoan and Heinz, 2012; Picton, 2013) and abnormal GDTs prevent the phonological processing that allows consistent detection of the boundaries between speech sounds in variable phonetic contexts (Ben-Artzi et al., 2005). Normal GDTs are achieved when SGNs are able to synchronously recover from refractoriness of the initial stimuli and subsequently encode the start of the second stimuli within the time frame that the gap exists (Kirby and Middlebrooks, 2010). CI users may require longer gaps in between stimuli to be able to reliably and consistently detect separations between sounds as damage to the peripheral and central pathways may result in altered temporal discharge patterns, this is most likely due to the dys-synchronous response of the SGNs to the gap. There is currently a small body of evidence regarding temporal resolution abilities in CI users and our understanding of how this impacts the speech perception is limited. This thesis provides insight on how GDTs can be utilised as an index to the integrity of the central auditory system and as a predictor of speech perception.

A critical parameter of speech processing strategies is stimulation rate as it plays a vital role in transferring temporal cues from rapidly changing speech signals. In CI programming software this is controlled by the per channel stimulation rate, which refers to the number of pulses per second delivered from an electrode pair to the ANFs. There are currently a wide range of stimulation rates available in current CI systems, ranging from low rates 200 pulses per second to high rates 5000 pulses per second, which can be adjusted to optimise performance. Studies have shown that speech perception varies as a function of stimulation rate both within and across recipients (Brill et al., 1997; Friesen et al., 2005; Holden et al., 2002; Kiefer et al., 2000; Loizou et al., 2000; Vandali et al., 2000) and this could be due to individual differences in the temporal response properties of the auditory nerve and/or temporal processing abilities (Cazals et al., 1994; Fu, 2002).

Temporal properties of ANFs responses are substantially different when the fibres are stimulated electrically with a CI than with acoustic stimulation in the NH ear. In a healthy cochlea SGNs fire spontaneously in an independent and stochastic nature which results in neurons remaining in varying states of refractoriness (Rubinstein et al., 1994); and enables high rates of temporal coding in the auditory system to up 4kHz due to the summation of neural responses across the neural population. However, in the typically pathologic cochlea of CI recipients this ability is greatly reduced and SGNs stimulated electrically fire in a highly synchronous manner; as shown by Moxon (1971) who measured the discharges of 19 single ANFs in cats and found phase locking of ANFs prevents coding of high frequency temporal information and fine structure, therefore transmission of high frequency temporal information is likely compromised in CI users. This is supported by the findings of Liberman and Dodd (1984) who compared spontaneous activity in 24 single ANFs from pathological ears in cats and showed a significant decrease in the mean rates of spontaneous discharge in ANFs associated with the selective loss of the tallest row of stereocilia from the IHCs. Furthermore, Dynes and Delgutte (1991) completed systematic measurements of 140 single ANFs in 12 anaesthetised cats and found significant phase locking to electric stimuli above 1 kHz, suggesting that poor frequency discrimination in CI users above this frequency is not due to a lack of temporal information but may be due to the inability of the central processes to make effective use of the available phase locking information. It is important to note that the cats used in these animal studies had NH prior to insertion of the stimulation electrodes into the cochlea, in contrast, human CI users are likely to have longer durations of deafness prior to implantation so neural degeneration and discharge rates are likely to differ between animal and human subjects.

There is some evidence to support the theory that higher stimulation rates in CI users can induce stochastic firing of SGNs (Wilson et al., 1997; Rubsinstein et al., 1999), which would provide more detailed temporal sampling and could improve speech performance (Dawson et al., 2000; Dorman et al., 1997; Dorman et al., 2000; Loizou et al., 1999). It is important to note that there are no clear or consistent advantages reported for the use of high stimulation rates, and incomplete recovery of neural responsiveness between speech segments could potentially blur the neural code for speech onsets. Therefore, choosing an optimal stimulation rate requires a subjective process of trial and error which can be time consuming. In this study we examine the extent to which temporal neural response patterns, measured by eCAP recovery function, correlate to behavioural measures of temporal resolution and speech perception as a function of stimulation rate in CI users.

1.1 Overall contributions to knowledge

The overarching question which motivates this research is “To what extent does temporal processing influence speech performance in CI users?” The central aims of this study were to determine if there was a correlation between objective and behavioural measures of temporal processing and if these were predictive of speech perception. To the author’s knowledge no other study has attempted this.

The work described in this thesis contributes to the existing literature in several ways. Neither electrophysiological nor behavioural measures of temporal processing are included in standard clinical practice to evaluate speech perception in CI users. Therefore, the results of this work show that both can be employed reliably and consistently in a clinical setting. The findings of this work add to the knowledge base on methodology, demonstrating that eCAP recovery function measurements can be completed with relative ease and do not require any additional equipment. The results also highlight the potential clinical application of the Random Gap Detection Test (RGDT) as a strong predictor for speech performance. An additional contribution to methodology is the successful measurement of acoustic GDTs utilising circumaural headphones, a method which has had limited use as most clinical testing with CI users is completed in a soundfield environment. This study adds to the six studies which have previously investigated the correlation between recovery function and speech perception in humans. Similar to five of these studies we have found no significant correlation between recovery time constants and speech perception results (Fulmer et al., 2011; Lee et al., 2012; Gantz et al., 1994; Brown et al., 1990; Kiefer et al., 2001; Turner et al., 2002).

Furthermore, this work improves our understanding of temporal resolution abilities in CI users, and the factors such as deafness onset and stimulation rate which contribute to the individual differences in performance. This research revealed a very strong correlation between impaired temporal resolution and speech perception and supports the idea that temporal resolution abilities are likely to account for the large variation in speech performance between CI users. This study found overwhelming evidence that GDTs were predictive of speech performance across a range of scenarios, but eCAP based objective measurements were not. A paper based on the original work in this thesis is currently being prepared for publication.

1.2 Structure of this thesis

This thesis is concerned with investigating how the temporal properties of the auditory nerve impact temporal processing and speech perception outcomes in CI users. The present chapter has introduced the topic of the thesis and summarised its main aims and objectives.

Chapter 2 – Background: introduces the anatomy and physiology of the normal functioning ear and outlines how the temporal properties of the auditory nerve differ between the normal functioning and impaired auditory system.

Chapter 3 – Electrical Hearing in the Auditory System: details how electrical hearing with a CI works and provides a description of the different facets of signal processing and the perceptual effects of these parameters.

Chapter 4 – Objective and Behavioural Measures of Temporal Processing: Drawing on evidence from previous studies this chapter provides an overview of how objective and behavioural measures of temporal processing can be utilised to address gaps in knowledge.

Chapter 5– Methodology: describes the development and design of the experimental work

Chapter 6 – Results: This chapter reports results from the experimental work

Chapter 7 – Discussion: This chapter discusses the results of the experimental work and describes the limitations and advantages of this work when compared to previous studies, alongside recommendations for further work.

Chapter 8 – Conclusion: This chapter contains a general summary of the key findings from this experimental work.

Chapter 2: Background

This chapter focuses on the neural mechanisms of information transfer through the different levels of the normally functioning auditory system; beginning with the passage of mechanical impulses through the middle and inner ear, and continuing with non-linear mechanoelectric transduction within the organ of Corti, which gives rise to neural impulses in ANFs that are subsequently received by higher levels of the central auditory system. An outline of how changes to these physiological mechanisms following SNHL, lead to impairments in the auditory pathway as well as the limitations these impose to temporal processing are described. In CI users the cessation of afferent inputs to the auditory system following SNHL leads to a series of anatomical, physiological, and cognitive changes in both the peripheral and the central auditory pathways. These alterations are likely to contribute to the deterioration of speech performance with increasing duration of auditory deprivation.

2.1 The Cochlea

The cochlea is a bony structure embedded in the temporal bone, which spirals for two and a half turns and contains three fluid filled chambers, the scala vestibuli (SV), scala tympani (ST), and scala media (SM). The ST and SV are continuous with one another, via a foramen known as the helicotrema. Both these scalae contain perilymph fluid which has a composition that is rich in sodium (Na+) and poor in potassium (K+) concentration. The SM lies between these two chambers and is separated from the SV via Reissner's Membrane (RM) and from the ST via the Basilar Membrane (BM). The SM contains the organ of Corti (OC), which contains the receptor cells also known as hair cells (Pickles, 1988). The SM does not directly communicate with the other scalae and contains endolymph fluid which is rich in potassium (K+) and poor in sodium (Na+) concentration which makes the potential difference between the endolymph and the perilymph +80 mV (Pickles 1988). This endolymphatic potential appears to be due to the selective secretion and absorption of ions by the stria vascularis (Pickles, 1988). Damage to the stria vascularis results in loss of the endolymphatic potential and failure of mechanoelectrical transduction (Pauler et al.,1988).

The cochlea acts as a frequency filter that separates and analyses individual frequencies from complex sounds. These tuning properties result from anatomic and physiologic characteristics of sensory hair cells and the BM. Movement of the stapes at the oval window, causes it to move back and forth which results in a corresponding forward movement at the round window. This oscillation causes compression of the perilymph and this pressure variation causes

displacement of the BM, which generates a traveling wave along its length. Because motion of the BM reflects the frequency–intensity pattern of the sound initiating the wave, distinct populations of cochlear hair cells in the organ of Corti will be set in motion by different sound stimuli. The BM is tonotopically organised, from 20 Hz to 20,000 Hz (20 kHz), the base, which is nearest the oval window, is selective for high frequencies, whereas the apex, the end nearest the helicotrema, is selective for low frequencies. The differential displacement of the BM is the basis of frequency specificity in auditory function (Pickles, 1988). See figure 5.

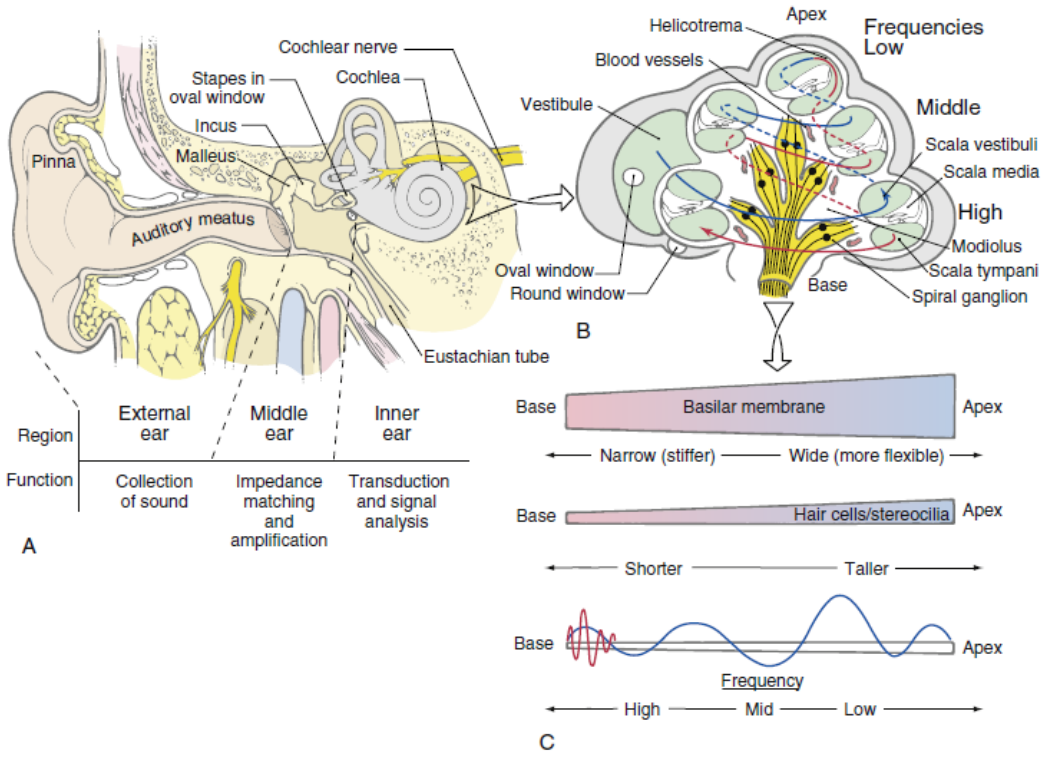

Figure 5: Displacement of the basilar membrane and frequency specificity. (A) The route of sound signals as it progresses from the external ear, through the middle ear into the inner ear. (B) A Cross section of the cochlea from apex to base. The blue and red lines represent the spiral course of the scala vestibule and scala tympani. (C) The basilar membrane separates sound waves into different frequencies. It is narrow and stiff at the base and becomes wider and more flexible towards the apex. The hair cell stereocilia also increase in height from base to apex and when excited produce an action potential. From Henkel (2018). Reproduced with permission, copyright Elsevier

Transduction, the conversion of mechanical energy to intracellular electrochemical events, occurs in the organ of Corti, which is the highly specialised sensory epithelium that rests on top of the BM (Hudspeth and Jacobs, 1979). It is composed of IHCs, outer hair cells (OHCs), supporting cells, and the tectorial membrane (TM). IHCs form a single row spiralling from base to apex, and the OHCs form three parallel rows that follow the same course. These cells are separated by the tunnel of Corti, which is formed by the filamentous arches of the inner and outer pillar cells and is filled with fluid similar to perilymph (Belyantseva et al., 2005). Each hair cell has a bundle of projections called stereocilia which are filled with a microfilament called actin and each stereocilium is connected by tip links that are graduated in height order, so that the longest stereocilia are on the outer border and in contact with or embedded in the TM which is the gelatinous arm that extends over the organ of Corti (Flock et al., 1981; Belyantseva et al., 2005). In humans, there are approximately 12 000 OHCs per cochlea and each OHC has approximately 140 stereocilia; in comparison there are approximately 3500 IHCs, each with approximately 40 stereocilia (Pickles, 1988). Stereocilia are surrounded by endolymph, whereas the remainder of the hair cell is surrounded by perilymph. See figure 6.

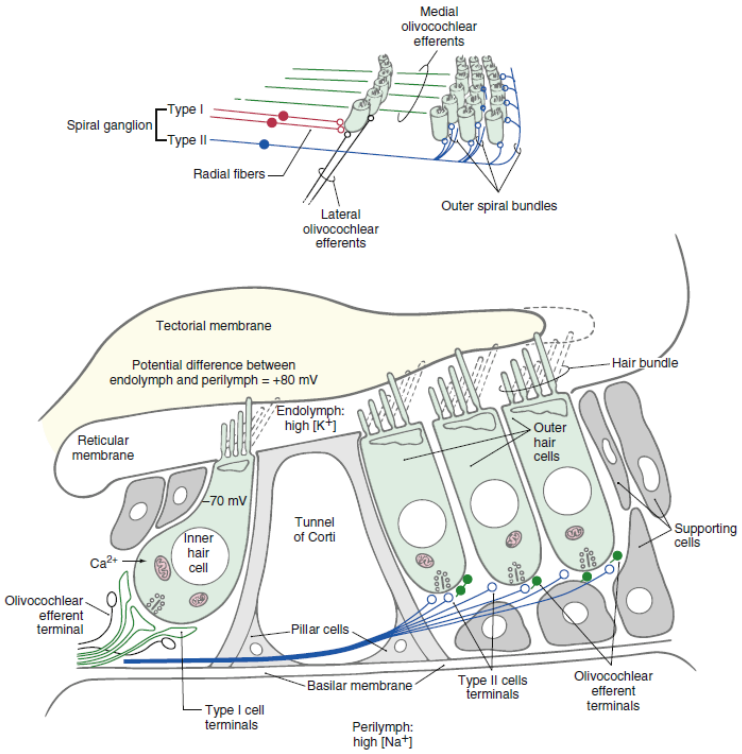

Figure 6: Structure of the organ of Corti and the relation of type I and type II afferent fibres to the spiralling ranks of inner and outer hair cells. From Henkel (2018). Reproduced with permission, copyright Elsevier

Movement of the BM causes a shearing motion between the TM and organ of Corti which causes the hair bundle to deflect (Pickles, 1988), this process results in a graded depolarisation of the hair cells due to the opening of ion gated channels at the tips of the stereocilia. Stretching of the tip links towards the tallest stereocilia open the membrane channels and results in cell depolarisation. The large potential difference between the endolymph and the hair cell interior creates a force of 150 mV that drives potassium ions into the cell and increases the range of the cell's graded electrical response to mechanical displacement (Hudspeth, 1989; Denk et al., 1995). Subsequently, when a hair cell depolarises, voltage gated calcium channels at the base of the cell open, and the resulting influx of calcium causes synaptic vesicles to fuse to the cell membrane which triggers the release a neurotransmitter at the glutamatergic synapses that causes specialised ion channels to open on the postsynaptic neuron cell membrane and initiates signal propagation to afferent neurons (Ottersen et al., 1998), see figure 4. Conversely when the hair cell deflects in the opposite direction, toward the short stereocilia, this contracts the tip link and closes the membrane channels, resulting in hyperpolarisation (Nadol, 1990). See figure 7 and 8.

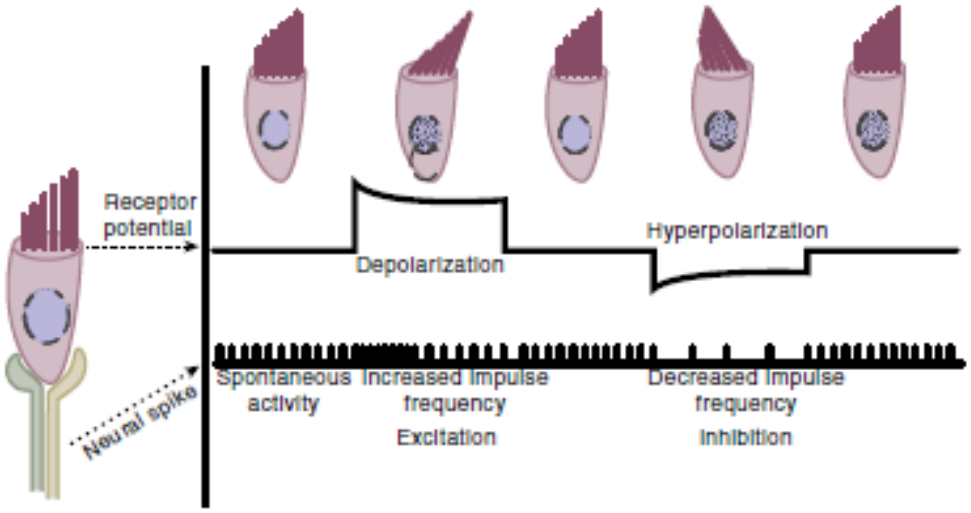

Figure 7: Illustration of hair cell stimulation, receptor potential and auditory nerve fiber discharge. The tip links tense during displacement toward the taller stereocilium, thus increasing the probability that the ion gated channel will open.

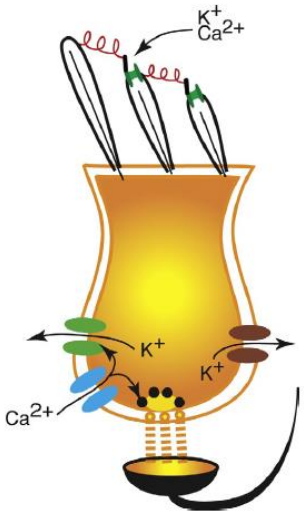

Figure 8: Illustration of how deflection of the hair bundle towards the tallest stereocilia causes potassium channels to open at the tip links, the influx of potassium ions causes the cell membrane to depolarise which results in and the influx of calcium ions. These fuse to the synaptic vesicles in the cell which triggers the release of the neurotransmitter glutamate into the synaptic cleft between the hair cell and SGN which causes a neural spike in the ANF.

2.2 The auditory nerve

The vestibulocochlear nerve (cranial nerve VIII) is derived from the embryonic placode. It emerges from the pontomedullary junction and exits the skull via the internal auditory meatus in the temporal bone. Inner and outer hair cells receive their primary afferent innervation from SGNs, these bipolar neurons send peripheral axons to the hair cells and their central axons form the main component of the cochlear nerve. There are two types of afferent neurons which separately stimulate the inner and outer hair cells and have distinctly different structures, vary in volume and innervation patterns (Spoendlin, 1985). The first type, Type I neurons send processes to contact the IHCs in a highly convergent manner, contacting a single cell that is innervated by approximately 20 afferent fibres (Spoendlin 1975; Kujawa and Liberman 2009; Meyer et al., 2009). Type 1 neurons make up 90-95% of the afferent population, are relatively large in diameter and myelinated; thus, their information reaches the brain quickly, within a few tenths of a millisecond (Matthews and Fuchs 2010). In contrast the second type, Type II neurons send processes to contact approximately 10 OHCs that are innervated by approximately 6 auditory fibres (Weisz et al., 2012 and Spoendlin 1975). Type II SGNs make up the remaining 5-10% of the afferent population, they are unipolar, smaller in diameter and unmyelinated, hence transmit neural information at a much slower rate. (Benson and Brown 2004). OHCs are therefore innervated only by a small minority of the afferent neurons which highlights the functional importance of the role of the IHCs and Type I neurons as the

predominate mechanism for neural transmission to the brain (Kiang et al., 1967; Sachs and Abbas, 1974; Sachs and Young, 1979; Young and Sachs, 1979; Young, 2008). Merchan-Perez and Liberman, 1996). See Figure 9.

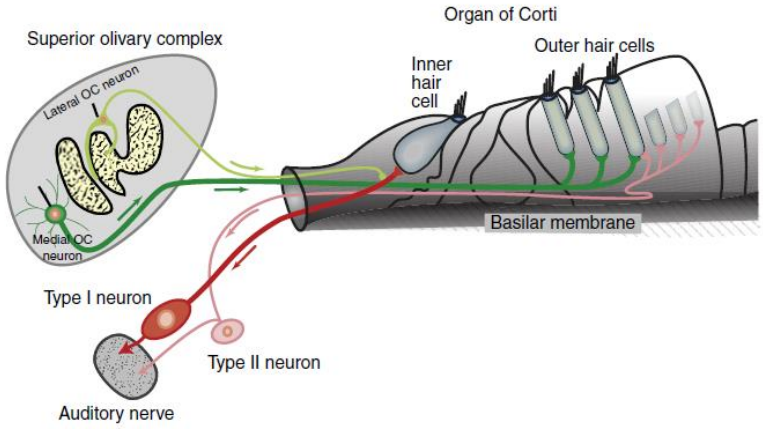

Figure 9: Innervation patterns of the afferent and efferent neurons in the organ of Corti. Afferent innervation is provided by the SGNs which have central axons that form the AN. There are two types of afferent neurons, Type I neurons which receive synapses from the IHCs and Type II neurons which receive synapses from the OHCs. Efferent innervation is provided by a subgroup of neurons in the superior olivery complex that send axons to the OHCs.

Frequency is coded in the auditory nerve based on the position of ANFs along the cochlear spiral. At high intensities, each fibre responds over a large range of frequencies but at the intensity drops the response range narrows and is therefore most sensitive at its characteristic frequency (Evans, 1975). The characteristic frequency (CF) is the frequency at which the fibre has the lowest spike threshold. ANFs are spontaneously active and discharge at rates that vary from 0 to more than 120 spikes per second. Sound levels must therefore exceed the ANFs threshold before they discharge above their spontaneous rate. As the intensity of a single tone increases so does the rate of firing for the ANF at that CF, the firing rate is the highest at the start of the stimulus and then adapts over tens of milliseconds. When the sound intensity rises beyond the saturation point the ANFs are unable to fire any faster as they are refractory (Evans, 1975). ANFs differ in spontaneous discharge rate (SR) and threshold to stimuli; Liberman (1978) demonstrated that there are three classes of afferent fibers in the auditory nerve of the cat. The classes were discovered by obtaining spontaneous rates and tuning curves from a large population of fibers (100-150 ANFs) which showed ANFs are bimodal with low SR fibres (< 18 spikes per second) associated with high absolute thresholds and high SR fibres (> 18 spikes per second) associated with low absolute thresholds. Most ANFs have high spontaneous rates (70%) and saturate rapidly, in contrast those with low

spontaneous rates saturate more slowly. High spontaneous rate fibres code intensity changes at low levels, and the low spontaneous rate fibres code intensity changes at high levels (Evans 1975). The range over which the ANF changes its firing rate in response to changes in intensity of sounds is called the dynamic range. The dynamic range is narrow for high spontaneous rate fibres and wider for Medium and low SR ANFs. Previous animal studies suggest that the high-threshold, low-SR fibres are important for hearing in background noise as they have larger dynamic ranges and are not as affected by the presence of masking but they are more prone to damage following noise exposure and as a result of aging (Costalupes et al., 1984). Therefore, loss of low SR auditory fibres would be expected to show decreased ability to understand speech in noise (Schmiedt et al., 1996). There is a generalisation that has been assumed in literature that the different spontaneous classes found in the cat are also found in other mammals, however, there are some studies that show no evidence of these categories in other species, notably guinea pig (Manley and Robertson, 1976) and gerbil (Ohlemiller and Echteler, 1987) The differences between the results of those studies and Liberman (1978) may be due to differences in methodology, threshold algorithms, or an inadequate sample of fibers in one animal.

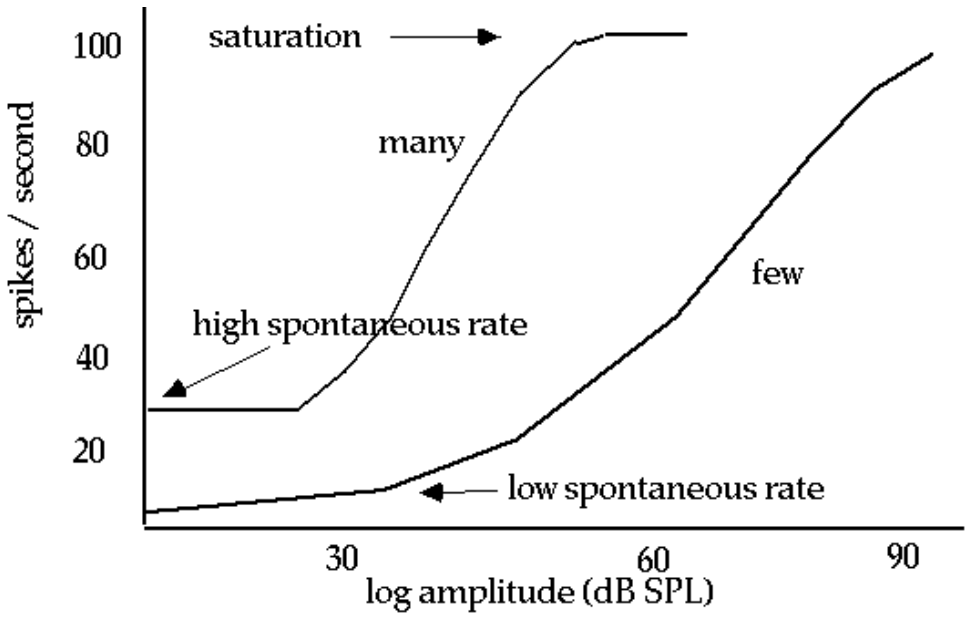

Figure 10: Illustrates the difference in APs between High SR ANFs and Low SR ANFs

The place code, reflects the mechanical filtering that occurs in the cochlea, the responses of the basilar membrane are sharply tuned and highly specific, the apical end of the basilar membrane responds best to low frequencies, whereas the basal end responds to high frequencies. Thus, every place along the basilar membrane has its CF, the frequency to which

that place responds most strongly, this is known as tonotopic organisation, and it is maintained throughout the auditory pathways up to primary auditory cortex, thereby providing a potential neural code for the pitch of sounds (Ohm 1843, Helmholtz 1863). The temporal code depends on the rate with which ANFs generate APs at a certain phase within the period of the sound (Seebeck, 1843). At low frequencies the ANFs fire at preferred phases of the sound wave at each cycle, this is usually at the peak amplitude. At low frequencies the ANFs are phase locked to the stimulus waveform, (Rose et al. 1967) and the neurons are able to generate APs at almost every cycle, as shown in Figure 11a. By phase locking, the response pattern of the ANF accurately reflects the frequency code of the signal. Phase locking has been extensively researched in all vertebrate classes; squirrel monkey (Rose et al., 1967; Geisler et al., 1974) cat (Galambos and Davis. 1943; Rupert et al., 1963; Kiang et al., 1965; Pfeiffer and Molnar, 1970; Kim and Molnar. 1979; Evans, 1980; Johnson, 1980), chinchilla (Woolf et al., 1981; Oshima and Strelioff, 1983) guinea-pig (Tasaki, 1954; Harrison and Evans, 1979). birds (Sachs et al., 1974. 1980; Sullivan and Konishi, 1984) crocodile (Klinke and Pause, 1980; Smolders and Klinke. 1985) turtle (Crawford and Fettiplace. 1980) frog (Narins and Hillery, 1983) and fish (Fay, 1978). Phase locking in response to low frequencies can be observed in all ANfs irrespective of their CF; but is less effective at higher frequencies (> 4 kHz) as ANFs are unable to fire at each phase of the cycle, as they are limited by the refractory period and APs cannot be generated rapidly, At higher frequencies groups of ANFs respond to specific phases of the sound wave and when grouped provide a representation of the frequency, this is known as the volley principle (Wever and Bray, 1930; Evans, 1979) see figure 11b; suggesting the cochlea might possess different physiological transduction mechanisms for low and high frequencies, with a possible transition from temporal code to place code between 4-5kHz (Moore, 1993).

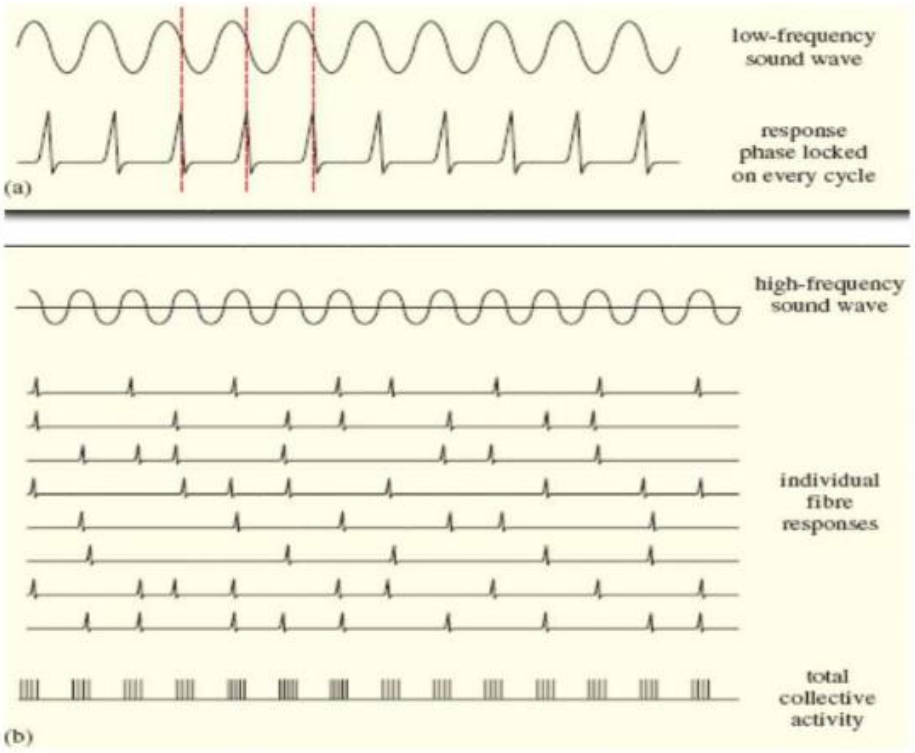

Figure 11: (A) Each of the eight ANFs are firing in phase with the incoming signal and demonstrate phase locking (at low frequency) where the inter-spike interval is sufficient for the ANFs to recover and be non-refractory allowing them to generate a subsequent AP at the next phase of the stimulus cycle. (B) At higher frequencies up to 4kHz, the volley principle is shown with each of the eight ANFs firing at random time intervals as the inter-spike interval is too short and a larger number of ANFs are refractory. The bottom trace in the figure shows the combined responses of all eight ANFs, which is sufficient to reproduce the frequency of the incoming signal.

Phase locking is essential in order to separate components of complex speech. Two tone suppression is a nonlinear mechanical process caused by the interactions between the vibrations in the cochlear. This is demonstrated when a second tone (suppressor) is introduced just above or below the CF of an ANF and results in at least a 20% reduction in the firing rate of the ANF (Pfeiffer and Suga, 1971) see figure 12. Suppression is important in the coding of speech as stronger components of the signal are likely to be supressed as a result of a reduction in the ANF firing rate due to the presence of less-intense components (Delgutte, 1990).

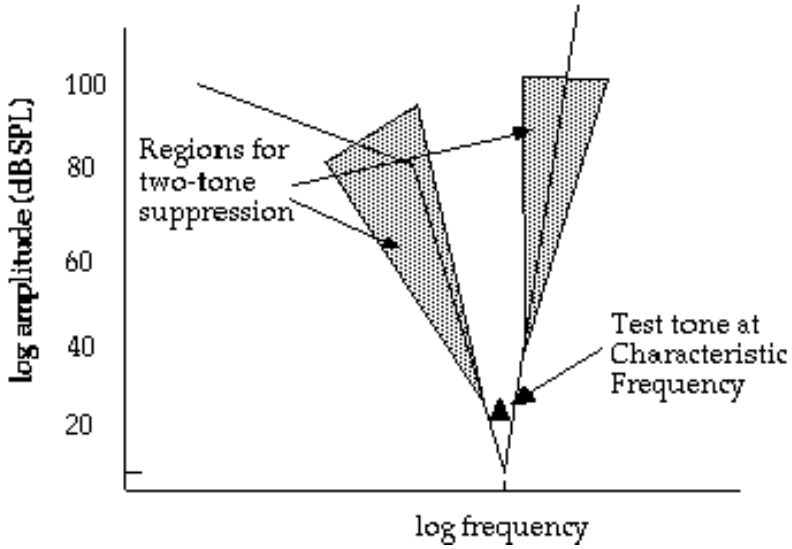

Figure 12: Suppression areas of an ANF. The continuous line shows the tuning curve of the ANF. When a second tone is added with a level and frequency within the shaded area the firing rate of the ANF is reduced.

2.3 Refractoriness

The refractory period of SGN starts when an action potential has been generated and is a momentary decrease in the SGN's discharge probability (Hodgkin and Huxley, 1952; Gray, 1967), which prevents it from spiking twice in rapid succession. The duration of the refractory period is approximately 1 ms (Gray, 1967). In CI users this period can be estimated based on eCAP measurements and lasts approximately 400 ms (Morsnowski et al., 2006). See chapter 4. The initial period following a spike forms the absolute refractory period, during which period the SGN is unresponsive and is unable to fire another action potential regardless of the intensity of the stimulus. The absolute refractory period is followed by the relative refractory period, during which period the SGN starts to regain its resting state responsiveness and the spike probability to a stimulus increases from 0 and returns to 1 at full recovery (Boulet et al., 2016). Within the relative refractory period the SGN is able to generate a spike but at an elevated threshold (see figure 13). The duration of the stimulus and the interval between the spikes can occur within the refractory period, thereby, preventing spikes to consecutive pulses which could also result in a shift in the phase alignment between pulses. Therefore, refractoriness is likely to play a significant role in temporal coding within SGNs as it can affect both synchronisation and entrainment of pulses.

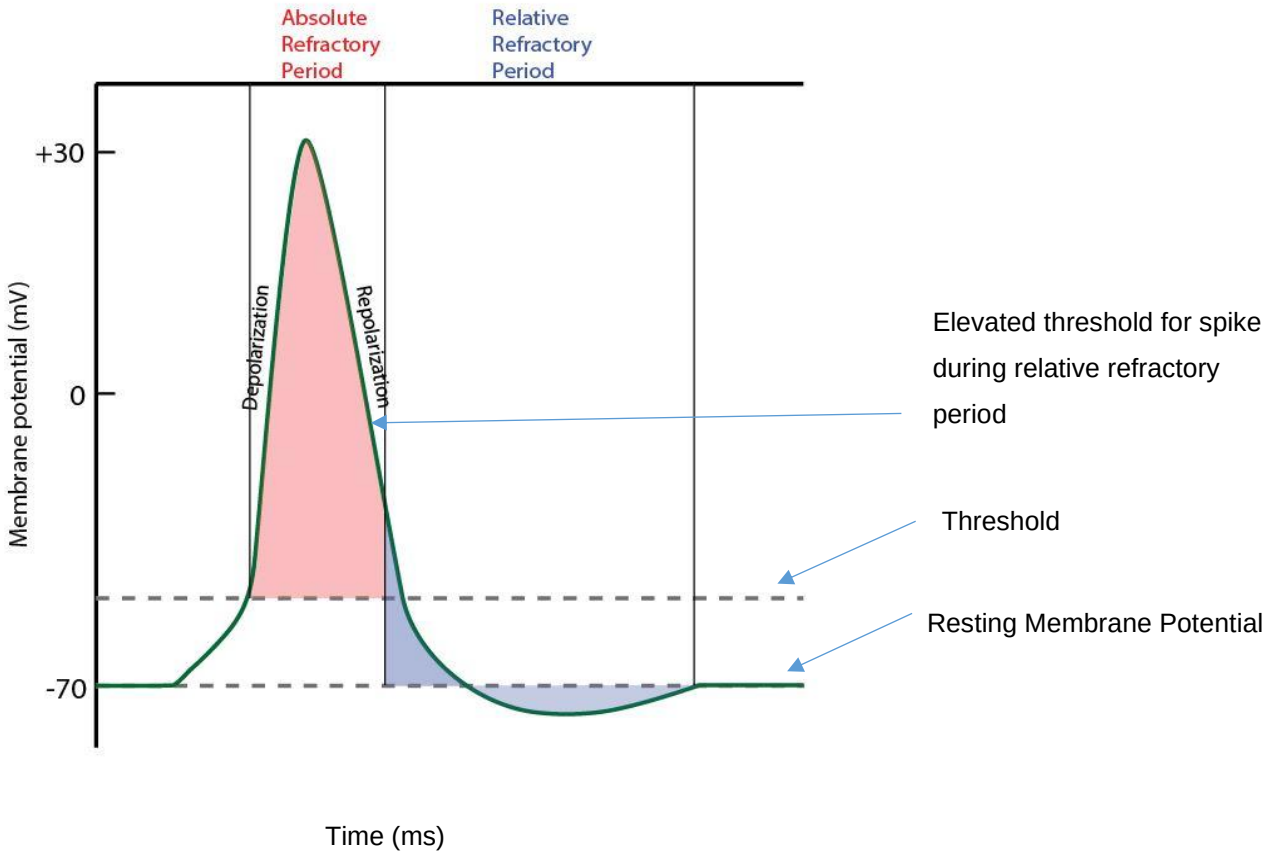

Figure 13: Recovery from inactivation is a time and voltage-dependent process. During the refractory period, sodium channel inactivation prevents an increase in sodium channel conductance, which results in the absolute refractory period during which period the SGN is unable to generate an action potential. During the relative refractory period sodium channels are deactivated and there is a large potassium conductance which produces an increased threshold for an action potential initiation.

2.4 Central auditory pathways

A complex chain of nerve cells helps to process and relay auditory information, encoded in the form of nerve impulses, directly to the highest cerebral levels in the auditory cortex. These dynamic processes enable perceptual acuity such as pitch recognition, melody recognition and being able to hear in noise. These perceptual tasks are complex and one critical aspect of the high temporal resolution of the auditory system is the rapid and accurate transmission of sound information throughout its many pathways and the ability to combine and integrate the auditory streams from both ears (Gage and Roberts, 2000; Gage et al., 2006). SNHL may results in changes in the central pathways that can change how sound is processed in the

cortex and effect auditory perception, speech discrimination and temporal mechanisms involved in audition such as integration, ordering and masking (Phillips, 2002).

The cochlear nerve enters the brain stem at the pontomedullary junction, where it bifurcates and terminates in the two major subdivisions of the cochlear nucleus, the dorsal and ventral cochlear nuclei. The neurons arising from the cochlear nucleus project to the superior olivary nuclei in the brainstem (Pickles, 1988). The superior olivary complex (SOC) receives binaural input and is concerned with sound localisation, based on interaural time and intensity differences. Neuronal fibres from the SOC ascend with fibres from the cochlear nucleus forming the pathway of the lateral lemniscus. Many neurons in the lateral lemniscus complex are specialised for extracting temporal patterns in complex sounds, which are transmitted to the inferior colliculus (Malmierca et al., 1998). The tonotopic mapping of the cochlea is strictly maintained in the cochlear nucleus, lateral lemniscus, and reticular formation and this finding supports the theory of a place code for sound frequency (Ehret and Romand, 1997; Popper and Fay, 1992; Webster et al,.1992). The inferior colliculus is the primary site for integrating inhibitory and excitatory inputs, which themselves have different temporal properties, and so interact to produce filters for temporal features of sound. The time constants of the filters suggest that they are relevant for the analysis of sound envelope, such as the estimation of the duration, the amplitude modulation rate, or the rate of frequency modulation (Covey and Casseday, 1999). Activity from the inferior colliculus ascends to the medial geniculate body of the thalamus, which continues the integration of the spatial, spectral, and temporal features that have been extracted separately and partially reintegrated within the nuclei of the lower levels of the auditory system, to refine the neural coding of specific sound which is then presented to the auditory cortex (Gruters and Groh, 2012), see figure 14. In parallel with ascending pathways are descending pathways that originate from regions in the Cortical and subcortical auditory system cortex to the periphery (Bajo and King, 2013; Usrey and Sherman, 2019). One important function of the descending pathway is to provide top down information and exhibits inhibitory functions that can affect many aspects of subcortical performance such as filtering (Diamond et al., 1992), sharpness of tuning (Villa et al.,1991), and response plasticity (Ma and Suga, 2001).

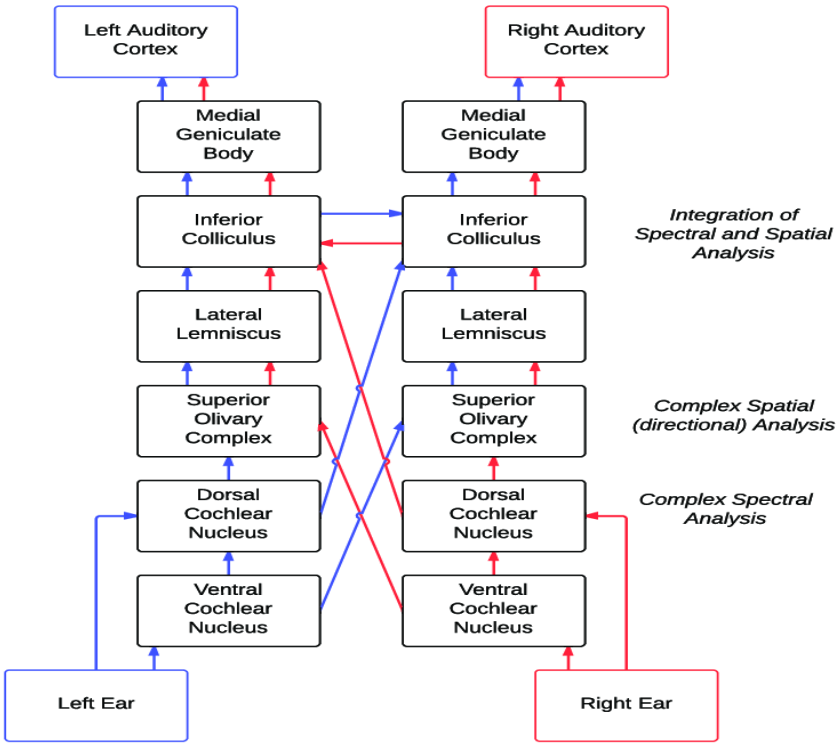

Figure 14: Schematic of the various central auditory nuclei and the ascending pathways

2.5 The likely limitations imposed by impairments in the auditory pathway

SGCs are the first order target neurons for CIs that are responsible for transmitting electrical stimuli to the central nervous system (Kalkman et al., 2014). Studies using animal models have shown that IHC loss induces retrograde neural degeneration which results in a substantial reduction in the activity of SGNs (Liberman and Kiang, 1978; Hartmann and Klinke, 1984; Hinojosa et al., 1983; Shepherd and Javel; 1997). It has been suggested that this degeneration is a gradual process which initially involves the loss of the peripheral process, followed by a significant reduction in soma area and partial demyelination; ultimately resulting in cell death (Terayama et al., 1977; Spoendlin, 1984; Leake and Hradek, 1988; Spoendlin and Schrott, 1989; Shepherd and Javel, 1997; Hardie and Shepherd, 1999). The preservation of SGCs has been shown to be negatively correlated with the duration of deafness (Nadol et al., 2006), therefore, it is reasonable to assume that the volume of SGCs will strongly influence the level of speech perception achieved by CI users. Subjects with shorter durations of deafness are likely to have better neural survival compared to those with longer durations of deafness, resulting in better speech performance. Differences in neural survival patterns at the periphery could elucidate the large individual variability in speech performance reported in adult CI users.

A number of post mortem examinations of temporal bones of post-lingually deaf adults have shown varied histological results and it has not been possible to reveal a consistent relationship between the degree of SGC survival and speech performance in CI users. Some studies have concluded that there is no relationship between the SGC population and speech perception scores (Khan et al., 2005; Blamey et al., 1997; Xu et al., 2012; Seyyedi et al., 2014). In contrast Fayad et al (2006) demonstrated a statistically significant negative correlation between total SGC count and word recognition scores in histologic examination of 14 implanted temporal bones. There was an inverse relationship between SGC count and performance suggesting that central and cognitive factors are likely to contribute to the variability seen in CI users. Nadol et al., (1989) reported that subjects with different aetiologies had varying SGC counts, in the ninety-three temporal bones they examined, they found subjects with sudden idiopathic deafness had the highest residual SGC count and subjects with deafness due to pre-lingual or genetic causes had the lowest residual SGC count, with the diagnostic group accounting for 57% of the variability in SGC count. Similarly, Xu et al., (2012) showed there was great variability in the residual SGC count of the 4 temporal bones they examined. They found surviving dendrites varied from 5% to 30% and there was no correlation to speech performance. The speech recognition scores varied from 4% to 89% and the cases with the highest number of SGCs had better speech scores. However, as this study only examined four cases it is considerably weaker when compared to the findings of Nadol et al., (1989).

Possible reasons for the variability in the results of these studies is that when comparing SGC count and word recognition scores, subjects were not always matched for confounding factors such as duration of deafness, age at implantation, deafness onset and cognitive ability. Additionally, in some studies with unilaterally implanted subject's researchers compared the SGC count in the implanted ear with the contralateral ear and assumed both ears would have had the same number of SGCs prior to implantation (Khan et al., 2005; Fayad et al., 2006). It is possible that the large across subject variability seen in SGC count (Hinojosa and Marion, 1983), may also be present between ears in the same subject, therefore these comparisons may have weakened the statistical power in these studies.

Seyyedi et al., (2011) compared the temporal bones of 21 bilaterally implanted subjects and reported that one ear could be used as a control ear for each subject and demonstrated that the number of surviving SGCs was similar between the ears when both ears were deafened by the same deafness onset and had the same level of hearing loss. A later study by the same

author (Seyyedi et al., 2014) examined the relationship between SGC count and word recognition by comparing the temporal bones of six bilaterally implanted subjects. The results showed that there was a significant positive correlation between the differences of word recognition scores and SGC counts between the ears of each patient. Interestingly, the four ears with the largest number of residual SGCs did not have the highest word recognition scores and there was still great variability in SGC count between three subjects in their series, as shown in Table 1.

Subject	SGC count right ear	Word Recognition Score	SGC count Left ear	Word Recognition Score
1	2326	5	5916	25
2	2326	28	2611	30
3	11635	66	12546	66
4	16000	56	16401	60
5	10064	86	8364	80
6	7548	57	8500	58

Table1: The word recognition scores based on SGC count in 6 bilaterally implanted subjects. Reproduced from Seyyedi et al., 2014

Collectively, these results suggest that the residual SGC count following hearing loss cannot solely explain the differences in speech perception scores and long durations of deafness do not necessarily result in significant neural degeneration. None of these studies have calculated the minimum number of SGCs that would be required for satisfactory speech perception in CI users. Temporal bone studies of NH subjects have documented the SGC count to be in the range of 23,193 to 39,114 (Guild, 1932); a later study by Otte et al (1978) reported the range as 19,000 to 38,000 SGCs. In CI users Hinojosa and Marion (1983) reported SGC counts ranging from 0 to 25,873. In a limited case series, Linthicum et al (2009) reported that two out of four subjects in their study with fewer than 3,000 SGCs were still able to achieve relatively good word recognition scores. Therefore, it is likely that the central auditory system, contributes significantly to how successful a recipient is with processing the signal provided by a CI. It is possible that input from a fewer number of SGCs is adequate in subjects with better central processing, which might explain why some of the subjects in these studies were able to achieve relatively good speech performance despite having a lower volume of SGCs.

The relationship between the number of surviving SGCs and speech performance is not clear in CI users, however, some of these studies have shown that the cochlear pathology and neural survival patterns are also highly variable along the length of the cochlea (Hinojosa and Marion 1983; Khan et al., 2005; Fayad et al., 2009). This suggests that individual CI users will have differing neural survival patterns at each electrode location, which leads to variation in the function of each electrode-neural interface (see section 3.12). It is likely that individuals with longer durations of deafness will have a fewer number of well-functioning channels across electrodes due to the sparser neural survival. Poor functioning electrode-neural interfaces are likely to result in reduced temporal acuity for CI users. In the subsequent chapter we discuss how channel interactions may contribute to errors in speech perception in CI users and describe how temporal coding with a CI differs from acoustic hearing, and how these factors are likely to impede temporal transmission in CI users. As maturation of the neural peripheral and central auditory pathways is dependent on auditory stimulation, auditory deprivation is likely to compromise both pathways and therefore limit the benefit that can be achieved with a CI. In comparison, these pathways are already formed in post-lingually deafened CI users, who have an auditory memory, and considering SGCs are the main responders to electrical stimulation, robust pre-existing pathways are likely to result in better outcomes with CIs.

Chapter 3: Electric Hearing in the Auditory System

This chapter describes the components of a CI system, the mechanisms of operation and the psychophysics. A description of the different facets of signal processing and the perceptual effects of these parameters are provided.

3.1 Cochlear implant

Severe-profound SNHL often results in substantial loss, damage and dysfunction of hair cells and can also lead to degeneration of the peripheral portion of the auditory neurons, reducing the volume of SGNs; in such cases some degree of hearing can be restored with a CI (Merchant and Nadol, 2010). A CI bypasses the deficient transducer structures and directly stimulates the SGNs via electrical current which generates an action potential in lieu of the neural transmitter that would have been released by normal functioning IHCs. CIs consist of three parts: an external sound processor, a subcutaneous receiver, and an intra-cochlear electrode array (see figure 15). Most CI systems use electrode arrays that are surgically inserted into the scala tympani and extend one to one and half turns from the base to the apex. Commercially available CI electrodes consist of 12-22 electrode contacts. An implant channel comprises one active electrode along the cochlear array and one reference electrode, which may be inside or outside the cochlea. The stimulation mode determines the current flow between an active and a reference electrode. The most commonly used stimulation mode in cochlear implant systems from all manufacturers is monopolar mode, where current flows between an intra-cochlear (active) electrode and an extra-cochlear (reference) electrode. The active electrode typically delivers a train of biphasic pulses. Most of the current flows along the fluid-filled scala tympani, but some also flows into the less conductive osseous spiral lamina adjacent to it. Within this bone lie the SGNs, whose axons form the auditory nerve (Bierer, 2010), see figure 16. The proximity of the electrodes to the different subpopulations of SGNs, global neural survival and fibrosis around the electrode array are likely to affect how well the neural elements of the auditory nerve are innervated. One of the main aims of a CI is to replicate the coding of speech that occurs in the normal functioning auditory system however; this is a challenging task as speech is a complex signal that is coded into patterns of neural discharge in approximately 20,000 ANFs (Pickles 1983) and a CI is limited by the number of spatial contacts, which cannot fully replicate the robustness of the peripheral auditory system. Thus, spectral coding in the cochlea is restricted however, temporal coding of frequency can be reproduced by electrical stimulation of the ANFs.

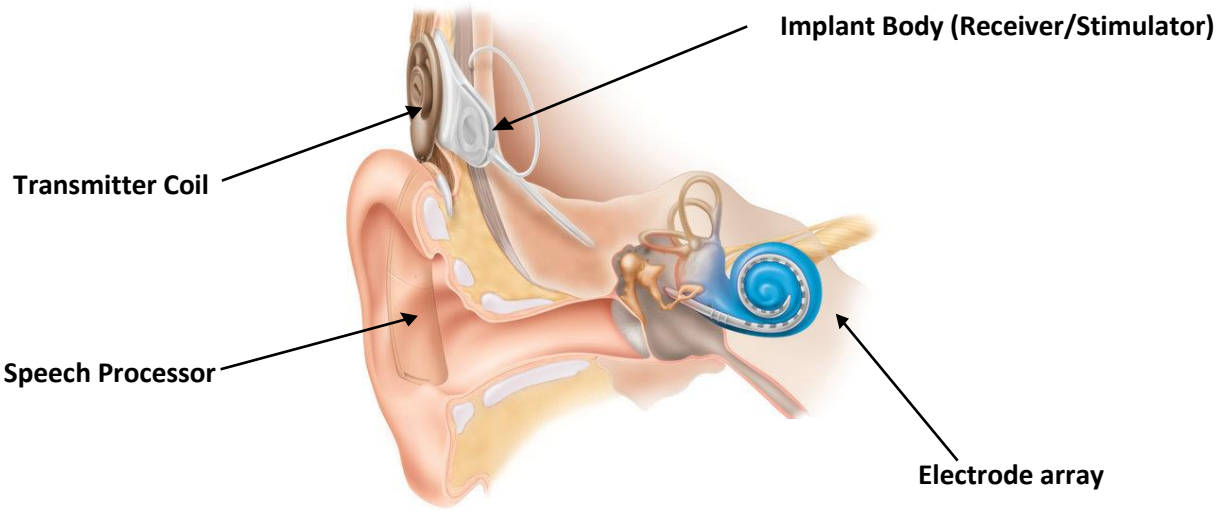

Figure 15: Components of a CI system. The speech processor captures, digitises and encodes sound. The speech processor transmits the encoded sound through the coil to the implant just under the skin. The implant transmits the encoded sound along the electrode array which is positioned in the cochlea. The electrodes stimulate the ANFs, which relay the signals to the brain to produce hearing sensations.

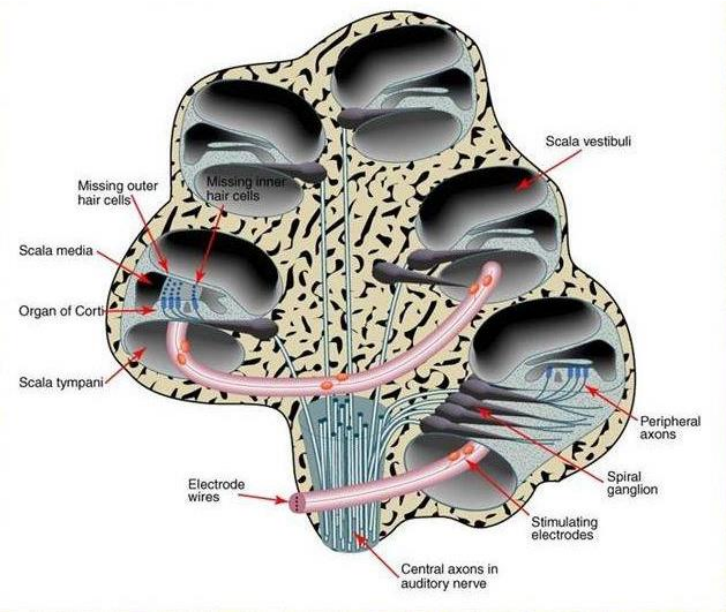

Figure 16: Cross section of the cochlea showing an electrode array inserted in the scala tympani. The electrode contacts stimulate peripheral axons of the SGNs, whose central axons send neural impulses to the brain. The electrode array is designed to stimulate groups of nerve fibres in the same tonotopic manner as the BM.

3.2 The sound processor

The speech processor uses a microphone to detect sounds and splits these into channels by band pass filtering. The signal is then compressed and sent to the transmitter coil where the receiver converts them into electrical signals which are processed using pre-defined coding strategy. The electrical current is delivered to individual electrodes (see figure 15). Stimulation of basal electrodes represents high frequency sounds and more apically located electrodes represent lower frequency sounds in line with the tonotopic arrangement of the basilar membrane (Niparko et al., 2000).

There are three main stages of processing the sound signals, the spectral pattern representation by band-pass filtering, the coding of sound signals by the band envelope and amplitude compression to map the large acoustic dynamic range (100-120dB in NH listeners) to the narrow electrical dynamic range of 15dB in CI users (Nelson et al., 1995).

3.3 Spectral representation

The frequency coding in CIs is achieved by distribution of electrical energy at multiple electrodes which provides a spectral code (Burian et al., 1979) and temporal code is attained when the amplitude of the pulse trains on each electrode are modulated by the amplitude envelope of the acoustic signal (Rosen 1992). Each electrode carries information in a frequency range that, in NH, would be transduced by hair cells and ANFs at a place of the basilar membrane in the vicinity of the electrode (Bierer, 2010). The clinical map sets out the tonotopic arrangement in the CI and assigns a frequency band to each channel. The electrodes that form the channel affect how the electrical current delivered by that channel activates the ANFs (Bierer, 2010). Most CI users appear to reach optimum performance with six to eight channels, and there do not appear to be any significant advantages of having all channels active for speech perception measured in quiet and background noise (Dorman and Loizou, 1997; Fishman et al., 1997; Dorman and Loizou, 1998; Loizou et al., 1999 and Friesen et al., 2001).

3.4 Place code

The place code in a CI is crude due to the small number of electrodes; excitation of discrete SGNs is inadequate due to the spread of electrical current which stimulates a broader number of SGNs and reduces the fine frequency discrimination abilities of a CI user (Clarke, 2013), due to cross-channel interaction (Throckmorton and Collins, 2002). Differences in channel interaction patterns may help to explain variations in CI user performance but the evidence base for this is limited (this is discussed in more detail in the temporal coding section).

Envelope and temporal fine structure are known to be two important acoustic cues, especially for speech intelligibility and are represented in the timing of neural firing (Chen & Zhang 2008). Envelope refers to the relatively slow rate fluctuations in the overall amplitude of speech over time, while temporal fine structure is defined as the rapid oscillations with which the signal crosses zero (Rosen 1992; Moore 2008). Temporal fine structure processing is reflected in the synchronised firing patterns (phase locking) of ANs to a specific phase of the carrier (Zeng, 2002; Moore et al. 2012). Temporal fine structure processing is known to play an important role in pitch perception, which is important for speech perception (McDermott& Oxenham 2008; Moore 2008). Current CI processing mainly conveys mainly envelope information for a number of different frequency bands and temporal fine structure cues are largely discarded (Qin and Oxenham 2003; Nie, Barco and Zeng 2006). Therefore, the lack of TFS cues in conventional CI encoding strategies reduces temporal pitch cues and may contribute to poor speech understanding. Low frequencies can be coded by the periodicity in the signal applied to an electrode but due to the limited number of channels spectral resolution is reduced and pitch perception is poor. Coding of the periodicity of complex sounds in CIs depends almost entirely on a temporal code and does not extend above about 300 Hz (Moore, 2003). Buchman et al., (2014) reported that deeper electrode insertion angles provide greater cochlear coverage in the apical regions, thus better tonotopic place representation which results in better speech perception in CI users, discussed in further detail in (see temporal coding section).

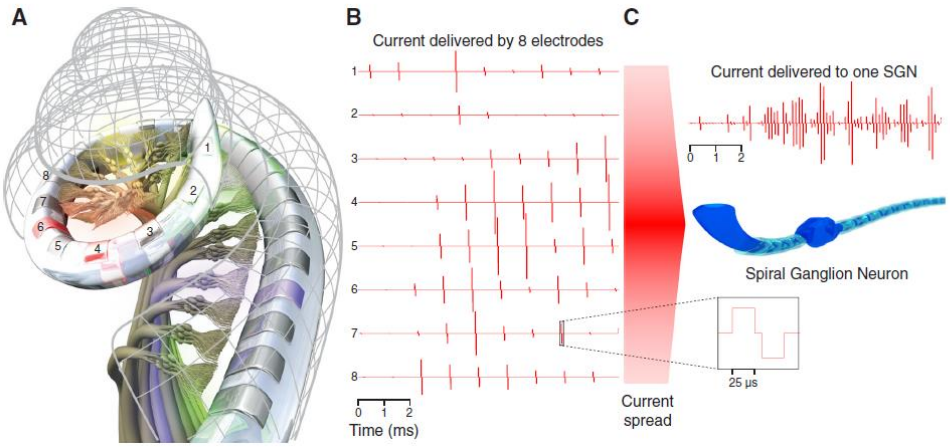

Figure 17: Illustration of electrical stimulation of SGNs by a CI. A) The different electrodes stimulate subpopulations of SGNs (highlighted in blue, green, yellow and red). Due to current spreading in the cochlea, such that a single SGN is subjected to a weighted sum of the currents delivered by the nearby electrodes, this is shown in B) which shows pulse trains delivered by electrodes 1-8 for a speech segment, encoded at a rate of 900 pulses per seconds on each electrode. C) The current spread profile is shown in red that smears the contributions of all 8 electrodes, in this example when the SGN is located between electrodes 4 and 5. From Boulet et al,. (2016) Reproduced with permission, copyright Springer Nature

3.5 Amplitude compression

Acoustic information carried in speech is complex and varies over time in spectral content and intensity (Oxenham and Bacon 2004). Under acoustic stimulation, SGNs have a greater dynamic range, a more variable firing rate, and undergo weaker phase locking (Boulet et al, 2016). In contrast CI users have a narrow dynamic range as electrical stimulation by passes the chemical synapse between the IHCs and SGCs, hence presenting the information in acoustic signals onto electrodes remains a challenge and an amplitude gain compressor (AGC) is used to compress signals into the narrow dynamic range of electrically evoked hearing. A measurable auditory percept (MAP) is a set of processing parameters unique to an individual CI user, which includes the minimal permissible current level (T level) for each electrode to elicit a soft sound percept, and the maximum permissible current level (C level) to elicit a comfortable loudness percept. The range of acoustic input levels that are mapped onto the CI user's electrical dynamic range, during front end processing are referred to as the input dynamic range. The Nucleus devices used in the present study implement a fixed 40dB input dynamic range, which is determined by the range of input signals between the C-SPL and T-SPL see figure 18, that would be stimulated within the electrical dynamic range

(between C-level and T-level). In the present study the standard fixed input dynamic range was used.

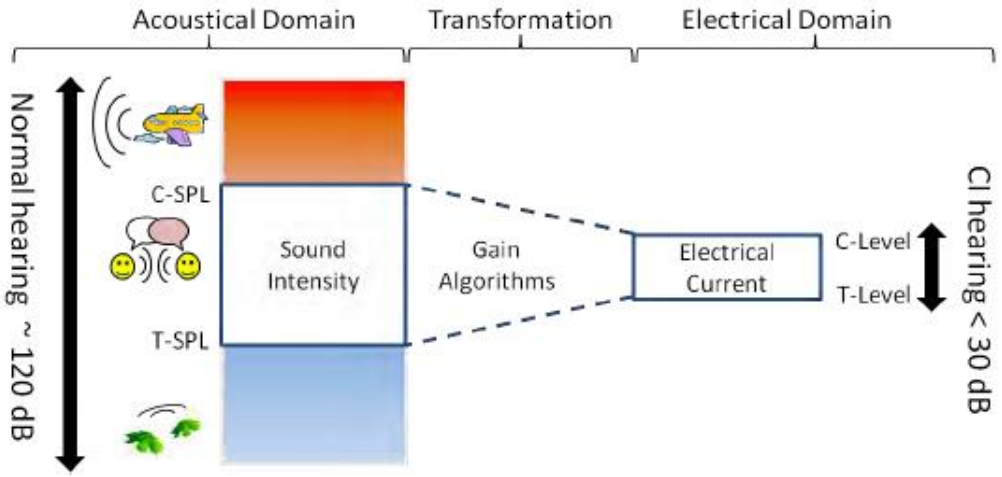

Figure 18: Dynamic range requirements in cochlear implant users.

Nelson et al., (1995) have shown that the main limitation to amplitude coding in CI user's is their ability to discriminate the number of amplitude steps. CI users who performed well could discriminate 40-50 amplitude steps, the Nucleus devices used in this study implement 256 steps which suggests that a large number of discriminable current steps being available within the electrical dynamic range is unlikely to impact performance. It is likely that the input dynamic range therefore plays a key role in how spectro-temporal information is mapped into electrical hearing. A narrow input dynamic range may compromise a CI user's ability to detect soft speech because less of the acoustic signal is being mapped into the CI user's electrical dynamic range (Holden et al, 2011). This is supported by the findings of Dawson et al (2007) who showed that when the input dynamic range was progressively increased from 31dB to 56dB, CI users demonstrated improved word recognition at low presentation levels in quiet.

3.6 Speech coding strategies

Speech processing strategies for CIs determine the excitation patterns within the cochlea and subsequently have a strong influence on speech perception. The main aim of filter bank based speech processing strategies is to provide the vital cues of speech waveform for speech understanding. All subjects in this study were recipients of Nucleus CI512 and CI532 devices and used the Advanced Combinational Encoder (ACE) sound coding strategy. Therefore, we focus here on the specific coding strategies employed in this device, noting there are some differences with other manufacturers' devices which are not covered here. The acoustic signal

received by the Nucleus CP910 sound processor used in this study can be split into a maximum of 22 frequency channels which match the number of active intracochlear electrodes. ACE is an n-of-m (channel selection/peak clipping) envelope extraction strategy which separates speech signals into sub-bands (M) and derive envelope information from each band signal. N bands with the largest amplitude are then selected for stimulation (N out of M) in each time window (see channel selection section). It is designed to increase temporal resolution by reducing the density of electrical stimulation thus concentrating on the most important spectral components of the speech signal (Wilson and Dorman, 2008). The signal processing framework of the ACE strategy is shown in Figure 19 and a description of the stages in signal processing are described below.

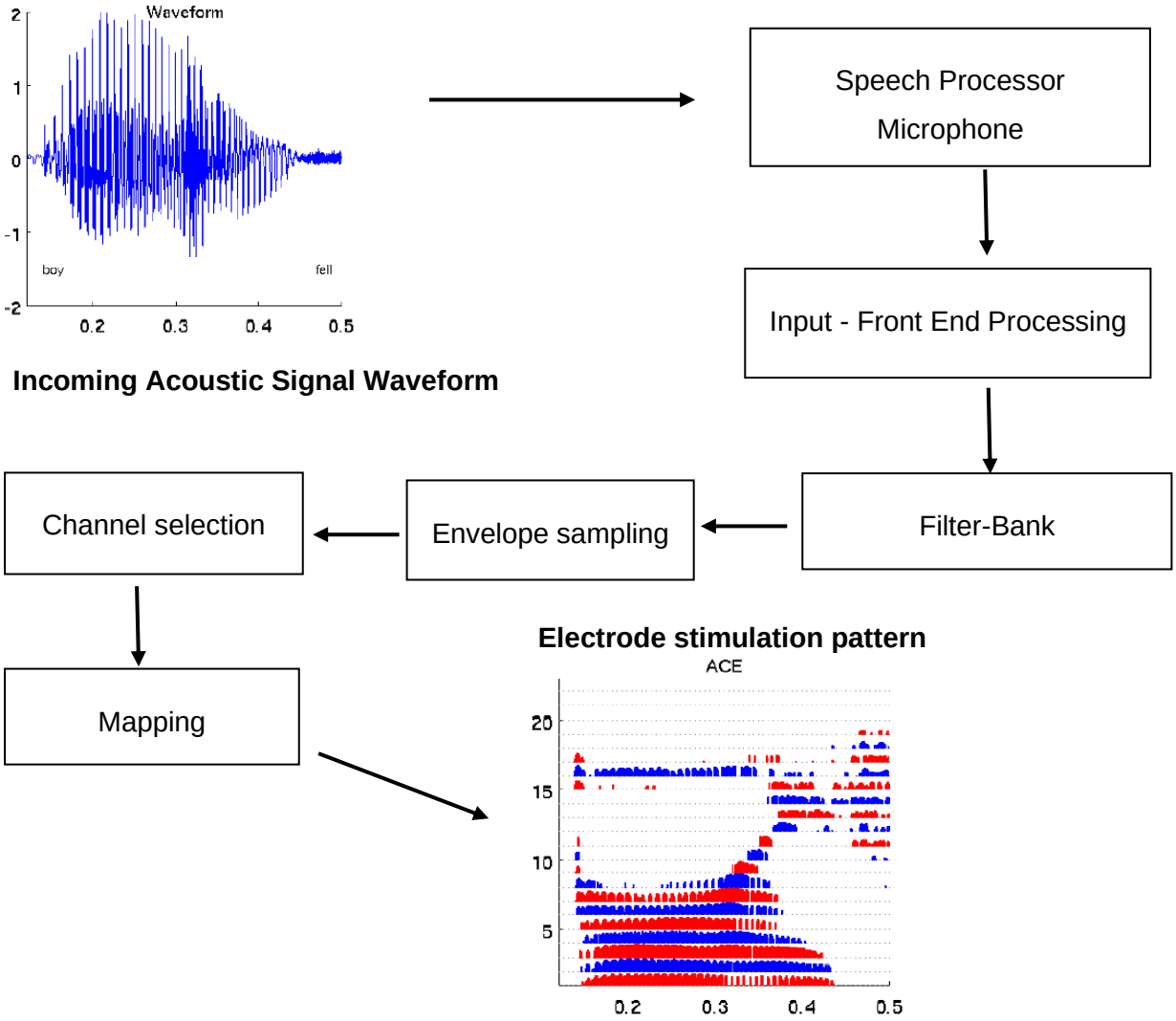

Figure 19: Block diagram of main stages of CI speech processing

3.7 Front end processing

At the input stage or front end processing the acoustic signal detected by the microphone is converted to a digital signal, frequency shaping and level adjustments are completed at this stage. The front-end block typically involves a pre-emphasis filter, a sensitivity control and an AGC system. During the signal transformation high frequencies are removed beyond 8kHz due to an anti-aliasing filter within the CP910 speech processor which is required prior to analog-to-digital conversion. The pre-emphasis filter plays a key role in emphasising the high frequency components within the signal in order to increase the audibility of high frequency spectral content. The limited dynamic range and reduction in amplitude coding in CI users which subsequently requires implementation of AGC has been discussed above (see amplitude compression section).

3.8 Filter bank and envelope sampling

At the next stage of signal processing the digital signal is sent through a filter bank. The Nucleus filter bank implements a fast fourier transform (FFT) for the frequency analysis of the signal. The filter bank splits the signal into frequency bands so that each frequency band is allocated to one stimulation channel. The FFT is performed on windowed input blocks of 128 samples (8 ms at 16 kHz) of the signal. A Hann window is applied and gives each bin a 6 dB bandwidth of 250 Hz. Each analysis frame is overlapped with the previous frame to make the analysis rate or the envelope sample rate close to the stimulation rate. For a fixed 128 point FFT analysis, there are 64 bins for real components with frequencies spaced linearly at multiples of 125 Hz, but this exceeds the number of channels in the Nucleus implant (maximum of 22) so the channel envelope is calculated by combining the sum of powers which provides a set of frequency bands. The bands are spaced linearly below 1 kHz and logarithmically spaced above 1 kHz. For the bands below 1 kHz, each band is assigned to one FFT bin. Bin 0 and 1 are discarded and the assignment starts from bin 2. For frequency bands above 1 kHz, two or more consecutive FFT bins are combined to produce wider bands. The default frequency range in the Nucleus implant is 187 – 7937 Hz. The frequency allocation for a 22 channel filter bank is shown in Figure 20.

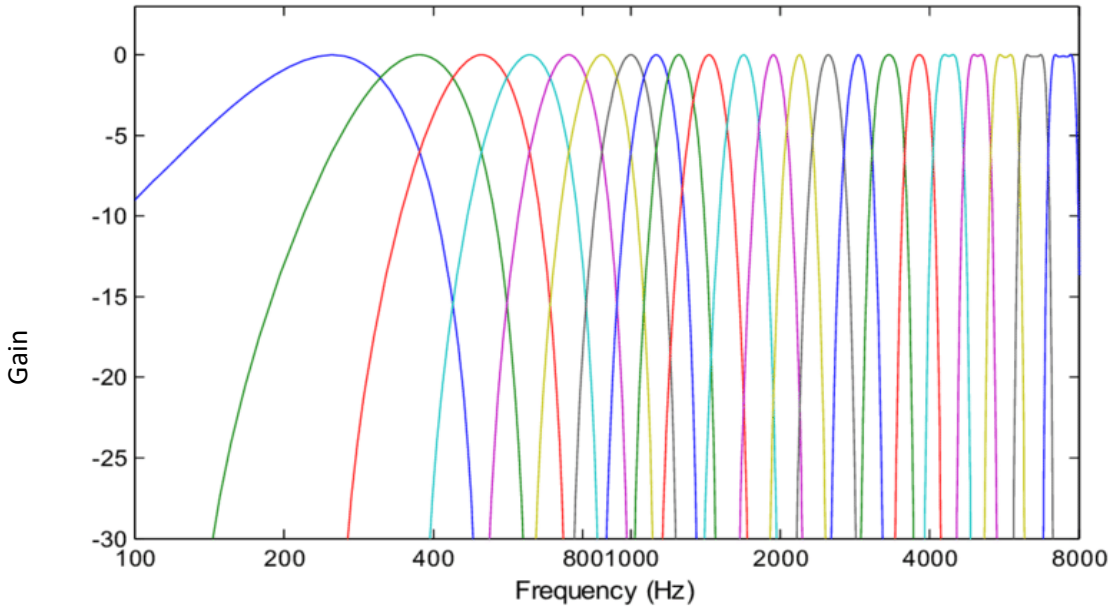

Figure 20: 22 channel FFT filter bank used with ACE and resulting frequency response. From Laneau et al., (2006). Reproduced with permission, copyright Acoustic Society of America.

3.9 Channel selection and mapping

The channel selection method for the ACE strategy is called maxima selection, which scans the amplitudes of the channel envelopes and selects the channels with the highest amplitudes, stimulus pulses are delivered only to the electrodes that correspond to the channels with those highest amplitudes. For each frame of the audio signal, N electrodes are stimulated sequentially and one cycle of stimulation is completed. The number of cycles per second therefore determines the rate of stimulation on a single channel, also known as channel stimulation rate, which represents the temporal resolution of the implant (Nogueira et al., 2005). The standard ACE strategy uses the length of the processed segment 128 samples and overlap 32 samples. Therefore, if the channel stimulation rate is increased this leads to a corresponding increase in the overlap between the FFT analyses, hence frequency components that occur within the same channel are unlikely to be resolved accurately. The total number of electrodes (M) represents the frequency resolution, only a sub set of electrodes (N), out of (M) electrodes, with the largest amplitude are selected in each cycle. There is therefore a trade-off between the spectral and temporal representation of the signal. If N is decreased there is a loss of spectral content however, as channel stimulation rate can be increased there is a better temporal representation of the signal. Equally if the channel stimulation rate is decreased, N can be increased giving a better spectral representation of

the signal. The number of maxima is a clinical parameter and can be different between CI users. In the present study the default maxima of 8 was used for all subjects. In the final stage of signal processing envelope fluctuations are coded to the corresponding electrode channel. See section 3.5 on amplitude compression.

3.10 Temporal structure of speech: Coding and relevance to perception

The temporal structure of speech provides important linguistic contrasts which are crucial for speech perception. Rosen (1992), developed a framework for describing the acoustic structure of speech based purely on temporal features. The temporal structure of speech is classified into three categories of speech cues based on dominant temporal fluctuation rates, they are envelope, periodicity, and fine structure cues (Van Tasell et al., 1987, Rosen, 1992). In the framework postulated by Rosen (1992) the envelope cues contain modulation frequencies from 2 to 50 Hz, representing acoustic aspects of phonetic segments combined with stress and voicing information (Mermelstien, 1975; Howell and Rosen, 1983; Delgutte and Kiang, 1987; Doman et al., 2008 and Miller, 2008). The temporal envelope represents the timing of events in the speech stream, and provides the temporal framework in which the fine structure of linguistic content is delivered (Dullman et al., 1994). Periodicity cues exist from 50 to 500 Hz and convey information about voicing and intonation. Periodicities of higher frequencies, from 0.6 to 10 kHz, comprise the fine structure of the speech signal and convey information related to aspects of consonant place and vowel identity. These temporal features are discussed below and the framework formulated by Rosen (1992), is shown in figure 21 which summarises the importance and relationships between each feature.

The temporal envelope:

Conveys four main types of linguistic information:

1. Segmental cues that assist with identifying the place of articulation such as voiceless fricatives (Dorman et al., 1980) based on rise and fall time of the fricative based on rise and fall time as well as duration, for example short release transients are indicative of plosive sounds. Rapid changes in overall amplitude distinguish consonants from non-consonants (Stevens, 1980,1981; Stevens and Blumstein, 1981), or continuants from non-continuants (Shinn and Blumstein, 1984).

2. Segmental cues for voicing, vowels typically have a greater amplitude than voiceless obstruents. It is thought that the existence and duration of the silent gap is important for distinguishing voiced from unvoiced plosives (Umeda, 1975).

3. Segmental cues that allow vowel identity based on the duration and quality change in the vowel sound, for example the vowel in “heed” is of significantly longer in duration than that in “hid” (Lehiste, 1970).

4. Prosodic cues that assist with syllabification. Dynamic envelope cues and relative amplitude provide some information on where stress is assigned in words, providing distinctions in meaning (Crystal, 1969). Information on speech rate can assist listeners distinguishing between segmental and prosodic contrasts (Miller, 1981).

Periodicity:

Includes the properties of speech which are periodic (sounds fluctuating at rates between 50-500Hz) and aperiodic (sounds fluctuating at rates between 2Hz up to 5-10kHz). As both sounds differ greatly in rate of fluctuation, the acoustic contrast of periodicity versus aperiodicity is reflected in the time domain as regularity versus irregularity of the speech signal, and in the frequency domain as the distinction between the harmonic and continuous spectrum (Rosen, 1992). Periodicity information conveys two main types of linguistic information:

1. Segmental information about voicing manner, the presence of low frequency quasi-periodic acoustic energy in a speech signal reflects the vibrations of the vocal folds (for example, the /m/ of mate). These voiced sounds provide the most important cue to the phonological feature in voicing and the most basic distinction between manner and voice features obtained from phonetic voicing patterns. Speech segments that are aperiodic are a result of noise generated by aerodynamic flow between closely spaced articulators, and provide a strong cue for voicelessness, or the fricative manner of articulation (Rosen, 1992).

2. Prosodic information associated with intonation and stress, the fundamental frequency of quasi-periodic energy in speech reflects the rate of vocal fold vibration and provides the perception of voice pitch. Linguistically meaningful patterns of voice pitch are known as intonation and tone, both play a crucial role in accenting syllables in words and sentences, in clarifying pronoun references and in marking syntactic units, and separating questions from statements (Fry, 1986; Rosen and Fourcin, 1986; Lehiste, 1970 and Rosen, 1992).

Temporal fine structure:

Rosen (1992), refers to variations of wave shape within single periods of periodic sounds, or over short time intervals of aperiodic ones as fine structure information, which informs about the spectrum of sound (amplitude and phase) and contain the formant patterns. Fine structure relates to timbre and quality of speech which conveys two types of segmental linguistic information:

1. Segmental cues to place of articulation and vowel quality, this is considered the most important function of fine structure as spectral shape variations are the only acoustic cues to place. Voiceless fricatives in English can be distinguished from one another on the basis of static spectral shape or the formant transitions in the following vowel, with the importance of each cue strongly dependent on the particular place of articulation (Harris, 1956). Spectral shape is the major cue to vowel identity.

2. Segmental cues to voicing and manner, voiced sounds have a spectrum that is heavily weighted below 1kHz, hence tend to have low fluctuation rates, whereas voiceless sounds have peak energies at considerably higher frequencies, thus higher fluctuation rates. Studies have shown that first formant transitions play some role in distinguishing English voiced from voiceless plosives in initial prevocalic position (Soli, 1983; Stevens and Klatt, 1974). The shape of the spectrum can also signal cues to manner, for example, nasals, are characterised by low first formant frequency, broad resonances, and zeros in the spectrum (Fujimura, 1962). Additionally, sudden spectral changes that occur in conjunction with sudden envelope changes can assist with distinguishing consonant sounds from non-consonant sounds (Stevens, 1980, 1981)

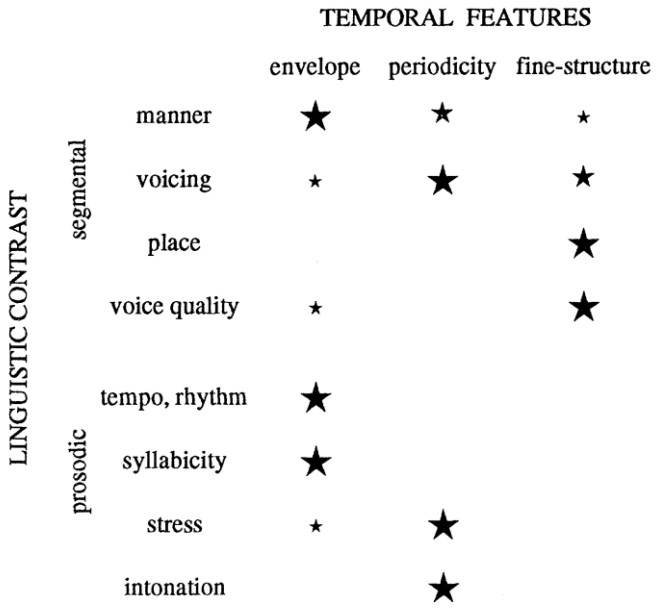

Figure 21: The temporal features of speech in linguistic contrasts. The size of the stars indicates the extent to which a particular feature operates in a linguistic contrast, with a blank space indicating very weak or non-existent cues. Periodic cues, which occur across a number of segments, are cued by slow rate categories. From Rosen (1992). Reproduced with permission, copyright The Royal Society (U.K).

Studies have shown that spectral cues alone are insufficient for robust speech decoding (McDermott, 2009; Moore & Gockel, 2002) and emphasise the central role of temporal cues in in providing a contact within which the spectral content is processed. Several psychophysical studies have demonstrated that speech becomes less intelligible when the temporal structure of speech is modified and presented at unnaturally slow or fast rates, even when the fine structure is preserved (Ahissar et al., 2001; Ghitza & Greenberg, 2009) or if its temporal envelope is smeared (Arai & Greenberg, 1998; Drullman, 2006; Drullman, Festen, & Plomp, 1994a, 1994b; Greenberg, Arai, & Silipo, 1998; Stone, Fullgrabe, & Moore, 2010). These findings show the critical importance of the temporal structure of speech for its intelligibility. In contrast previous studies have investigated the minimal information required to comprehend speech in NH listeners in conditions of reduced spectral information and demonstrated that a high level of speech recognition is maintained even when all spectral cues in speech were removed as long as the temporal envelope is preserved (Drullman et al., 1994; Shannon et al., 1995). Shannon et al., (1995) presented envelope information that was low-pass filtered at successively lower frequencies and used to modulate bands of noise as a carrier. Listeners were able to decode continuous speech with remarkable accuracy, and no change in performance was observed when the low pass filter cut off was 50Hz or higher.

Removing envelope fluctuations above 50 Hz had no effect on recognition, while removing envelope fluctuations between 20 and 50 Hz resulted in reduced phoneme discrimination and reduced speech recognition. Therefore, speech recognition is possible with only three spectrally adjacent bands of noise, even when each band is modulated by the low frequency envelope information below 50 Hz. Drullman et al., (1994) measured speech recognition in NH listeners when slow or fast envelope modulations were removed from the speech signal. The speech recognition score remained the same when the envelope fluctuations below 16 Hz were preserved. Reductions in envelope frequencies below 16 Hz resulted in a significant decrement for consonant recognition. This work indicates that while spectral information is of course important in decoding speech, it is not vital and the temporal envelope carries more relevant information for speech recognition.

3.11 Temporal coding in cochlear implants

CI users have limited spectral resolution therefore the reliance on temporal information is heightened. Two areas relevant to temporal coding in CI devices that have received attention in the literature are pulsatile stimulation rate and modulation depth perception. In CIs current is delivered to the electrodes in the form of amplitude modulated trains of biphasic pulses. The modulation waveforms are generated proportional to the temporal envelopes of band-pass filtered components of the acoustic signal. Therefore, the extent to which CI recipients are able to efficiently process temporal envelope information is likely to influence their overall benefit with a CI. Although speech coding strategies such as ACE extract the temporal envelope of speech, CI users are restricted by the temporal response of a fixed FFT and sampling rate. The Nucleus 512 and 532 devices implement an audio sampling rate of 16 kHz and a fixed FFT length of 128 points (see FFT section above) and completes 125 analyses per second (1600/128). The temporal response of the filter is similar to a low-pass filter with a cut off at 125 Hz, which would suggest the envelope bandwidth is effectively limited to 125 Hz and minimal information is available in the envelope above 125Hz. To increase the temporal information there would need to be an increasing overlap between each FFT analysis with the previous frame so that the number of overlapping analyses is equal or close to the stimulation rate. The Nucleus 6 processor used in the present study can employ a range of stimulation rates from 250 pulses per second per channel (pps/ch) up to 3500 pps/ch. As the stimulation rate is increased there is less overlap between the data points with each analysis, this suggests that unless filter bank parameter such as the sampling rate (are shortened) or FFT length (is decreased) is co-varied with higher stimulation rates there is likely to be minimal benefit in temporal detail for the envelope.

Limitations in filterbank technology may explain why studies using Nucleus devices and the ACE strategy show variable benefits of increased pulsatile stimulation rates (Vandali et al, 2000; Holden et al, 2002; Weber et al, 2007; Plant et al, 2007; Arora et al., 2009). Vandali et al., (2000) investigated the effect of varying stimulation rate from 250, 807, and 1,615 pps/ch on speech comprehension of five listeners using the Nucleus 24 cochlear implant. Open-set monosyllabic words in quiet and open-set sentences at different signal-to-noise ratios were used. The study showed no significant difference in speech recognition between 250 and 807 pps/ch and significantly poorer performance in noise was obtained for the 1,615 pps/ch rate, although this is largely attributed to the result of one subject in the study. A questionnaire completed by subjects in the study also showed a preference for lower rates of stimulation compared to the 1615 pps/ch rate.

However, Holden et al., (2002) compared stimulation rates of 720 pps/ch and 1800 pps/ch in eight adult subjects using Nucleus 24 implants with the ACE strategy and found that two subjects obtained better performance with 1800 pps/ch compared to 720 pps/ch, at lower intensity levels (50dB SPL). Testing in noise showed significantly higher scores with the 720 pps/ch rate for two subjects, whereas one subject performed better with the 1800 pps/ch, and similar to Vandali et al., (2000) the preference for stimulation rate also varied. Both the studies by Vandali et al (2000) and Holden et al (2002) are unlikely to have been able to demonstrate the effects of higher stimulation rates due to the limited analysis rate of 760 Hz employed in the SPRINT processor used in those studies. Due to the small sample size in both studies neither are able to demonstrate a robust relationship between stimulation rate and speech performance.

Likewise, Plant et al (2007) compared high and low rate stimulation rates in fifteen subjects and also varied the maxima. No significant differences were observed in speech recognition between stimulation rates but five subjects showed individual benefits and obtained significantly better scores with higher rates (2400 pps/ch and 10 maxima, or 3500 pps/ch and 9 maxima) compared to lower rates (1200 pps/ch and 10 maxima, or 1200 pps/ch and 12 maxima) for speech tests conducted in either quiet or noise. Two subjects obtained significant benefit in both quiet and noise with the higher set of rates. However, four subjects in the study remained on the lower rate program for an additional three-twelve weeks which resulted in significant learning and three of these subjects reported preferring the lower rate program.

Similarly, Weber et al (2007), did not demonstrate a significant difference between stimulation rates of 500, 1200, and 3500 pps/ch using the ACE strategy and speech perception scores in quiet and noise. Although, some variability in individual scores was observed for sentences in noise with six of the fourteen subjects obtaining benefit with the higher rate programme. Arora et al., (2009) investigated low to moderate stimulation rates of 275, 350, 500, and 900 pps/ch and compared speech perception performance for eight subjects with the Nucleus CI24 CI using the ESPrit 3G processor. The majority of subjects showed a preference for 500 pps/ch and achieved better performance on speech perception in noise with rates of 500 or 900 pps/ch but no significant effect of rate was found for monosyllabic word tests. Collectively these studies show the benefit of higher stimulation rates are not conclusive although one reason for individual variations could be attributed to the effects of channel interaction (see channel interaction section), which is greater at higher stimulation rates (Brill et al., 1997).

Other studies have evaluated stimulation rate in Med-el CI devices using the continuous interleaved sampling (CIS) speech coding strategy and have shown benefits for moderate and high stimulation rates (Loizou et al, 2000; Verschuur, 2005; Nie et al, 2006). Verschuur (2005) evaluated speech perception performance across various rates of stimulation (ranging from 400-2020 pps/ch) for six users of the Med-El Ineraid and Combi 40 + CI. Subject performance displayed no effects of stimulation rate for sentence testing, consonant recognition and categorical identification of acoustic speech cues. However, two subjects showed significantly reduced sentence scores at lower rates, which would suggest that sentence testing is more sensitive to rate changes and higher stimulation rates may be advantageous for certain individuals.

In contrast, Loizou et al., (2000) found a significant effect of rate on speech performance of six Med-el CI users on a number of speech materials. Speech scores were obtained at stimulation rates of 400, 800, 1400, and 2100 pps/ch and results showed that higher stimulation rates between 800-2100 pps/ch produced a significantly higher performance on word and consonant recognition than lower stimulation rates lower than 800 pps/ch. The VCV consonant test with the aCa context showed less sensitivity to changes in rate in comparison to when used in the iCi or uCu context. The authors suggested that this may be due to the formant transition being more critical in the aCa context as a signal to place of articulation. However, it is likely that the place of articulation is dependent on spectral resolution so higher rates would enable better coding of the onset frequency of the formant transition and would have therefore been expected to have a larger impact on place of discrimination.

Nie et al., (2006) varied the stimulation rate from 1000 to 4000 pps/ch on four pairs of fixed electrodes in five users of the Med-El COMBI 40+ and reported a significant advantage of higher stimulation rates for consonant recognition and sentence scores in noise. These results add weight to the findings of Shannon et al., (1995) and support the argument that temporal cues from limited spectral bands are adequate for speech perception in quiet, however, speech recognition in noise is more dependent on spectral resolution (Dorman et al, 1999; Qin and Oxenham, 2003).

The effect of stimulation rate on speech perception does not show a clear trend and comparisons are complicated by the use of different CI systems. Differences in results between studies may be caused by factors such as stimulation mode, number of electrodes used, stimulus intensity, the speech coding strategy used, speech material used, amount of practice with a given stimulation rate and prior experience with a CI. Studies which found a significant effect of rate on speech recognition used with higher rates (Loizou et al., 2000), 2100 pps/ch), in comparison to most of the studies with the Nucleus devices which have used lower rates (Fu and Shannon, 2000; Vandali et al., 2000; Holden et al., 2002; Arora et al., 2009). It is possible that some of these studies did not use a high enough stimulation rate to cause desynchronisation of the SGNs and are therefore not close enough to the subject's stochastic rate which prevents any benefit in speech performance.

3.12 Channel interaction

The Nucleus Ltd implants have 22 intra-cochlear electrode sites and each electrode conveys information for a specific frequency range (Henry et al., 2000; Nelson et al., 2011). Typically, electrodes are positioned in relatively close proximity to adjacent electrodes, hence the electrical current fields are not distinct and broader stimulation can cause increased channel interaction, which is defined as any effect that the stimulation of one electrode channel has on the activation of a spatially separated channel (Cohen et al., 2003). It has been suggested that higher levels of channel interaction lead to spectral blurring of the speech signal which leads to degraded speech perception in CI users (Friesen et al., 2001; Stickney et al., 2006; Jones et al., 2013). Earlier studies of channel interaction have shown that speech outcomes do not improve when the number of channels increase above 10 (Dorman and Loizou 1997; Hanekom and Shannon 1998; Friesen et al., 2001; Fu and Nogaki, 2005; Fishman et al., 1997; Shannon et al., 2011), suggesting that channel interaction makes neighbouring electrodes less distinguishable and therefore limits speech perception.

Friesen et al., (2001), varied the number of channels for NH subjects (listening to acoustic vocoder simulations of CIs) and post-lingually deafened CI subjects to determine the number of effective channels that could be accessed by CI users. For NH subjects, average sentence recognition scores of 100% were reached with 6–8 channels in quiet, and 8–10 channels in noise (+10 dB signal-to-noise ratio). CI users were able to obtain an average score of 80% correct in quiet and 60% in noise for eight channels or greater. These findings suggest that increasing the number of available electrodes past eight does not increase performance as CI users cannot access more than eight effective channels even when a higher number of electrode sites are available (16-22 electrodes in the devices included in their study). These results are consistent with other studies that speech recognition does not improve beyond 8–10 spectral channels for CI users (Fishman et al., 1997; Friesen et al., 2005; Shannon et al., 2011). However, more recent studies have demonstrated that with newer pre-curved electrode arrays, speech perception increased when the number of channels were increased beyond 12 (Croghan et al., 2017; Berg et al., 2019a). In contrast, Berg et al., (2019b) demonstrated there was no significant benefit in speech performance when the number of channels was increased beyond 8-10 in CI users with a pre-curved electrode array.

The variability seen in speech performance across CI users (Blamey et al., 1996; Holden et al., 2013) may be explained by the differences in the conditions of neural function near each individual electrode (Pfingst et al., 2015). CI users are limited by the electrode-neural interface, which refers to the interface between the CI electrode and the target SGNs (Bierer 2010), hence a well-functioning electro-neural interface is a critical component for the transmission of speech signals through a CI. It is likely that all electrode-neural interfaces in an implant cochlea are not equally effective, with some stimulation sites contributing more significantly than others to a subject's speech perception. Several peripheral factors contribute to sub-optimal interfaces such as the degree of SGN degeneration inherent to CI users (Pfingst et al., 2011); and how far the electrodes are positioned from the target SGNs (Bierer 2010; Miura et al., 2002; Finley et al., 2008; Long et al., 2014). Degeneration of SGNs and central auditory system neurons occurs in the absence of auditory input (Otte et al., 1978), therefore the duration of auditory deprivation prior to cochlear implantation is likely to contribute to the quality of the electro-neural interface.

Longer durations of auditory deprivation are likely to result in suboptimal interfaces, thus, the efficacy of each channel of stimulation differs between individuals. It is quite possible that spectral speech cues transmitted via channels with poor quality interfaces are smeared due to the overlap of current between channels. Previous studies have shown that sparser neural

survival results in higher detection threshold (requiring more electrical current) which results in a greater spread of excitation resulting in poorer spectral resolution (Bierer and Faulkner 2010; Long et al., 2014, DiNino et al., 2019). The hypothesis that the variability in speech performance can be explained by duration of deafness is supported by Leung et al. (2005) who examined a large group of CI recipients between the ages of 14 to 91 years in a multicentre study. CI users were divided into a younger group (<65 years of age, n = 491) and an older group (≥65 years of age, n = 258). Post implant monosyllabic word scores significantly declined with longer duration of deafness in both groups.

Several studies have investigated if speech perception scores can be improved by using site-selection strategies that disable poor performing channels in a subject's MAP, thereby reducing channel interaction (Zwolan et al., 1997; Noble et al., 2013, 2014; Bierer and Litvak 2016; Garadat et al., 2013; Vickers et al., 2016; Goehring et al., 2019b). Some of these studies demonstrated improvements in speech perception (Zwolan et al., 1997; Garadat et al., 2013; Saleh et al., 2013; Noble et al., 2013, 2014) and others did not find significant improvements (Henshall and McKay, 2001; Vickers et al., 2016; Bierer and Litvak 2016; Goehring et al., 2019b).

For example, Zwolan et al (1997) assessed users with an older generation Cochlear Ltd device, Mini-22 and deactivated channels based on poor electrode discrimination. They found a significant improvement in speech perception for seven out of the nine participants in their study, however there was considerable individual variability in the benefit obtained. Similarly, in the study by Garadat et al., (2013), speech perception improved in all 12 subjects when the electrodes with the high amplitude modulation detection thresholds (poor temporal sensitivity) were deactivated. They reported significant benefit for consonant recognition and sentence scores in noise for eight out of twelve subjects, although they showed a deterioration in vowel recognition scores in seven out 7 out of twelve subjects. Other studies showed improved speech performance among CI users when electrode sites were deactivated based on the results of computed tomography imaging (Noble et al., 2013, 2014); which predicted which channels had the highest degree of interaction with other channels. However, the authors do not provide any psychophysical or electrophysiological evidence to support that the channels selected by their computational model for deactivation were in fact those with high levels of channel interaction.

Some studies have not found any benefit from electrode deactivation, Henshall and McKay (2001) disabled electrodes with poor pitch precepts and demonstrated no improvements in

speech perception scores, and some subjects' showed performance deteriorated. Although not statistically significant, Bierer and Litvak (2016) found that deactivating channels with high focused thresholds, increased consonant and vowel identification scores for poor performing subjects which suggests that channel reduction has the potential to benefit certain CI users. Similarly, Vickers et al., (2016) deactivated in-discriminable electrodes in thirteen subjects with Cochlear Ltd devices and compared speech perception scores with their optimised clinical maps. They found there were no significant benefits of electrode deactivation on speech perception which may suggest that channel reduction is not beneficial for users of n-of-m speech coding strategies.

Some methodological differences between studies are likely to account for some of these mixed results. Most of these studies used different devices and measures to select the channels for deactivation which makes comparison of results more difficult. Additionally, factors such as neural survival and the distance of the electrode from the SGNs were not taken into account in most of these studies. Studies have shown that electrodes that are further away from neural tissue have a wider spread of excitation leading to higher channel interaction (Long et al., 2014). When electrodes are deactivated the frequency allocation of the remaining channels is broadened and shifted apically, resulting in the experimental MAP sounding significantly different to the subjects optimised MAP. Most studies did not account for learning effects and subjects were not given an adequate period of time to adapt to their experimental MAPs; it is therefore possible that speech scores may have been better than reported in some studies if subjects were provided an acclimatisation period.

Other researchers have explored another approach to improving the electrode-neuron interface by using current focusing methods which simultaneously stimulate a number of neighbouring electrode channels to restrict the spread of neural excitation, hence reducing channel interaction. Computational modelling studies have demonstrated that current level requirements are higher and the spread of excitation is broader for electrodes further away from the SGNs or near a region of neural degeneration (Goldwyn et al., 2010; Kalkman et al., 2015). Models of electrical current flow have demonstrated the broadest spatial extent of electrical fields with monopolar (MP) stimulation modes, and progressively more narrow fields with bipolar (BP) stimulation. All subjects in the present study used MP stimulation which would suggest a larger number of SGNs are likely to be recruited due to the increased spread in excitation (Spelman et al., 1995; Jolly et al., 1996; Kral et al., 1998; Briare and Frjins, 2000). Overlapping excitation patterns between adjacent electrodes may distort spectral and

temporal information resulting in decreased pitch and speech perception (Favre and Pelizzone, 1993; Abbas et al., 2004; Boex 2003; Crew et al., 2012; Hughes 2008; Jones et al., 2013; Pfingst et al., 2004; Snel-Bongers et al., 2012).

Similar to channel deactivation, results of studies investigating the relationship between focused stimulation and speech perception have shown mixed outcomes. Most studies have not demonstrated a benefit (Mens and Berenstein 2005; Berenstein et al., 2008; Bierer and Litvak 2016; Langner et al., 2017; DeVries and Arenberg 2018) and only one study has demonstrated significant benefit in individual subjects (Srinivasan et al., 2013). Srinivasan et al., (2013) compared speech perception in noise in six CI users with an experimental monopolar and partial tripolar strategy and demonstrated a significant improvement in speech perception in noise with partial tripolar stimulation, with a mean improvement in speech sentence recognition thresholds of 3dB. The authors suggest that as partial tripolar stimulation uses two intra-cochlear electrodes, this reduces current spread in the cochlea in comparison to monopolar strategies where the ground electrode is extra-cochlear which results in a wider spread of current. Studies have shown than partial tripolar stimulation requires larger current levels to reach adequate loudness levels, which could lead to greater power consumption and issues with voltage compliance limits (Bierer and Litvak, 2016).

Berenstein et al., (2008) compared speech perception with monopolar and partial tripolar speech processing strategies in steady and fluctuating noise and found no benefit with focused stimulation in speech perception., although they reported that CI users with relatively poor speech perception performed better with speech recognition tasks when using the focused stimulation strategy. More recently, DeVries et al., (2016) found a relationship between electrode position, current spread, and focused behavioural thresholds using eCAP measurements and computed tomography, in ten unilaterally implanted adults with Advanced Bionics HiRes90k devices. The width of the eCAP spread of excitation was positively correlated with the electrode-to modiolus distance in most subjects. The eCAP peak amplitudes were negatively correlated with behavioural thresholds, and channels with smaller amplitudes had higher behavioural threshold indicative of poor neural survival and or synchrony in those region. Subjects with larger eCAP peak amplitudes and lower behavioural thresholds demonstrated better speech perception scores, which suggest that the eCAP peak amplitude may be sensitive to neural status and can be used as a proxy for neural health.

With simultaneous stimulation, current fields can interact by summing or subtracting prior to neural stimulation, which may cause over stimulation or an insufficient amount of current

(White et al., 1984; Abbas and Brown, 1988; Boex et al., 2003a; Middlebrooks, 2004;). In order to reduce these effects, speech processing strategies such as ACE use sequential pulse presentation, however, non-simultaneous channel interaction can still occur due to forward masking effects within the stimulated neural population. Forward masking is the mechanism by which the SGNs respond to the first stimulus but are unable to respond to the following stimulus due to neural refractory properties (see section on eCAP and refractory properties). When a stimulus is presented at a supra-threshold level the SGNs ability to respond to the second stimuli is depressed (Shannon 1999). Throckmorton and Collins (1999) demonstrated that forward masking of one pulse over a successive pulse serves to blur between-channel amplitude differences, which may lead to reduced speech perception. They reported a significant correlation between average psychophysical forward-masking levels and speech recognition for sentences, consonants, and phonemes in seven Nucleus 22 recipients using BP stimulation and found 3 of the subjects with the narrowest stimulation patterns demonstrated better spatial selectivity and had the highest speech perception scores. This is similar to the findings of Chatterjee and Shannon (1998) who showed higher degrees of neural overlap compromised speech recognition scores, although they found that the effects of forward masking were reduced as the interval between the masker and probe increased.

3.13 Amplitude modulation detection

Speech signals display prominent low frequency modulations in their temporal envelope. Modulation frequencies which are close to the average syllabic rate of 3-4Hz are the most pronounced. When these are modulation frequencies are degraded there is a marked reduction in speech intelligibility (Drullman et al., 1994; Drullman et al., 1994; Houtgast and Steeneken, 1973). Amplitude modulation detection is a measure of temporal sensitivity and NH listeners can perceive amplitude fluctuations as shallow as 5% for modulation frequencies below 60 Hz. Above that frequency, modulation sensitivity decreases by about 3 dB per octave, until they reach 1 kHz, at which modulations evoke a percept of a steady sound, rather than rough fluctuations (Viemeister, 1979). Variations in amplitude over time are salient for speech perception because components of prosodic and segmental information are provided by fluctuations in the amplitude envelope (Blamey et al., 1985; Grant et al., 1985; Van Tasell et al., 1987; Freyman et al., 1991). Temporal modulation transfer function (TMTF) can be used to determine the temporal resolution of the auditory system and is a physical measure of the amplitude modulation (AM) detection thresholds as a function of modulation rate (Galvin and Fu 2005). The TMTF is a plot of modulation detection threshold as a function of modulation frequency and has been described in both normal (Viemeister., 1979; Bacon and Viemeister, 1985,

Moore and Glasberg, 2001) and electric hearing (Cazals et al., 1991; Shannon, 1992; Busby et al., 1993; Fu, 2002).

It was shown that TMTFs from CI users have higher cut off frequencies (between 100 and 200 Hz) than the typical acoustic TMTFs in NH listeners, which is approximately 68.8 Hz (Bacon and Viemeister, 1985) and the TMTF function is independent of stimulus level (Viemeister 1979; Moore and Glasberg, 2001). In comparison Shannon (1992) measured TMTFs in post-lingually deaf CI users by taking three types of measurements, detection of amplitude modulation, detection of low-frequency sinusoidal waves and detection of beats in two-tone complexes. The response pattern of the TMTF was similar across the three tasks and CI users typically demonstrate similar low pass filter characteristics to those obtained in NH listeners. These results would suggest that temporal envelope cues are largely dependent on amplitude coding can be conveyed by relatively low stimulation rates. However, the TMTFs had a higher mean cut off frequency of 140 Hz and varied as a function of stimulus level, with poorer temporal modulation detection thresholds at lower stimulus levels.

Busby et al., (1993) measured perception of temporal modulations in 7 CI users for a series of modulation frequencies, pulse rates and pulse durations. They estimated the low pass filter cut off frequency was between 50-100Hz (lower in comparison to Shannon, 1992). Of relevance to the present study, Busby et al., (1993) used duration of deafness as a predictor of temporal processing, three of the subjects in the study were pre-lingually deaf and their overall perception of temporal information was poorer in comparison to the four post-lingually deafened subjects. However, it should be noted that the deafness onset of deafness for the three pre-lingually deaf subjects was meningitis which can cause a significant loss of SGNs (Nadol et al., 1989). These results suggest that there is considerable variation in temporal processing between individual CI users although it is not clear if these differences are due to central or peripheral contributions.

Other studies which have investigated the relationship between temporal processing and speech recognition abilities. Cazals et al., (1991) investigated the correlation between basic temporal psychophysical abilities and speech perception in 5 Ineraid CI users. They measured the detection of a silent gap in noise and interval between two. The results showed a significant correlation between the temporal resolution of clicks at the most basal cochlear electrode and the perception of place of articulation of consonants. Fu and Shannon (2000) measured phoneme recognition in CI users and NH listeners as a function of the low-pass cut off

frequency and found no significant difference in performance in both groups for cut off frequencies above 20 Hz. Both vowel and consonant scores dropped significantly when the cut off frequency was reduced from 20 Hz to 2 Hz, this is interesting as it would suggest that only very low level modulation rates are required for phoneme recognition and increasing the envelope cut off frequency above 20Hz does not provide additional temporal information,

Of significance are the findings of Fu (2002), previous studies measured modulation detection performance at higher stimulus levels closer to the C (comfort) level of the MAP, in contrast Fu (2002) measured the modulation detection thresholds across a range of stimulus levels. A strong correlation was found between phoneme recognition scores and mean modulation thresholds in 9 CI users who were recipients of the Nucleus 22 CI and were using the SPEAK processing strategy. The results showed that the mean modulation detection threshold averaged across all input levels was a strong predictor of phoneme recognition, which highlights the importance of temporal processing abilities in CI users. These results suggest that CI users' psychophysically measured temporal resolution is related to their speech recognition abilities.

Use of high rate pulse trains may provide better temporal sampling of the speech signal and is likely to increase the stochastic response properties of the activated SGNs (Rubinstein et al., 1999; Wilson et al., 1997). In doing so this reduces atypical phase locking which desynchronises neural firing patterns without excessive reductions in the probability of firing across the neural population; so that the rapid amplitude modulations of speech may be encoded more accurately by the auditory nerve. However, as mentioned, high rate stimulation in CI users has not consistently shown to improve speech recognition in CI users.

Neural firing has been shown to synchronize with rate cycles of up to 1000 Hz in human electric hearing (Wilson et al.,1997). CI users who typically lack synaptic noise which is a caused by the release of neurotransmitter at the synaptic cleft between the IHC and SGN and results in spontaneous neural firing. Thereby, placing ANFs in varying states of refractoriness and hence limiting the synchronous response to a stimulus. In CI users, a potential source of noise is the voltage sensitive sodium channels at the neural membrane (Wilson et al, 1994; Rubinstein et al, 1999). Wilson et al (1994) suggested that for pulses presented at high rates, low levels of neural noise "jitter" may be introduced due to refractoriness and/or discharge of the neural membrane. This jitter is likely to increase with time and interact with pulses to produce levels of stochastic independence among SGNs. Hence, if a greater population of

SGNs are kept out of their absolute refractory period it is possible to reduce the amount of a temporal smearing, which weakens the salience of the amplitude envelope, consequently this would allow a better neural representation of the temporal fluctuations in the speech signal.

Fu and Shannon (2000) also evaluated the effect of stimulation rate on consonant and vowel recognition in CI users and found that recognition improved as stimulation rate was increased from 50 to 150 pps/ch, but no further significant improvements were seen when the rate was increased from 150 to 500 pps/ch. Similarly, Pfingst et al., (2007) found subjects had better modulation detections for lower rates (250 pps/ch) compared to higher rates (4000 pps/ch), although the authors reported a significant effect of stimulation site, and modulation detection abilities were better at the apical stimulation site. This finding may be attributed to the differences in neural survival patterns between individuals (Hinojosa and Lindsay, 1980; Nadol, 1997) and across site variations in modulation detections suggest that testing at one or two sites (as in the studies by Shannon, 1992; Busby et al, 1993; Cazals et al, 1994; Fu, 2002; Galvin and Fu, 2005) may not provide a complete assessment of a CI recipient's modulation sensitivity.

Galvin and Fu (2005) examined the effects of stimulation rate and level on modulation detection thresholds in CI users and found a significant correlation between stimulation rate and level, with an improvement in modulation detection at low stimulus levels when using a low stimulation rate (250 pps/ch) compared to a high rate (2000 pps/ch), suggesting that the carrier rate strongly affects modulation sensitivity. Consistent with the findings of Shannon (1999) they reported that modulation sensitivity was poorest at quiet listening levels. Which would suggest that CI users may not have access to the enhanced temporal cues provided by high stimulation rates especially nearer their T (Threshold) levels. It should be noted that the results in this study were obtained by direct stimulation which therefore does not take into account the impact of CI signal processing.

Based on the evidence it is not clear how much temporal information CI users have access to, with perceptual measures (such as the psychophysically measured TMTF) it is not possible to delineate if temporal information loss is due to limitations in CI signal processing or due to the underlying neural physiology (loss of information at the electro-neural interface). Given the large variability in TMTFs reported in the above studies it is possible the electro-neural interface plays a more significant role in accounting for temporal information loss. To date there have been no studies which have utilised objective measures (such as eCAP recovery function) in combination with psychophysical measures of temporal processing which could

assist with identifying the source of temporal information loss. Therefore, the question of how much access a given individual has to temporal information remains unanswered. In the following chapter methods in which these measurements can be completed are discussed.

Chapter 4: Objective and Behavioural Measures of Temporal Processing

There is currently not a strong evidence base to account for the large individual differences and variability in speech recognition among CI users. In current clinical practice most speech outcome measures are also not directly linked to the underlying mechanisms that may contribute to variations in outcomes. The following chapter provides an overview of the literature on how temporal processing can be measured both objectively and behaviourally in CI users in an attempt to identify the possible sources of individual differences in performance.

The two main questions which drive this review are:

1. What are the individual differences in temporal processing that may influence speech perception?

2. Are there intra-cochlear regional differences in temporal processing in CI users that may influence speech perception?

4.1 What are the individual differences in temporal processing that may influence speech perception?

As described in Chapter 2, section 2.5, it is hypothesised that one reason for the large individual variability in CI users is the difference in neural survival patterns across different subjects. Although a firm connection between SGC count and speech perception has not been established (Fayad et al., 2006; Khan et al., 2005) it is likely that the success with a CI depends on the presence of an adequate number of healthy SGCs. Poor neural function is likely to impede the transmission of speech information to the auditory nerve and limit outcomes with a CI. It is not clear how patterns of neural survival affect speech performance, objective and behavioural measures could assist clinicians optimise programming parameters in order to improve information transfer in CI users. It is hypothesised that neural health will be more significantly compromised in CI users with pre-lingual deafness and longer periods of auditory deprivation prior to cochlear implantation when compared to post-lingually implanted CI users. We would therefore expect temporal processing abilities to vary between these subjects.

As it is not feasible to directly measure the SGC count in CI users, information regarding the synchronous firing of a population of ANFs and temporal response properties can be obtained by measuring the eCAP recovery function. The refractory recovery of the auditory nerve can be evaluated using the single-pulse forward masking paradigm for eCAP measurement (Brown et al., 1990; Miller 2001). This technique utilises a masking pulse that causes the ANFs to enter a refractory state where they are unable to generate an action potential to the subsequent probe pulse. As eCAPs are generated within the cochlea they are likely to reflect the quality of the neural structures at the electrode-neural interface, there is currently insufficient evidence on how eCAP recovery time constants vary along the cochlea. The eCAP recovery function is not routinely used in clinical practice and we are still limited in our knowledge on its characterisation in CI users and its utilisation as a predictor of speech performance. Robust eCAP response depends on highly synchronised neural activity, therefore predicted poor neural survival in the pre-lingual group is likely to result in less synchronised neural responses which may reduce neuronal refractoriness and result in eCAPs with a smaller overall amplitude and prolonged eCAP latencies. The purposes of this study is to evaluate refractory properties of the auditory nerve in adult CI users with pre-lingual and post lingual deafness using the eCAP recovery function and to investigate the correlation between eCAP recovery time constants, behavioural measures of temporal resolution and speech perception abilities.

It is also plausible that subjects with pre-lingual deafness will have greater central temporal processing deficits due to a reduced number of effective channels being available to relay spectro-temporal information to the central auditory system; therefore, we hypothesis that behavioural measures of temporal resolution may be a useful tool in reflecting such impairments. It is hypothesised that objective measures of temporal processing, measured by eCAP recovery function are correlated to behavioural measures of temporal resolution, measured by GDTs. It is hypothesised that subjects with pre-lingual deafness will have slower eCAP recovery functions and elevated GDTs which is likely to result in poorer speech performance. This leads us to the second question:

4.2 Are there intra-cochlear regional differences in temporal processing in CI users that may influence speech perception?

Studies have shown that the cochlear pathology and neural survival patterns are highly variable along the length of the cochlea (Hinojosa and Marion 1983; Khan et al., 2005; Fayad et al., 2009). Therefore, localised differences in neural survival are likely to result in different

neural firing patterns. There is limited evidence regarding the variation of GDTs at different stimulation sites, some studies have suggested across site differences may relate to the difference in neural function in the cochlea near the stimulating electrode (Pfingst et al., 2008). By measuring the eCAP recovery function and GDTs at different locations along the implant array the aim is to determine whether the two measurements are correlated with each other, since they could both be influenced by neural survival. We hypothesise that eCAP recovery times will be faster and GDT thresholds will be shorter in apical regions compared to basal regions as SGC survival tends to be higher in this region (Khan et al., 2005; Fayad et al., 2009).

Theoretically, high stimulation rates available in CIs should enable better sampling of the speech signals by reducing synchronous firing of SGNs. However, as outlined later on in this chapter this has not been a consistent finding in previous studies. Individuals with sparser localised neural populations, may not benefit from higher stimulation rates due to spatial overlap of excitation (see section 3.12) and it is unclear if stimulation rates that produce different neural firing patterns (stochastic firing) are correlated to better speech perception. It is possible that GDTs at high stimulation rates may be poorer in some subjects as temporal characteristics such as fine structure are compromised when the time interval between pulses reaches the refractory period which would compromise the transfer of the temporal gap. Javel (1990) showed a reduction in the synchronisation of discharge probability of auditory neurons as the pulse rate reached the refractory period and pathological changes, such as demyelination that are associated with long durations of deafness lead to an increase in the refractory period (Shepherd and Javel 1997), which is likely to compromise representation of the temporal structure of the stimuli. This study therefore examined if there were any differences between the objective and behaviour measures between subjects based on their existing stimulation rates and if this was correlated to their speech performance.

4.3 Current evidence base for eCAP recovery function and speech perception

There are only six studies (Brown et al., 1990; Gantz 1994; Keifer et al., 2001; Turner et al., 2002; Fulmer et al., 2011 and Lee et al., 2012) which have investigated the correlation between eCAP recovery function and speech perception in CI users. Keifer et al., (2001) found a significant correlation in speech performance, for three speech coding strategies; spectral peak, continuous interleaved sampling, and advanced combination encoders in nine post-lingually deaf adults. Brown et al., (1990), found a significant correlation between the slope of

eCAP recovery and speech perception scores and postulated that subjects with steep recovery curves are likely to perform better with electrical stimulation compared to subjects with shallow recovery functions. The other studies (Gantz 1994; Keifer et al, 2001; Turner et al, 2002 and Lee et al, 2012) found no significant correlation, however, Fulmer et al (2011) found significantly faster recovery functions were associated with better speech recognition thresholds in noise for children with Auditory Neuropathy Spectrum Disorder (ANSD) and SNHL. Although not significant Gantz (1994) showed a moderate correlation between speech perception and recovery time constants, both studies suggested that faster recovery times resulted in better speech perception performance. Table 2 provides a summary of these six studies**.**

Study	Population	CI Device	Recovery Parameter	Speech Perception vs. Recovery Parameter		P
Brown et al., (1990)	10 subjects	S Ineraid	Slope of recovery curve		Iowa NU-6 words R= 0.85 Iowa sentences R = 0.74	0.02 0.01
Fulmer et al., (2011)	20 children	AB 90K/CII, Med-EL Pulsar/Sonata, Cochlear Nucleus Freedom	Recovery function constant	ANSD SNHL Total ANSD SNHL Total	SRT in quiet R=0.10 R=0.03 R=0.21 SRT in noise R=0.85 R=0.25 R=0.45	0.78 0.94 0.38 0.08 0.49 0.04
Gantz et al., (1994)	10 adults	S Ineraid	Recovery time constant		Iowa NU-6 words	0.09

					R=0.57 Iowa sentences R=0.51 Iowa medial consonants R=0.62	0.13 0.56
Kiefer et al., (2001)	9 adults	Cochlear Nucleus CI24M	ISIma50	Speech coding Strategy SPEAK CIS ACE	Average of speech perception tests R= - 0.756 R = - 0.708 R = -0.780	0.02 0.03 0.01
Lee et al., (2012)	12 adults	AB CII/HiRes 90K	Recovery function constant		CNC Words R^2 = 0.03 HINT in quiet R^2 = 0.02 HINT in noise R^2 = 0.003	0.60 0.68 0.86
Turner et al., (2002)	5	Cochlear Nucleus CI24M	Recovery time		Deviation from the normal speech weighted function R=0.05	0.94

Table 2: Summary of studies investigating the relationship between eCAP recovery function and speech recognition in human CI users. Redrawn from van Eijl et al., (2017).

Brown et al (1990) reported that faster recovery functions in 10 Ineraid CI users correlated with better speech performance scores, this finding was corroborated by Kiefer et al (2001) who found short recovery periods were associated with better speech recognition for different speech coding strategies (spectral peak coding - Speak, continuous interleaved sampling – CIS and advanced combination encoders - ACE). It should be noted that there are significant differences between the Ineraid CI system and Nucleus 24M implant used in the Keifer et al (2001) study. The Ineraid implant consists of 6 intra-cochlear electrodes in comparison to the Nucleus 24M which has 22 intra-cochlear electrodes, which is likely to lead to differences in the site of stimulation, spread of current and therefore the number of neural fibres recruited. Additionally, the method used to obtain the recovery function varied between both studies, Keifer et al., (2001) used the NRT software, whereas Brown et al (1990) used an analog–to-digital converter interfacing with a computer. Due to the difference in devices, and the eCAP recovery extraction method, factors such as sampling rate, filter settings and gain control are not comparable between both data sets.

Brown et al (1990) assessed word recognition using the Iowa NU6 word list and the Iowa Sentence test, which were presented in quiet at 73dB SPL in the sound field. In comparison, Keifer et al (2001) completed a more thorough assessment of speech perception, testing vowel and consonant identification, monosyllabic words and numbers as well as two sentence tests in quiet and noise at 70dB HL. In both studies the speech material was presented in the sound field and it is not clear if or how the non-test ear was controlled for in either study. Brown et al (1990) scored speech tests based on the words identified correctly rather than phonemes, this may have resulted in lower scores on the Iowa NU6 word test which could bias the correlation observed with the slope of recovery.

Furthermore, there was no attempt made to control for the amount of experience subjects' had with their CI (minimum use was 1 month) and it is not known if the subject group was pre or post lingually deaf. There is substantial evidence that suggests pre-lingually deafened adults attain poorer levels of speech perception with their CIs than post-lingually deaf adults (Klop et al., 2007; Teoh et al., 2004) and may therefore take a longer time to acclimatise to their cochlear implant, hence, a shorter duration of device use may also have resulted in poorer speech scores which may also bias the correlation observed with the slope of recovery. The 11 subjects tested in the study by Keifer et al (2001) were all post-lingually deaf and the duration of use with cochlear implantation ranged from 3 months to 12 years and subjects were given 4-6 weeks to adjust to a new MAP for each speech coding strategy prior to testing. In order to correlate the eCAP to speech performance, Kiefer et al (2001) averaged the results

of speech tests in each subject to find the best overall performance strategy. Of Importance, the eCAP recovery function could not be used to predict which strategy would provide the best performance as it correlated to a similar extent across all stimulation rates and coding strategies, although subjective preference and performance indicated a clear advantage of the ACE strategy

Fulmer et al (2011) investigated the relationship between the eCAP recovery function and speech recognition thresholds in both quiet and noise in 10 children with ANSD and a control group of children with SNHL. No difference was found in eCAP recovery function in the ANSD group compared to the SNHL group and similarly there was no difference in the speech recognition threshold in quiet; however, there was a significant effect of lower speech recognition threshold in noise with faster eCAP recovery function for all subjects. Participants in this study were recipients of 3 different implant systems and due to differences in technology and variations in measurement algorithms, the eCAP recovery function is less comparable between devices with a small sample size. The eCAP recovery function was also only measured at one mid-range electrode therefore any changes in recovery function based on site of stimulation were not observed, considering the significant variability in the site of lesion in patients with ANSD multiple electrode measurements may have provided further information on overall neural recovery in this patient group

Psychophysical pulse train forward masking (PTFM) recovery, is a measure that reflects single channel temporal processing abilities and refers to the increase in detection threshold of a probe when presented after a masker, compared with the probe's unmasked threshold. Electrical stimulation of ANFs with a CI shows this effect can persist up to several hundreds of milliseconds in both NH and CI users and is dependent on the duration and level of the masker (Plomp 1964; Shannon 1990). In comparison, recovery from eCAPs (single pulse forward masking) has been shown to be more rapid with time constants no greater than a few milliseconds (Brown et al, 1990; Morsnowski et al., 2006), see to section 4.4. It is thought that the eCAP recovery from a single pulse masker provides a direct measure of the short term recovery processes in surviving ANFs (Nelson and Donaldson 2001) where as there are two main contributors to PTFM, a rapid recovery process due to refractory properties of the ANFs and a slow recovery process arising from more central mechanisms (Nelson and Donaldson 2002), which is thought to reflect neural adaptation (Shannon 1990).

Lee et al (2012) examined the link between age, eCAP recovery time constants and PFTM recovery in CI users with the aim to identify the relative importance of each measure on speech performance. Their study consisted of a sample of 14 post-lingually deaf subjects who were grouped by age as older (>60 yr old, n=9, mean age 73.44) and younger (<60yr old, n=5, mean age 46.8yrs), and all subjects were Advance Bionic device users. The recovery time constant (eCAP and PFTM) was recorded at a single mid-electrode in all subjects in monopolar mode. The eCAP recovery showed no difference between groups, however, the psychophysical recovery from (PFTM), was significantly slower in older adults compared with the younger subjects ($p < 0.0005$), with a significant effect of age ($R^2 = 0.70$, $p < 0.0005$). There was also a significant positive relationship between psychophysical recovery and word scores ($R^2 = 0.62$, $p < 0.001$), although no relationship was found with sentences in noise. Due to these differences the authors therefore postulate that the eCAP recovery function time constant is more indicative of peripheral temporal processing and that the central auditory system is the dominant contributor to the slow recovery from PTFM, accounting for the differences in speech performance in both groups.

In humans age related loss of SGNs is commonly observed with neural presbycusis (Schuknect and Gacek, 1993; Makary et al., 2011) suggesting age is a stronger predictor of neural health, therefore the findings by Lee at al., (2012) are unexpected. They found eCAP recovery was not associated with age, however, it should be noted only12 eCAP recovery measurements were analysed as measurements could not be obtained in 2 subjects due to stimulus artifact interference. Additionally, the 5 subjects in the younger group had longer mean durations of deafness (23.2 years) compared to the 7 subjects in the older group (13 years), hence it is possible that differences in the population of SGNs at the one electrode site measured were not detected, it is therefore important to assess eCAP recovery constants at more than one electrode location, with a larger sample size.

Due to the limited number of studies with small sample sizes and inconsistent findings it is not clear if eCAP recovery functions can serve as both an objective measure of temporal processing and a reasonable index with which to predict speech perception abilities in CI users. These studies span a large period of time during which significant advances in technology and modifications in the methodology used to measure recovery function have occurred; which makes comparison between studies more challenging. For example, in earlier studies Brown et al., (1990) used electrodes connected in a voltage controlled feedback loop and Gantz et al., (1994) used a temporary electrode to measure eCAP recovery functions, whereas more recent studies (Keifer et al, 2001; Turner et al, 2002; Fulmer et al, 2011 and

Lee et al, 2012) have used telemetry technology incorporated in modern CIs. Additionally, the differences in devices used in these studies further limits comparisons, as there is insufficient evidence for eCAP recovery function as a predictor for speech perception, hence the author propose a study where all subjects are recipients of a Cochlear Ltd Nucleus device, use the same speech processing strategy and speech processor and are assessed using the same speech outcome measures.

4.4 The eCAP recovery function background

The eCAP represents a synchronised response generated by a group of electrically activated ANFs to the presentation of an electrical stimulus. It is not possible to directly measure the neural population in human subjects and the eCAP is a direct measurement of neural responses generated by ANs which allows evaluation of the physiological status of the auditory nerve (Brown et al. 1990). Near field recording of eCAPs is possible using intra-cochlear electrodes utilising the Neural Response Telemetry (NRT) function implemented in programming software, which became commercially available for eCAP recording in 1998, when Cochlear Ltd incorporated two-way telemetry in the Nucleus R CI24 cochlear implant system. In CI users, the absolute recovery period (ARP) and the RRP can be estimated based on the eCAP recovery function (Gantz et al., 1994; Miller et al., 2000; Charasse et al., 2003; Battmer et al., 2004; Shpak et al., 2004; Morsnowski et al., 2006; Cohen, 2009; Botros and Psarros, 2010; Fulmer et al., 2011; Kim et al., 2011; Lee et al., 2012). Most studies of the neural refractoriness of the electrically stimulated auditory nerve have been carried out using either a two-pulse masker–probe paradigm or multi-pulse stimulation masker-probe paradigms. The pulse that causes a refractory state in an ANF is referred to as the masker pulse while the subsequent pulse that is used to assess the state of refractoriness is referred to as the probe. The eCAP amplitude may be examined as a function of the masker-probe interval (MPI) to estimate recovery of the fibre population. Mechanisms of voltage gated-ion channels give rise to refractoriness (Hodgkin and Huxley 1952) therefore the recovery function is dependent on the stimulus level at the neural membrane as well as the membrane properties, both of which may differ across the neural population (Miller et al 2001).

Measuring eCAPs has historically been difficult due to the lack of a method for recognising and minimising contamination of the stimulus artefact on the recorded response (He et al., 2017). The forward masking method (see section 4.4.3) was first developed by Brown et al., (1990) for measuring the eCAP from an intra-cochlear electrode in human CI patients. This technique was further developed by a modified template subtraction (Miller et al., 2000) which allows artefact free eCAPs to be recorded. Cochlear Ltd incorporated these techniques in their

two-way telemetry function software, Neural Response Telemetry (NRT), see section 4.4.2. Similarly, other manufacturers have their own telemetry capabilities although the methods for stimulus extraction vary between devices. Advanced Bionics Ltd utilise Neural Response Imaging (NRI) and Med-el Ltd use Auditory Response Telemetry (ART). For the purpose of this research we focus on NRT as all the subjects in this study were implanted with Cochlear Ltd devices.

4.4.1 The eCAP morphology

The eCAP recorded in CI users usually shows a biphasic morphology that consists of one negative peak (N1) occurring around 0.2-0.4 ms following stimulus onset, followed by a much smaller positive peak (P2) occurring around 0.6-0.8 ms, and eCAP amplitudes can be as large as 1-2mV (Brown and Abbas, 1990; Brown et al., 1990, 1998; and Abbas et al., 1999). This singe peak morphology occurs in 80% of all measureable eCAPs (Lai and Dillier, 2000; and Miller et al., 2008). Double peak eCAP responses are rarer with an incidence of 10-20% (Lai and Dillier, 2000) and consist of two positive peaks, P1 occurring at about 0.4–0.5 ms and the P2 typically occurring around 0.6–0.7 ms (Lai and Dillier, 2000). See figure 22.

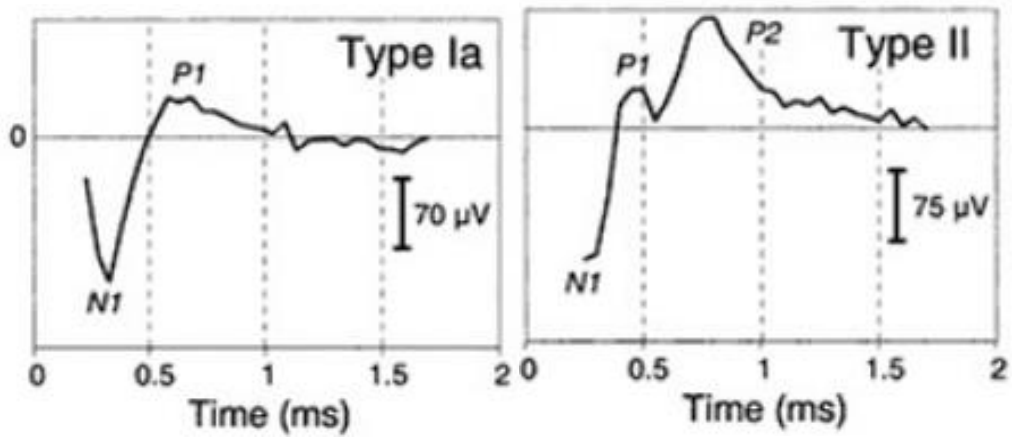

Figure 22: Typical eCAP waveform (Type 1a) the amplitude of the eCAP is defined as the voltage difference between N1 and P2 and Type II double peak eCAP waveform.

4.4.2 Neural Response Telemetry

The NRT software consists of a bidirectional telemetry circuit and has been developed by Dillier et al (1995) at Zurich University in collaboration with Cochlear Ltd. It was validated by Lai et al (1997) as a technique to directly measure the eCAP of the stimulated ANs in response to electrical stimulation from a single electrode contact. Several studies have found a strong

correlation between the eCAP threshold and the predicted Threshold (T) and Comfort (C) levels which can assist in the programming process (Brown et al., 1996, 1998; Abbas et al., 1999). The compound action potential that results from a stimulus applied on a given intra-cochlear electrode is recorded from a neighbouring electrode as voltages. These voltages are amplified and encoded for transmission back over the radio frequency (RF) link to the storage buffer in the speech processor. These measurement data are retrieved by the NRT software for further processing, display and storage. See figure 23.

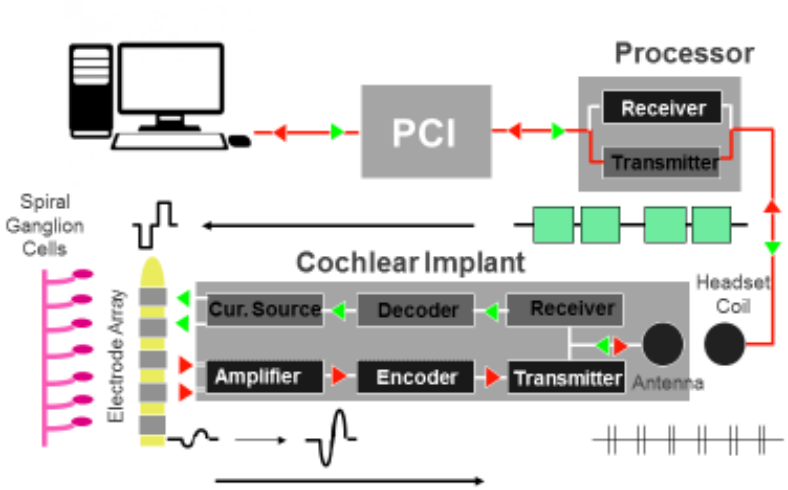

Figure 23: The NRT software communicates with the cochlear implant via the speech processor. Stimulation is initiated by the software and the resulting eCAP is measured by an amplifier in the implant and the data is transmitted back to the speech processor, which sends it to the software which then processes the incoming data.

The typical neural action potential which is produced is very small (approximately 100uV) in amplitude compared to the stimulus artefact which is several times larger and occurs close to the evoked neural response. To ensure the recording of the neural response is not contaminated with the stimulus artefact the NRT software implements a forward masking paradigm (see section 4.4.3) described by Charlet de Sauvage et al (1983) and Brown et al (1990) in order to extract the neural response.

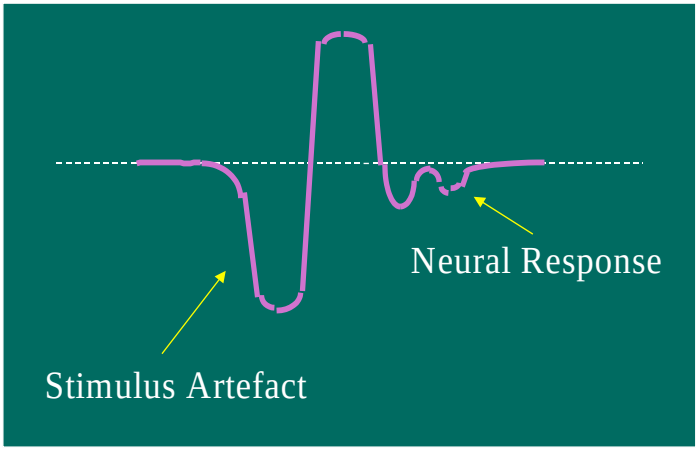

Figure 24: The neural response amplitude is very small compared to the electrical stimulation which makes it difficult to extract the neural response from stimulus artefact.

4.4.3 Forward masking paradigm

Forward masking is a phenomenon in which one stimulus (masker) suppresses the detection of a subsequent sound (probe). The shorter the interval between the masker and probe, the more suppression occurs. Forward masking tasks generally measure how intense the probe signal needs to be in order to be detectable in the presence of the masker as a function of the silent interval between them. In the NRT algorithm, the forward masking paradigm includes four stimulation intervals. The first interval (A) the probe stimulus is presented alone and the recording contains the neural response and the probe stimulus artefact. The second interval B, presents a masker stimulus followed by the probe stimulus, after a specified interval between the masker and the probe, known as the masker probe interval. With adequate forward masking, this recording only contains the stimulus artefacts from the masker and the probe. In the third interval (C), the masker and the probe sequence (as B) is repeated and the probe is set to a minimum level in order to extract the probe artefact, therefore the masker is presented alone. This recording contains the stimulus artefact from the masker. Subtracting the (C) recording from (B) yields the probe stimulus artefact alone, subtracting this from (A) yields the neural response to the probe (A) final recording (D) is taken to record the artefact produced from the measurement amplifier, at interval (D) both the masker and probe are presented at minimal levels in order to prevent any stimulus artefacts from either the masker or the probe. The subtraction (A-(B-(C-D))) then yields the desired neural response (Abbas et al., 1999; Brown et al., 1990, 1998, 2000; Dillier et al., 2002). See figure 25.

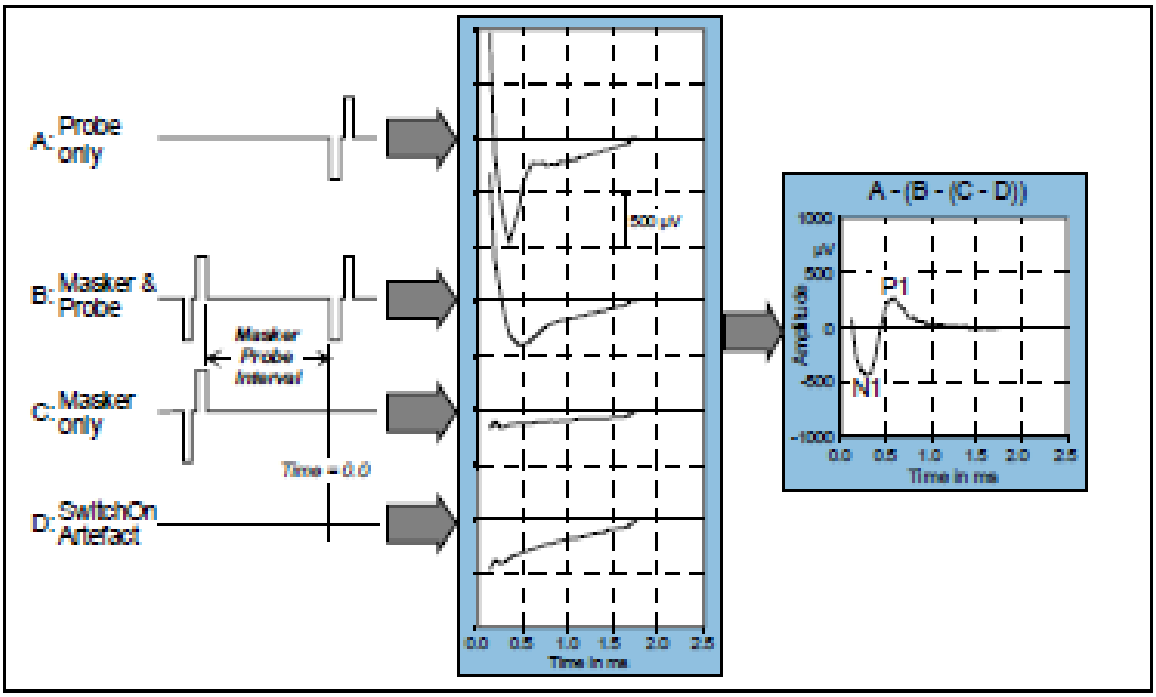

Figure 25: The diagram above illustrates how the forward masking algorithm functions. **A.** The probe stimulus is presented alone. The probe recruits auditory nerve fibres near the stimulated electrode. The measured wave form contains the neural response as well as the stimulus artifact. **B.** A masker stimulus is presented followed by the probe stimulus. The masker stimulus recruits the same auditory nerve fibres as in condition *(MPI: masker-probe time interval),* only stimulus artifact (no neural response) is recorded for the probe stimulus in this condition. **C.** The masker stimulus is presented alone. The probe is then presented shortly after the masker within the refractory period of those fibres. **D.** Zero current pulse to elicit system artifact

4.5 Two pulse experimental paradigm to estimate refractory function

Numerous studies have used a two pulse masker pulse paradigm to estimate the refractory function of the auditory nerve to electrical stimulation. Studies in animals (Hartmann et al., 1984b; Stypulkowski and van den Honert, 1984; Dynes, 1996; Brown and Abbas, 1999; Cartee et al., 2000; Miller et al., 2001; Cartee et al., 2006) have been used to infer single-fibre refractory properties. Analyses of the cat's electrically eCAP RRF suggest that the ARP typically ranges from 600 to 700 µs (Dynes, 1996) and full recovery occurs within 1.5-2ms (Dynes, 1996, Cartee et al., 2000). Other studies have yielded lower estimates closer to 350 µs (Miller et al., 2001; Stypulkowski and van den Honert, 1984). Miller et al., (2001) determined the single pulse threshold (the current level) at which the AN spikes 50 % of the time to a pulse while the neuron is at rest, and demonstrated that complete recovery is restored by 3 ms after the masker pulse is presented. They were also found that some fibres may fire at 100% efficiency even at MPIs as short as 500 µs and more than a third of their sampled fibres responded at that interval without a significant decrease in spike efficiency. This is consistent

with the findings of Brown and Abbas (1990) who reported that a 500 μs MPI typically produced maximum refractoriness.

Cartee et al., (2000) obtained threshold vs MPI data for 25 single fibres and estimated a RRP time constant of 0.7ms. Cartee et al., (2000) used the same recovery equation as Miller et al., 2001 but did not include an ARP, which could have biased the time constant estimate upward. Miller et al., (2001) obtained recovery time constants at a shorter minimum MPI in comparison to Cartee et al., (2000) and found that the accuracy of the ARP is strongly dependent on the minimum MPI. These studies used cats that were acutely deafened during the experiment and therefore, did not evaluate the impact of long standing degenerative changes within the cochlea. Shepherd et al (2004) found a positive correlation between the duration of deafness and absolute refractory periods in ANs of rats. Despite the varied estimates of the recovery time constants in these studies, there is consensus that the AN thresholds decrease exponentially as the MPI increases and faster recovery of fibre threshold can be caused by higher probe levels (Matusoka et al., 2000; Miller et al., 2001; Shepherd et al., 2004). At longer MPIs, there will be a larger number of ANs that have recovered and are ready to respond to the second stimulus; which results in a larger amplitude response.

Immenov and Rubinstein (2009) suggest that sodium ion inactivity may not be the sole channel activity within the SGN which accounts for refractoriness. They used a computational model of SGNs in a cat embedded with rapid sodium channels that activated the transient potassium channels, and delayed the receptor channels. They yielded an ARP of 750μs, similar to the values of 700 μs reported by Cartee et al., (2000) but longer than the ARP (~ 450 μs) reported by Miller et al., (2001). Their model also predicted a RRP of 4.6ms which is close to the 5ms RRP reported by Hartman et al., (1984) and Dyne (1996).

The eCAP recovery function measures in human subjects have yielded median values of ARP (276 - 645 μs) and RRP (600 to 1350 μs) and recovery of the eCAP appears to be complete by about 4ms (Brown et al., 1996, Pesch et al., 2005; Morsnowski et al., 2006; Hughes et al., 2012; Wiemes et al., 2016). The eCAP is an aggregate response which is dependent on the number and function of surviving SGNs and their properties such as fibre thresholds, fibre diameter and the distribution of high or low spontaneous- rate fibres. All of these variables are likely to effect the spike threshold and speed of action potential propagation (Rhode and Smith, 1985; Muller and Robertson, 1991). Loss of peripheral processes may lead to a greater spread of excitation which may cause the site of action potential generation to move to a central axon

(Javel and Shepherd, 2000) and higher current levels may be required to induce an action potential. Additionally, demyelination observed studies in deafened animals (Elverland and Mair, 1980; Leake and Hradek, 1988), is likely to result in a large increase in membrane capacitance (England et al., 1990; Vabnick et al., 1997), consequently, more charge is required at the neural membrane to initiate depolarization (Smith and McDonald, 1999). There are currently a limited number of studies on eCAP RRF in human subjects and they are restricted by their small sample size. It remains unclear how the pathological and atrophic changes within the cochlea following SNHL effect temporal response properties in CI users.

4.6 Multi-pulse experimental paradigm to estimate refractory function

Refractory properties appear to have an alternating effect on the responses to pulse trains of pulses at rates of that 1000 pps/ch and above (Hay-McCutcheon et al.,2005; Hughes et al., 2012; Wilson et al.,1997). Wilson et al., (1997) examined eCAP amplitudes in response to increasing stimulation rates in ten subjects. At slow rates (100-200 pps/ch]), nearly all ANs fired with each pulse resulting in eCAPs that were similar in amplitude. This would indicate that the same population of ANs are depolarised and then fully recover following each pulse in the train. When the stimulation rate was increased (400 – 1500 pps/ch), an alternating eCAP amplitude pattern emerged due to the heterogeneous refractory recovery periods across the population of ANs. This resulted in subsets of ANs entering a refractory period and not recovering in time to discharge with every pulse. Consequently, the eCAP response to the first pulse was high in amplitude because many ANs were non refractory and were able to discharge to the stimulus but the response to the second pulse was lower as many of the ANs that discharged to the first stimulus were in a refractory period but recovered in time to respond to the third pulse and this alternating pattern then continued for pulses. When the stimulation rate was increased further (2000 – 3000 pps/ch), the alternating pattern diminished and the eCAP amplitude reduced and remained consistently smaller due to stochastic independence among ANs; likely due to the effects of incomplete refractory recovery, increased adaptation, and increased temporal jitter (Hay-McCutcheon et al., 2005; Mino and Rubinstein, 2006; Miller et al., 2008; and Wilson et al., 1997). Wilson et al., (1997) did not measure the eCAP recovery function in their study so it is not clear to what extent the temporal response patterns varied across individuals.

Hughes et al., (2012) defined the stimulation rate where the eCAP response discontinues this alternating amplitude pattern (desynchronization) as the stochastic rate, when a sub-population of ANFs is available to respond at any given point in time. Hughes et al., (2012) determined the stochastic rate for 29 subjects (27 with Nucleus devices and 2 with Advanced

Bionic devices) by measuring eCAPs in response to pulse train (containing 21 pulses) at rates of 900, 1200, 1800, 2400, and 3500 pps/ch at three electrode locations (basal, middle, and apical). Consistent with the findings of Wilson et al., (1997), an alternating amplitude pattern was observed for slow rates reflecting the refractory properties of the responding ANFs. At faster rates the overall amplitude was lower to the first pulse and the alternating pattern ceased. The stochastic rate varied across individuals and for the three electrode locations, 79% of subjects had different stochastic rates across the three regions of the cochlea. The stochastic rate occurred most frequently at 2400 pps for basal and middle electrodes, and at 3500 pps for apical electrodes. Hughes et al., (2012) also measured the eCAP recovery time constants at the three electrode locations, basal (1032.4 ms), middle (990.4 ms) and apical (774.4 ms) which are consistent with the finding of faster stochastic rates at the apical electrode. The authors suggest this may be due to better neural survival in the apical region with a more heterogeneous population of ANFs. This study did not evaluate rates lower than 900 pps/ch based on the alternating pattern observed in the study by Wilson et al., (1997) therefore, it is not clear if desynchronization could have been reached at rates slower than 900 pps/ch. Although the study indicates it may be possible to identify an optimal rate as speech recognition was not evaluated in the study it is not clear if the stochastic rate led to improved functional benefit. Additionally, as the pulse train was short in duration (21 pulses), the sampling window was limited so it is not known if the alternation pattern would continue across longer duration pulse trains. Hay-McCutcheon et al., (2005) showed moderately stable alteration patterns across a series of 100 pulses for a 1000-pps train however, other rates were not assessed.

Furthermore, as the rate varied across cochlea region consideration needs to be given to which region should be used to identify the optimal rate for the entire electrode array, and this is region is likely to be different across individuals. It would therefore be ideal to identify the region which provides the best speech recognition in a CI user. Studies have previously examined speech perception abilities in CI users by stimulating a specific selection of electrodes (Fu and Shannon, 1999; Pfingst et al., 2001; Shannon et al., 2001; Hochmair et al., 2003) and results have been varied. Fu and Shannon (1999) stimulated sets of four widely-spaced electrodes in three users of the Nucleus 22 CI. Maps were shifted basally to apically along the cochlea and the authors found that vowel and consonant recognition scores improved as the stimulated electrodes moved to a more apical location. All subjects had >100 hours' experience with the experimental tasks before the start of data collection. Similarly, other studies have deactivated sections of the electrode array (Geier and Norton, 1992;

Shannon et al., 2001) in order to stimulate isolated regions in the cochlea. Geier and Norton (1992), deactivated five electrodes in each region of the cochlea (apical, middle and basal) for six subjects. Shannon et al., (2001) varied the number (2-8) of electrodes that were deactivated in five subjects. Subjects in both studies were recipients of the Nucleus 22 implant. Both studies demonstrated that speech recognition scores worsened with the deactivation of apical electrodes, with better performance reported when middle electrodes were deactivated by Geier and Norton (1992) and when basal electrodes were deactivated by Shannon et al., (2001), although there was considerable variability between subjects.

In contrast two studies (Hochmair et al., 2003; Pfingst et al.,2001) found that stimulating the mid region of the cochlea resulted in better speech perception. Hochmair et al., (2003) assessed speech perception in ten users of the Med-El COMBI 40+ CI with a fixed number of equally spaced channels (8) concentrated in the basal, middle and apical regions and compared these with the users every day MAP, which had all 12 channels active. The results showed that stimulation of the apical region of the cochlea resulted in better speech understanding, and that distributing the channels over the whole length of the cochlea improved speech perception in quiet and in noise. It should be noted that the full input frequency was compressed in the test conditions which would have introduced spectral mismatch, therefore the middle array maps may have produced better speech recognition scores as it is less sensitive to spectral compression, and the changes in the place code may be minimal in comparison to the apical and basal regions (Fu and Shannon, 1999a; Fu et al., 2002)

Similarly, Pfingst et al., (2001) stimulated basal, middle, and apical regions of the cochlea by with half the electrodes activated (11) in ten subjects implanted with either the Nucleus CIs. The highest sentence recognition scores were obtained using the middle region of the electrode array, and no difference was found between the scores obtained with the apical and basal MAPs. The variations in the results of these studies may be attributed to the differences in the distribution and number of stimulating electrodes, the studies with the Nucleus devices had covered a larger portion of the cochlea compared to the MAPs used by Hochmair et al., (2003).

Other studies have investigated the use of eCAP recovery function as a predictor of preferred stimulation rate (Kiefer et al., 2001; Shpak et al., 2004). Shpak et al., (2004) compared the eCAP responses of eleven Nucleus 24 recipients using the ACE processing strategy at rates

of 900, 1200 and 1800 pps/ch to each subject's preferred stimulation rate. Consistent with the findings of Hughes et al., (2012) the eCAPs varied based on electrode location however electrodes 7, 11, and 15 (mid electrodes) were found to be predictive of preferred stimulation rate. Subjects who preferred lower stimulation rates (900 and 1200 pps) demonstrated longer eCAP recovery times than those subjects preferring a higher stimulation rate of 1800 pps. This study assessed subjective preference and no speech perception assessments were completed so it is not clear if a subject's preferred rate equates to better performance. Likewise, Keifer et al., (2001) reported an association between short recovery time constants and higher levels of speech recognition. however, as stimulation rate preferences and performance were relatively uniform across subjects eCAP RRF could not be related to preferences of speech-coding strategy.

Although high stimulation rates may improve temporal representation and stochastic responses (Rubinstein et al., 1999), the evidence base for this is currently limited. The neural survival pattern and the condition of the surviving SGNs varies considerably between subjects (Hinojosa and Lindsay, 1980; Nadol, 1997), therefore, individual variance in the electrode neural interface and the condition of the AN are likely to contribute to the trade-off between channel number and stimulation rate. As discussed in section 3.12, higher stimulation rates produce greater electrode interaction which reduces the number of functional channels (Brill et al., 1997; Boex et al., 2003; Middlebrooks, 2004), hence individual CI users may be restricted by this upper limit. Collectively, these studies demonstrate that the eCAP recovery function is a feasible measurement however, it's potential clinical application is unclear due to limited research findings and there is also insufficient evidence for eCAPs as a predictive factor for speech perception

4.7 Behavioural measures of temporal processing

Auditory temporal processing refers to the perception of sound or the alteration of sound within a restricted or defined time domain (Musiek et al., 2005). Temporal processing consists of four sub-processes:

1. Temporal Ordering

Temporal ordering (or sequencing) refers to the processing of two or more auditory stimuli in their order of occurrence in time (Pinheiro and Musiek, 1985a). Research has shown that the ability to recognise, identify and sequence auditory patterns involves cognitive processes that are require integration of information from both hemispheres across the corpus calloum

(Musiek et al.,1980). Therefore, pattern (sequencing) tests are sensitive to hemispheric lesions, as well as interhemispheric dysfunction (Musiek and Pinheiro, 1987; Musiek et al.,1990). The most widely used clinical tests of temporal ordering are the Frequency Pattern Test and the Duration Pattern Test (Emanuel et al., 2011). Both tests have been used widely in the assessment of central auditory processing disorders in subjects with peripheral hearing loss (Musiek and Pinheiro, 1987; Musiek et al., 1990). and in individuals with cerebral lesions who demonstrate temporal ordering deficits (Belmont and Handler, 1971; Karaseva, 1972; Swisher and Hirsch, 1972; DeRenzi et al., 1977).

2. Temporal Resolution

Temporal resolution (or discrimination) refers to the shortest duration of time in which a listener can discriminate between two auditory signals (Gelfand, 1998). The threshold for detection is approximately 2-3 milliseconds in NH subjects (Philips, 1999) and is known as the temporal auditory acuity or minimum integration time (Greene, 1971). The most commonly used clinical tests of temporal resolution are two measures of gap detection, the Gaps-in-Noise (GIN) test (Musiek et al., 2005) and the RGDT (Keith, 2000). Another measure of temporal discrimination is the TMTF, discussed in section 3.13, there are however, no clinically available tests using TMTF.

3. Temporal Integration

Temporal integration is caused by the summation or aggregation of neuronal activity resulting from the additional duration of sound energy (Gelfand, 1998). This results in threshold improvement as duration increases up to about 200–300 msec in NH listeners (Durrant and Lovrinic, 1995). It has been observed that as a sound is decreased to one tenth of its original duration, the subject's threshold worsens by approximately 10 dB; the reverse occurs when duration increases. This phenomenon is referred to as a time intensity trade off (Durrant and Lovrinic, 1995). This same phenomenon holds true for intensity, as the duration of a brief signal is increased at suprathreshold levels, the sound is perceived as being louder. If the duration of a stimulus is decreased to less than 20 msec, threshold levels increase in NH listeners (Durrant and Lovrinic, 1977).

4. Temporal masking

Temporal masking (obscuring of one sound by another) is the threshold shift of one sound in the presence of other subsequent stimuli. This occurs when a stimulus, generally a tone, is presented with duration and intensity sufficient to reduce the sensitivity of a stimulus presented either before

or after the initial stimulus. The effect depends on the frequency region of the masking tone, with the most significant loss of sensitivity occurring within the same frequency region. Several parameters determine temporal masking, including the time interval between the masker and signal, masker level, masker duration, and the acoustic similarity between the masker and the signal. When these parameters are kept constant, temporal masking has been shown to decrease rapidly as the time interval between the masker and signal is increases (Durrant and Lovrinic, 1995). Geland (1998) found that the amount of masking increases as the intensity of the masker increases, however the relationship was nonlinear, a 10 decibel increase in masking level resulted in a threshold shift of approximately 3 decibels.

Currently, clinically feasible measures of temporal processing are limited to temporal ordering and resolution. Although there are a number of paradigms reported in the literature for assessment of temporal integration and temporal masking they are not clinically feasible due to the necessary equipment interfacing, as well as subject training and time requirements (Musiek et al., 2005).

The integrity of these sub-processes are essential for phoneme discrimination, speech in noise perception, duration discrimination, rhythm perception, and prosodic distinction (Phillips, 2002; Chermak and Musiek, 1997). Temporal resolution defines the capacity the auditory system has to detect the occurrence of two consecutive auditory events and, consequently, avoid them being detected as a single event (William et al., 1972; Gelfand, 2004). It is a critical skill for speech recognition, which depends on the listener being able to process temporal information at varying stimulation rates. In particular, fluctuations in the speech envelope contain lexical and syntactic information; segmental cues such as gap duration provide information about phoneme identity; and sub segmental information derived from the periodic vibrations of the vocal folds conveys voice pitch and sound quality (Teoh et al., 2003; Munson and Nelson, 2005; Langovan and Stuart, 2008). Furthermore, there is some evidence to suggest that normal temporal resolution allows the listener to detect fluctuations in the dips of background noise in order to acquire segmental cues which is important for speech recognition in noise (Bernstein and Grant, 2009; Rosen et al., 2013).

GDTs are a psychophysical task which measures temporal resolution and are determined by the shortest interval a person can detect between a pair of stimuli (Green, 1971; Eddins et al., 1992; Moore, 2005), and are used clinically as an index of the integrity of central auditory temporal processing mechanisms. Gap detection tasks which require the subject to detect the

presence of a gap between two sounds that are spectrally identical, stimulate the same set of SGNs and are referred to as a within channel task. The detection of the gap is thought to be limited only by the ability of the SGNs to encode the onset of the second stimuli (post gap) while recovering from the first stimuli (Phillips et al., 1997; Chatterjee et al.,1998). Within channel gap detection tasks therefore involve recovery from forward masking (Kirby and Middlebrooks, 2010). In contrast when the two stimuli are spectrally different, the subject is required to detect a gap between the offset of excitation in one frequency region, and an onset in a different channel, this is referred to as a between channel task (Phillips et al., 1997). Temporal resolution is therefore completed across channels requiring more processing at higher central levels as the stimuli are processed through independent neural pathways. GDT can therefore indicate the degree of neural overlap between the two stimuli (Heinz et al., 1996).

For within channel tasks NH listeners can detect gaps between 3-5 ms at moderate to high presentation levels regardless of the frequency of the stimuli (Penner, 1976; Fitzgibbons, 1983; Florentine and Buus, 1984; Hall et al., 1996; Shailer and Moore, 1983). However, when the two stimuli that bound the gap are different spectrally or in level, GDTs increase to 30-50ms (Divenyi and Danner, 1977; Divenyi and Sachs, 1978; Formby and Forrest, 1991; Formby et al., 1992). In CI users, Chatterjee et al., (1998) showed that within channel GDTs were longer when the stimuli bounding the gap was of unequal amplitude or unequal pulse rate. They concluded that the perceptual discontinuity caused by dissimilar markers complicated the gap detection task, and suggested that under these conditions GDTs may be a function of limitations caused by peripheral mechanisms as well as central processing. Figure 26 shows a schematic depiction of the differences between the two gap detection designs.

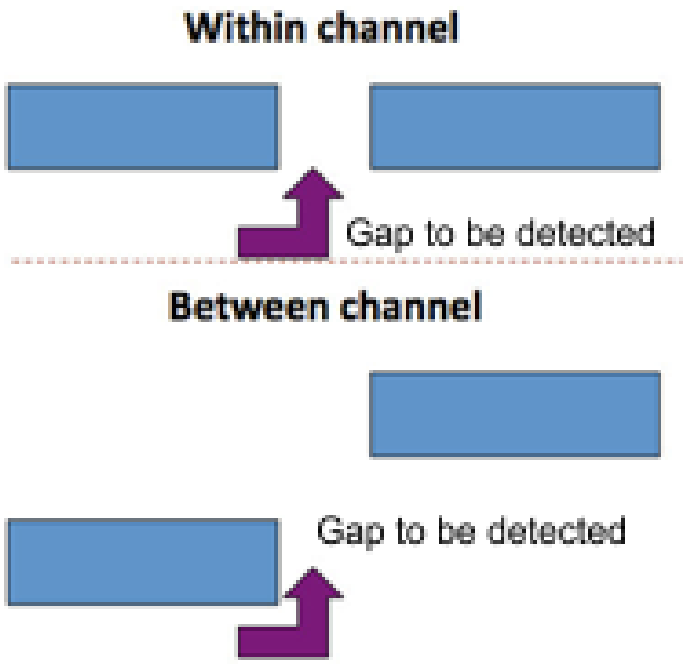

Figure 26: Illustration of gap detection stimuli for within-channel and between-channel designs. In the within-channel design, the leading and trailing markers of the gap have the same spectral content with the same duration. In the between-channel design, the leading and trailing markers of the gap differ, in this case the leading marker is shorter in duration that of the trailing one.

In NH listeners the neural responses from the peripheral auditory system to the brain operate synchronously and are able to switch off and back on within the time frame of the gap (Moore 1993). Forward masking and gap detection likely result from the same neural mechanisms, as these stimuli share a common temporal structure and have been shown to give consistent results in human psychophysical studies (Plomp, 1964). However, in subjects with SNHL alterations in peripheral pathways and central hearing abilities are likely to contribute to deficits in temporal resolution. They are also likely to affect both bottom-up sensory processing and top-down cognitive modulation of sounds, which can result in elevated GDTs in CI users (Kral and Eggermont, 2007). Previous studies have shown that hearing loss can lead to degraded neural encoding of temporal cues, psychoacoustic temporal processing abilities, and decreased speech perception performance in hearing impaired individuals (George et al, 2006; Anderson et al, 2013). When SGNs are unable to respond synchronously, sensitivity is compromised and it is not possible for listeners to reliably and consistently detect gaps, making it more challenging for them to detect shorter gaps.

The effect of stimulation rate on GDT in CI users has been investigated with mixed results (Preece and Tyler, 1989; Busby and Clark, 1999; van Wieringen and Wouters, 1999). All of these studies measured GDTs at stimulation rates no higher than 1250 pps/ch, hence SGNs may not have achieved stochastic independence. Wieringen and Wouters (1999), found GDTS of 2-8ms at 400 pps/ch. Although a consistent relationship between GDT and stimulation rate has been found, overall psychophysical studies of gap detection, show a trend towards increased temporal acuity (decreased GDTs) associated with higher pulse rates van Wieringen and Wouters 1999; Grose and Buss, 2007; Garadat et al., 2010). One possible explanation for this is that the recovery from forward masking might be faster when pulse rates are higher.

In CI users, the majority of previous studies have measured GDTs using direct electrical stimulation delivered to an electrode contact (Shannon, 1989; Garadat and Pfingst, 2011; Bierer et al, 2015) and only a few have measured GDTs using acoustic stimuli presented through a CI speech processor (Tyler et al, 1989; Muchnik et al, 1994; Wei et al, 2007, Zhang et al, 2013), therefore GDTs recorded using these approaches differ considerably. Unlike the electrical GDT that can only reflect restraints of temporal processing abilities in the auditory pathway, the acoustic GDT reflects both the limitations of CI speech processing strategy and the limitations of temporal processing abilities of the auditory system, which may account for some of the variability in the results of the above studies.

Electrically measured GDTs in CI users appear much lower and do not show as much variability as those measured acoustically and are similar to NH listeners. Studies have shown that the GDTs of post-lingually deaf adults using electric stimulation (Moore and Glasberg, 1988; Preece and Tyler, 1989; Shannon, 1989, Garadat and Pfingst, 2011; Bierer et al, 2015) are similar to NH listeners using acoustic (Fitzgibbons and Gordon-Salant, 1987; Fitzgibbons and Wightman, 1982; Florentine and Buus, 1984; Hall and Grose, 1997; Penner, 1977) ranging from 1.8 – 32.1 ms for different pulse rates and stimulus durations (Busby and Clark 1999). These results infer that that temporal resolution as measured by electrical gap detection is not impaired by peripheral damage.

In comparison, GDTs measured with an acoustic stimuli showed CI users had a longer average GDT of 30 ms, ranging from 4 to 128 ms (Tyler et al., 1989; Wei et al., 2007; Zhang et al., 2013; Blakenship et al., 2016). Given that CI users perceive speech that is processed through their speech processor for day to day listening it seems reasonable to evaluate the

acoustic GDT as it has the advantage of reflecting the limitation of CI processing as well as the limitations of temporal processing abilities of the auditory system. The difference in GDTs between the two stimulation methods may suggest that the limitations of CI speech processing strategies may further contribute to deficits of temporal processing. Gaudrain (2016) investigated the origin of the differences between the GDTs obtained by direct electrical stimulation and stimulation via a clinical processor and compared the resulting electrodograms. The results showed that certain aspects of front end processing likely related to automatic gain control, reduce the depth of the gap, which is consistent with a reduction in gap detectability.

Due the differences in the stimulation approach (electric vs acoustic) and the differences in speech materials used across studies, there are mixed results in the correlation between the GDT and speech perception in CI users. Muchnik et al (1994) found a negative correlation between open set speech recognition and GDT. Busby and Clark (1999) found a significant negative correlation between the GDT and word scores for Bamford-Kowal-Bench (BKB) sentences in the auditory-visual condition. Tyler et al (1989) reported that individuals with acoustic GDTs less than 40 ms showed a wide range of performance on speech perception measures whereas subjects with GDTs greater than 40 ms showed poor speech recognition. More recently Blakenship et al (2016) compared acoustically measured GDTs in CI users and NH listeners and found that CI users displayed temporal processing impairments when GDTs were greater than 20ms and poorer speech performance than NH listeners. These results support the theory that temporal processing abilities in CI users contribute to the individual differences in speech performance.

4.8 Gaps in knowledge:

The literature has therefore raised the following questions:

1. Can eCAP recovery functions be measured reliably in CI users using NRT

2. Does eCAP recovery function inform us of the underlying neural physiology in CI users

3. Does eCAP recovery function predict psychophysical performance as measured by GDT? And if it does is that because the neural circuits that mediate recovery function and temporal processing are the same in individual subjects?

4. Does eCAP recovery function predict speech performance? And if it does can this information be utilised to optimise programming parameters in CI devices to enhance performance?

5. Do acoustically measured GDT thresholds inform us regarding temporal processing abilities in CI users?

6. Do these behavioural measures of temporal processing predict speech performance?

4.9 Conceptual model and hypotheses

To answer these questions, the conceptual model shown in figure 27 was designed, which aims to utilise the eCAP recovery function to measure the status of the underlying neural physiology in individual CI users. It was hypothesised that neural health is a key contributor to behavioural measures of temporal processing; hence, deficits in neural function associated with longer durations of auditory deafness are likely to be correlated to behaviourally measured performance of temporal processing as measured by RGDT. Furthermore, it was hypothesised that both measures could in turn affect speech performance as measured by AB word phoneme scores.

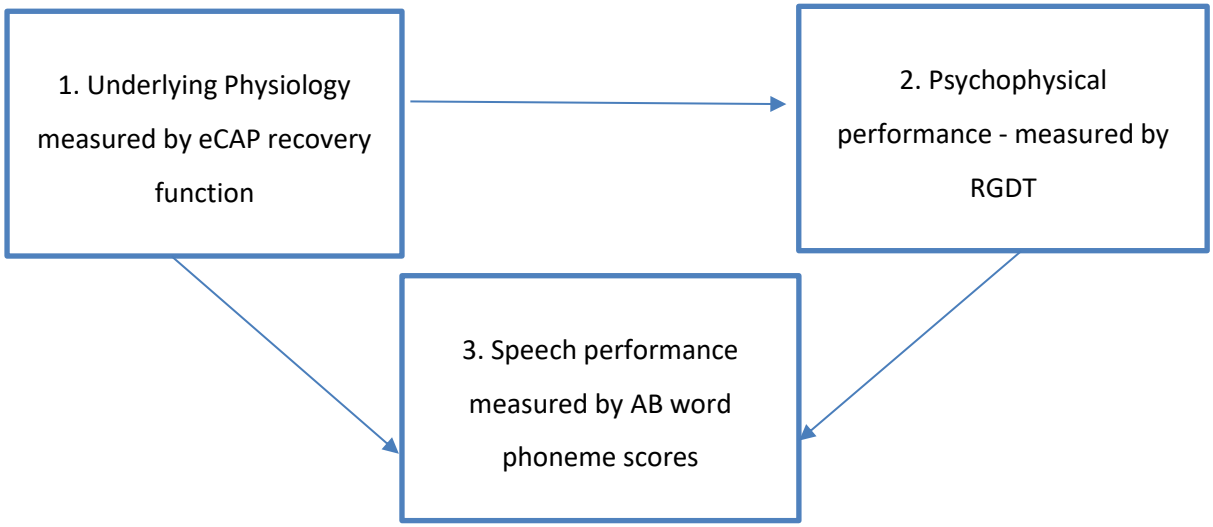

Figure 27: The conceptual model for an experiment where measurement (1) predicts (2) and both (1) and (2) predict speech performance (3). The factors that are likely to influence each measurement and how they may be associated with each other are discussed below:

The following hypotheses were drawn:

1. Longer durations of auditory deprivation are more likely to significantly compromise refractory properties due to the predictable pathological changes and associated neural degeneration in the auditory periphery. It was hypothesised that these alterations would result in longer recovery function time constants in pre-lingually deafened CI users with low stimulation rates, as measured by the eCAP recovery function.

2.. As the same neural deficits are likely to also compromise central auditory processing, it was hypothesised that the eCAP recovery function measurement would be predictive of the behaviourally measured temporal processing abilities in the same individual and longer GDTs were expected in individuals with pre-lingual deafness and low stimulation rates

3. It was hypothesised that both objective (eCAP recovery function) and behavioural (RGDT) measures would predict speech perception as measured by AB word phoneme scores. Lower speech recognition scores were anticipated in individuals with pre-lingual deafness and low stimulation rates (who based on the above hypothesises would demonstrate longer eCAP recovery function time constants and longer GDTs in comparison to post-lingually deafened subjects).

The next chapter describes the experimental design the methods used for this study.

Chapter 5: Methodology

In the previous chapter several questions were formulated based on the gaps identified in the literature. This chapter details the experimental design and methods developed to answer the questions raised and outlines a test-battery approach which investigates the relationship between objective and behavioural measures of temporal processing and their contribution to speech perception, providing justification for certain methodological decisions.

5.1 Developments in methodology

Different approaches were considered for the objective and behavioural measurements of temporal processing. The advantage of eCAPs over other electrophysiological measurements such as electrically evoked auditory brainstem responses or electrically evoked Cortical potentials is that eCAPs are evoked from the ANFs and therefore provide a more direct measure of the residual number and quality of SGCs, which constitute the electrode neural interface. Additionally, the measurement is fast and requires minimal patient co-operation; and does not require special equipment to be obtained as is the case with electrically evoked auditory brainstem responses or electrically evoked Cortical potentials. Furthermore, the eCAP response is not affected by factors such a level of alertness and muscle artefact, both of which can impact the quality of the responses obtained from electrically evoked auditory brainstem responses or electrically evoked Cortical potentials.

Most of the studies reviewed in chapter 4 used relatively heterogeneous groups of CI users, and of significant importance to the present study, most had CI users that used different cochlear implant devices, hence used different signal processing parameters. In order to control for these variations, the present study reports findings from subjects' with either the Nucleus CI532 or Nucleus CI512 device. In order to ensure the effects of front end processing were uniform, every subject was tested with the same clinical processor, a CP910 speech processor, with fixed microphone sensitivity and orientation to ensure any differences in processor technology, such a microphone quality and location did not contribute to the variability in behavioural responses; and all subjects used the ACE speech coding strategy.

5.2 Pilot Study

Prior to the main experiment a small pilot study with 5 CI users was undertaken to assess how robust the test methodology was and to ensure appropriate modifications could be made prior to the completion of the main experiment. As it was anticipated that the main experiment would

have a range of participants with varying durations of hearing loss and stimulation rates it was important to check the feasibility and range of the proposed measures. The main aims of the pilot study were:

1. The duration of time it would take to undertake the experiment

2. To assist with the sample size calculation for the main experiment

3. As discussed in chapter 4, eCAP measurements can be used for several purposes although little information is available on the clinical utility of the eCAP refractory recovery function in CI users and it is not clear if it can be employed in a routine clinical setting. Previous studies have shown a lower success rate for obtaining responses (Bostros and Psarros 2010) when compared to threshold eCAP measurements, the pilot study therefore aimed to determine if it was feasible to obtain eCAP recovery function measurements successfully using the existing methods in the NRT software and to see if any of the test parameters required optimisation.

5.3 General method

The following section outlines the methods used for the pilot and main experiment, there were some modifications made to the methodology following the pilot study and these are outlined in the introduction of the main experiment. All tests were completed in a sound proof audiology booth.

5.3.1 The eCAP recovery function

All the subject's in the pilot and main study were recipients of Cochlear Nucleus Ltd devices. Subjects were unilaterally implanted with either a Nucleus profile (CI 512 or CI532) Contour Advance all of which are modiolar electrode arrays. Therefore, for the purpose of both experiments, the eCAP recovery function was measured using advanced NRT in Custom Sound Electrophysiology (CS EP) Software Version 5.2 (Cochlear Ltd), which controlled for stimulation and recording parameters, and was installed on a computer coupled with a portable programming interface and a CP910 Sound Processor (Cochlear Ltd). This allowed for a better comparison of results as it ruled out differences in technology between CI manufacturers that could contribute to variations in results; such as the type of speech processor, number of electrodes, electrode array position, channel frequency allocation and the software algorithms used to calculate neural recovery functions.

Each eCAP recovery function measurement involves presenting a masker and probe stimuli to an electrode pair and subsequently recording the resultant neural response (see chapter

4). The recording electrode was set two electrodes away apically from the stimulation active electrode, which is the default setting in CS EP software. The masker precedes the probe stimuli and the software automatically varies the MPI as well as the pulse width (pulse width per phase). Once the probe stimulus is completed, a measurement delay is introduced so that the stimulus artefact can decay which prevents saturation of the measurement amplifier. At the end of the delay interval, the compound action potential is measured as a sequence of 16 voltage samples collected at regular intervals corresponding to the sampling period (Lai 2009). The amplitude of each voltage sample is coded for transmission back to the speech processor by 16 pairs of pulses at the sampling period. At the default sampling rate of 10Hz, the 16 samples span a measurement period about 1.5 millisecond (Lai 2009). The probe stimulation rate defines the time from one probe stimulus to the next probe stimulus and the masker rate defines the time between consecutive masker stimuli (Lai 2009), see figure 28.

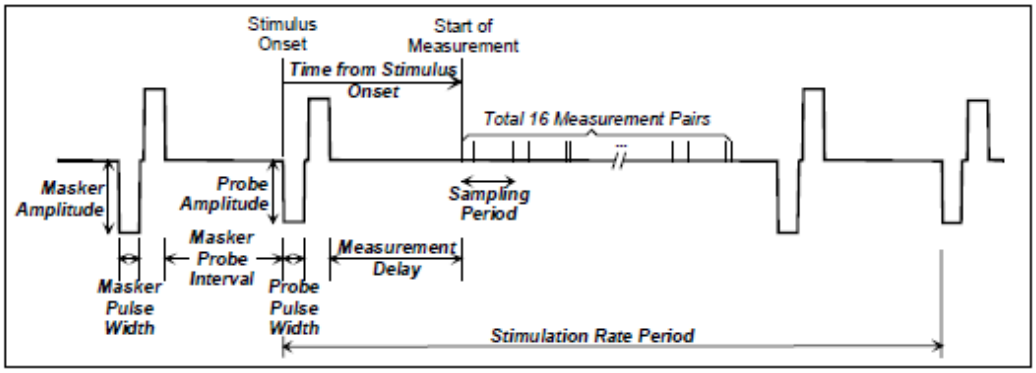

Figure 28: NRT stimulation and measurement sequence. Constant interphase Gap (IPG) of 25 µs is used for the masker and probe stimuli. 1) The MPI measured from the end of the masker to the onset of the probe, 2) The measurement delay started at the end of the probe stimulus.3) Stimulation rate time is as the interval between the start of the probe stimulus to the start of the next probe stimulus

In the CS EP software electrodes 6, 10, 16 and 19 were selected for eCAP recovery function measurements as these channels have the allocated frequencies (0.5,1,2,4 kHz) that correspond with the test frequencies on the RGDT (see table 3). Higher stimulus levels evoke larger eCAPs and thereby clearer recovery functions. Recovery function is dependent on the intensity of the probe stimulus, therefore, indirectly on loudness, hence for each subject eCAP recovery function measurements were completed at the current level they identified as the loudest acceptable presentation level (LAPL). To determine the subjects LAPL at each electrode, stimulation was initiated at 100 current levels, and increased in 5 current level steps until a response trace was observed and the subject indicated that the presentation level was

at a comfortably acceptable loudness level; the eCAP recovery function measurements were completed at this LAPL. Each recovery function consists of eCAP measurements obtained at MPIs ranging from 100 to 10,000 milliseconds. The NRT software automatically fits the recovery function measurement into an exponential function, using a mathematical model proposed by Müller-Deile et al (2003) which defines that:

F Masker Probe Interval (MPI) = A (1-exp [(-1/tau) (MPI-T0)])

	Electrode 19	**Electrode 16**	**Electrode 10**	**Electrode 6**
Lower Frequency (Hz)	563	938	2188	3938
Upper Frequency (Hz)	688	1063	2563	4563
Corresponding RGDT frequency (Hz)	500	1000	2000	4000

Table 3: The lower and upper frequency distributions of electrodes 19,16,10 and 6, which correspond to the test frequencies used in the RGDT 500,1000, 2000 and 4000Hz.

The recovery function has three parameters: ‘T0’, ‘A’ and ‘tau’. T0 is the absolute refractory period (in µs); A is the maximum amplitude of the neural response at the maximum saturation level (in µV); and tau is the recovery time constant during the relative refractory period (in µs), see figure 29.

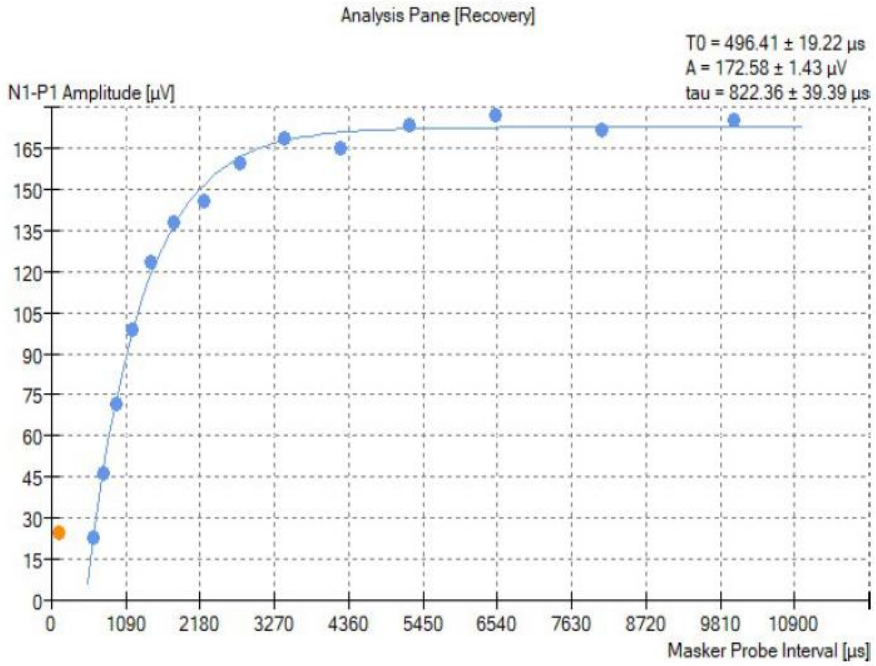

Figure 29: Fitted exponential recovery function: F (MPI) = A (1-exp [(-1/tau) (MPI-T0)]) at a reference MPI of 300 µs. The neural response becomes measurable above the threshold T0 and the eCAP amplitude increases with a time constant (Tau) up to an asymptotical limit, the saturation level A. Parameters: T0 = 496.41 µs; A = 172.58 µV, Tau = 822.36 µs

5.3.2 The eCAP recovery function stimuli and recording of parameters

In order to record a valid eCAP the following recording parameters were controlled according to the methodology described by Abbas et al. (1999) and Lai et al (2009). Biphasic stimulus pulses with a pulse width of 25 µs per phase and an interphase gap of 7 µs were used and the frame rate was 80Hz between the stimuli. The recording electrode was located two locations apically from the stimulated electrode. The default amplifier gain was set at 60dB and the number of sweeps (averaging) was set at 100, averaging assists with the removal of the noise that accompanies the eCAP response. The eCAPs were measured and recorded (2 electrodes apically from the stimulating electrode) in response to a stimuli presented in monopolar mode at electrode 6 (basal), electrode 10 (mid), electrode 16 (apical) and electrode 19 (apical), the extra-cochlear ball electrode (MP1) served as the reference electrode. NRT uses a forward masking paradigm described in chapter 4 which consists of eCAP recordings under four stimulus frames to remove stimulus artifact: probe alone (A), masker plus- probe (B), masker alone (C), and zero-amplitude pulse (D). The masker stimulus level was set 10 current levels above the probe stimulus level, by using a masker level greater than the probe level allows adequate forward masking to be achieved (Lai et al, 2009). Forward masking is

also dependent on the MPI, at shorter MPIs up to 300 µs facilitation effects are observed, which is thought to be caused by residual subthreshold depolarisation of ANs in which the masker stimulus does not generate an action potential (Finley et al., 1997), hence this depolarisation facilitates the probability of an action potential to the probe stimulus. Therefore, some ANs will be excited by the masker and go into absolute refractoriness, while others are depolarised below the excitation threshold which will facilitate the response to the consecutive probe stimulus. The absolute refractory period lasts between MPIs of 300 – 500 µs, which is followed by the relative refractory period at MPIs >500 µs and lasts up to 3-4 µs. The default MPI for the reference measurement was 300 µs. Changes were not made to the default parameters as the aim was to investigate if modifications were needed to these defaults based on the results of the pilot study.

5.3.3 Random Gap Detection Test

The RGDT is designed to identify temporal processing deficits that may be linked to poor phonologic processing and auditory discrimination, it is viewed as a test of temporal integrity at the level of the cortex (Keith, 2000). Previous studies have linked elevated GDTs to central auditory processing disorders, language delays, and aging-related decrements in temporal processing (Jerger et al., 2002; Smith et al., 2008; Lister et al., 2011b). Data on GDTs in CI users has been relatively limited with mixed results, as mentioned in chapter 4, this may partially be attributed to the variety of stimulus parameters used in studies. The purpose of the RGDT is to identify the listener's auditory gap detection threshold and is the most commonly used clinical measure of temporal resolution. It has been used extensively in diagnosing central auditory processing deficits (Jerger et al, 2002; Chermak and Lee, 2005; Queiroz et al., 2010; Iliadou et al., 2014); however, it has limited use in the CI population (Zhang, 2013). There is currently limited data on the sensitivity of the RGDT (Chermak and Lee, 2005). The validity of the RGDT's ability to correctly identify individuals with temporal resolution difficulties was established by examining its predictive validity, using the Auditory Fusion Test-Revised (The RGDT is a revision of this test) as the criterion measure. Keith (2000) reported that gap detection thresholds obtained on the RGDT for tonal stimuli were comparable to fusion thresholds reported for the Auditory Fusion Test-Revised as published by McCroskey and Kidder (1980).

The RGDT, like eCAP recovery, depends on forward masking, where one stimulus (masker) suppresses the detection of the sound stimulus (probe) and is a within channel task (see figure 27). The shorter the interval between the masker and probe the greater the level of suppression, and the greater likelihood of both stimuli activating the same ANFs, with the

RGDT as the stimuli are identical (within channel) the task relies on the ability of the ANs to encode the start of the second stimuli whilst recovering from the first stimuli, and therefore requires recovery from forward masking (Kirby & Middlebrooks, 2010). Normal GDTs are typically less than 20ms and are vital for speech perception which requires rapid separation of speech segments.

Several studies have demonstrated that temporal resolution improves substantially with increasing stimulus level (Preece and Tyler,1989; Shannon,1989; Pfingst et al., 2007; Galvin and Fu, 2009). In a CI increasing the current level leads to the recruitment of more ANFs and increases the perception of loudness. Variations in loudness growth are likely due to the differing patterns of neural survival among CI users. Previous studies have shown that elevated GDTs and limited temporal processing are related to poor neural function (Moore, 1996; Moore and Oxenham 1998). It is plausible that GDTs obtained at low stimulation levels are more sensitive to the effects of local neural pathology as stimulation is more focused with less spread of excitation hence more precise stimulation of a narrow subset of ANFs close to the recording electrode. The RGDT was administered at 60dB HL in this experiment, as this level would likely demonstrate the best performance of temporal resolution in all subjects.

The RGDT was presented via free field sound speakers 1 meter away from test ear in the sound field through an audiometer using a CD player (using RGDT on the Auditec St. Louis CD) after calibration was successfully completed. The advantage of measuring GDT acoustically is that it is reflective of the limitations imposed by front end signal processing in speech processors as well as those imposed by electrical stimulation, hence results are able to provide information on temporal processing skills in CI users for routine daily use. During the practice screen, the researcher provided the subject information on the test and ensured they had a good understanding of the task and were able to respond appropriately. The subjects were instructed to verbally identify if they heard one or two sounds or hold up one finger if they heard one tone, or hold up two fingers if they heard two tones. The practice and main section of the test consists of pairs of pure tones separated by silent intervals, the silent intervals for the practice section begin at 0 μs and gradually increase to 40 ms (0, 2, 5, 10, 15, 20, 25, 30 or 40 ms). In the main section of the test, the silent intervals were presented in random order for each of the following pure tones, 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz, which were tested in sequence and not counter balanced across subjects. Each stimulus in the signal pairs has the same frequency and the same duration (17 ms, including a 1-ms rise-fall time). A 4.5 second inter-trial interval was used to allow subjects time to respond between presentations. The practice as well as the main section of the test (each frequency) was only

administered once. The smallest detectable gap was scored based on the subject's response for each frequency and compound score was also calculated across the four frequencies. For subjects who were unable to detect gaps at 40 ms, the RGDT-Expanded Test was administered which has longer silent intervals between stimuli, 50, 60, 70, 80, 90, 100, 150, 200, or 300 ms. At each frequency the RGDT threshold was calculated as the interval where the subject consistently identified two rather than one tones.

For scoring, at each frequency the GDT was defined as the interval where the subject consistently identified two rather than one tones. When completing the RGDT, it is not unusual for there to be uncertainty at the threshold between one and two tones, and some subjects may be inconsistent in their decision on whether they heard one or two tones. Below are examples of scoring in such cases, responses marked in red are considered the GDT:

If the subject reports hearing gaps as below:

Gap interval msec	0	2	5	10	15	20	25	30	40
Response	1	2	1	1	1	**2**	2	2	2

The response at 2msec would be considered an outlier and the GDT would be scored at 20 msec.

If the subject reports hearing gaps as below:

Gap interval msec	0	2	5	10	15	20	25	30	40
Response	2	1	**2**	2	2	2	2	2	2

The response at 0msec would be considered an outlier and the GDT would be scores at 5msec.

If the subject reports hearing gaps as below:

Gap interval msec	0	2	5	10	15	20	25	30	40
Response	1	2	**1**	1	2	2	1	1	**2**

The GDT would be scored at 40msec

If the subject reports hearing gaps as below:

Gap interval msec	0	2	5	10	15	20	25	30	40
Response	1	1	1	1	2	1	2	1	1

The GDT is not established and the Expanded GDT would need to be administered as this subject has a GDT >40 msec.

If the subject reports hearing gaps as below:

Gap interval msec	0	2	5	10	15	20	25	30	40
Response	1	1	2	1	**2**	2	2	2	2

The GDT would be scored as 15 msec as the subject displays uncertain responses at 5 and 10msec but more consistent responses at 15 msec and above.

Shannon (1989) obtained electrical GDTs for both closely spaced (bipolar) and widely spaced (monopolar) electrode configurations to assess the effects of the electrical field and neural activation using sinusoidal and pulsatile stimuli. GDT were found to be strongly dependent on stimulus level and the shortest gaps (1.5 - 3.1 ms) did not differ based on the separation between the stimulating and recording electrode. This study used direct electrical stimulation and measurements were completed with the stimuli marking the gap at a single electrode pair therefore across channel processing was not assessed. Measurements were also obtained from two different devices, the GDTs were lower for the Symbion device (monopolar, sinusoidal stimulation) compared to the Nucleus device (bipolar, biphasic stimulation). This difference in GDTs was as expected, as monopolar thresholds tend to be lower due to widespread neural activation compared to bipolar thresholds, which are the result of more focused electrical stimulation that activates fewer ANs (van den Honert and Stypulkowski,1987; Shannon, 1983), and sinusoidal GDTs are slower than or equal to pulsatile GDTs for the same stimulating frequency (Shannon, 1985). The stimulation mode for all of the subjects in this study was monopolar mode (MP1 +2) which is the clinical default stimulation mode for Cochlear Nucleus devices.

5.3.4 Speech perception tests

The most commonly used clinical tests to assess speech perception in adult CI users are sentence and word lists. In the UK the most frequently used standardised tests to assess candidacy and monitor progress are the Bamford-Kowal-Bench (BKB) sentences (Bench et al., 1979) and Arthur Boothroyd (AB) word lists (Boothroyd, 1968). BKB sentences are highly

predictable as they contain contextual cues, therefore individuals with higher cognition and linguistic knowledge are able to predict the content of the sentence despite only accessing minimal speech cues (Kalikow et al., 1977). When administering BKB sentences in quiet for high preforming CI users it is easy to reach a ceiling which means the test lacks sensitivity in tracking progress over time. Furthermore, BKB sentences may not reflect the speech perception abilities in non-native English speakers and in subjects who are poorer performers.

AB Word lists therefore provide a better measure of speech perception because context cues are not available and are therefore not predictable. An additional advantage of word lists is that they can be scored based on the proportion of phonemes correct rather than words correct and therefore provide a better indication of speech performance. Scoring in phonemes is appropriate for a wide range of people and is also suitable for participants with English as a second language or pre-lingually deafened adults who are unable to report whole words. For these reasons AB word lists in quiet were used to assess speech perception in our subject group. There is minimal evidence on the correlation between the objective and behavioural measures of temporal resolution and speech perception in quiet, therefore speech perception was assessed in quiet in this experiment. It is likely that speech testing in noise will be more difficult for CI users and temporal resolution may play a greater role in predicting performance in more complex listening environments, however, we propose that the results of this study may form the basis of further studies investigating speech perception in noise. An additional reason for completing speech testing in quiet is that it allowed for the best performance in an optimal listening environment across subjects. Pre-lingual subjects who are usually at the lower end of the performance scale would have been unlikely to have complete speech perception testing in noise.

The AB word test comprises fifteen lists containing ten words, each word is made up of three phonemes. Each list has a total of 30 phonemes constructed from the same 10 vowels and 20 consonants. The AB word test (female speaker, audition alone) was administered via free field speakers 1 meter away from the test ear through a CD player. An AB word list was presented at sound presentation levels, 70, 60, 50, and 40dBA. The participant was asked to listen to each word in the list and then repeat what they heard, each word was scored based on the phonemes identified correctly, a maximum score of 30 phonemes was achievable per list presented. The presentation level was decreased in 10dB steps for each subsequent word list until the minimal presentation level of 40dBA was reached.

5.4 Results of the pilot study

Of the 5 subjects in the pilot study, three were pre-lingually deaf and two were post-lingually deaf. The results of the pilot experiment are shown in table 4 and figure 30. The eCAP recovery function was obtained successfully in all five subjects, however in some subjects the eCAP recovery function could not be measured at all electrodes, on a two occasions this was due to electrode compliance issues and on all other occasions it would appear that the stimulation current level at the test electrode was not adequate to elicit a neural response. In the pilot study eCAP recovery function was obtained for 45/60 of the measurements completed, providing a 75% success rate. The eCAP recovery function measurement took approximately 10 minutes to complete at four electrode locations and was not time consuming in a clinical setting.

	Subject 1	**Subject 2**	**Subject 3**	**Subject 4**	**Subject 5**
Deafness onset	Post-lingual	Pre-lingual	Pre-lingual	Post-lingual	Pre-lingual
Electrode 19 Tau	1075.27 ms	515.38 ms	899.70 ms	82.10 ms	1104.46 ms
Electrode 19 T0	536.74 ms	374.41 ms	187.05 ms	569.95 ms	494.72 ms
Electrode 19 Amplitude	80.36 mv	191.40 mv	54.58 mv	14.97 mv	96.96 mv
Electrode 16 Tau	822.36 ms	674.06 ms	Response not obtained	Response not obtained	772.01 ms
Electrode 16 T0	496.41 ms	330.99 ms	Response not obtained	Response not obtained	647.29 ms
Electrode 16 Amplitude	172.58 mv	177.32 mv	Response not obtained	Response not obtained	74.44 mv
Electrode 10 Tau	1212.70 ms	Response not obtained	1257.30 ms	729.01 ms	Response not obtained
Electrode 10 T0	520.90 ms	Response not obtained	528.81 ms	417.20 ms	Response not obtained
Electrode 10 Amplitude	66.74 mv	Response not obtained	21.70 mv	27.53 mv	Response not obtained

Electrode 6 Tau	1507.44 ms	13.71 ms	1181.59 ms	558.64 ms	Response not obtained
Electrode 6 T0	241.40 ms	548.72 ms	560.46 ms	449.03 ms	Response not obtained
Electrode 6 Amplitude	47.19 mv	16.54 mv	21.70 mv	42.79 mv	Response not obtained
Compound RDGT Score	30 ms	55 ms	60 ms	20 ms	60 ms
Compound AB Word Score	50%	23%	10%	57%	42%

Table 4. eCAP recovery function measurements and mean RGDT and AB word phoneme scores for subjects in the pilot study.

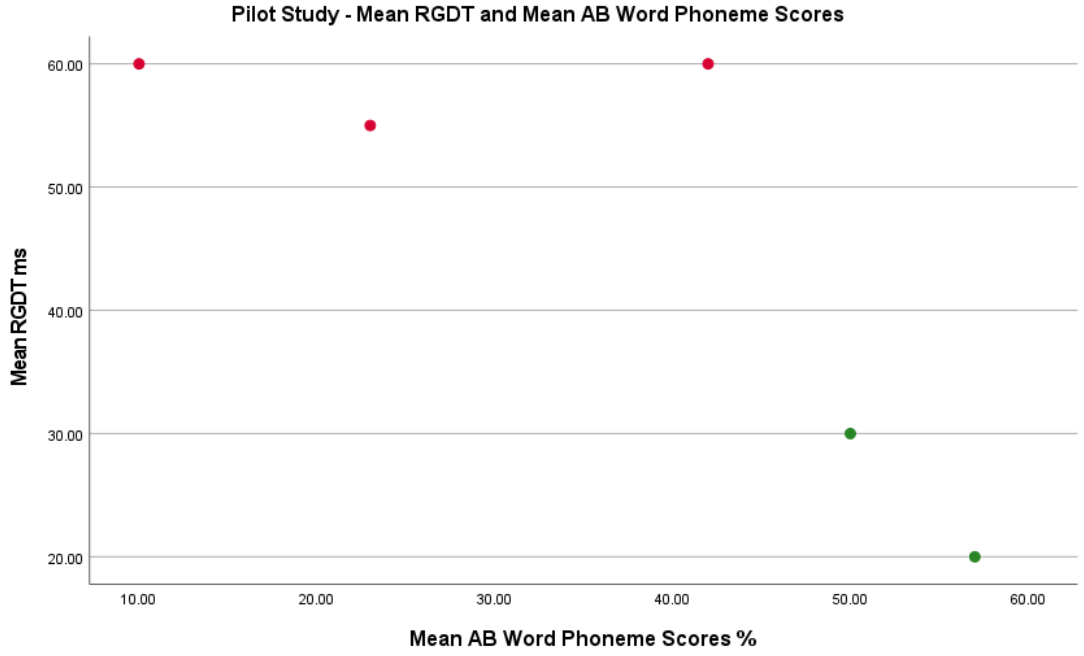

Figure 30: The mean RGDT and AB word phoneme scores for the 5 subjects in the pilot study. The red circles represent the pre-lingual subjects and the green circles represent the post-lingual subjects. The pre-lingual subjects have larger GDTs and lower AB word phoneme scores when compared to the post-lingual subjects.

The results of the pilot study were in line with expectation, and appeared to support the hypotheses proposed for the main study. Figure 30 shows that the pre-lingual subjects had longer RGDT thresholds with lower AB word phoneme scores in comparison to the post-lingual

subjects. The average RGDT thresholds were higher in the pre-lingual subjects when compared to the post-lingual subjects and the average AB word phoneme scores were lower in the pre-lingual subjects when compared to the post-lingual subjects. Based on the existing methodology the evidence from the pilot study demonstrated that all the measurements were appropriate to answer the questions raised in chapter 4.

5.5 Subjects and sample size calculation

The sample size calculation used to determine subject numbers for the main experiment was based on the mean RDGT and mean AB word scores obtained from the pilot study. Sample size was calculated based on an anticipated large size regression effect, f2 = 0.70, the required sample to obtain a power of 80% was 18.

Consequently, 18 subjects (13 females and 5 males, mean age of 64.5 years, minimum age 31 years, maximum age 90 years) were recruited between August 2018 - January 2019 to the main study from the Auditory Implant Service at St George's University Hospitals NHS Foundation Trust, following ethical approval from NHS National Research Ethics, reference 18/LO/12/41, local safety and ethics committee approval and from the University's Research Governance Office. See Appendix A.

5.6 Study participants

Understanding the prediction of performance was of most importance in this experimental work therefore subjects were recruited on the basis that their underlying physiology would be the main predictor of performance. Subjects were therefore recruited by convenience sampling and stratified by deafness onset and stimulation rate. For the purpose of this experimental work pre-lingual CI users had congenital HL or HL that occurred before the acquisition of language and post-lingual CI users had HL that occurred after the acquisition of language at any age. It was expected that the pre-lingual group would demonstrate larger neural deficits impacting performance due to longer periods of auditory deprivation in comparison to the post-lingual group of subjects. Subjects were not paid to participate and were required to provide fully informed consent based on the safety and ethics application in order to participate in the study. Subjects had a minimum of 6 months' use with their CI to ensure their impedance profile was stable. Fluctuations in impedance and eCAP measurements are often observed in the early stages of CI use and these fluctuations can continue 3-6 months' post activation; it also takes time for CI users to acclimatise to their device before using the signal provided by the CI for speech discrimination. Additionally, it can

take pre-lingually deafened adults a longer time to acclimatise to a CI. Therefore, to obtain successful eCAP recovery measurement and accurate measures of behavioural temporal resolution and speech performance data was not collected from CI users who had less than 6 months of use with their device. Each subject had a fully inserted CI electrode array, with 22 intra cochlear electrodes and two extra cochlear electrodes that deliver stimulation in monopolar (MP) mode (Abbas et al. 1999) which was the default stimulation mode for all subjects. CI users who had partial insertion of a cochlear implant array, where all the electrodes cannot be accommodated in the cochlea were excluded from the study. In this group of people studies have shown that speech performance is poorer due to pitch mismatch therefore including these cases in the study was likely to skew the performance data. All subjects used the Advanced Combination Encoder (ACE) strategy and English was the first language for all subjects. No subjects were lost to follow up as data was collected at one visit, which lasted approximately 45 minutes.

Medical records and clinical history was reviewed for all subjects recruited to the study to ensure they met the inclusion criteria and to confirm accuracy for variables such as deafness onset. Of the 18 subjects that were recruited, 7 were pre-lingually deaf and 11 were post-lingually deaf, ideally both groups would have an equal number of subjects that are age matched but this was not possible as the recruiting centre had a fewer number of pre-lingual adult subjects that could be recruited when compared to post-lingual adults.

5.7 Main experiment

Based on the observations and methodological issues that were experienced in the pilot study the following changes were made to the general procedures for the main experiment:

Most clinical testing with CI users is conducted in soundfield but during the pilot study there was the presence of a low level hum from the sound field speakers which appeared to mask the presentation of shorter gaps on the RGDT and blur the AB word phoneme presentation at lower presentation levels; therefore, circumaural headphones that fit well around the speech processor were used in the main experiment. Calibration was completed with the test speech processor by using a custom leaf from the processor to the line of the operating computer. This had the added advantage of ensuring the contra-lateral ear did not contribute to results, especially in cases where there was some residual hearing.

5.8 Analysis

Before analysis the gathered data was prepared and the dataset was checked for missing data and outliers. The data was then analysed using statistical software SPSS (version 26) and the results of the experiment and analyses are presented in the next chapter.

Chapter 6: Results

This chapter is divided into several sections and provides the results obtained from the main experiment as follows:

Section 6.1 provides information on the subjects recruited to the study and provides details of the descriptive and statistical analysis used to assess the results.
The aim of analyses in section 6.2 was to explore the effects of deafness onset and stimulation rate on each parameter of the eCAP recovery function measurement and explore individual differences related to the hypotheses outline in section 4 and summarised below:

- The eCAP recovery function will be quicker in subjects with post-lingual deafness who have a high stimulation rate compared to subjects with pre-lingual deafness with low stimulation rates.

The aim of the analyses in section 6.3 was to explore the effects of deafness onset and stimulation rate on the RGDT thresholds in order to explore the individual difference in temporal resolution related to the hypotheses outlined in section 4 and summarised below:

- RGDT thresholds will be shorter at all frequencies in subjects with post-lingual deafness who have high stimulation rates compared to subjects with pre-lingual deafness with low stimulation rates.

The aim of the analyses in section 6.4 was to explore the effects of deafness onset and stimulation rate on the AB word phoneme scores in order to explore the individual differences in speech perception related to the hypotheses outlined in section 4 and summarised below:

- AB word phoneme scores will be higher in subjects with post-lingual deafness who have high stimulation rates compared to subjects with pre-lingual deafness with low stimulation rates.

Subsequently, in section 6.5 the results of multiple linear regression analyses are presented which explore the relationship between the variables that predict performance of eCAP recovery function, RGDT thresholds and AB word phoneme scores.

The dataset for this thesis - DOI: https://doi.org/10.5258/SOTON/D1558

6.1 Subject details

General details and values for the key variables for each subject are shown in table 5, the sample consists of 13 female subjects and 5 male subjects (with a mean age of 64.5 years, minimum age 31 years, maximum age 90 years) who are categorised by deafness onset (pre-lingual or post-lingual hearing loss) and by the rate of their MAP, those with rates of 900 pps/ch were classified as high rate and those with rates of 500 and 250 pps/ch were classified as low rate. The pre-lingual group consisted of 7 subjects (6 females and 1 male) with a rate of 900 pps/ch (2 females), 500 pps/ch (4 female) and 250 pps/ch (1 male). The post-lingual group consisted of 11 subjects (7 females and 4 males) with a rate of 900 pps/ch (6 females, 3 males), 500 pps/ch (1 female and 1 male), see table 6. All subjects were recipients of a profile series cochlear implant, the CI512 (7 females and 2 males) and the CI532 (6 females and 3 males). The mean age at implantation was 61.2 years (minimum age at implantation was 24 years and maximum age at implantation was 89 years) and the mean duration of cochlear implant use was 2.4 years (minimum time 9 months and maximum time 7.3 years).

Subject	Gender	Date of Birth	Deafness onset	Rate	Duration of amplification with hearing aids prior to CI	Implant Type	Age at implantation	Time with CI
1	Female	18/06/1958	Pre-lingual	500	48 years	512	53.1 years	7.3 years
2	Female	17/08/1962	Post-lingual	900	1 year	512	52.1 years	4.1 years
3	Male	08/07/1943	Post-lingual	900	6 years	512	67.6 years	7.9 years
4	Female	14/08/1944	Post-lingual	900	41 years	532	72.4 years	1.10 years
5	Female	13/01/1956	Pre-lingual	500	54 years	532	61.8 years	1.2 years
6	Female	09/09/1941	Post-lingual	900	31 years	512	72.4 years	4.1 years
7	Female	11/11/1971	Pre-lingual	500	43 years	532	45.2 years	1.10 years
8	Female	09/10/1946	Post-lingual	900	39 years	512	68.3 years	3.10 years
9	Female	24/12/1962	Pre-lingual	500	53 years	532	55.4 years	9 months
10	Male	04/09/1987	Pre-lingual	250	24 years	532	27.1 years	4.5 years
11	Female	18/09/1969	Post-lingual	900	3 years	532	47.8 years	9 months
12	Female	17/08/1983	Pre-lingual	900	31 years	532	34.3 years	1.4 years
13	Male	10/09/1946	Post-lingual	900	1 year	532	70.6 years	1.1 years
14	Male	06/06/1939	Post-lingual	900	47 years	512	78.8 years	1 year
15	Female	09/06/1938	Post-lingual	500	66 years	512	78.1 years	2.8 years
16	Female	04/05/1939	Post-lingual	900	31 years	512	77.3 years	2.9 years
17	Female	05/12/1951	Pre-lingual	900	48 years	512	66.1 years	1.2 years
18	Male	02/08/1928	Post-lingual	500	34 years	532	89 years	1.8 years

Table 5: General details and values of key variables for each subject recruited to the study.

	Number of subjects	High stimulation rate 900 pps/ch	Low stimulation rate 250/500 pps/ch
Pre-lingual	7	2	5
Post-lingual	11	9	2

Table 6: The number of subjects in the pre-lingual and post-lingual group based on stimulation rate.

6.1.1 General and descriptive statistics

The main aim of this analysis was to outline the differences observed in the eCAP recovery function, RGDT thresholds and AB word phoneme scores between subjects based on the two main predictor variables deafness onset and stimulation rate. This was achieved by measuring box plots for all measures, the box plots show the median (black bar), interquartile range (box ranges between 1st and 3rd quartile, whiskers represent highest and lowest values after exclusion of outliers). The outliers (circles, defined as any point which falls more than 1.5 times the interquartile range above the third quartile or below the first quartile) have subject numbers alongside for identification. Inspection of these outliers did not reveal them to be extreme and they were kept in the analysis as they did not unduly influence the mean difference and whilst they elicited an increase in variability, they did not change the conclusion of the statistical tests, described below.

6.1.2 Statistical analysis

Before statistical analysis was completed, data were tested for normality and homogeneity of variance. This was done by performing Levene's test, Shapiro-Wilks test and by visual inspection. It was found that all variables except AB word phoneme scores at 40dBA were distributed approximately normally. An attempt was made to transform this data using log 10 transformation and square root transformation but the Shapiro-Wilks test was still significant (p 0.02). The AB word phoneme scores at 40dBA are heavily influenced by floor effects in this small sample, therefore it has not been possible to normalise the data, 5 out of 18 subjects scored 0% for AB word scores and a further 3 subjects had scores of 3% which positively skews the data. Levene's test for AB word phoneme scores at 40dBA was not significant F (1,16), P 0.47. Although the AB word phoneme scores at 40dBA violated the assumption of normal distribution, as only one variable violated the assumption of normal distribution it was concluded that parametric statistical analysis with ANOVA would be appropriate. Many studies

have shown that for ANOVAs and t-tests, departures from normality are not critical (Rubinstein et al., 1992; Lix et al., 1996; Schmider et al 2010).

Statistical analysis was performed using repeated measures two-way ANOVA where results were normally distributed and Mauchly's test of sphericity gave a non-significant result; the effect sizes, were calculated from the *F*-values for within-subject's contrasts. Where this assumption was violated for two-way interaction, the Greenhouse-Geisser correction was applied. For *post-hoc* tests following ANOVA, the Bonferroni correction was applied controlling for type I errors as the result of making multiple comparisons. For all statistical tests, an alpha-level of 0.05 was used. In section 6.4, multiple linear regression was performed after data was checked for the assumption of normality by production of histograms and P-P Plots which showed the residuals were normally distributed.

6.2 The eCAP recovery function measurements

In this section the results obtained for each component of the eCAP recovery function measurement are detailed; where A (μV) is the maximal amplitude of the neural response at saturation level, T0 (μs) is a measure of the absolute refractory period and tau (μs) is the time constant of recovery during the relative refractory period Müller-Deile et al (2003). A full set of eCAP recovery function measurements were obtained in 14 of the 18 subjects (78%). Figure 31 illustrates the variance between each component measurement of the eCAP recovery function, which are presented in detail in subsequent sections below.

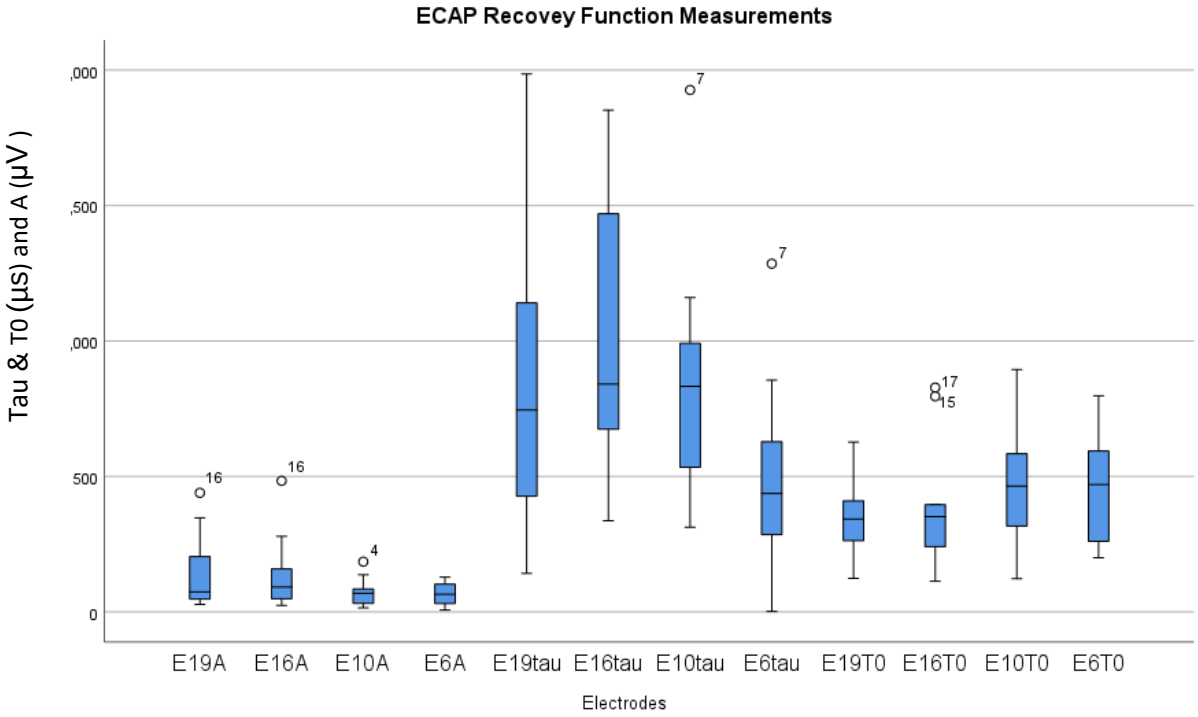

Figure 31: Box plots of the data obtained for each eCAP recovery function measurement component at the different electrode locations. A (µV) is the maximal amplitude of the neural response at saturation level, T0 (µs) is a measure of the absolute refractory period and tau (µs) is the time constant of recovery during the relative refractory period.

Figure 31 demonstrate that the Tau values vary considerably in our sample and across location, with faster recovery constants being observed at electrode 6 (basal) when compared to electrode 19,10, 6 which have similar median constants. The T0 values do not differ hugely between electrodes, but visually it would appear that the absolute refractory periods are slower for the basal electrodes. The A values do not differ significantly between electrodes but the responses at electrode 19 and 16 appear to vary more significantly between subjects.

Figure 32-35 show eCAP recovery function traces obtained from subject 2 in this study, which show the eCAP traces and the fitted exponential recovery function for each electrode when an recovery constant could be calculated.

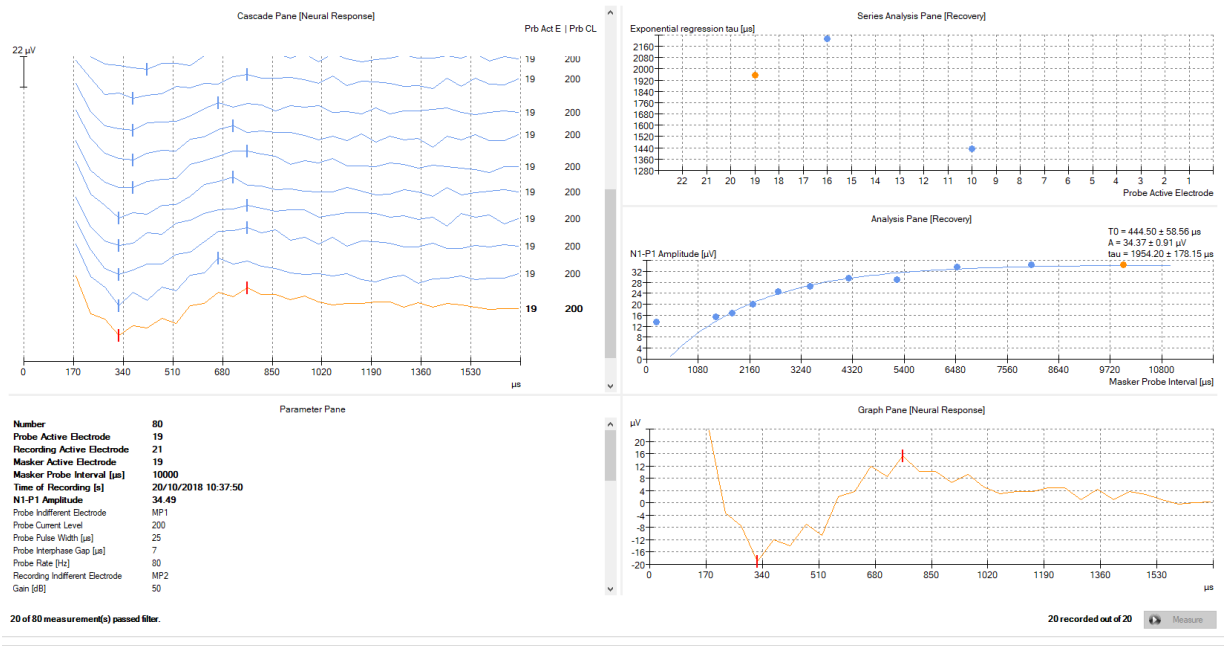

Figure 32: The eCAP recovery function measurements obtained for subject 2 at electrode 19.

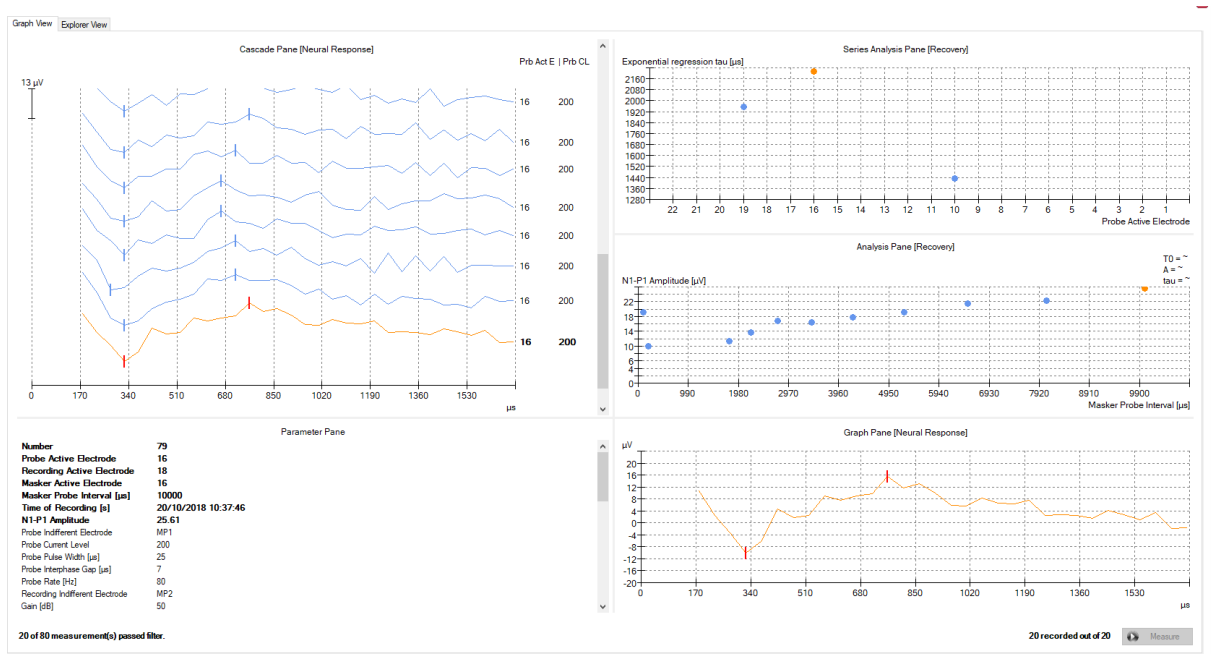

Figure 33: The eCAP recovery function measurements obtained for subject 2 at electrode 16. Note, recovery function could not be calculated at this electrode therefore an exponential curve is not fitted.

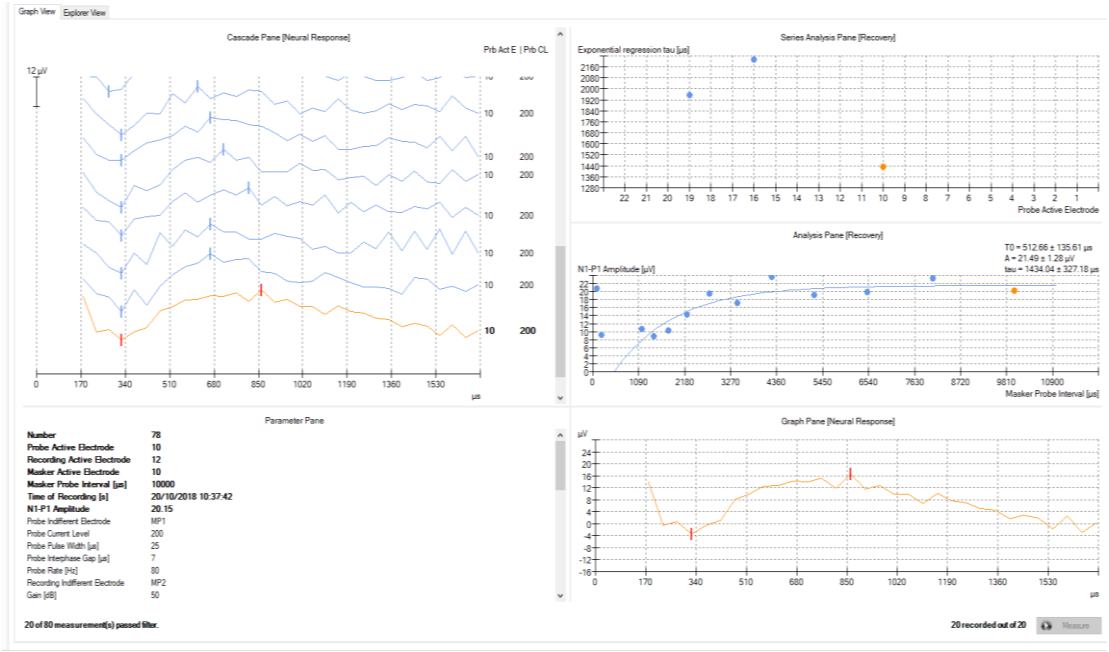

Figure 34: The eCAP recovery function measurements obtained for subject 2 at electrode 10.

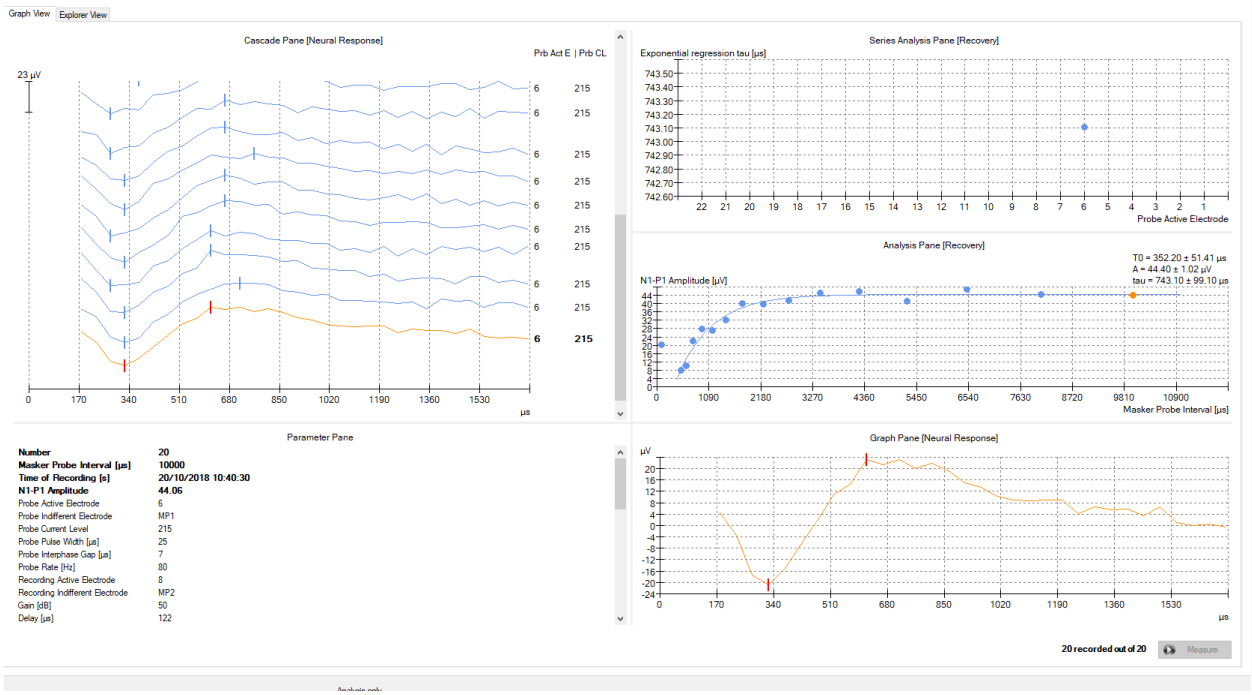

Figure 35: The eCAP recovery function measurements obtained for subject 2 at electrode 6.

6.2.1The eCAP recovery function Tau measurements and deafness onset

One aim of this experiment was to identify if the eCAP recovery function measurements differed in subjects based on deafness onset. It was hypothesised that individuals with pre-lingual hearing loss would have longer Tau measurements as the ANFs may be in a prolonged state of absolute refractory. The median Tau values at each electrode based on deafness onset are shown in figure 36.

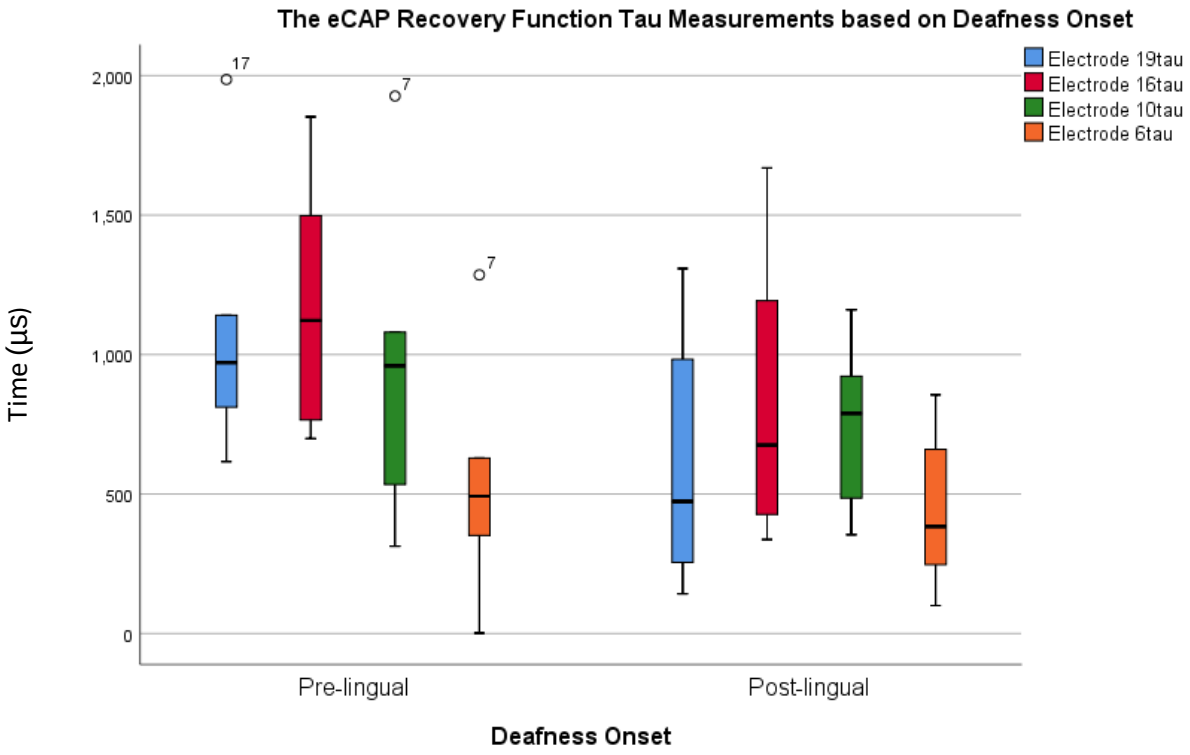

Figure 36: Median Tau Measurement at different electrode locations based on deafness onset

A two-way repeated measures analysis of variance was completed to determine the effect of deafness onset on Tau measurements at each electrode location (N =14). Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(5) = 21.01$, $P = <0.01$, therefore the Greenhouse-Geisser correction was applied. There was a significant main effect of electrode location on the Tau value, F (1.43, 17.13) = 5.32, P = <0.05. The *posthoc* tests are described in section 6.2.4. There was not a significant interaction between deafness onset and electrode location within subjects, F (1.43, 17.13) = 0.74, $P = 0.45$. Furthermore, there was not a significant difference between the Tau values at each electrode location in the pre-lingual (N=6) and post-lingual group (N=8) F (1, 12) = 3.03, $P = 0.11$.

6.2.2 The eCAP recovery function Tau measurements and stimulation rate

Another aim of this experiment was to identify if the eCAP recovery function measurements differed in subjects based on the rate of stimulation. It was hypothesised that the eCAP recovery function may be able to provide an indication of an optimal stimulation rate in subjects which could be correlated to better speech perception. The median and mean Tau values at each electrode location by stimulation rate are shown in Figure 37.

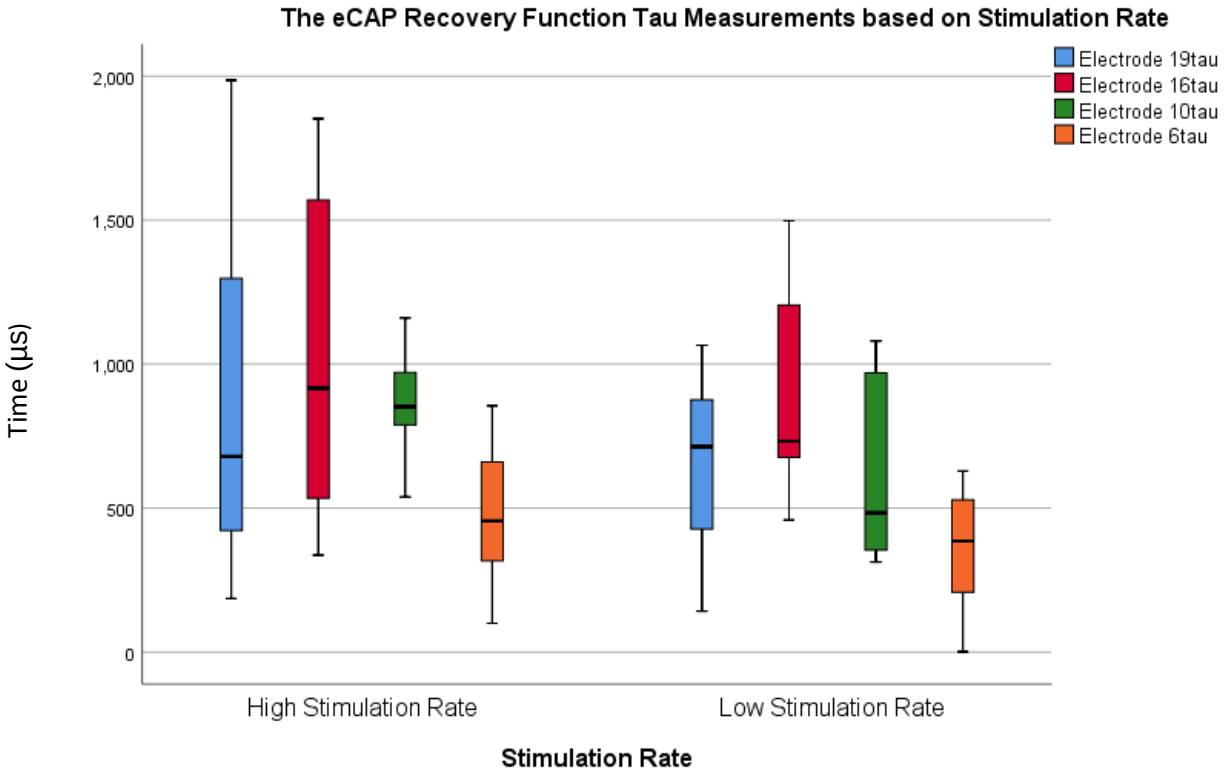

Figure 37: Median Tau measurements at different electrode locations based on rate

A two-way repeated measures analysis of variance was completed to determine the effect of rate on Tau values at different electrode locations (N=14). Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(5) = 21.00$, $P = <0.01$, therefore the Greenhouse-Geisser correction was applied. There was a statistically significant main effect of electrode location for Tau values, F (1.43, 17.26) = 4.80, P =<0.05. The *posthoc* tests are described in section 6.2.4. There was not a significant interaction between stimulation rate and electrode location within subjects, F (1.44, 17.26) = 0.18, $P = 0.76$. There was no significant difference between Tau values in the high rate (N=7) and low stimulation rate (N=7) group at each electrode location, F (1, 12) = 0.26, $P = 0.62$.

6.2.3 *Posthoc* analysis for eCAP recovery function Tau measures and electrode location

In order to further analyse the main effect of electrode location observed with deafness onset and rate, post hoc comparisons using paired t-tests were completed and are shown in figure 38 and Table 7 summarises the mean difference in Tau values between electrode pairs.

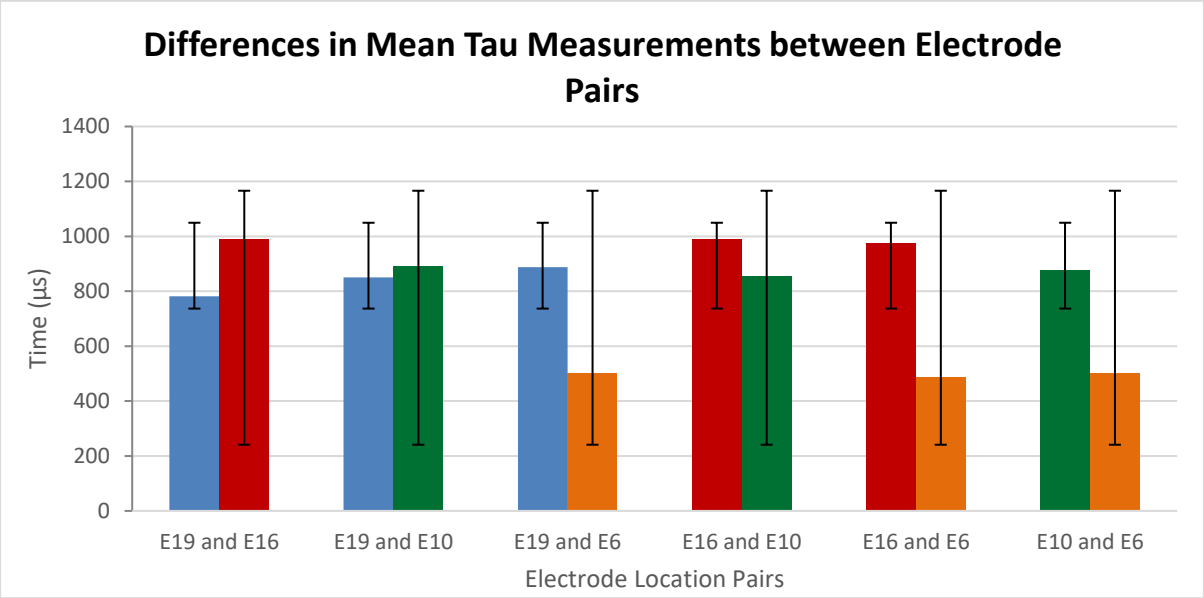

Figure 38: Mean (+ 2 SD) Differences in mean Tau measurements between electrode pairs

Electrode	Mean (Tau)	SD	Electrode	Mean (Tau)	SD	Mean Difference	T Value	Significance level (2-tail)
19	781.59	494.08	16	988.71	459.10	-207.11	-2.90	**0.01**
19	850.57	556.54	10	888.81	411.06	-38.24	-0.32	0.75
19	888.28	573.93	6	502.18	323.98	386.09	2.54	**0.02**
16	988.71	459.10	10	854.73	398.98	133.97	0.97	0.35
16	975.40	491.58	6	484.98	328.72	490.42	3.04	**0.01**
10	874.38	430.92	6	502.18	323.70	372.20	5.50	**0.00**

Table 7: *Posthoc* paired t-tests for eCAP recovery function Tau measures and electrode location. Differences reaching the Bonferroni-corrected significance level are given in bold.

There is a main effect of electrode location on the Tau values and paired sample *posthoc* T-tests show Tau values are significantly different between electrode 19 and 16, electrode 19 and 6, electrode 16 and 6 and electrode 10 and 6.

6.2.4 The eCAP recovery function T0 measurements and deafness onset

The median T0 values at different electrodes by deafness onset are shown in figure 39.

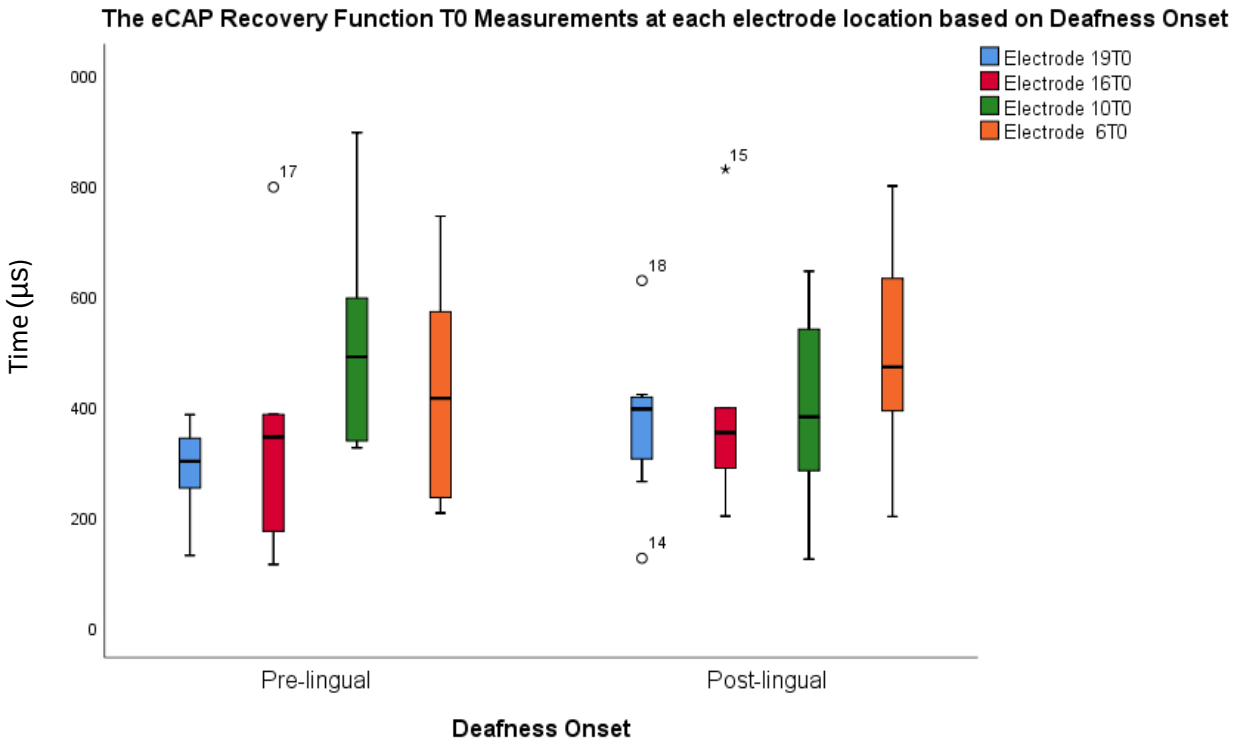

Figure 39: Median eCAP recovery function T0 measurements by deafness onset

A two-way repeated measures ANOVA was completed to determine the effect of deafness onset on T0 measurements at different electrode locations (N =14). Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi^2(5) = 1.27$, $P = 0.94$. There was not a statistically significant main effect of electrode location for T0 values, F (3, 36) = 2.72, $P = 0.59$. There was not a statistically significant interaction within subjects between deafness onset and T0 values at each electrode location, F (3, 36) = 1.43, $P = 0.25$. The T0 values were not significantly different between the pre-lingual (N=6) and post-lingual (N=8) groups, F (1,12) = 0.04, P = 0.84.

6.2.5 The eCAP recovery function T0 measurements and stimulation rate

The median T0 values at each electrode location based on stimulation rate are shown in figure 40.

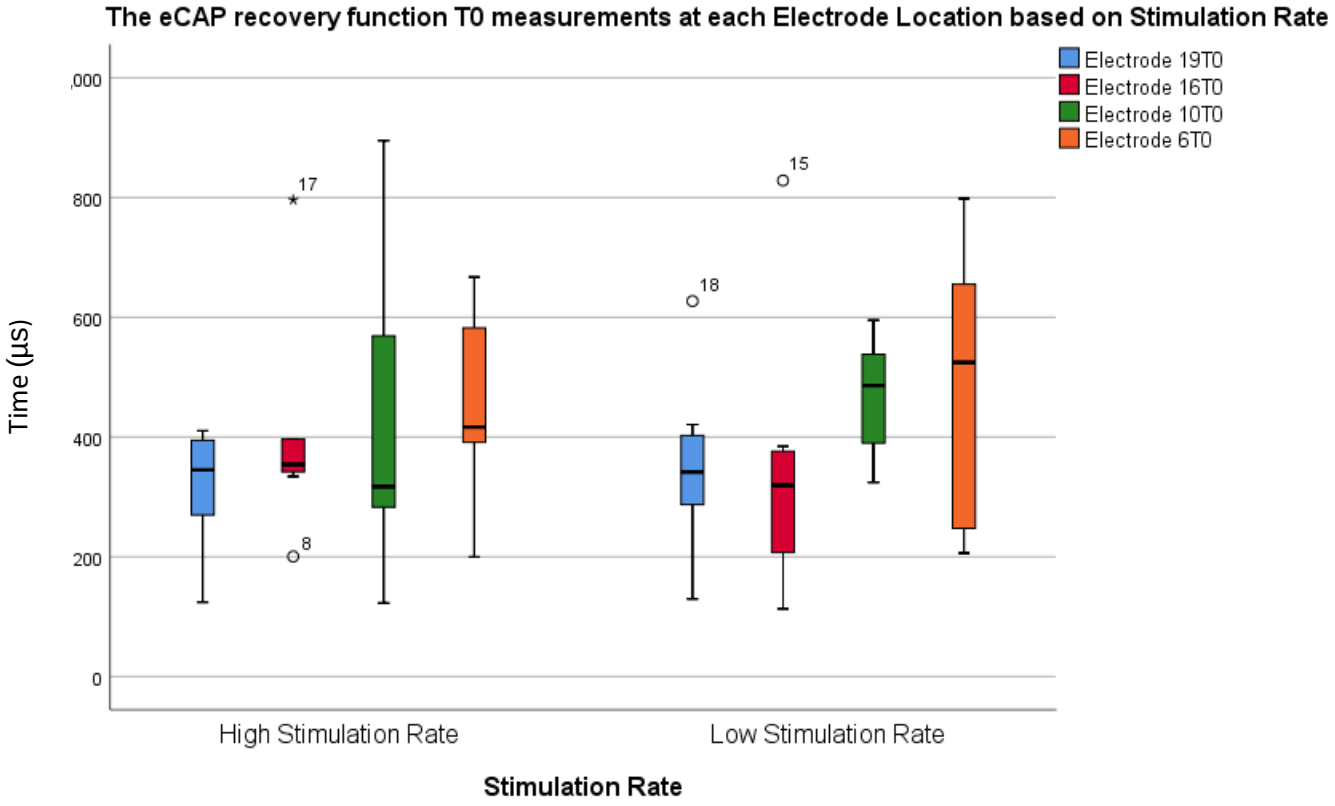

Figure 40: Median eCAP recovery function T0 values by rate

A two-way repeated measures ANOVA was completed to determine the effect of stimulation rate on T0 measurements at each electrode location (N=14). Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi^2(5) = 0.92$, $p = 0.97$. There was not a statistically significant main effect of electrode location for T0 values, F (3, 36) = 2.28, $P = 0.10$. There was not a statistically significant interaction within subjects between stimulation rate and T0 values at each electrode location, F (3, 36) = 0.28, $P = 0.84$. The T0 values were not significantly different between the high rate (N=7) and low stimulation rate (N=7) groups, F (1,12) = 0.10, P = 0.92.

6.2.6 The eCAP Recovery Function A Measurements and deafness onset

The median A values at different electrodes by deafness onset are shown in figure 41.

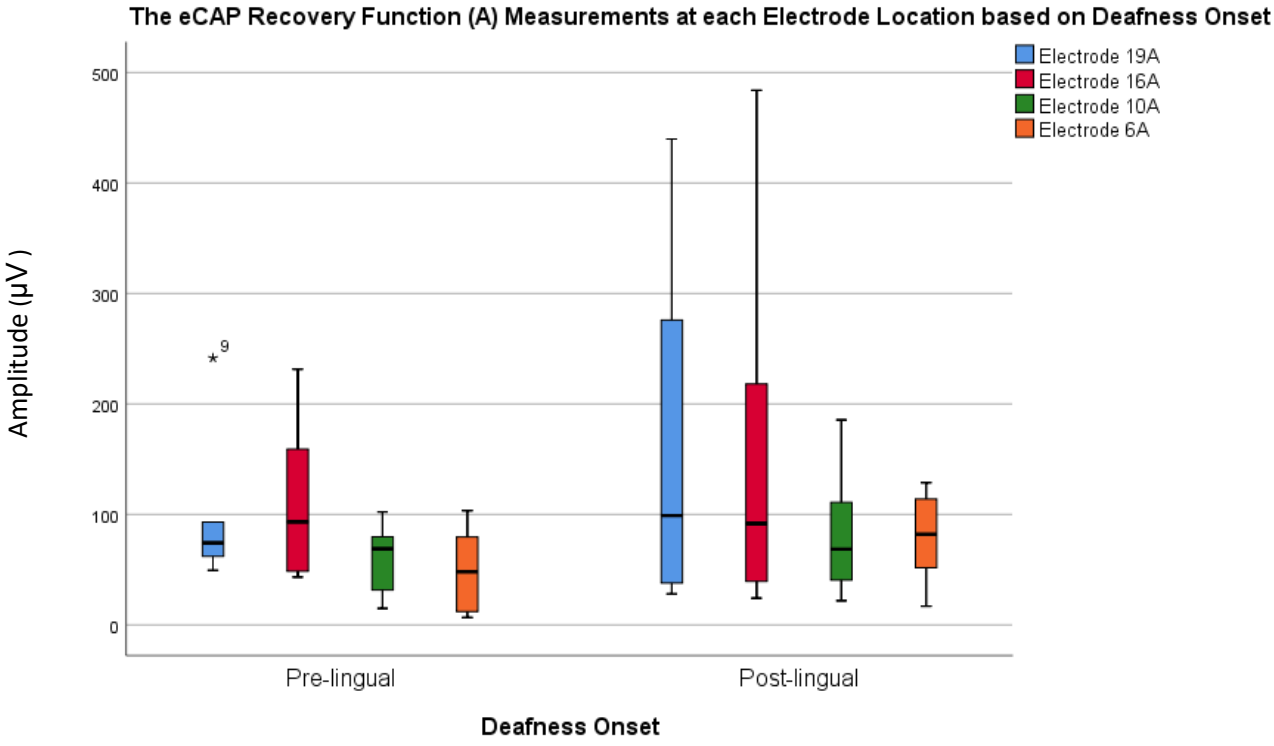

Figure 41: Box plot analysis of eCAP recovery function A values by deafness onset

A two-way repeated measures ANOVA was completed to determine the effect of deafness onset on A values at different electrode locations (N=14). Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(5) = 25.80$, $P = <0.01$, therefore the Greenhouse-Geisser correction was applied. There was not a statistically significant main effect of electrode location for A values, F (1.37, 16.47) = 2.60, $P = 0.12$. There was not a significant interaction between deafness onset and A values within subjects at each electrode location, F (1.37, 16.47) = 0.16, $P = 0.77$. The A values did not vary significantly between the pre-lingual (N=6) and post-lingual (N=8) groups, F (1,12) = 1.18, P =0.30.

6.2.7 The eCAP recovery function A measurements and stimulation rate

The median A values at different electrodes by rate are shown in figure 42.

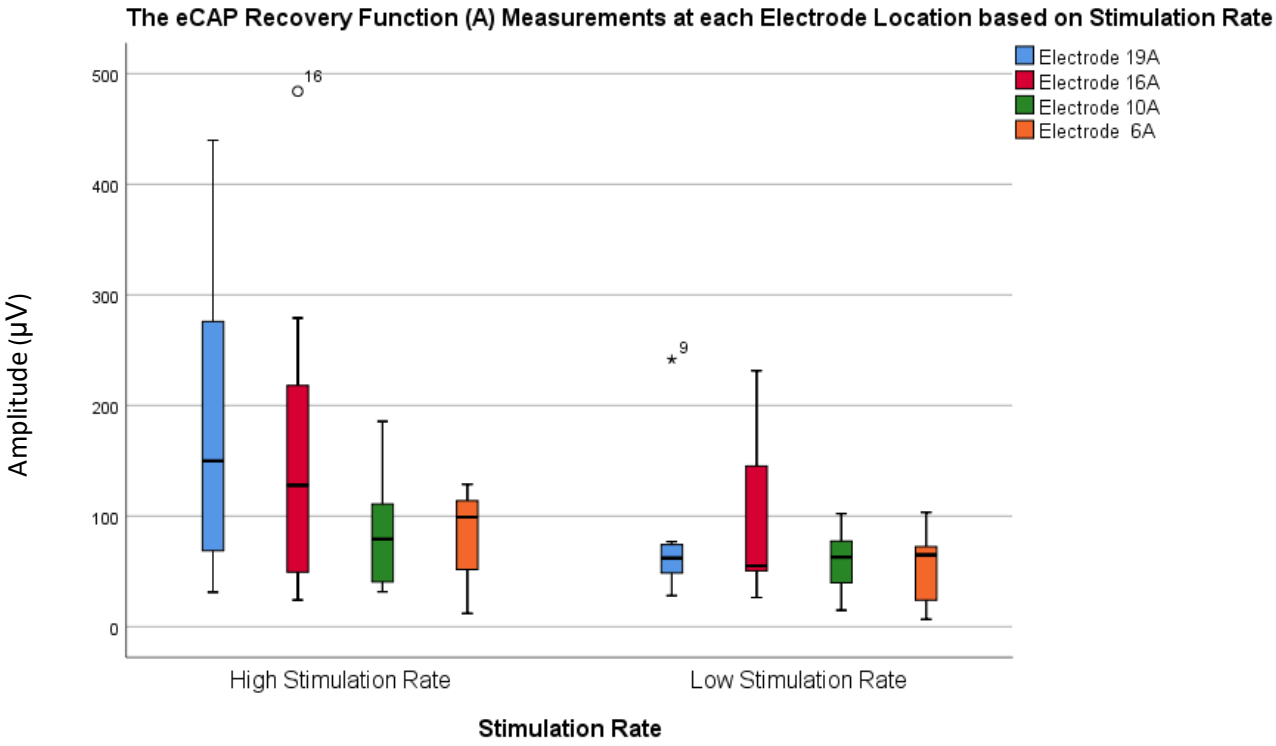

Figure 42. Box plot analysis of eCAP recovery function A values by stimulation rate

A two-way repeated measures ANOVA was completed to determine the effect of stimulation rate on A values at different electrode locations (N=14). Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(5) = 25.22$, $P = <0.01$, therefore the Greenhouse-Geisser correction was applied. There was not a statistically significant main effect of electrode location for A values, F (1.38, 16.50) = 2.93, $P = 0.96$. There was not a statistically significant interaction between stimulation rate and A values within subjects at each electrode location, F (1.38, 16.50) = 0.71, $P = 0.45$. The A values did not vary significantly between the high rate (N=7) and low stimulation rate (N=7) group F (1,12) = 3.05, p = 0.11.

6.2.8 Summary of results for eCAP recovery function measurements

The main effect of electrode location observed for Tau values indicates that mean measurements vary significantly between electrode pairs when they are spaced more widely apart, which in turn reflects the different regions of SGNs being stimulated. The more apical (E19) and mid electrodes (E16 &E10) have longer mean Tau values in comparison to the

basal electrode (E6), which suggests there may be a sparser neural population in the region of this recording location. Deafness onset and stimulation rate do not contribute to any component of the eCAP recovery function measurement.

6.3 RGDT thresholds

The thresholds obtained from the RGDT at each frequency for the 18 subjects are shown in figure 43. Of the 18 subjects, 10 completed the standard RGDT which consists of inter-stimulus intervals of 0-40 msec. 8 subjects gap detection thresholds exceeded 40msec and went on to complete the Expanded RGDT (EXP-RGDT) which includes time intervals between 40 – 300 msec. Analysis was completed with all 18 subjects as the EXP-RGDT is a different version of the same test but the outcome measure is the same regardless of which test is utilised to reach the subjects final RGDT threshold.

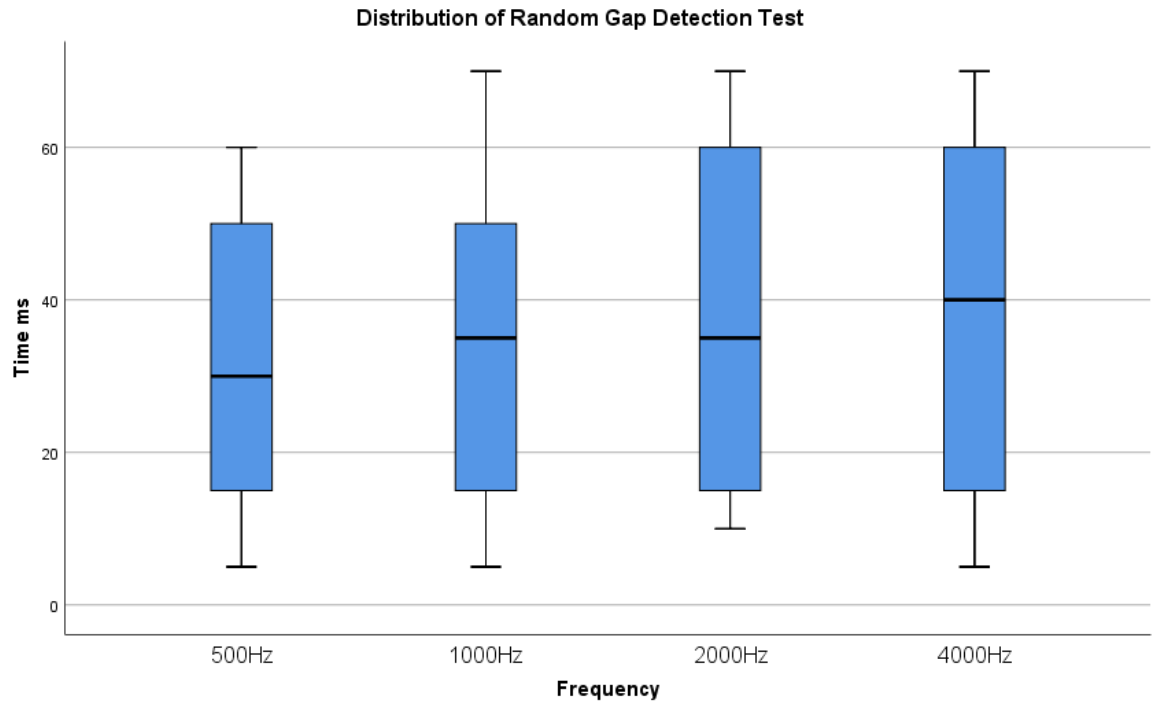

Figure 43: Box plot analysis of RGDT scores at each frequency

6.3.1 RGDT thresholds and deafness onset

The median RGDT scores at each frequency based on deafness onset are shown in figure 44.

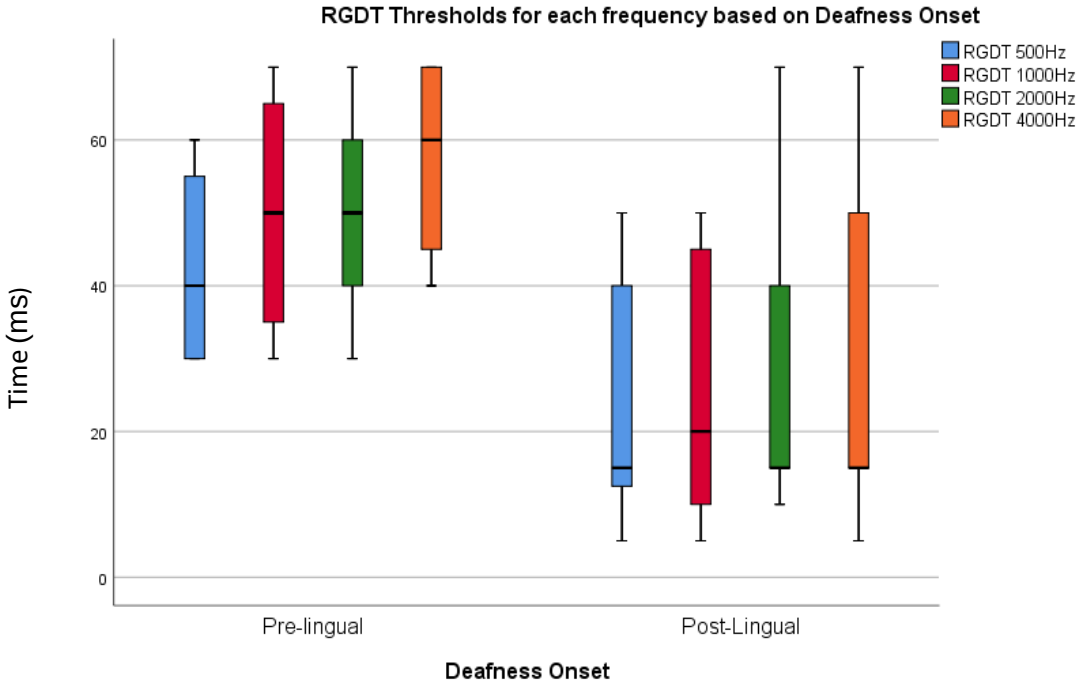

Figure 44: Median RGDT scores at each frequency based on deafness onset

A two-way repeated measures ANOVA was completed to determine the effect of deafness onset on RGDT at different frequencies (N=18). Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi^2(5) = 7.66$, $p = 0.18$. There was a statistically significant main effect of frequency on RGDT thresholds, F (2.27, 39.30) = 7.36, $P = <0.05$. There was not significant interaction within subjects between frequency and deafness onset on the RGDT, F (2.27, 39.30) = 1.86, $P = 0.17$. There was a significant difference in RGDT scores between the pre-lingual (N=7) and post-lingual (N=11) group, F (1,16) = 6.88, P= <0.05, and the post-lingual group had better (lower) GDT when compared to the pre-lingual group. The differences between RGDT at different frequencies is not dependent on deafness onset; and the differences between RGDT scores based on deafness onset are not dependent on frequency.

6.3.2 *Posthoc* analysis for RGDT frequencies and deafness onset

In order to analyse the main effect of frequency post hoc comparisons using paired t-tests were completed. See figure 45 and Table 8.

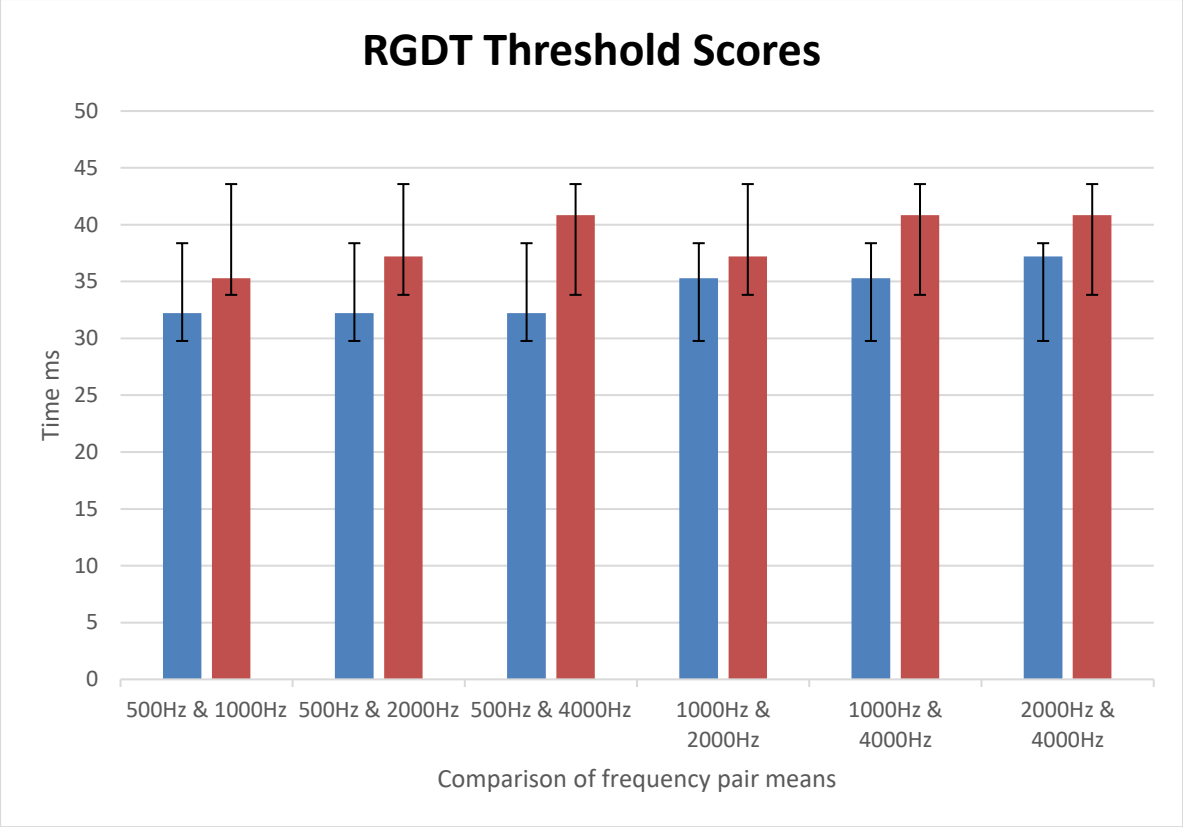

Figure 45: Mean (+ 2 SD) RGDT thresholds for paired t-tests for RGDT frequencies

Comparison (RDGT Frequency)	Mean	SD	Comparison (RDGT Frequency)	Mean	SD	Mean difference (m/sec)	T value	Significance level (2-tail)
500Hz	32.22	17.68	1000Hz	35.28	21.38	-3.06	-2.01	**0.06**
500Hz	32.22	17.68	2000Hz	37.22	21.02	-5.00	-2.26	**0.04**
500Hz	32.22	17.68	4000Hz	40.83	23.78	-8.61	-3.34	**0.00**
1000Hz	35.28	21.38	2000Hz	37.22	21.02	-1.94	-0.98	0.34
1000Hz	35.28	21.38	4000Hz	40.83	23.78	-5.56	-2.65	0.17
2000Hz	37.22	21.02	4000Hz	40.83	23.78	-3.61	-1.87	0.79

Table 8: *Posthoc* paired t-tests for RGDT frequencies, differences reaching the Bonferroni-corrected significance level are given in bold.

6.3.3 RGDT Thresholds and stimulation rate

The median RGDT scores at each frequency based on stimulation rate are shown in figure 46.

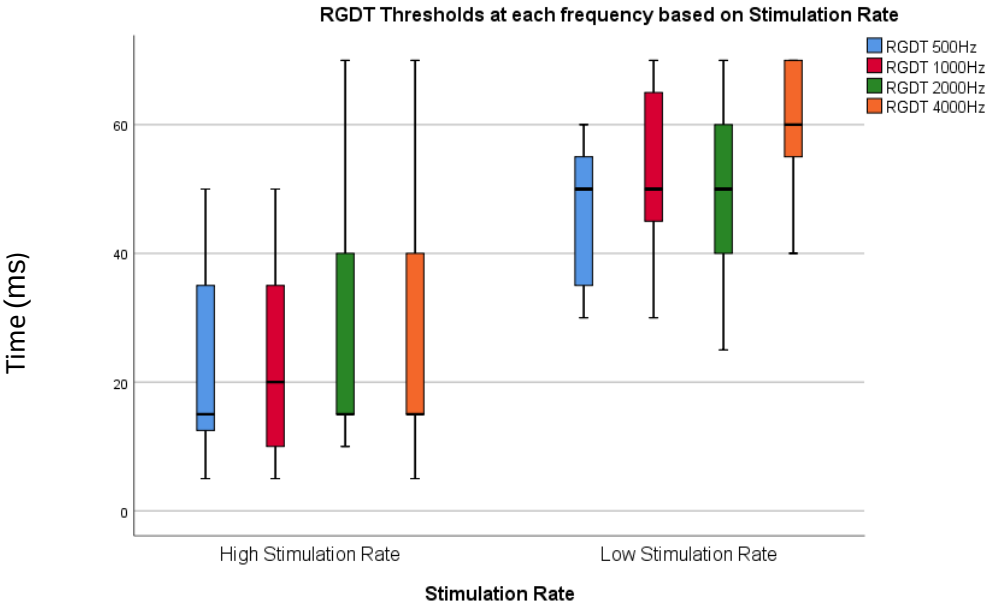

Figure 46: Median RGDT scores by stimulation rate

A two-way repeated measures ANOVA was completed to determine the effect of stimulation rate on RGDT at different frequencies. Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(5) = 14.16$, $p = <0.05$, therefore the Greenhouse-Geisser correction was applied. There was a statistically significant main effect of frequency on RGDT, F (1.87, 48) = 8.08, $P = <0.05$, which showed that RGDT scores increased (became longer) as frequency increased from 500Hz-4000Hz. As shown in figure 45 and table 8 the pairs of significance are 500-1000Hz, 500-2000Hz and 500-4000Hz. There was also a significant interaction within subjects between frequency and stimulation rate at the different electrode locations, F (1.87, 48) = 3.85, $P = <0.05$. There was a significant difference between the RGDT scores between the high stimulation rate (N=11) and low stimulation rate (N=7) group, $F\ (1,16) = 10.40$, $P = <0.05$, with lower RGDT scores observed in the high rate group.

6.3.4 *Posthoc* analysis for RGDT frequencies and stimulation rate

In order to analyse the significant interaction between frequency and stimulation rate, *posthoc* comparisons using independent paired t-tests were completed. An independent paired t-test

showed that the RGDT scores were significantly longer across all frequency pairs in the low stimulation rate group compared to the high stimulation rate group (see figure 47 and table 9).

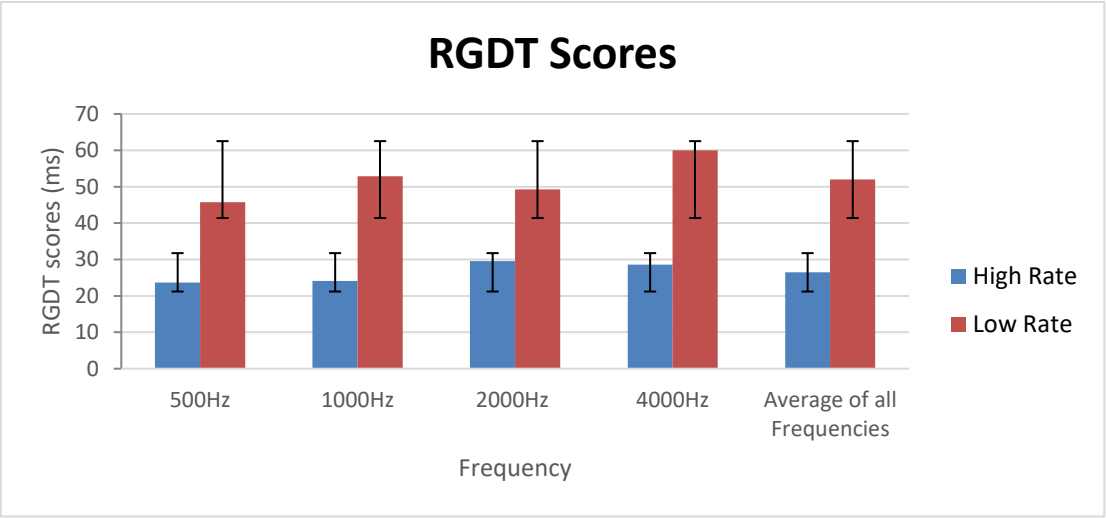

Figure 47: Mean (+ 2 SD) RGDT scores for independent t-tests for RGDT frequencies and stimulation rate

Comparison (RDGT Frequency)	Mean High Rate	SD	Mean Low Rate	SD	Mean difference between groups (m/sec)	T value	Significance level (2-tail)
500Hz	23.63	15.01	45.71	12.72	-22.08	-3.34	**0.05**
1000Hz	24.09	17.00	52.86	14.96	-28.77	-3.77	**0.02**
2000Hz	29.55	20.55	49.29	16.44	-19.74	-2.25	**0.04**
4000Hz	28.64	21.46	60.00	11.55	-31.36	-4.02	**0.00**

Table 9: *Posthoc* independent paired t-test, for RGDT frequencies and stimulation rate, differences reaching the Bonferroni-corrected significance level are given in bold.

6.3.5 Summary of results for RGDT thresholds

There was a significant effect of deafness onset on the RGDT thresholds, with longer GDTs in the pre-lingual group compared to the post-lingual group.

There was a significant effect of stimulation rate on the RGDT thresholds across all frequency pairs, with longer GDTs in the low stimulation rate group compared to the high stimulation rate group.

6.4 AB word phoneme score

The AB word phoneme scores at each presentation level is shown in figure 48;

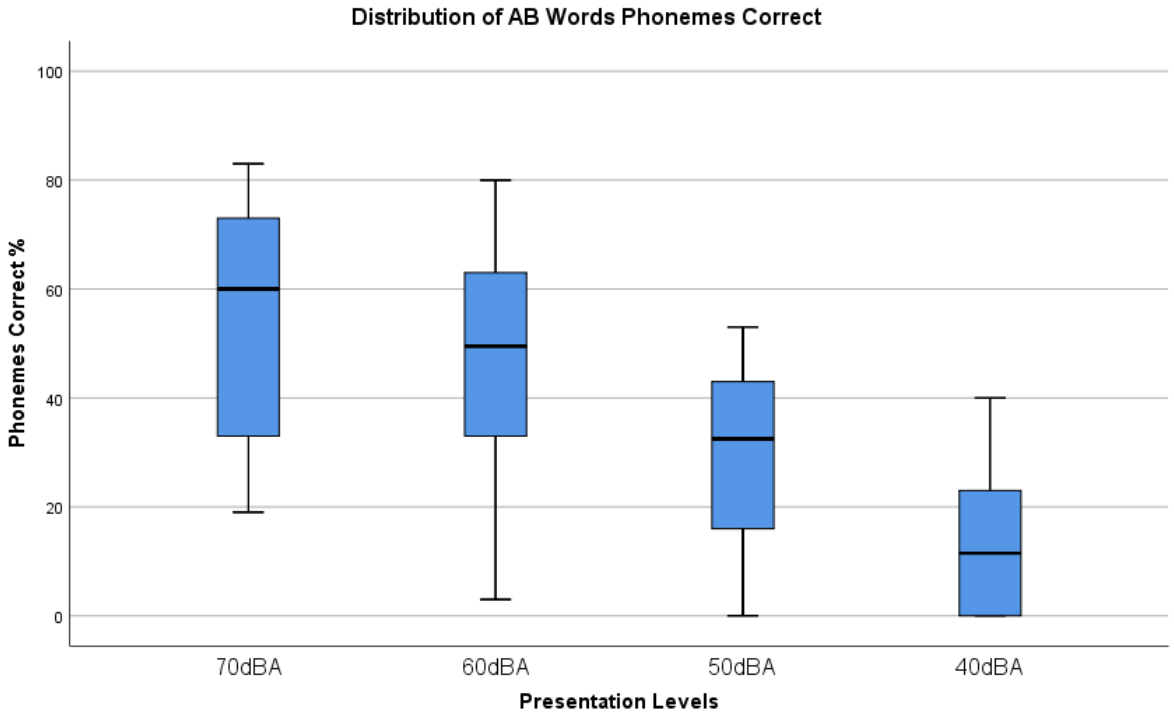

Figure 48: Box plot analysis of AB word phoneme scores across presentation levels

6.4.1 AB word phoneme score and deafness onset

The median AB word phoneme scores at each presentation level based on deafness onset are shown in Figure 49.

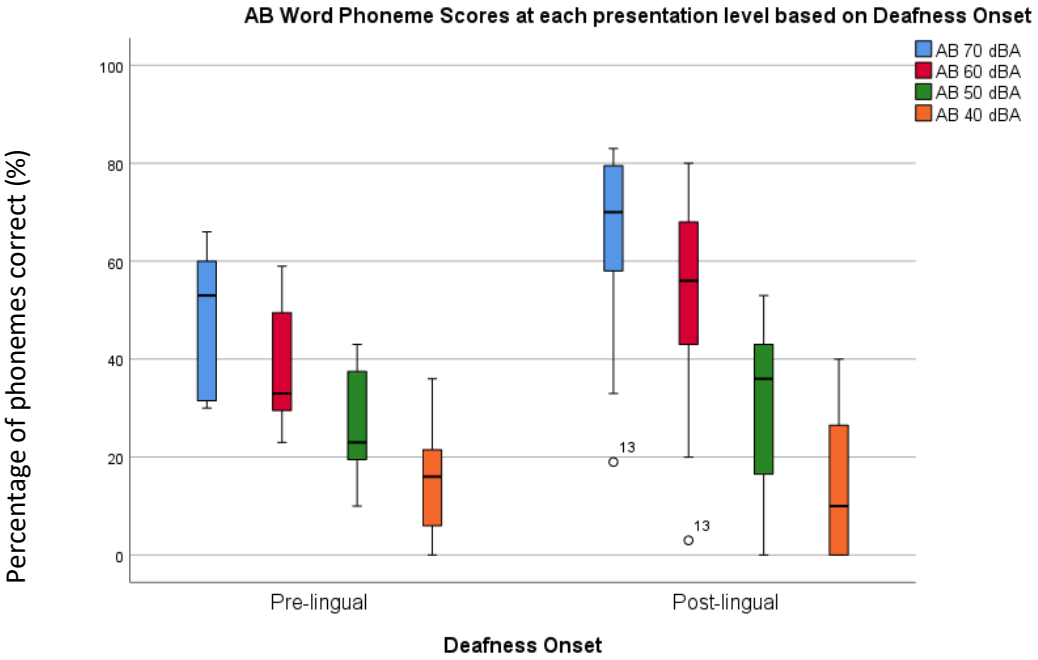

Figure 49: Median AB word scores based in deafness onset

A two-way repeated measures ANOVA was completed to determine the effect of deafness onset on AB word phoneme scores at different presentation levels (N=18). Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(5) = 17.11$, $p = <0.01$, therefore the Greenhouse-Geisser correction was applied. There was a statistically significant main effect of level on AB word phoneme scores, *F* (1.78, 28.51) = 69.05, *P = <0.05*. There was a statistically significant within subject interaction between deafness onset and AB word phoneme scores at the different presentation levels, *F* (1.78, 28.51) = 3.68, *P = <0.05*. The AB word phoneme scores were not significantly different between the pre-lingual (N=7) and post-lingual (N=11) group, *F* (1,16) = 1.01, P=*<0.33.*

6.4.2 *Posthoc* analysis for AB word phonemes presentation level and deafness onset

In order to analyse the main effect of presentation level *posthoc* comparisons using paired t-tests were completed. The mean AB word phoneme scores were significantly different across presentation level pairs (see figure 50 and table 10) The mean difference is the greatest between the AB word phoneme scores at presentation levels of 70dBA and 40dBA and the mean difference is the smallest between the AB word phoneme scores at presentation levels of 70dBA and 60dBA.

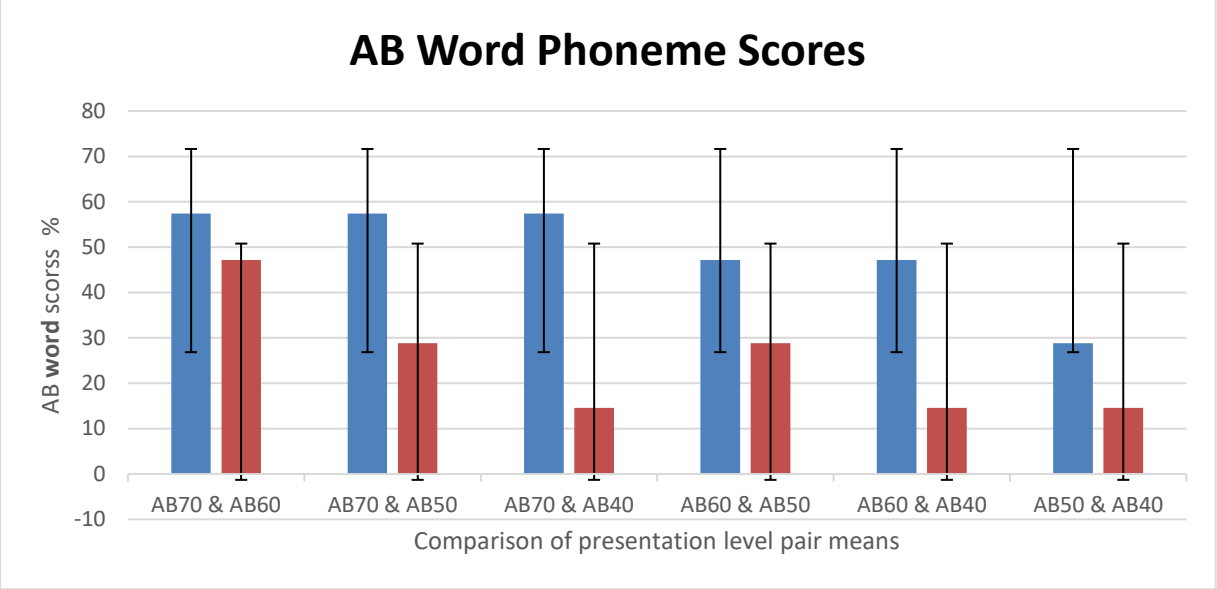

Figure 50: Mean AB word phoneme scores based on presentation level for paired t-tests

Mean (+ 2 SD) AB word Phoneme Score Comparison (Presentation levels)	Mean	SD	Mean (+ 2 SD) AB word Phoneme Score Comparison (Presentation levels)	Mean	SD	Mean difference (%)	T value	Significance level (2-tail)
AB70	57.44	20.39	AB60	47.17	21.12	10.28	6.89	**<0.01**
AB70	57.44	20.39	AB50	28.83	16.12	28.61	8.37	**<0.01**
AB70	57.44	20.39	AB40	14.56	14.15	42.89	10.05	**<0.01**
AB60	47.17	21.12	AB50	28.83	16.12	18.33	6.01	**<0.01**
AB60	47.17	21.12	AB40	14.56	14.15	32.61	8.36	**<0.01**
AB50	28.83	16.12	AB40	14.56	14.15	14.28	5.66	**<0.01**

Table 10: Post-hoc paired t-tests for AB word phonemes at different presentation levels, differences reaching the Bonferroni-corrected significance level are given in bold.

In order to analyse the significant interaction between deafness onset and AB word presentation level, *posthoc* comparisons using independent paired t-tests were completed. These showed that the AB word phoneme scores did not vary significantly across all presentation level pairs in the pre-lingual and post-lingual group. Visually, it can be seen that subjects with pre-lingual deafness have lower AB word phoneme scores in comparison to those with post-lingual deafness (see figure 51 and table 11).

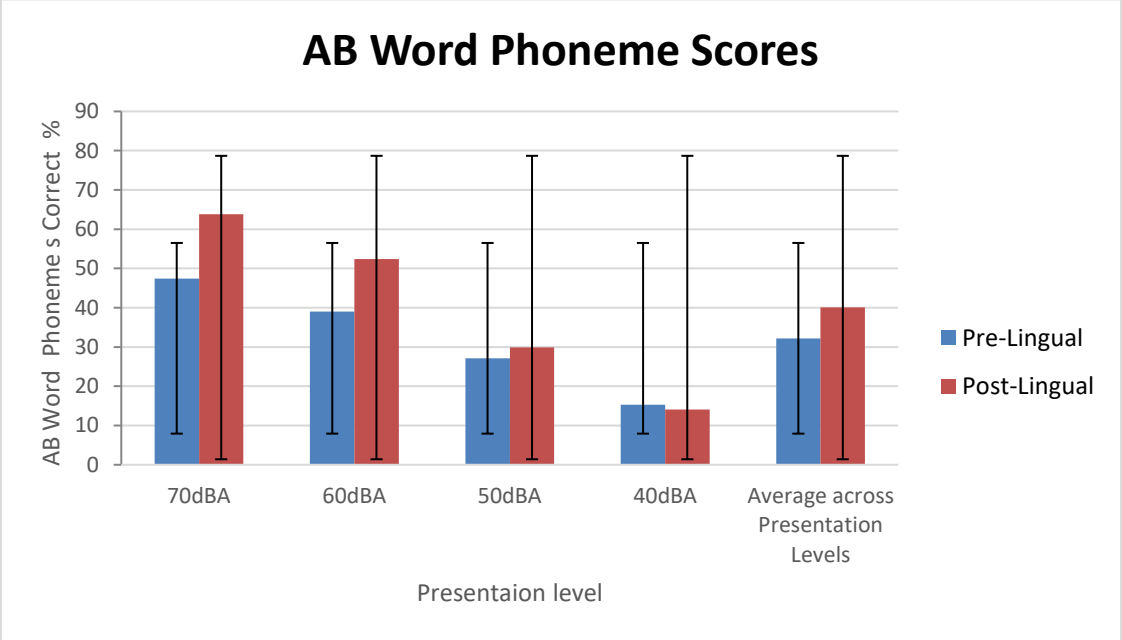

Figure 51: Mean (+ 2 SD) AB word phoneme scores for independent t-tests based on deafness onset.

Comparison (Presentation Levels)	Pre-Lingual	SD	Post-Lingual	SD	Mean difference between groups (%)	T value	Significance level (2-tail)
70dBA	47.43	15.85	63.82	21.01	-16.39	-1.88	0.08
60dBA	39.00	13.79	52.37	23.83	-13.36	-1.51	0.15
50dBA	27.14	12.40	29.91	18.61	-2.77	-0.38	0.71
40dBA	15.29	12.37	14.09	15.74	1.19	0.18	0.86

Table 11: *Posthoc* independent paired t-test for AB word phoneme scores based on deafness onset. Differences reaching the Bonferroni-corrected significance level are given in bold.

6.4.3 AB word phoneme scores and stimulation rate

The median AB word phoneme scores at each presentation level based on stimulation rate are shown in Figure 52.

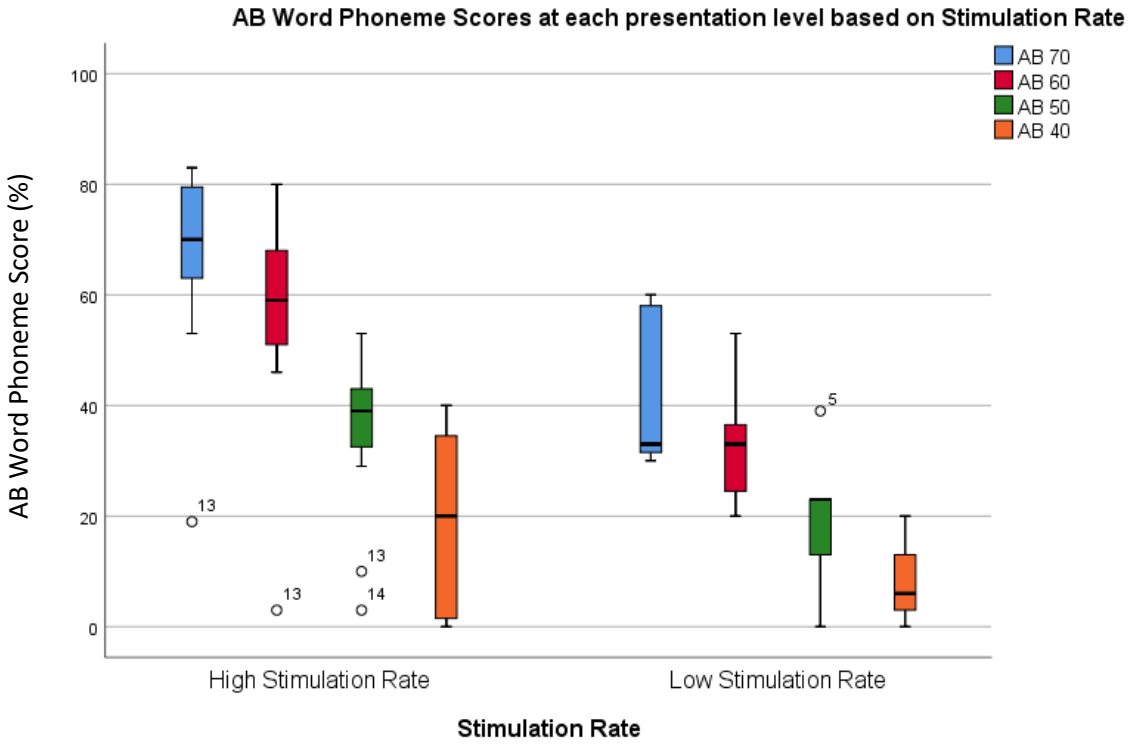

Figure 52: Median AB word scores based on stimulation rate

A two-way repeated measures ANOVA was completed to determine the effect of stimulation rate on AB word phoneme scores at different presentation levels (N=18). Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(5) = 19.44$, $p = <0.01$, therefore the Greenhouse-Geisser correction was applied. There was a statistically significant main effect of presentation level on AB word phoneme scores, *F* (1.69, 27.09) = 64.86, *P = <0.05.* There was a decrease in scores as presentation level decreased, table 10 and figure 50 show the presentation levels of significance. There was not a statistically significant within subject interaction between stimulation rate and AB word phoneme scores at the different presentation levels, *F* (1.69, 27.09) = 2.05, *P = 0.15.* There is a significant difference between the AB word phoneme scores in the high stimulation rate (N=11) and low stimulation rate (N=7) group, *F* (1,16) = 7.75, P = <0.05.

6.4.4 *Posthoc* analysis for AB word phoneme presentation level and stimulation rate

In order to analyse the between group effect of presentation level *posthoc* comparisons using paired t-tests were completed. An independent paired t-test showed that the AB words scores were significantly different across all levels in the high and low rate group with the exception of 40dBA (see figure 53 and table 12).

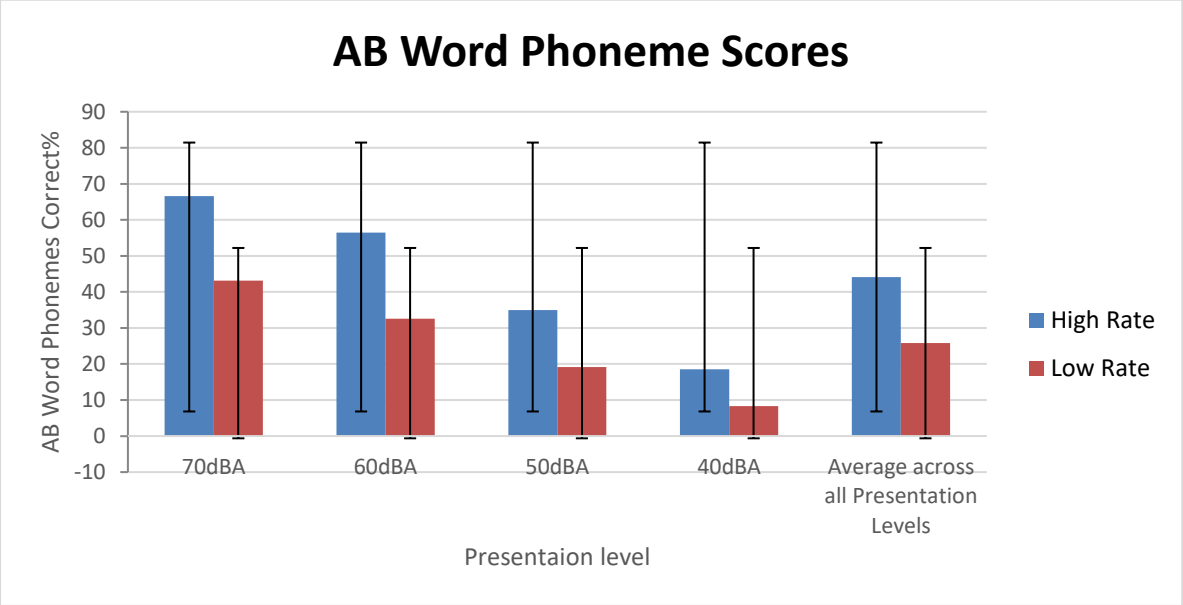

Figure 53: Mean (+ 2 SD) AB word phoneme scores for paired t-tests based on stimulation rate

Comparison (Presentation Levels)	High Rate	SD	Low Rate	SD	Mean difference between groups (%)	T value	Significance level (2-tail)
70dBA	66.55	18.55	43.14	14.63	23.40	2.98	**0.01**
60dBA	56.45	20.93	32.57	11.30	23.88	3.14	**0.01**
50dBA	35.00	15.63	19.14	12.24	15.86	2.40	**0.03**
40dBA	18.55	16.14	8.29	7.61	10.26	1.82	0.09

Table 12: *Posthoc* independent paired t-test for AB word phoneme scores based on stimulation rate, pairs which are significantly different are highlighted in red. Differences reaching the Bonferroni-corrected significance level are given in bold.

6.4.5 Summary of results for AB word phoneme scores

There was a significant effect of stimulation rate on AB word phoneme scores at presentation levels of 70,60 and 50dBA, with higher scores in the high stimulation rate group compared to the scores in the low stimulation rate group. There was no significant effect of stimulation rate on AB word phoneme scores at 40dBA and the scores are similar in both groups, likely due to floor effects

6.5 Multiple linear regression

The conceptual model for this study was that the underlying physiology as measured by eCAP recovery function is likely to affect psychophysical performance as measured by RGDT, and both in turn could affect performance as measured by AB word phoneme scores, no reverse effects were expected, hence multiple linear regression analyses were used to determine which variables predicted outcomes for each measurement.

Pearson's correlation coefficients were calculated to identify the degree of association between eCAP recovery function Tau measurements, RGDT thresholds and AB word phoneme scores. The univariate associations that were not significant were not added to the multiple regression model, to prevent overloading the analysis so that effects are not missed given the small sample size in this study. Rate and deafness onset were included in all analyses as they were the key hypothesis driven variables.

In the following section each of the results of the regression analyses are presented in the same format. For each dependent variable, the model summaries are shown with its explained variance (R^2). For realistic predictions of the variation the adjusted R^2 values are taken into account and highlighted in all tables. Also, the independent variables that were significantly associated with the dependents and their standardised coefficients (β) and unstandardised coefficients (B) with constant for the best predicting model are shown.

6.5.1 Electrode 19 eCAP recovery function Tau measurement

Pearson's Coefficients showed significant relationships between E19 Tau and the following variables:

- There was a very strong positive correlation between E19 Tau values and E16 Tau values, $r = 0.82$, $N=16$, $p < 0.01$

- There was a moderate positive correlation between E19 Tau values and E10Tau values, r = 0.51, N=17, p 0.04

Pearson's coefficients showed no significant relationships between E19 Tau and the following variables:

- There was no correlation between E19 Tau values and age, r = -2.55, N=18, p 0.31
- There was no correlation between E19 Tau values and implant type, r = -0.39, N=18, p 0.11
- There was no correlation between E19 Tau values and deafness onset, r = -0.29, N18, p 0.24
- There was no correlation between E19 Tau values and rate, r = -0.20, N18, p 0.21
- There was no correlation between E19 Tau values and average RGDT scores, r = 0.13, N18, p 0.62
- There was no correlation between E19 Tau values and average AB word scores, r = 0.36, N18, p 0.14

Based on these correlations a multiple linear regression was calculated to predict the Tau value at electrode 19 based on, deafness onset, stimulation rate, E16 Tau values, E10 Tau values and implant type. The overall regression model was significant $F(5,10) = 9.98$, $p<0.05$, with an adjusted R^2 of 0.75, indicating that collectively the predictor variables accounted for 75% of the variance seen in E19 Tau values, furthermore, E16 Tau values significantly contributed to this variance, highlighted in red in table 13.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.91 (a)	0.83	**0.75**	247.22

a. Predictors: (Constant), Implant Type, Deafness onset, Stimulation rate, E16tau, E10tau

Dependent Variable: E19 tau

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	802.08		0.30
Implant Type	-246.46	-0.26	0.11
Deafness onset	-291.82	-0.30	0.15
Stimulation Rate	-52.67	-0.06	0.76
E16 Tau	**0.66**	**0.61**	**0.00**
E10 Tau	0.29	0.23	0.14

Table 13: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for the dependent variable electrode 19 Tau

6.5.2 Electrode 16 eCAP recovery function Tau measurement

Pearson's coefficients showed significant relationships between E16 Tau and the following variables:

- There was a very strong positive correlation between E16 Tau values and E19 Tau values, r = 0.82, N=16, p < 0.01

Pearson's coefficients showed no significant relationships between E19 Tau and the following variables:

- There was no correlation between E16 Tau values and age, r = -0.92, N=16, p 0.29
- There was no correlation between E16 Tau values and implant type, r = -0.23, N=16, p 0.20
- There was no correlation between E16 Tau values and deafness onset, r = -0.35, N=16, p 0.09

- There was no correlation between E16 Tau values and rate, r = -0.16, N=16, p 0.27
- There was no correlation between E16 Tau values and average RGDT scores, r = -0.47, N16, p 0.43
- There was no correlation between E16 Tau values and average AB word scores, r = 0.15, N16, p 0.29

A multiple linear regression was calculated to predict the E16 Tau values based deafness onset, stimulation rate and implant type. The predictive relationship between E19 Tau values and E16 Tau values have already been analysed in the regression model shown in table 17. The overall regression model was significant F (3,12) = 2.23, p< 0.03, with an adjusted R^2 of 0.18, indicating that that collectively the predictor variables accounted for 18% of the variance seen in E16 Tau values. Furthermore, the multiple regression models showed deafness onset was a significant predictor of Tau at E16, highlighted in red in Table 14.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.588 (a)	.346	**.183**	415.03744

a. Predictors: (Constant), Stimulation rate, Implant type, Deafness onset

Dependent Variable: E16 tau

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	2764.351		.002
Implant Type	-259.315	-.289	.262
Deafness onset	**-555.068**	**-.619**	**.042**
Stimulation Rate	-350.032	-.391	.176

Table 14: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for the dependent variable electrode 16 Tau

6.5.3 Electrode 10 eCAP recovery function Tau measurement

Pearson's coefficients showed significant relationships between E10Tau and the following variables:

- There was a very strong positive correlation between E10 Tau values and E6 Tau values, $r = 0.80$, $N=15$, $p < 0.01$
- There was a moderate correlation between E10 Tau values and age, $r = -0.49$, $N=17$, $p < 0.05$

Pearson's coefficients showed no significant relationships between E10 Tau and the following variables:

- There was no correlation between E10 Tau values and implant type, $r = -0.03$, $N=17$, p 0.50
- There was no correlation between E10 Tau values and deafness onset, $r = -0.22$, $N=17$, p 0.19
- There was no correlation between E10 Tau values and rate, $r = -0.18$, $N=17$, p 0.24
- There was no correlation between E10 Tau values and average RGDT scores, $r = 0.09$, N17, p 0.37
- There was no correlation between E10 Tau values and average AB word scores, $r = -0.23$, N17, p 0.46

A multiple linear regression was calculated to predict the Tau values at electrode 10 based on implant type, deafness onset, E6 Tau values, age and stimulation rate. The overall regression model was significant $F(5,9) = 4.39$, p 0.02, with an adjusted R^2 of 0.55, indicating that that collectively the predictor variables accounted for 55% of the variance seen in E10Tau values, furthermore, E6 Tau values significantly contributed to this variance, highlighted in red in table 15.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.842 (a)	.709	0.55	289.911

a. Predictors: (Constant), Stimulation rate, Implant type, Deafness onset, E6 tau, Age

Dependent Variable: E10 tau

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	1218.60		0.12
E6 Tau	**1.02**	**0.77**	**<0.01**
Implant Type	-116.01	-0.14	0.54
Deafness onset	-226.15	-.0.27	0.38
Stimulation Rate	- 195.901	-0.24	0.37
Age	-0.58	-0.02	0.94

Table 15: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for the dependent variable electrode 10 Tau

6.5.4 Electrode 6 eCAP recovery function Tau measurement

Pearson's coefficients showed significant relationships between E6Tau and the following variables:

- There was a strong positive correlation between E6 Tau values and E10 Tau values, r = 0.67, N=15, p 0.03
- There was a moderate correlation between E6 Tau values and age, r = - 0.54, N=15, p 0.02

Pearson's coefficients showed no significant relationships between E10 Tau and the following variables:

- There was no correlation between E6 Tau values and implant type, r = 0.62, N=15, p 0.41
- There was no correlation between E6 Tau values and deafness onset, r = -0.63, N=15, p 0.41
- There was no correlation between E6 Tau values and rate, r = -0.12, N=15, p 0.33

- There was no correlation between E6 Tau values and average RGDT scores, r = -0.00, N15, p 0.50
- There was no correlation between E6 Tau values and average AB word scores, r = -0.19, N15, p 0.25

A multiple linear regression was calculated to predict the Tau values at electrode 6 based on age, implant type, deafness onset and stimulation rate. The predictive relationship between E6 Tau values and E10 Tau values have already been analysed in the regression model shown in table 19. The overall regression model was not significant, F (4,10) = 1.25, p 0.36, with an adjusted R^2 of 0.07. None of these predictor variables were significant. Regression coefficients and standard errors can be found in Table 16.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.58 (a)	0.33	0.07	312.83

a. Predictors: (Constant), Stimulation rate, Implant type, Deafness onset, Age

Dependent Variable: E6 tau

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	1242.00		0.08
Implant Type	-26.90	-0.43	0.89
Deafness onset	190.28	0.30	0.48
Stimulation Rate	-21.39	-0.03	0.93
Age	-14.90	-0.72	0.07

Table 16: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for the dependent variable electrode 6 Tau

6.5.5 RDGT thresholds

Pearson's correlation coefficients showed that the RGDT thresholds at each frequency were strongly correlated with each other, hence the average RGDT threshold was used for the multiple regression analysis in order to ensure the effects of other independent variables were

not diluted as these strong correlations were probably likely to make strong effects. The correlations are summarised below:

- There was a strong positive correlation between RGDT scores at 500Hz and RGDT scores at 1000Hz, r = 0.96, N=18, p <0.01
- There was a strong positive correlation between RGDT scores at 500Hz and RGDT scores at 2000Hz, r = 0.90, N=18, p <0.01
- There was a strong positive correlation between RGDT scores at 500Hz and RGDT scores at 4000Hz, r = 0.90, N=18, p <0.01
- There was a strong positive correlation between RGDT scores at 1000Hz and RGDT scores at 2000Hz, r = 0.92, N=18, p <0.01
- There was a strong positive correlation between RGDT scores at 1000Hz and RGDT scores at 4000Hz, r = 0.93, N=18, p <0.01
- There was a strong positive correlation between RGDT scores at 2000Hz and RGDT scores at 4000Hz, r = 0.94, N=18, p <0.01

Additionally, Pearson's correlations found:

- There was a moderate negative correlation between deafness onset and RGDT scores, r = 0.54, N = 18, p < 0.05
- There was a strong positive correlation between rate and RGDT scores, r = 0.63, N=18, p <0.05
- There was a strong positive correlation between RGDT scores and AB word scores, r = 0.74, N=18, p <0.01
- There was no correlation between RGDT scores and age, r = -0.30, N=18, p 0.12
- There was no correlation between RGDT scores and implant type, r = 0.13, N=18, p 0.31
- There was no correlation between RGDT scores and E19 Tau values, r = - 0.13, N=18, p 0.62
- There was no correlation between RGDT scores and E16 Tau values, r = - 0.45, N=16, p 0.86
- There was no correlation between RGDT scores and E10 Tau values, r = 0.88, N=17, p 0.74
- There was no correlation between RGDT scores and E10 Tau values, r = 0.11, N=15, p 0.70

A multiple linear regression was calculated to predict the average RGDT score based on deafness onset and stimulation rate. The overall regression model was significant, F (2,15) = 6.34, p 0.01, with an adjusted R^2 of 0.39. However, deafness onset and stimulation rate were not significant predictors of RGDT scores. This would indicate that both predictor variables are correlated with each other to such a degree that neither can offer any amount of significant variance in explaining the RGDT scores. Pearson's correlation showed there was a significant moderate, negative correlation between deafness onset and stimulation rate (r = -0.53, N = 18, p 0.02). The Regression coefficients and standard errors can be found in Table 17.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.68 (a)	.458	0.39	15.97

a. Predictors: (Constant), Stimulation rate, Deafness onset

Dependent Variable: Average RGDT threshold

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	29.54		0.24
Deafness onset	-12.15	-0.30	0.20
Stimulation Rate	19.02	0.47	0.05

Table 17: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for average RGDT threshold scores

6.5.6 AB word phoneme scores 40dBA

Pearson's coefficients showed a significant moderate positive correlation between average RGDT scores and AB word scores at 40dBA, r = 0.53, N=18, p < 0.05

Pearson's coefficients showed no significant relationships between AB word scores at 40dBA and the following variables:

- There was no correlation between AB word scores at 40dBA and age, r = -0.77, N=18, p 0.76
- There was no correlation between AB word scores at 40dBA and implant type, r = -0.19, N=18, p 0.44

- There was no correlation between AB word scores at 40dBA and deafness onset r = -0.42, N=18, p 0.87
- There was no correlation between AB word scores at 40dBA and rate r = -0.36, N=18, p 0.14
- There was no correlation between AB word scores at 40dBA and E19 Tau values, r = 0.27, N=18, p 0.13
- There was no correlation between AB word scores at 40dBA and E16 Tau values, r = 0.25, N=16, p 0.17
- There was no correlation between AB word scores at 40dBA and E10 Tau values, r = 0.25, N=17, p 0.46
- There was no correlation between AB word scores at 40dBA and E6 Tau values, r = -0.19, N=15, p 0.25

A multiple linear regression was calculated to predict the AB word phoneme scores at 40dBA based on deafness onset, stimulation rate and the average RGDT score. A significant regression equation was found F (3,14) = 4.01, p 0.03, with an adjusted with an adjusted R^2 of 0.35 indicating collectively the predictor variables explain 35% of the variance seen in AB word phoneme scores at 40dB. Average RGDT scores were a significant predictor of variance (p = 0.02). Regression coefficients and standard errors can be found in Table 18.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.68 (a)	0 .46	**0.35**	11.43

a. Predictors: (Constant), Average RGDT, Deafness onset, stimulation rate

Dependent Variable: AB word phoneme score at 40dBA

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	64.635		0.00
Average RGDT	**-0.47**	**-0.68**	**0.02**
Deafness onset	-15.04	-0.53	0.05
Stimulation Rate	-6.20	-0.22	0.42

Table 18: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for AB word phoneme scores at 40dBA.

6.5.7 AB word phoneme scores 50dBA

Pearson's coefficients showed significant relationships between AB word scores at 50dBA and the following variables:

- There was a moderate negative correlation between AB word scores at 50dBA and average RGDT scores, r = - 0.50, N=18, p 0.03
- There was a moderate negative correlation between AB word scores at 50dBA and stimulation rate, r = - 0.51, N=18, p 0.27

Pearson's coefficients showed no significant relationships between AB word scores at 50dBA and the following variables:

- There was no correlation between AB word scores at 50dBA and age, r = -0.01, N=18, p 0.98
- There was no correlation between AB word scores at 50dBA and implant type, r = -0.96, N=18, p 0.71
- There was no correlation between AB word scores at 50dBA and deafness onset, r = 0.86, N=18, p 0.73

- There was no correlation between AB word scores at 50dBA and E19 Tau values, r = 0.21, N=18, p 0.21
- There was no correlation between AB word scores at 50dBA and E16 Tau values, r = 0.21, N=16, p 0.47
- There was no correlation between AB word scores at 50dBA and E10 Tau values, r = -0.43, N=17, p 0.44
- There was no correlation between AB word scores at 50dBA and E6 Tau values, r = - 0.20, N=15, p 0.23

A multiple linear regression was calculated to predict the AB word phoneme scores at 50dBA based on deafness onset, stimulation rate and the average RGDT score. The overall regression model was not significant, F (3,14) = 3.07, p 0.06, with an adjusted R^2 of 0.27. None of these predictor variables were significant. Regression coefficients and standard errors can be found in Table 19

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.63 (a)	0.40	0.27	13.80

a. Predictors: (Constant), Average RGDT, Deafness onset, stimulation rate

Dependent Variable: AB word phoneme score at 50dBA

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	80.001		0.00
Average RGDT	-0.36	-0.45	0.13
Deafness onset	-12.24	-0.38	0.16
Stimulation Rate	-13.30	-0.41	0.16

Table 19: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for AB word phoneme scores at 50dBA

6.5.8 AB word phoneme scores 60dBA

Pearson's coefficients showed significant relationships between AB word scores at 60dBA and the following variables:

- There was a strong negative correlation between AB word scores at 60dBA and average RGDT scores, r = - 0.72, N=18, p <0.01
- There was a strong negative correlation between AB word scores at 60dBA and stimulation rate, r = - 0.65, N=18, p <0.05

Pearson's coefficients showed no significant relationships between AB word scores at 60dBA and the following variables:

- There was no correlation between AB word scores at 60dBA and age, r = 0.17, N=18, p 0.50
- There was no correlation between AB word scores at 60dBA and implant type, r = -0.33, N=18, p 0.18
- There was no correlation between AB word scores at 60dBA and deafness onset, r = 0.37, N=18, p 0.13
- There was no correlation between AB word scores at 60dBA and E19 Tau values, r = 0.31, N=18, p 0.10
- There was no correlation between AB word scores at 60dBA and E16 Tau values, r = 0.88, N=16, p 0.37
- There was no correlation between AB word scores at 60dBA and E10 Tau values, r = 0.65, N=17, p 0.40
- There was no correlation between AB word scores at 60dBA and E6 Tau values, r = - 0.68, N=15, p 0.41

A multiple linear regression was calculated to predict the AB word phoneme scores at 60dBA based on deafness onset, stimulation rate and the average RGDT score. The overall regression model was significant F (3,14) = 8.35, p< 0.01, with an adjusted R^2 of 0.57, indicating that collectively the predictor variables accounted for 57% of the variance seen in AB word phoneme scores at 60 dBA, furthermore, the average RGDT scores were a significant predictor, highlighted in red in Table 20.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.80 (a)	0.64	**0.57**	13.94

a. Predictors: (Constant), Average RGDT, Deafness onset, stimulation rate

Dependent Variable: AB word phoneme score at 60dBA

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	101.725		.000
Average RGDT	**-0.80**	**-0.77**	**0.00**
Deafness onset	-8.76	-.208	0.32
Stimulation Rate	-8.27	-.196	0.38

Table 20: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for AB word phoneme scores at 60dBA

6.5.9 AB word phoneme scores 70dBA

Pearson's coefficients showed significant relationships between AB word scores at 70dBA and the following variables:

- There was a strong negative correlation between AB word scores at 70dBA and average RGDT scores, r = - 0.73, N=18, p < 0.01
- There was a strong negative correlation between AB word scores at 70dBA and stimulation rate, r = - 0.60, N=18, p < 0.02

Pearson's coefficients showed no significant relationships between AB word scores at 70dBA and the following variables:

- There was no correlation between AB word scores at 70dBA and deafness onset, r = 0.48, N=18, p 0.05
- There was no correlation between AB word scores at 70dBA and age, r = 0.31, N=18, p 0.22
- There was no correlation between AB word scores at 70dBA and implant type, r = -0.39, N=18, p 0.11

- There was no correlation between AB word scores at 70dBA and E19 Tau values, r = 0.28, N=18, p 0.13
- There was no correlation between AB word scores at 70dBA and E16 Tau values, r = 0.06, N=16, p 0.49
- There was no correlation between AB word scores at 70dBA and E10 Tau values, r = 0.65, N=17, p 0.40
- There was no correlation between AB word scores at 70dBA and E6 Tau values, r = - 0.38, N=15, p 0.45

A multiple linear regression was calculated to predict the AB word phoneme scores at 70dBA based on deafness onset, stimulation rate and the average RGDT score. A significant regression equation was found F (3,14) = 7.84, p< 0.01, with an adjusted R^2 of 0.55, indicating collectively the predictor variables accounted for are predicted by average RGDT and the model explains 55% of all variance in the AB word phoneme scores at 70 dBA. Furthermore, the multiple regression models showed the average RGDT was a statistically significant predictor of the AB word phoneme scores at 70dBA. highlighted in red in Table 21.

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.79 (a)	0.63	**0.55**	13.73

a. Predictors: (Constant), Average RGDT, Deafness onset, stimulation rate

Dependent Variable: AB word phoneme score at 70dBA

	unstandardised coefficients (B)	standardised coefficients (β)	Sig.
(Constant)	98.406		.000
Average RGDT	**-0.72**	**-0.72**	**0.00**
Deafness onset	-3.30	-0.08	0.70
Stimulation Rate	-6.74	-0.17	0.45

Table 21: Summary of multiple regression analysis B = Unstandardized regression coefficient; SE_B = Standard error of the coefficient; β = standardized coefficient for AB word phoneme scores at 70dBA

6.6 RGDT thresholds and AB word phoneme scores

The relationship between RGDT and AB word phoneme scores based on deafness onset and stimulation rate are shown in figure 54-58.

Subject are represented using the following legend on each graph:

Pink Circle = Subjects in the pre-lingual and high stimulation rate group

Pink Triangle = Subjects in the pre-lingual and low stimulation rate group

Green Circle = Subjects in the post-lingual high stimulation rate group

Green Triangle = Subjects in the post-lingual low stimulation rate group

Figure 54 shows the distribution of scores show that the majority of the subjects in the post-lingual group with high stimulation rates had shorter average RGDT thresholds and these correlated to higher percentage AB word phoneme scores. In contrast, subjects in the pre-lingual group with low stimulation rates had longer average RGDT scores which correlated to lower percentage AB word phonemes correct scores. The two subjects in the post-lingual low rate group had higher RGDT scores compared to the majority of the post-lingual high rate group and one of these subjects had AB word phoneme scores similar to those of the pre-lingual low rate group. Two of the subjects in the post-lingual high rate group had similar RGDT scores as those in the pre-lingual low rate group, but interestingly one of these subjects was able to achieve a relatively high AB word phoneme score despite the general trend of decreased AB word phoneme scores with higher RGDT thresholds.

Figure 54-58 show the distribution of results across the different presentation levels which shows a similar trend across all levels with the exception of 40dBA where subjects in the post-lingual high rate group did not appear to have a significant performance advantage to the pre-lingual group.

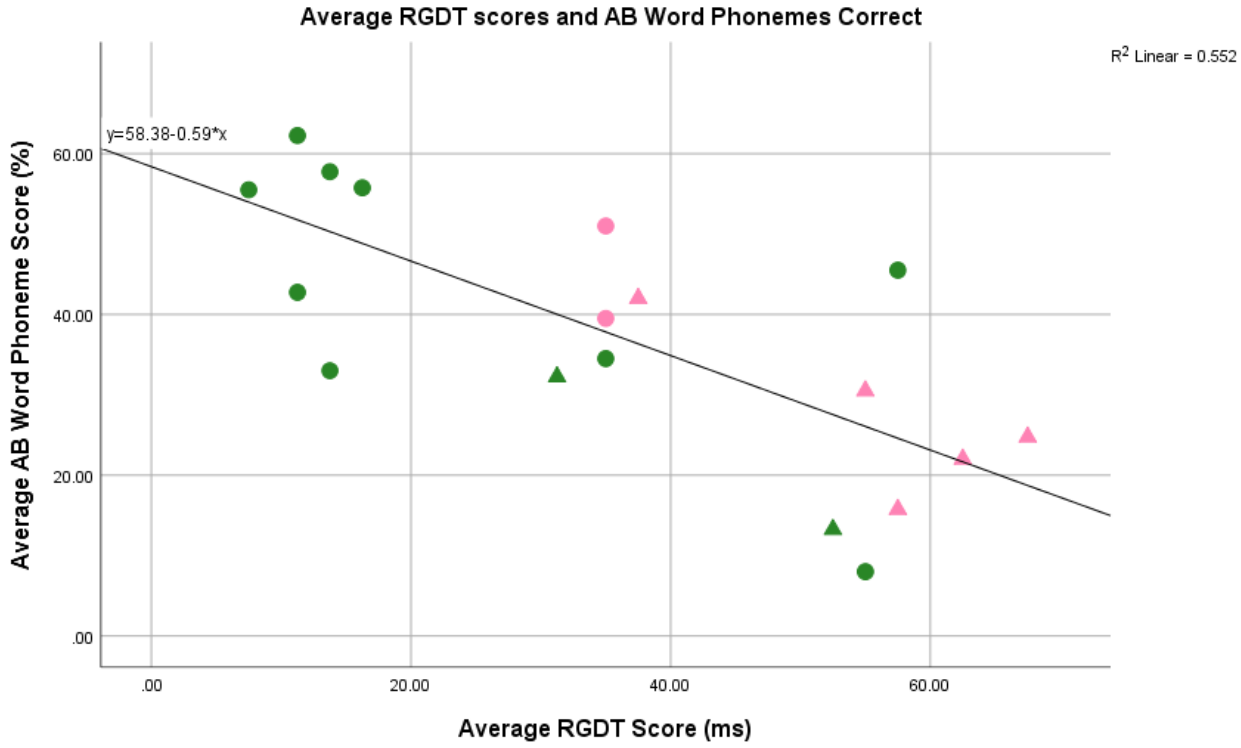

Figure 54: Average RGDT thresholds and average AB Word phoneme scores for each subject by deafness onset and stimulation rate

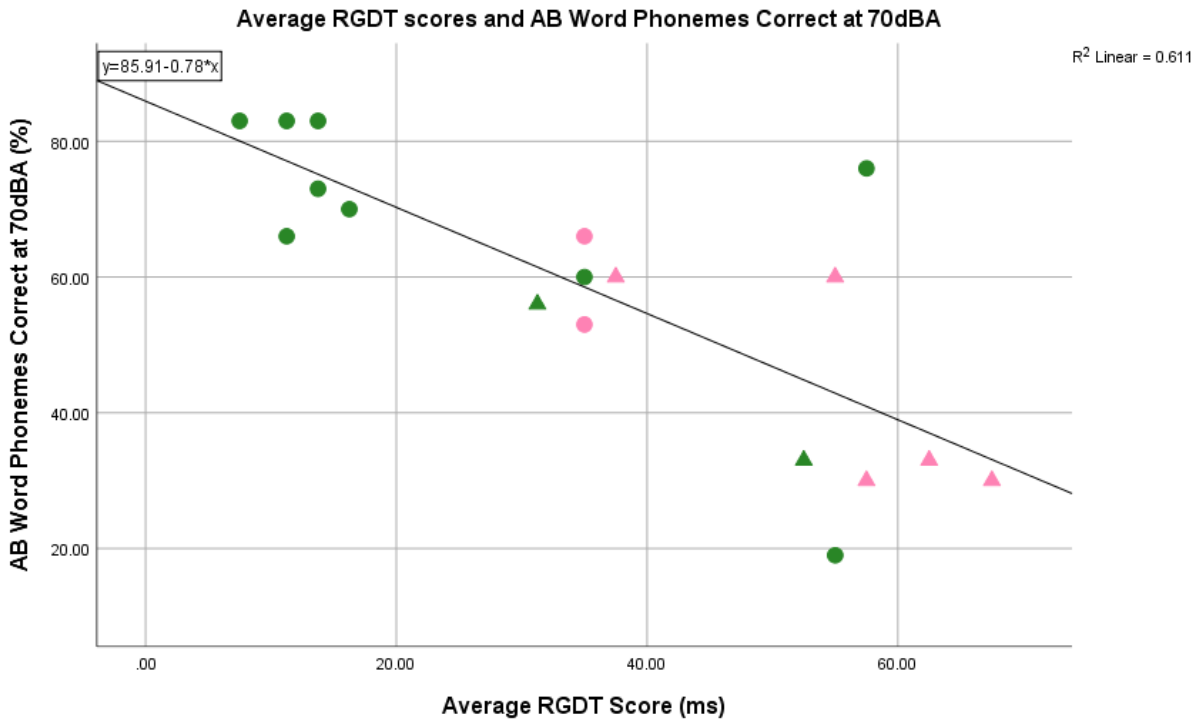

Figure 55: AB Word Phoneme Scores at 70dBA for each subject by deafness onset and stimulation rate

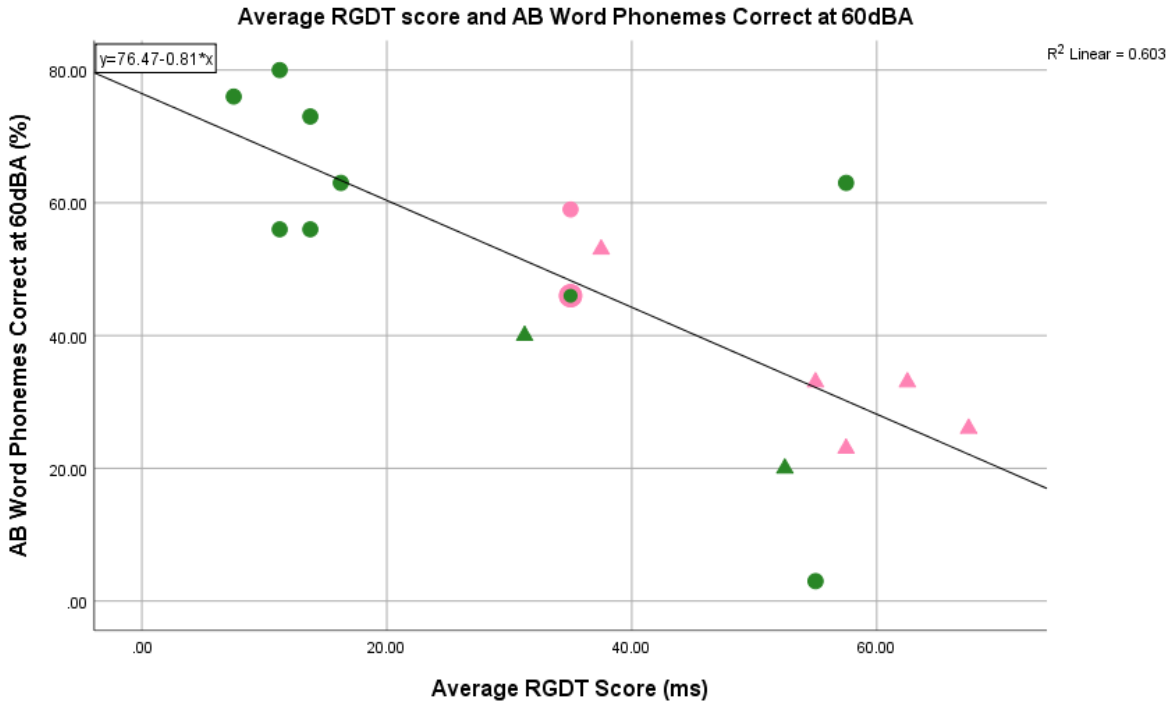

Figure 56: AB Word Phoneme Scores at 60dBA for each subject by deafness onset and stimulation rate. Represents the score achieved by 1 subject in post-lingual high stimulation rate group and 1 subject in the pre-lingual high stimulation rate group.

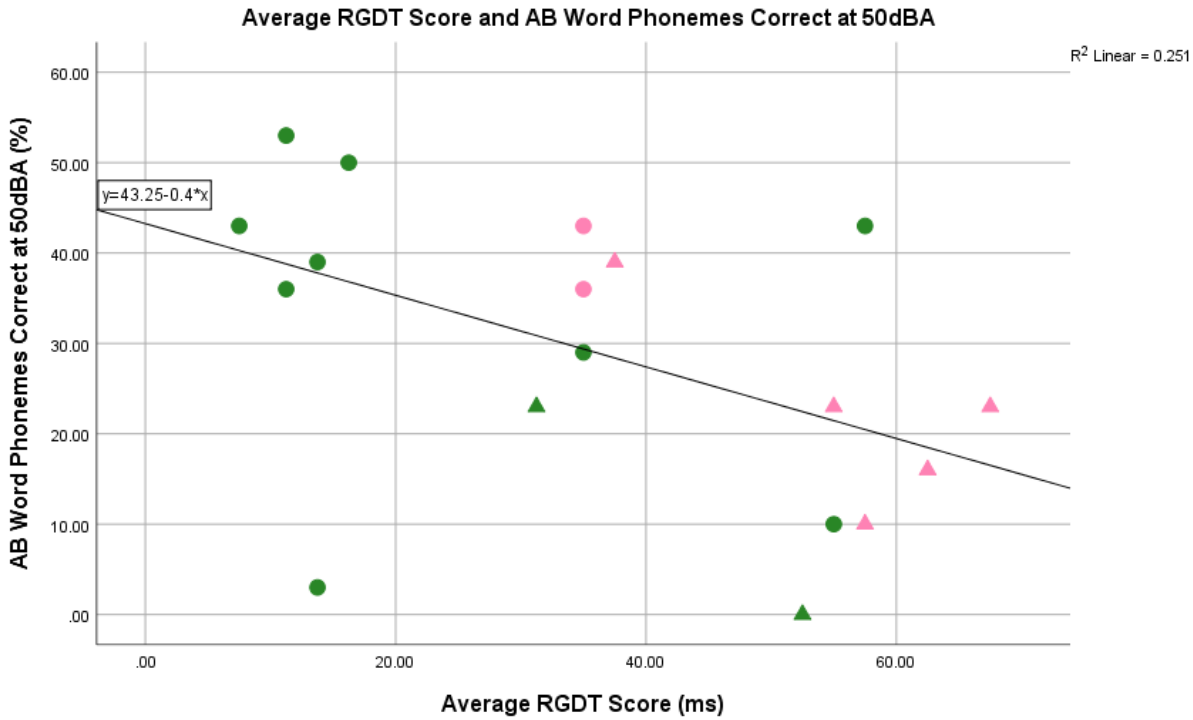

Figure 57: AB Word Phoneme Scores at 50dBA for each subject by deafness onset and stimulation rate

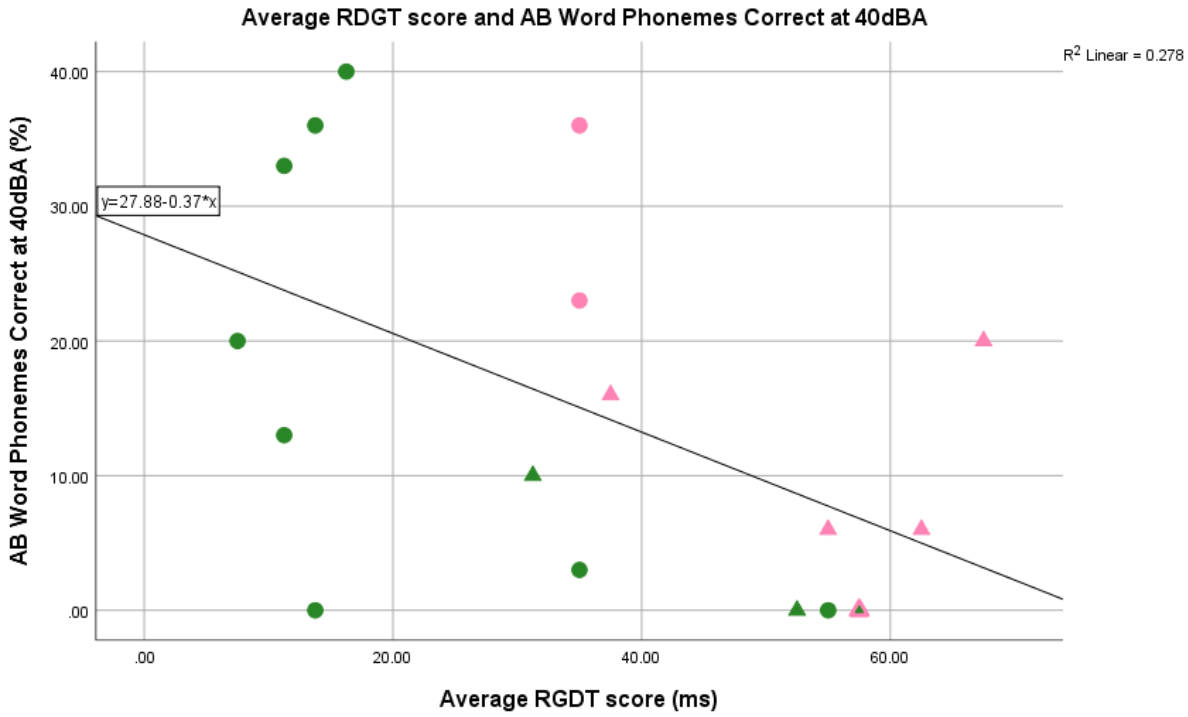

Figure 58: AB Word Phoneme Scores at 40dBA for each subject by deafness onset and stimulation rate. Represents the score achieved by 1 subject in the post-lingual high stimulation rate group and 1 subject in the pre-lingual low stimulation rate group.

Figure 59 shows the distribution of RGDT thresholds and AB word phoneme scores in the pre-lingual group. The two subjects in the pre-lingual group with high stimulation rates had the shortest RGDT thresholds (35msecs) and had higher AB word phoneme scores in comparison to the rest of the pre-lingual group. All of the subjects with low stimulation rates had longer RGDT thresholds and lower AB word phonemes correct scores, with the exception of one subject who performed similarly to the subjects with high stimulation rates.

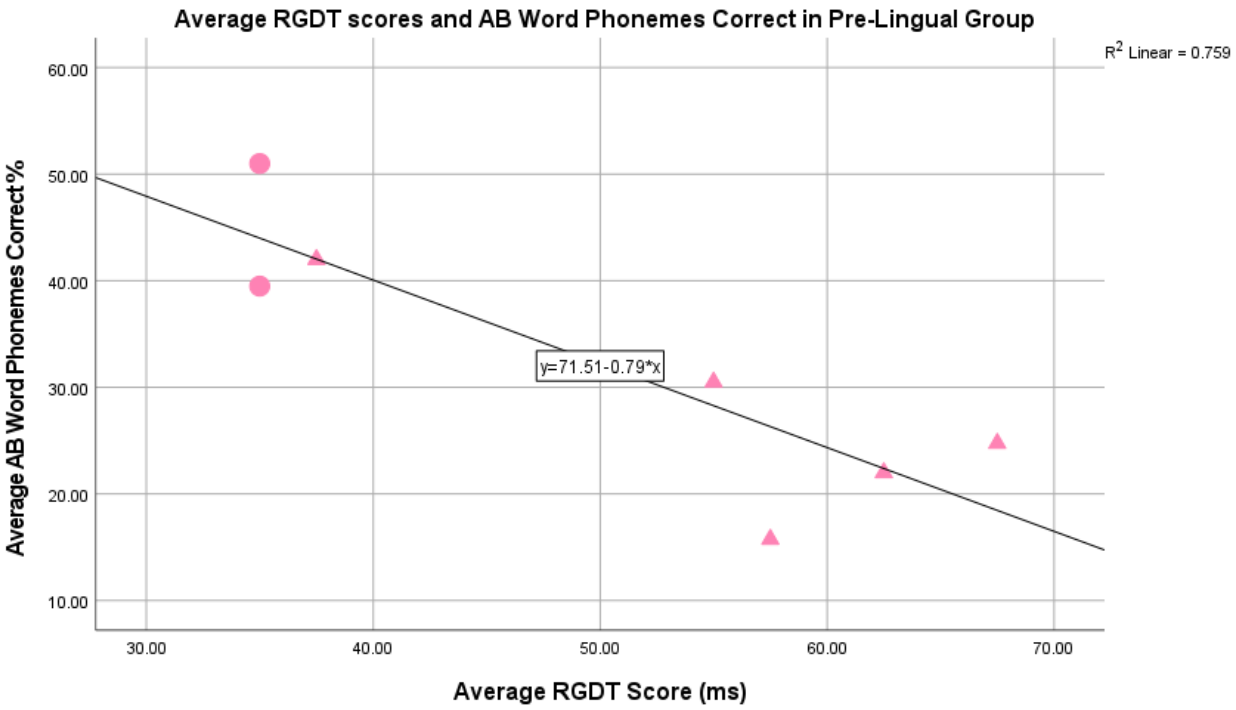

Figure 59: Average AB word phoneme scores in the pre-lingual group by average RDGT thresholds

Figure 60 shows the distribution of the RGDT thresholds and AB word phonemes scores in the post lingual group. Two subjects in the post-lingual group had low stimulation rates, one of these subjects had RGDT thresholds and AB word phoneme scores in the mid-range, whilst the other showed longer RGDT thresholds and lower AB word phonemes correct score.

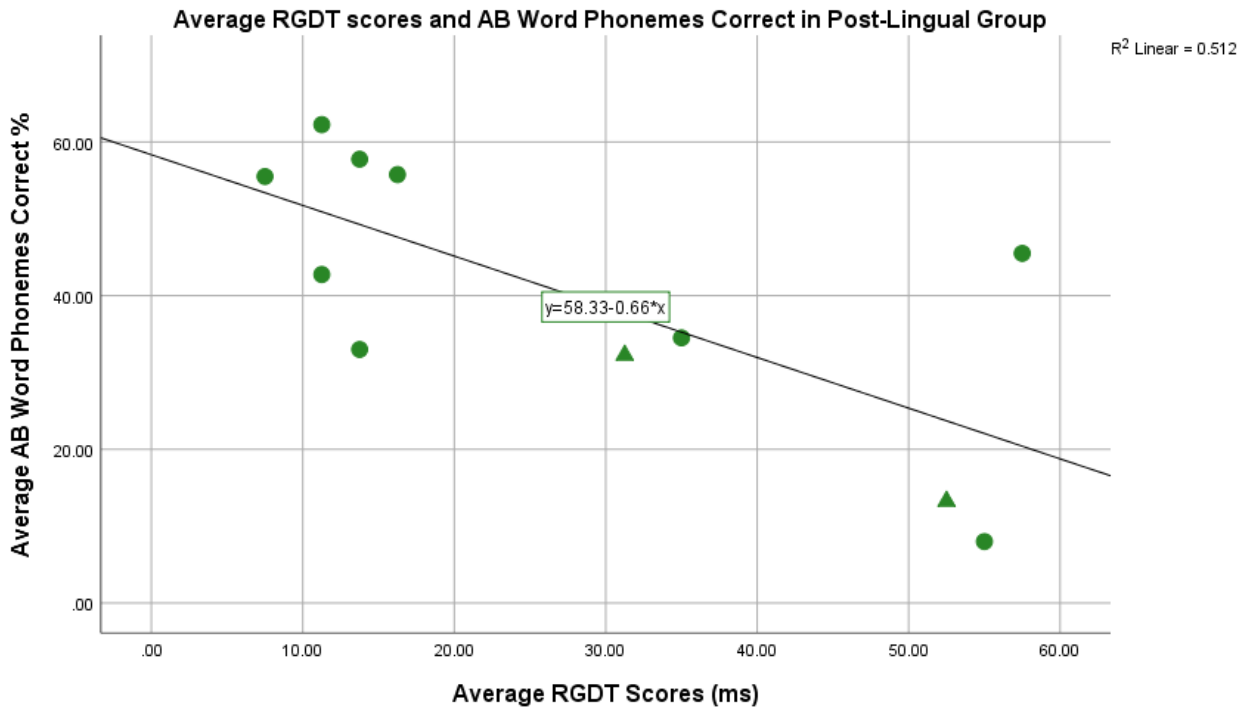

Figure 60: Average AB word phoneme scores in the post-lingual group by average RDGT thresholds

Chapter 7: Discussion

7.1 Summary of thesis and overall findings

The primary purpose of the present thesis was to investigate if objective and behavioural measurements of temporal processing were predictive of speech performance and to see if these measures were correlated to each other. To the authors knowledge, this is the first study which has investigated this and the findings of this research provide a novel contribution to the existing literature, which is currently limited in this area. The main aims of this research were to answer the following questions:

1. Can objective intracochlear measurements of the eCAP recovery function be completed successfully in a clinical setting?

2. Does this objective measurement inform us about the underlying physiology and temporal response properties of ANFs at a peripheral level based on deafness onset and stimulation rate?

3. Do eCAP recovery function measurements predict psychophysical performance as measured by RGDT?

4. Do deafness onset and stimulation rate effect RGDT thresholds?

5. Do these objective and behavioural measurements predict speech performance, as measured by AB word phoneme scores?

Below is a summary of the findings of this study that answer the above questions:

1. The eCAP recovery function can be measured reliably and successfully in CI users without the need of any additional testing equipment in a routine clinical setting. The measurement was relatively quick to complete and it took approximately 10 minutes to collect eCAP recovery function recordings at the four test electrodes.

2. There was not a significant interaction between eCAP recovery function measurements and duration of deafness (with the exception of Tau values at E16, which were predicted by deafness onset) or stimulation rate. A significant difference was found in the eCAP Tau value, which is a proxy for the RRP, at each electrode location. Longer Tau time constants

were found in the apical electrode when compared to the basal electrode across all subjects.

3. The eCAP recovery function and RGDT scores were not correlated, hence our study could not establish if a neural-behavioural relationship existed.

4. The eCAP recovery function was not correlated to speech performance, but RGDT was in the same individuals. There was a significant effect of deafness onset and stimulation rate on RGDT scores; with shorter gap detection thresholds in subjects with post-lingual deafness and high stimulation rates and we found overwhelming evidence that this was predictive of speech perception across a range of scenarios. Additionally, there was a significant effect of frequency, with shorter RGDT thresholds recorded at 500Hz when compared to 4000Hz across all subjects.

In this chapter the above findings are discussed, taking into consideration what impact particular methodological choices had and how this compares with previous studies. The results are discussed in the following subsections:

7.2 the results of the eCAP recovery function measurement,
7.3 the results of the RGDT thresholds,
7.4 the results of the RGDT threshold and AB word phoneme scores,
7.5 the limitations of the current study are outlined,
7.6 a proposal for a future study is outlined.

7.2 The eCAP recovery function

The author acknowledges that the current study was under powered as the sample was made up of pre and post lingually deafened adults, with different durations of deafness and age which increases between subject variability, and this may explain why highly variable eCAP recovery function measurements were obtained in this group of subjects. Due to the low power, it is possible that the effect of deafness onset and stimulation rate for the eCAP recovery function may have been altered or diminished. A *posthoc* sample size calculation for multiple regression showed that for the medium effect (R^2 =0.35) observed in the present study for eCAP recovery Tau measurements, a much larger sample of 36 subjects would be needed to achieve a power of 0.8. Although no relationship was found between eCAP recovery function and speech perception, there was a significant difference in Tau measurements based on electrode location, which may be indicative of the function of the underlying neural

structures and is discussed in further detail below, however, due to low power in the current study this finding needs to be replicated in future studies with a larger sample size and better control for between subject variability.

7.2.1 Feasibility of measuring the eCAP recovery function

The present study demonstrated the eCAP recovery function could be measured with relative ease and with a high success rate. The eCAP recovery function was recorded in 92% of electrodes tested in comparison to 52% of electrodes tested in the study by Botros and Psarros (2010). The eCAP recovery function is a more complex measurement in comparison to the routinely used eCAP threshold measurement, which has a reported success rate in excess of 90% (Botros et al., 2007; van Dijk et al., 2007); the results of the present study show that the eCAP recovery function can be measured successfully in a clinical setting without the need for any additional equipment. Many of the earlier eCAP recovery function studies have been conducted using older implant models CI24M or CI24R (Battmer et al., 2004; Charasse et al., 2003; Morsnowski et al., 2006), as we used newer models (CI512 and CI532) they provided the methodological advantage of measurements at shorter MPIs, 13ms versus 250ms for the CI24Mand CI24R (Gordon and Papsin, 2013) which may also account for some of the variability seen between the results of these studies.

7.2.2 The eCAP recovery function and deafness onset

As discussed in chapter 2, section 2.5, SGC survival is likely to play a critical role in determining performance with a CI, and is negatively correlated with the duration of deafness prior to cochlear implantation (Gantz et al. 1988; Blamey et al., 1996; Nadol et al., 1989). There is currently a limited amount of evidence on the correlation between speech perception and residual SGC counts in CI users. As SGC count cannot be measured directly in CI users, in this study, we utilised the eCAP recovery function as a measure of the underlying neural physiology in CI users with both pre and post lingual deafness. It was hypothesised that subjects with pre-lingual deafness would have poorer neural function, resulting in compromised temporal processing, slower eCAP recovery functions and limited speech perception abilities when compared to post-lingually deafened CI users. The results of the eCAP recovery function measurements in the present study did not support this hypothesis.

This study evaluated the refractory recovery time constants in adult CI users by measuring the eCAP recovery function; which reflects the integrity of the peripheral auditory system

(Brown et al 1990; Gantz et al 1994; Kiefer et al 2001 and Nelson and Donaldson 2001) and estimates how fast stimulated ANs are able to recover from a single biphasic pulse. Numerous animal studies (Terayama et al, 1977; Spoendlin, 1984, Leake and Hradek, 1988; Shepherd and Javel, 1997; Hardie and Shepherd, 1999, Shepherd et al 2004) have shown that there is a rapid and extensive loss of peripheral processes in the organ of Corti which innervates the ANs following hearing loss; and this pattern is also observed in the human cochlea (Felix et al., 1990; Nadol, 1990; Felder et al., 1997). It was therefore hypothesised that the pre-lingual group in this study, with longer durations of profound deafness, would be impacted more significantly by these pathological changes; which are likely to reduce the efficiency with which ANs respond to electrical stimulation (Koles and Rasminsky, 1972; Zhou et al, 1995). The results of the present study indicate that the recovery time constant is not affected by deafness onset, as mentioned this could be due to the low power of the study, but when compared to other studies which have investigated the refractory time constants in human CI users; (Miller et al.,, 2000; Charasse et al., 2003; Battmer et al., 2004; Shpak et al., 2004; Morsnowski et al., 2006; Cohen, 2009; Botros and Psarros, 2010; Fulmer et al., 2011; Kim et al., 2011; Lee et al., 2012, He et al., 2017 and Hey et al., 2017) some key methodological differences might also account for the discrepancy in results between studies.

Simulated results based on a computational model of the cat auditory nerve, show that prolonged RRPs are associated with better neural survival in CI users (Botros and Psarros 2010). This finding was not replicated in our study and we found evidence for the converse, with longer Tau values in subjects with pre-lingual deafness. The computational model used by Bostros and Psarros (2010) assumes that the firing rate of the ANs is independent of the neural population, our results show there is no statistically significant correlation between T0 (a proxy for ARP) and tau (a proxy for RRP). This would suggest that the firing rate of ANs could vary as a function of the size of the neural population; this is supported by the finding of normal RRPs in children with CND who presumably have reduced nerve density (He et al., 2017). Additionally, there are anatomical differences between the ANs examined in animal studies and the human cochlea (Nadol, 1988; Felix, 2002), which may account for this difference in results.

Furthermore, the simulated model used in Botros and Psarros (2010) was heavily based on the assumption that eCAP amplitude is the sole determinant of loudness perception, that eCAPs of equal amplitude correspond to equal loudness (Fletcher and Munson 1933). While this assumption is reasonable for an idealised model in which all ANs are characterised by the

same parameters using a single auditory nerve replica; in human CI users equal firing rates are not possible across different subjects due to variations in the degree of damage to the neural population. The eCAP amplitude is dependent on the number of ANs recruited as well the firing rate of each of these ANs. McKay and McDermott (1998) investigated how mechanisms of loudness affected the firing probability based on the duration of hearing loss and postulated that the firing rate plays the dominant role when neural survival is poor, with a high firing rate corresponding to longer durations of deafness. In the present study although not statistically significant, there was a trend for higher eCAP amplitudes in the post-lingual group compared to the pre-lingual group, which might suggest, there is a greater density of excitable neural fibres in the post-lingual group.

In cats, Li and Young (1993) showed that ANs with high firing rates had fast recovery from relative refractoriness, and the ARP was independent of firing rate. In this study there was a statistically significant difference in the eCAP Tau values at each electrode location, the RRP decreased as the stimulating site moved in an apical to basal direction, which supports the possibility that ANs near the apical electrode have a lower firing rate than those near the basal electrode in our subject group, assuming that the loss of the peripheral processes is greater towards the more basal regions of the cochlea over time. Due to the large variability in the results of the present study, this finding needs to be replicated in future studies to strengthen the argument that the eCAP Tau provides a direct measure of the function of the underlying neural population.

Lai and Dillier (2010) measured eCAP recovery function and found large variations in the recovery time constant at lower eCAP response amplitudes (<100 μV). As eCAP recovery function is dependent on the synchrony of the responding ANs, a possible explanation for this observation is that larger amplitudes are likely to be associated with ANs that respond in a highly synchronised and deterministic manner, whereas smaller response amplitudes may be associated with more stochastic firing and therefore produce larger variations in the eCAP recovery function. In comparison, 66 amplitude measurements were collected in this study, of which 25 had responding amplitudes lower than 100uV, the majority of which were obtained at electrodes 10 and 6. This would suggest that in the current sample the eCAP recovery function is showing highly synchronised and deterministic activity at electrode 19 and 16, which may also be reflective of the neural survival in this region as more ANs can be recruited. In contrast electrode 10 and 6 appear to be showing more stochastic firing patterns, however this experiment lacks power so further studies are required to demonstrate this effect. It is also

important to note that the eCAP recovery function is unable to inform us regarding where the deterministic vs stochastic activity originates within the ANs as it is an aggregate response, so it is most probably reflective of the density of the underlying neural population.

7.2.3 The eCAP recovery function and implant type

Botros and Psarros (2010) compared the eCAP recovery function obtained for different electrode array designs, Cochlear Nucleus Freedom Implants contour vs straight electrode array. Based on the findings of previous studies (Cohen et al., 2003; Hughes and Abbas, 2006) it was assumed that fewer neurons would be activated in subjects with a contour electrode array as they exhibit a reduction in the spread of excitation on stimulation. However, Cohen et al (2005) reported no difference in the spread of neural excitation measured between CI users with these two electrode arrays. More importantly, the spread of neural excitation was not measured in Botros and Psarros (2010), they reported a faster rate of recovery with the contour array compared to the straight array, but the assumed difference in neural population between implant model remains unverified. In the present study all subjects were recipients of a contour modiolar implant, the Nucleus CI532 or Nucleus CI512 device, so the results do not provide insight on the effect of intracochlear electrode position on eCAP refractory recovery function recordings. However, the multiple regression analysis showed a significant effect of implant type for the Tau measurement on electrode 19. The Nucleus CI532 has a is thinner, less stiff electrode array and is 60% of the volume of Nucleus CI512, it is designed to be inserted atraumatically, bringing electrode contacts closer to the modiolus, hence closer to the SGCs (Aschendorff et al., 2017; Shaul et al., 2018; McJunkin et al., 2018). Electrode contacts closer to the target neuronal population reduces the spread of excitation, resulting in more focused stimulation (Jeong et al., 2015) and potentially better speech perception (Hey et al., 2019). As implant type was not a predictor variable for any of the other eCAP recovery function measurements, and because in the present study there is a confound with the majority of the pre-lingual subjects being Nucleus CI532 recipients and the majority of the post-lingual subjects being Nucleus CI512 recipients the author is not confident regarding the robustness of this finding in the present study.

7.2.4 The eCAP recovery function and stimulation rate

The was no significant effect of stimulation rate on the eCAP recovery function. Few studies have characterised the temporal response properties of ANs for human CI users by measuring the eCAP recovery function at different stimulation rates, with variable results (Brown et al.,

1990; 1994; Wilson et al., 1997; Rubinstein et al., 1999; Kiefer et al, 2001; Shpak et al 2004; Fulmer et al., 2011; Hughes et al., 2012; Lee et al., 2012). Shpak et al (2004) measured the eCAP recovery function based on subjectively preferred rates and reported significantly longer recovery time constants in subjects' who preferred slower stimulation rates (900Hz or 1200Hz) than those in subjects' who preferred faster stimulation rates (1800Hz). As the authors did not examine preference at lower rates (250Hz or 500Hz) and did not perform any formal speech perception assessments, we are unable to make a direct comparison with the findings of the current study, furthermore, this positive correlation was not replicated in a follow-up study by the same author (Shpak, 2005).

7.2.5 The eCAP recovery function and speech perception

One shortcoming of the present study is that the stimulation rate was not systematically varied, therefore it is not possible to postulate if differences in performance as a function of stimulation rate result from underlying temporal response properties of the auditory nerve. Furthermore, there is a confound in the present study as the majority of the subjects in the low rate group had pre-lingual deafness; therefore, their ability to attain the same level of speech perception as the post-lingually deaf subjects is likely to be compromised (Teoh et al., 2004; Klop et al, 2007). In hindsight had the same subjects been tested with different stimulation rates, it may have been possible to provide findings on the clinical applications of the eCAP recovery function in optimising stimulation rates and speech performance. For these reasons future studies are needed with a larger sample size without the confound of deafness onset to identify if eCAP recovery function can help predict the stimulation rate that will provide optimal speech performance.

The lack of correlation between the eCAP recovery function and speech scores could be because measurements were obtained for a single masker-probe pulse pair rather than pulse trains, which are used for everyday listening. Single pulse eCAP recovery function measurements represent the aggregate response across a collection of ANs that vary in diameter, discharge thresholds, firing probability and recovery time (Brown et al., 1990) and is therefore not a measure of central temporal processing. By using different stimulation paradigms, eCAP measurements can inform us regarding different aspects of temporal processing, this study focused on recovery from refractoriness. Continuous stimulation with pulse trains is likely to result in adaptation due to depletion of neurotransmitters at the synaptic gap between the ANs and ANFs (Fruhstorfer, 1971; Smith 1977; Smith and Brachman 1982; Boettcher et al., 1990; Javel, 1996; Loquet et al., 2004; Morsnowski et al., 2006; Zhang et al., 2007). Adaptation is a ANs tendency to lower its excitability in response to sustained action

potentials and is thought to play an important role in speech encoding at the level of the auditory nerve as it removes redundant information (Geurts and Wouters, 1999; Fairhall et al., 2001; Avissar et al., 2007). Fast neural adaptation and recovery from prior stimulation have been proposed to enhance acoustic onsets in the speech waveform (Delgutte, 1997). Abnormal neural adaptation patterns, excessive adaptation and/or slow recovery from adaptation could potentially cause poor representation of temporal envelopes at the auditory nerve (Jeng et al., 2009), and might contribute to poor speech perception in some CI users (Wilson et al., 1994; Nelson and Donaldson, 2002). Recovery from refractoriness and adaptation are therefore likely to involve different phenomena; and we propose a further study which investigates eCAP recovery function from neural adaptation later on in this chapter which may provide insight on temporal integration and speech performance.

It is quite possible that the relationship between SGC count and speech perception is not linear and processed speech delivered by CIs may contain redundant information that can mask functional changes that occur at the peripheral level. As speech perception is measured using the entire electrode array, these variations could impact performance and may account for the lack of correlation between the eCAP recovery function and speech perception (Miller 2008). Furthermore, speech perception is influenced by factors such as neural plasticity and cognition which are independent of the auditory periphery so it is plausible that the eCAP recovery function lacks sensitivity to correlate with behavioural measures of temporal resolution and speech perception. Further studies with a larger sample and sufficient power would be required before any conclusions can be drawn.

7.2.6 The eCAP recovery function and RGDT thresholds

The eCAP recovery function was not correlated to the RGDT thresholds. To date, there is only one study which has examined the relationship between recovery from neural adaptation, RGDTs and speech perception in CI users (Zhang et al., 2013). Although Zhang et al (2013), investigated a different aspect of temporal processing (adaptation) to the present study (refractoriness), there are several key methodological similarities and differences of importance. Zhang et al (2013) measured the neural adaptation of the auditory nerve induced by a 50-ms pulse train with a pulse rate of 1,000 pps at a single electrode in 14 post-lingually deaf CI users. Similar to the present study they utilised the NRT software, therefore, only included subjects with a Cochlear corporation device. Their results showed no association between the amount of neural adaptation of the auditory nerve and RGDT thresholds or speech perception, similar to the findings of the present study. In the present study the eCAP recovery function was measured at 4 electrode locations corresponding to the frequency

allocation of the RGDT test, in order to capture the variability in neural health along the length of the electrode array, which presumably is relevant for both temporal resolution and processing of complex speech signals (Scheperle and Abbas, 2015); and other studies have shown that neural adaptation varies across stimulation sites within individual patients (Hughes et al., 2012; He et al., 2016a). As speech perception requires the listener to attend to changes in stimulation patterns across multiple electrode sites and levels, measurements at more than one electrode location are likely to reflect the perceptual differences amongst CI users more accurately. However, in our study the RGDT thresholds were similar across the array, with longer RGDT thresholds in the basal region, which could suggest that there are more complex interactions involved in speech perception and other measures may assist with disentangling the peripheral and central contributions.

Zhang et al (2013) also measured the late latency auditory evoked potential (LAEP) in a group of 10 NH subjects who served as a control, however, the effect of age on temporal processing was not accounted for effectively, as these subjects were not age matched controls. The NH group were aged between 20-30 year and the CI group were aged 24-83 years, studies have demonstrated that temporal processing abilities deteriorate as age increases (Kumar and AVS, 2011). It should be noted that while Zhang et al (2013) obtained both eCAP and cortical physiological potentials within the same subjects, the degree of adaptation was not compared between the two physiological measures, therefore it is not possible to clarify the relative contributions of peripheral versus central adaptation to perceptual measures of temporal processing.

7.3 RGDT thresholds

Statistical analysis revealed that RGDT thresholds had a significant correlation with both deafness onset and stimulation rate and there was a significant effect of frequency across all subjects. Furthermore, multiple regression analysis revealed that stimulation rate significantly predicted RGDT thresholds. These findings are compared with previous studies below.

7.3.1 RGDT thresholds and deafness onset

The results of this study show that deafness onset significantly effects RGDT threshold and found longer RGDT thresholds in the pre-lingual group compared to the post-lingual group which is reflective of reduced central temporal resolution in subjects with prolonged periods of auditory deprivation likely due to the physiological and morphological differences in neural structures in the auditory pathway between the two groups. In subjects with pre-lingual deafness RGDT thresholds may be more significantly impaired due to greater and more

widespread neural pathology which results in altered temporal discharge patterns (Shepherd and Javel 1997) and this is consistent with experimental animal studies which have shown that auditory deprivation results in incomplete maturation and, or degeneration within the auditory system (Harrison et al, 1991; Moore, 1990; Seldon et al, 1996; Webster and Webster, 1977).

In electric stimulation, loudness is regulated by controlling the amount of charge delivered by each current pulse or current amplitude and is equated across electrodes in the recipient's clinical map by setting threshold (T) and comfortable levels (C). Individual variations regarding how loudness grows with current has been widely reported and attributed to differences in the spatial distribution of the surviving neurons and current spread (McKay, 2004). With electrical stimulation, all neurons in the electrical field fire synchronously (Kiang and Moxon, 1972; van den Honert and Stypulkowski, 1984; Javel et al., 1987), when the stimulus intensity is increased, more auditory neurons are stimulated which results in an increased perception of loudness (Javel and Viemeister, 2000). Studies which have measured electrical gap detection as a function of stimulus intensity have demonstrated that temporal acuity substantially improved with increasing stimulus level (Preece and Tyler,1989; Shannon,1989; Pfingst et al., 2007; Galvin and Fu, 2009). In the present study, a fixed presentation level of 60dBA was used as it was likely to reflect the maximum performance and would allow individual variation in speech perception to be shown. At higher presentation levels there is a greater spread of excitation (Bierer and Middlebrooks, 2002; Snyder et al., 2004) which leads to a larger number of ANs being stimulated which consequently leads to an increase in loudness. Stimulation at low presentation levels is likely to activate a smaller number of ANs due to more focused stimulation which may reflect the localised health of the neural population at the site of stimulation; we would therefore expect the largest variance in RGDT thresholds at low presentation levels. The findings of Garadat and Pfingst (2011) support the theory that the same pathological processes in the cochlea that facilitate loudness also affect GDTs similarly and would imply that there is variation in temporal processing along the tonotopic electrode array. They reported a reduction in the GDTs as electrodes were tested at higher levels of their dynamic range which would support the idea that the central auditory system may improve temporal acuity by merging responses from multiple neurons. As we did not assess GDTs as a function of intensity we are unable to postulate the relationship between the stimulus intensity and potential variations in GDTs, one shortcoming of this study is that despite expecting a floor effect, we are unable to demonstrate if the striking predictive power of RGDT threshold for speech performance is maintained at lower presentations levels.

7.3.2 RGDT thresholds and frequency

Shannon (1989) reported there was no marked difference in electrically measured GDTs at apical and basal electrodes in post-lingual CI users, which is consistent with previous findings, (Green, 1973; Shailer and Moore, 1983; Moore and Glasberg, 1988) suggesting that there is no inherent difference in gap detection in the central auditory system when using information from apical or basal regions of the cochlea. We examined the variability in RGDT thresholds at different sites along the electrode array and observed significantly lower acoustic RGDT thresholds at the lower frequency electrode (500Hz) compared to the mid frequency electrode (2000Hz) and high frequency electrode (4000Hz). The same difference was observed at the mid frequency electrode (1000Hz) and the high frequency electrode (4000Hz). These difference in RGDTs thresholds whilst significant and elude to better neural survival in the apical region in the authors opinion they are unlikely to demonstrate that the RGDT thresholds can be utilised as a peripheral measure. As the RGDT thresholds were measured via a speech processor they do not provide a direct measure of neural health and function of the mechanisms that underlie gap detection ability.

7.3.3 RGDT thresholds and stimulation rate

The results of the present study indicate that there is a significant effect of stimulation rate on RGDT thresholds at all frequencies. The subjects with high stimulation rates show shorter RGDT thresholds and better temporal resolution when compared to subjects with low stimulation rates; however, it is important to mention the confound of deafness onset in this study when the effects of stimulation rate on RGDT scores are considered. The high stimulation rate group consisted of 11 subjects, 9 of whom were post-lingually deaf and 2 were pre-lingually deaf (subject 12 and 17). When the RGDT scores for subject 12 and 17 are examined more closely, their composite RGDT scores are longer compared to the rest of the group with the exception of subject 6 and 13 who despite being post-lingually deaf have much longer composite RGDT thresholds, similar to those observed in the low stimulation rate group, see table 22 and figure 61. In comparison to the low stimulation rate group subject 12 and 17 still had shorter RGDT thresholds compared to the rest of the subjects in that group, however, the rate of their map was not adjusted in this study, hence RGDT scores were not re-tested with a lower rate MAP. Closer examination of the RGDT scores in the low stimulation rate group, which consisted of 7 subjects, 4 of these subjects were pre-lingually deaf and 2 were post-lingually deaf (subject 15 and 18), show that subject 15 had similar RGDT scores to the rest of the group but subject 18 had the shortest RGDT scores in comparison to the rest of the group, see table 23 and figure 62 below.

Busby and Clark (1999) reported that pulse rate had no influence on the electric GDTs of pre-lingually deafened adults up to 1000 pps, however, GDTs were only obtained from a single electrode (14) and therefore differences in GDTs across the electrode array were not examined. It is possible that the GDTs could be elevated in areas of poor neural survival, however, studies examining neural responses to electrical stimulation in animals have shown that rates above 800 pps lead to less effective phase locking and entrainment of neurons due to refractory properties being more dominant (Parkins, 1989; Dynes and Delgutte, 1992). As RGDTs were measured acoustically and at one stimulation rate for each subject in the present study, no inferences can be made, further research is required to corroborate the stimulation rate effect, a larger sample size where subjects' GDTs are measured for a range of stimulation rates is likely to provide more information on the optimal stimulation rate for the effective transfer of temporal information in auditory system.

	Subject 2	Subject 3	Subject 4	Subject 6	Subject 8	Subject 11	Subject 12	Subject 13	Subject 14	Subject 16	Subject 17
500Hz	15	5	10	40	15	10	30	50	15	40	30
1000Hz	20	5	5	50	15	10	30	50	10	40	30
2000Hz	15	15	15	70	15	10	40	60	15	30	40
4000Hz	15	5	15	70	10	15	40	60	15	30	40
Composite	16.25	7.5	11.25	57.5	13.75	11.25	35	55	13.75	35	35

Table 22: RGDT thresholds in high stimulation rate group. Subjects 12 and 17 are pre-lingually deaf

	Subject 1	Subject 5	Subject 7	Subject 9	Subject 10	Subject 15	Subject 18
500Hz	60	30	60	50	40	50	30
1000Hz	70	40	70	50	60	50	30
2000Hz	70	30	60	50	60	50	25
4000Hz	70	50	60	70	70	60	40
Composite	67.5	37.5	62.5	55	57.5	52.5	31.25

Table 23: RGDT thresholds in low stimulation rate group. Subjects 15 and 18 are post-lingually deaf.

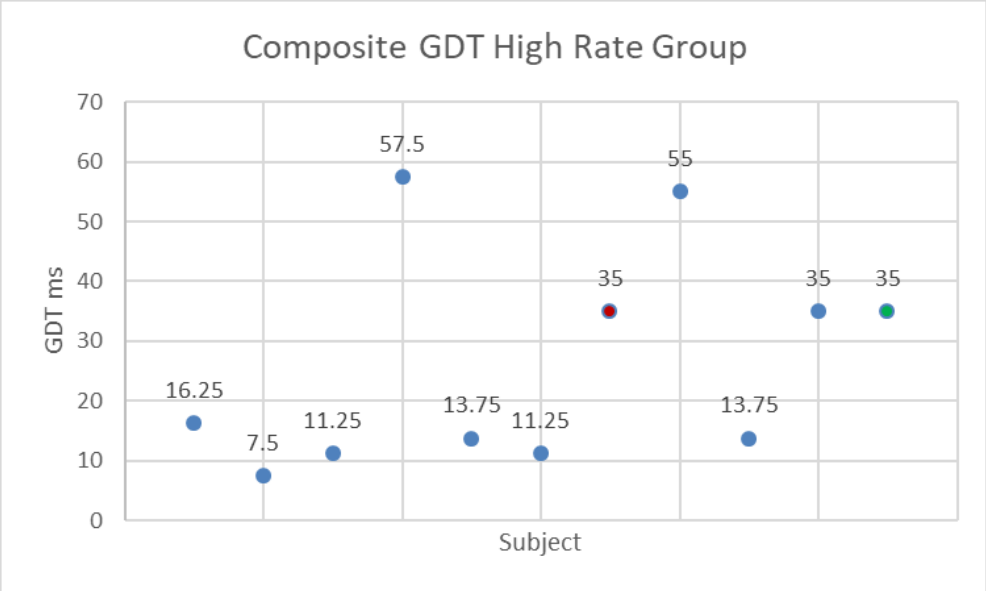

Figure 61: Composite RGDT thresholds for subjects in the high stimulation rate group. Data for Subject 12 (red circle) and Subject 17 (green circle)

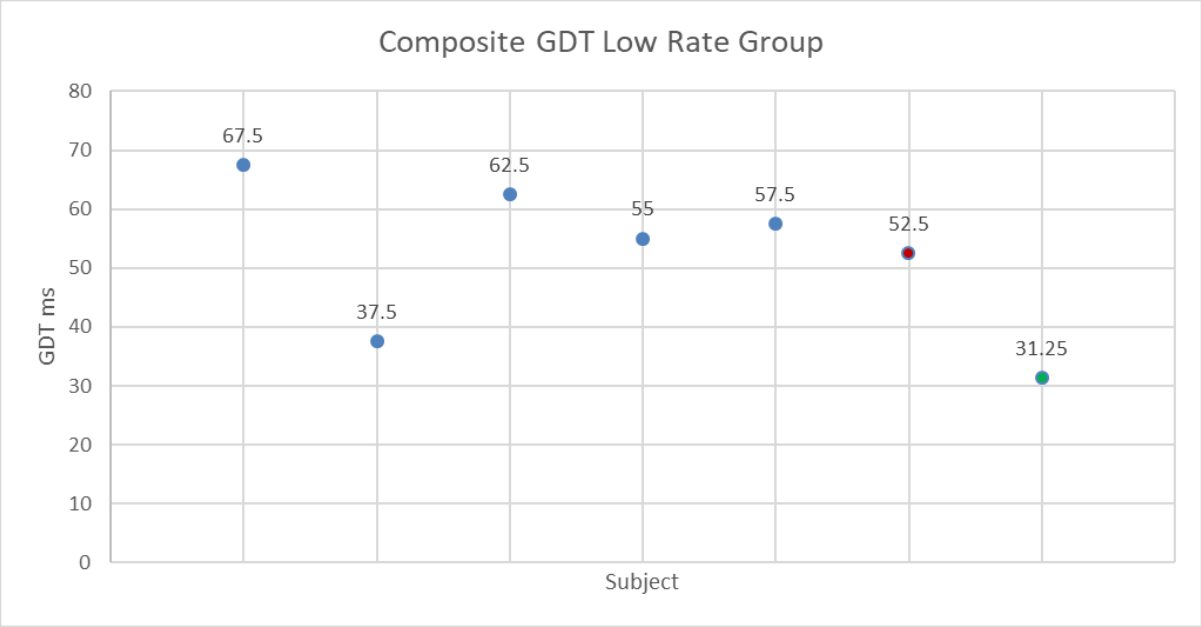

Figure 62: Composite RGDT thresholds for subjects in the low stimulation rate group. Data for Subject 15 (red circle) and Subject 18 (green circle)

7.3.4 The RGDT thresholds and age

In this study, age and RGDT scores were not correlated however; it is well established in the literature that there is a decline in the ability to process temporal properties of sound with advancing age. It has been reported that temporal processing ability declines after the fourth decade of life and deterioration accelerates after 70 years of age (Snell, 1997; Pichora-Fuller et al., 2006; Humes et al., 2010; Kumar and Sangamanatha, 2011), even after peripheral hearing loss has been factored in (Grose et al., 2001; Roberts and Lister, 2004; Queiroz et al., 2010). In this study, the mean age was 64.5 years, with a range of 31-90 years. In the present study cognition was not formally assessed, it is therefore not possible to know what the influence of cognitive abilities and working memory on temporal resolution and speech perception were in the current subject group. Future studies could examine GDTs in different age groups, for example, CI users divided into three groups, a young group (18-40), a middle age group (40-60) and an elderly group (over 60) matched with non-implanted controls, which would aim to assess the impact of aging on the relationship between temporal resolution, cognition and the perception of speech. An additional limitation to the current study is that only one trial of the RGDT was administered which is likely to impact test repeatability.

7.4 RGDT thresholds and AB word phoneme scores

Despite the variability in age and deafness onset in the sample of the present study, RGDT thresholds significantly predicted speech performance at 70, 60 and 40dBA. The results of the present study show an extremely strong negative correlation between RGDT thresholds and AB word phoneme scores, with a notable effect of stimulation rate and infer that the extent to which CI users are able to resolve gap detections strongly predicts speech performance. As speech intelligibility relies on temporal features in speech, these findings confirm that poor temporal resolution reduces speech perception, which is dependent on the utilisation of several neural networks which involve processing at a central level (Tremblay et al., 2004; Wong et al., 2009). As anticipated peak speech performance was seen for all subjects with AB word phoneme scores at mid-high levels. All subjects scored relatively poorly when the presentation level dropped to 40dBA likely due to floor effects and levels being close to the subjects' MAP threshold levels.

6 subjects had normal RGDT thresholds <20 ms across all test frequencies and had correspondingly higher AB word phoneme scores compared to the rest of the subjects (see figures 63-66). 5 subjects had RGDT thresholds between 20-40ms and 7 subjects had RGDT thresholds > 40ms. Previous studies which have investigated the relationship between acoustic GDTs and speech perception have found that when the deficit in gap detection reached 40 msec, there was a noticeable adverse effect on CI users' speech performance (Tyler et al., 1989; Muchnik et al., 1994; Wei et al., 2007; Blakenship et al., 2016). Eggermont (1995) reported that a GDT of 40 msec is critical for accurate speech performance because this value is close to the common duration found for voice onset times and forms the temporal boundary for categorical perception of some fricative/plosive contrasts. The results of the present study corroborate these findings and show subjects with RGDT scores >40 msec demonstrate poorer speech perception (see figures 63-66). The presentation level effect on speech recognition for subjects based on RGDT scores shows variance in performance, suggesting that some individuals are impacted by the reduction in presentation level more significantly than others. This may in part be attributed to the limitations in the information provided by the speech processing strategy but could also be caused as a result of spectral smearing, channel interaction, and limitations of fine structure information.

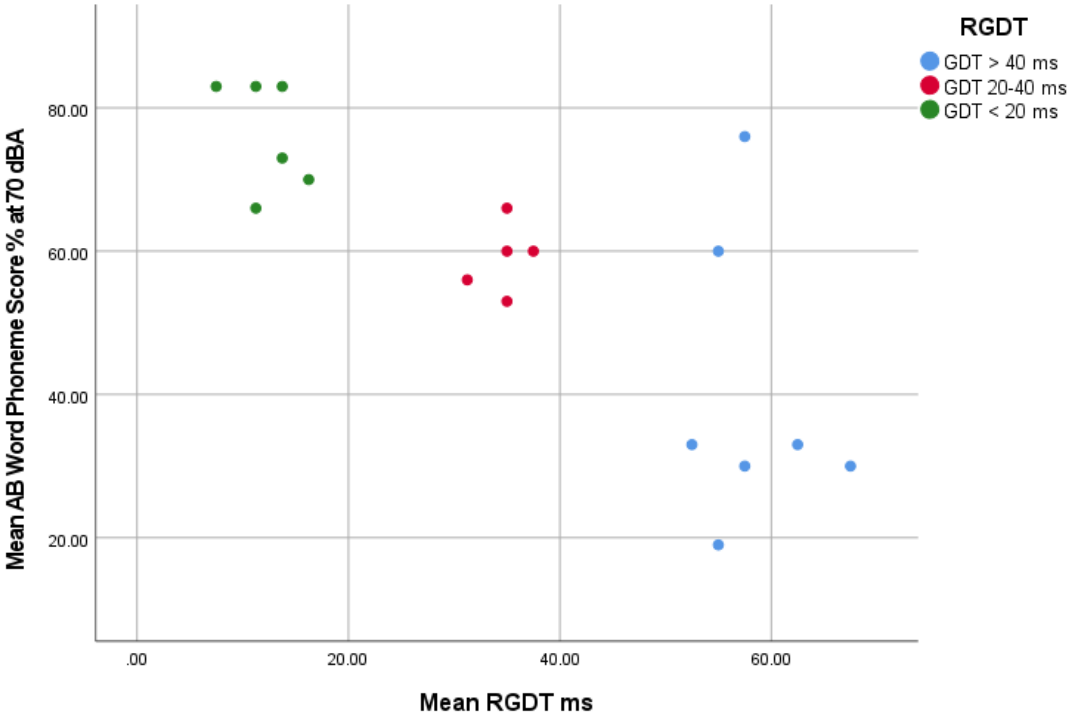

Figure 63: The AB word phoneme scores at 70dBA shown for each subject based on individual RGDT thresholds

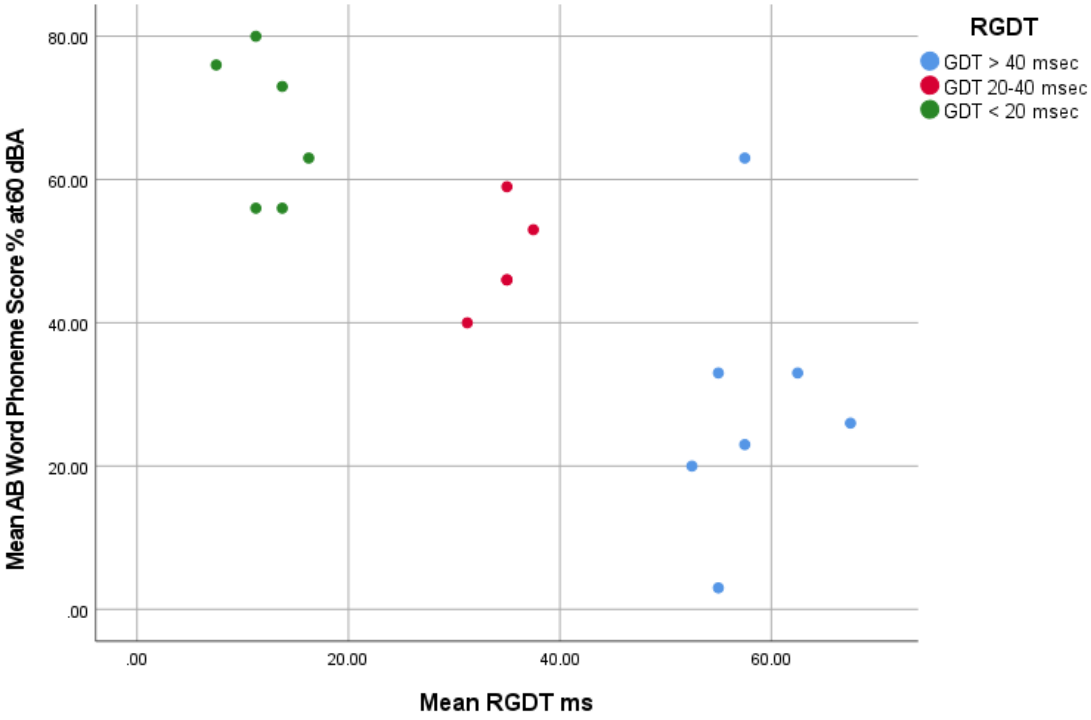

Figure 64: The AB word phoneme scores at 60dBA shown for each subject based on individual RGDT thresholds

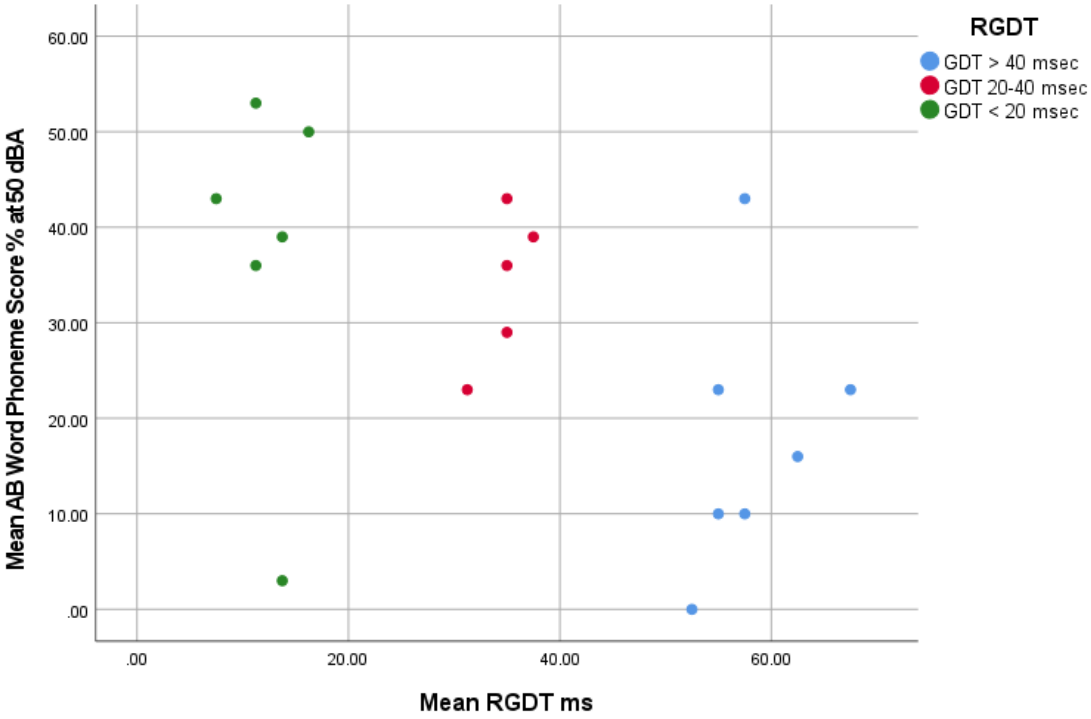

Figure 65: The AB word phoneme scores at 50dBA shown for each subject based on individual RGDT thresholds

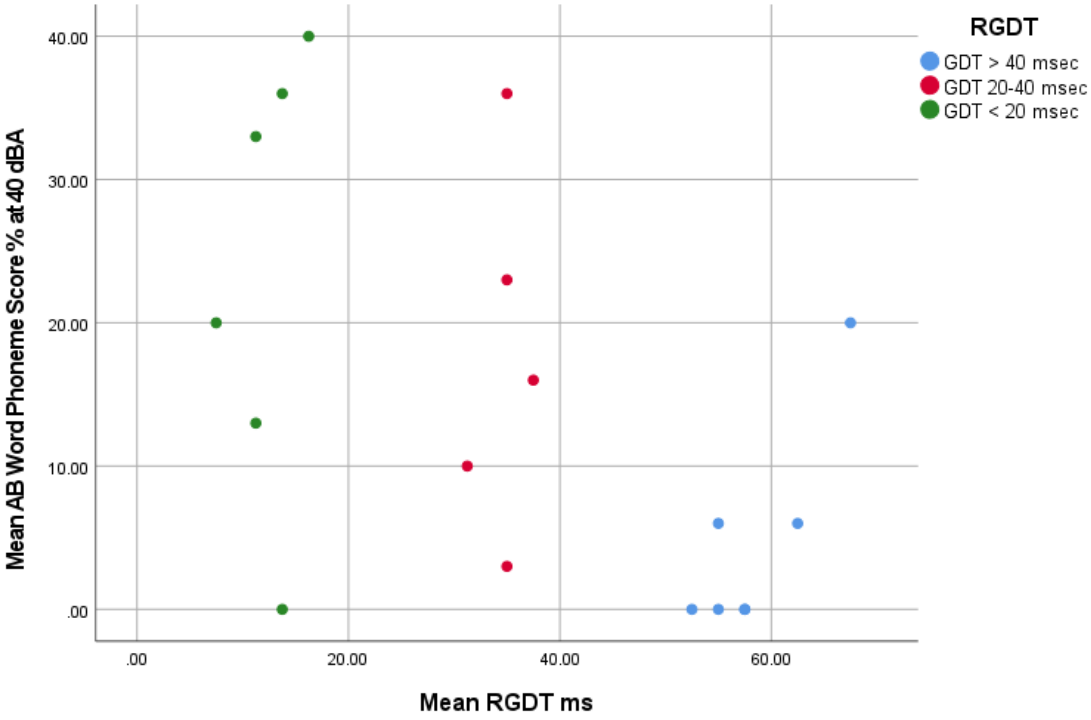

Figure 66: The AB word phoneme scores at 40dBA shown for each subject based on individual RGDT thresholds

Blakenship et al (2016) examined the relationship between behavioural GDTs (using the RDGT as in this study) and a range of commonly used speech perception measures in the USA (Speech Recognition Test [SRT], Central Institute for the Deaf W-22 Word Recognition Test [W-22], Consonant-Nucleus-Consonant Test [CNC], Arizona Biomedical Sentence Recognition Test [AzBio], Bamford-Kowal-Bench Speech-in-Noise Test [BKB-SIN]). Their sample consisted of 12 post-lingually deaf adult CI users (24-83 years) and 10 NH (22-30 years) subjects. Three of the main methodological differences in their study in comparison to the present study is that the RGDT was presented via a speaker and the present study used a circumaural headphones over the speech processor for reasons described in section 5.7. The MCL was not measured in our subjects to minimise the loudness across subjects, however, the presentation level for CI users was 60 dB HL and Blakenship et al (2016) ranged from 60-75dB HL. Furthermore, as the present study did not have a NH group we did not need to accommodate for the potential differences in audiometric thresholds between a NH and CI group. A sound field CI assisted audiogram was not completed prior to completion of testing in the present study as it was assumed that the subjects' map was optimised as they all had a minimum period of 9 months of use with their device.

Similar to the findings of this research Blakenship et al (2016) found there was a significant negative relationship between the RGDT thresholds and speech perception performance on the CNC-Phoneme (which is a monosyllabic speech test similar to AB words) and AzBio test (which is a sentence test). They additionally reported a positive correlation between RGDT thresholds and the signal to noise ratio for performance on the BKB-SIN speech perception test. Subjects with better temporal resolution (shorter RGDT thresholds) were able to discriminate 50% of the target words in the BKB-SIN sentences correctly at a lower signal-to-noise ratio. The present study did not examine the effect of RGDT thresholds on speech performance in noise and further studies investigating this with a range of speech materials in quiet and noise may help better identify temporal deficits that can assist with post-operative rehabilitation.

As hypothesised Blakenship et al (2016) found that there was a statistically significant difference in RGDT thresholds between the NH and CI group and poorer speech performance was found on all speech tests in the CI group compared to the NH group. They reported CI users had an average composite gap detection threshold of 24.96 ms with a range of 7.5 to 67.5 ms which is consistent with the findings of the present study, which found an average composite acoustic RGDT threshold of 36.39ms with a range of 7.5-67.5ms. There was a

difference between the average composite acoustic GDT in the pre-lingual (50.31ms, range 35-67.5ms) and post-lingual group (25.25, range 7.5 – 57.5ms), which is similar to the results reported by other researchers (Wei et al., 2007; Zhang et al., 2015) who measured acoustic GDTs in CI users. The significantly longer GDTs in CI users compared to NH controls in the study by Blakenship et al (2016) could be attributed to the limitations in CI technology where a reduced number of electrode contacts (a maximum of 22 in Cochlear Ltd devices) are available to stimulate the surviving auditory neurons in comparison to the abundant and normally functioning cochlear hair cells in NH listeners.

Similar to the present study, Blakenship et al (2016) obtained measurement from CI users who received Cochlear Ltd devices. They used the subject's own speech processor for testing, the models used were Freedom and Nucleus 5, so some of the variance in their results within the CI group may be due to differences in microphone technology between the processor models. The freedom processor only has a rear omnidirectional microphone whereas the Nucleus 5 has both rear and front microphones in omnidirectional mode. This may have affected results of the RGDT where stimuli were presented via a speaker at 0 degrees' azimuth and for speech testing in noise as the Freedom processor front mic may not have been in the same directional mode as the Nucleus 5 processor. In our sample all subjects were recipients of peri-modiolar electrode array, whereas the participants in the Blakenship et al (2016) study had a range of internal devices including straight electrode arrays. This is likely to be of more importance when considering electrically measured GDTs where the distance from the stimulated electrode contact and target neurons may affect GDTs (Mino et al., 2004) more significantly.

Similar to the present study, Blakenship et al (2016), did not find that deafness onset was a predictor of performance, this may be due the more varied aetiology (Rubella, Meniere's disease, genetic hearing loss, Alport's syndrome, Noise and MMR) in their subject group which may lead to different deficits in the auditory pathway. Most of the subject's in the present study had unknown aetiology of hearing loss and the finding of longer RGDT thresholds and poorer speech performance in pre-lingually deaf subjects is supported by previous work which has shown individuals with long term deafness take a longer time to acclimatise to the signal provided by a cochlear implant, with the duration of auditory deprivation being reported to be correlated to speech perception performance in multiple studies (Blamey et al., 1996; Rubinstein et al., 1999; Holden et al., 2013). Some studies assessing pre-lingual CI users over time found that auditory performance continued to improve beyond 6 months or even 1 year

after implantation (Santarelli et al., 2008; Shpak et al., 2009; Zeitler et al., 2012), In the present study, the pre-lingual group consisted of subjects with a range (9 months – 7 years) of experience with their CIs. However, in this small sample of 7 subjects, 5 had less than 16 months of use with their device and only 2 had > 3years of use with their device. Therefore, duration of implant use is a possible confound in this study as the pre-lingual group may not have achieved peak performance with their device at the time of testing in comparison to the post-lingual group who reach optimal performance faster.

7.5 Limitations of current study

There are a few limitations in the present study, firstly, subjects were recruited by convenience sampling and were stratified by deafness onset. Other factors such as age, sex and aetiology of hearing impairment were not closely monitored when recruiting subjects. The author acknowledges that any of these factors could have resulted in greater variability in data, thereby reducing the statistical power of the findings. As reported in section 7.2 a *posthoc* power calculation showed the study lacked power to show an effect of deafness onset and stimulation rate for eCAP recovery function measurements. Sampling was conducted in this manner, to ensure an adequate number of subjects could be recruited from a small sample population. A high degree of variability in individual performance was expected so an attempt was made to control for as many factors that could predict performance, such as deafness onset, device type and stimulation rate and a balanced experiment was designed. It is difficult to compare results across studies very closely as there are large differences in test methodology and CI user processing characteristics as discussed in chapter 7. This was the first study to investigate if objective and behavioural measures of temporal processing in CI users could predict speech performance and had the methodological advantage of recording the eCAP recovery function measurements using the same NRT software across subjects with a peri-modiolar implant device. Despite being underpowered the results of this study still provide the largest sample of eCAP recovery function recordings in human subjects and confirm that the current methodology is appropriate to obtain measurements. However, further studies are needed to answer whether the eCAP recovery function is able to inform us regarding temporal processing at a peripheral level.

A further methodological weakness in this study was that speech perception testing was completed in quiet, the main reason for this was given the lack of evidence currently available between objective and behavioural measures of temporal processing and speech perception, it seemed reasonable to investigate and establish if any relationship existed for performance

in quiet. Additionally, the aim of the study was to find the best speech perception scores in order to elucidate which factors might contribute to or predict performance, and poorer performance would be expected across CI subjects for speech performance in noise. In the next section a further study to examine the relationship between RGDT and speech testing in noise is proposed.

During the course of the present study, there was an update to the National Institute for Health and Care Excellence (NICE) (2019) technology appraisal guidance (TA566), cochlear implants for children and adults with severe to profound hearing loss; which resulted in AB word tests replacing the BKB sentence test for assessing benefit with hearing aids and are now used to assess candidacy for cochlear implantation in the UK. Given the strong predictive power of RGDT for AB word phoneme scores, the findings of the present study may inform clinical decision making, as there is currently limited evidence that would allow prediction of AB word phoneme scores post implantation. Further studies are needed to calculate such predictions.

7.6 Future studies

The current study demonstrates that stimulation rate is a determinant of RGDT thresholds, which in turn are an extremely strong predictor of speech performance in quiet. A possible further study could examine these effects for speech performance in noise, it is well documented that speech categorisation in noise is a more complex temporal task (Gordon-Salant and Fitzgibbons, 1993 Swaminathoan and Heinz, 2012; Picton, 2013), Additionally, temporal auditory processing is crucial for speech perception ability and understanding speech in noise (Rawool, 2007), therefore further investigation may provide more comprehensive information on whether RGDT (within-channel) and speech in noise use the same temporal mechanisms. Based on the very strong relationship between the RGDT and AB word phoneme scores in quiet in the current study, it is hypothesised that the same temporal resolution abilities are required for both tasks, it would therefore hold to reason that this relationship will be maintained for AB word phoneme scores in noise, with shorter RGDT thresholds associated with higher AB word phoneme scores with decreasing signal-to-noise ratio.

Previous studies which have investigated speech performance in noise in post-lingually deaf CI users have reported similar results. For example, Blakenship et al (2016) reported significantly poorer performance on all speech tests compared to their NH group. Their results for the BKB-SIN was 9.12 dB SNR-50 (SD = 5.52), which is slightly better but comparable to

the results of Donaldson et al (2009) who reported values of BKB-SIN SNR-50 value of 11.9 dB SNR and Gifford et al (2008) reported values of BKB-SIN (11.4 dB SNR-50 for unilateral CI users, 9.8 dB SNR-50 for bilateral CI users) in a large group of subjects (n=156). Blakenship et al (2016) may have reported slightly better results that both Donaldson et al (2009) and Gifford et al (2008) as 5 out of their 12 subjects were bilateral cochlear implant users and are likely to have had an advantage compared to unilaterally implanted subjects.

As discussed the subject's stimulation rate was not changed and testing was not repeated, therefore a follow-up study, ideally with the same subject group would examine the effect of rate on speech performance in quiet, as well as in noise. In the first step, the subject's map rates would be varied systematically (between 250Hz, 500Hz, 900Hz and 1200Hz) and the subject will be given a period of 4 weeks to acclimatise to each map change. Following this period of adjustment, the existing methodology can be used to measure eCAP recovery function, RGDT thresholds and AB word phoneme scores in quiet. Additionally, AB word phoneme scores in noise (adult babble +SNR20, +SNR15, +SNR10, +SNR5 dBHL) can be measured at each rate.

Future studies could utilise the same NRT software used in the current study to complete eCAP measurements for other temporal response properties of the ANFs, such as adaptation and facilitation. This may allow comparison of different temporal measures in CI users that may be predictive of speech performance. Recovery from neural adaptation at the level of the auditory nerve can be evaluated by measuring eCAP amplitude in response to the probe pulse at different time points after the masker-pulse-train ceases. The forward masking paradigm used in this study requires a further modification in order to complete this measurement, specifically the single pulse masker (used in this study) is replaced by a pulse train and the MPI is set to equal the interpulse interval (IPI) of the pulse train (see figure 70), which is the same methodology used by Zhang et al (2013). To assess the degree of auditory-nerve adaptation it is possible to change the duration of the pulse train (thereby the number of pulses), which makes it possible to obtain eCAP measurements evoked by individual pulses in the train.

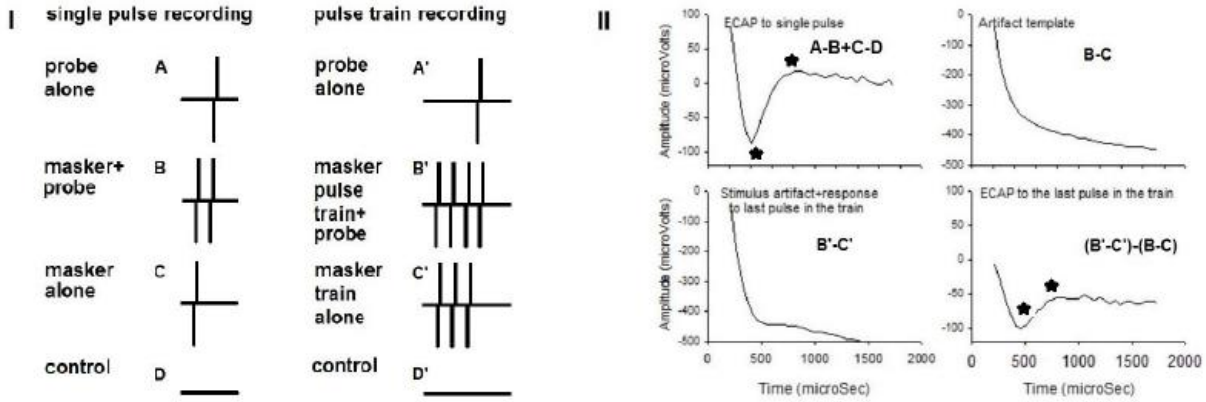

Figure 67: **(I)**The recording conditions used to obtain single pulse recordings (RRF) and pulse train recordings (Adaptation) and **(II)** How the eCAP to an individual pulse train would be derived

The NRT uses a forward masking method that consists of recordings under 4 stimulus frames to remove stimulus artefact, see figure 67. The probe alone (A), masker plus- probe (B), masker alone (C), and zero-amplitude pulse (D). From the single pulse recording, the eCAP response derived by using subtraction (A-B+C-D) was used as the response to the first pulse in the train when evaluating adaptation. Also the single pulse recording provides an artefact template that was derived by subtracting the recording frame for the masker alone condition from the recording frame for the masker-plus-probe condition (B-C). In the pulse train recording, the last pulse in the train was treated as the probe and the preceding pulses were treated as the masker pulse train. After the data were collected, the recording from the masker pulse train-alone condition was subtracted from the masker pulse train-plus probe condition (B'-C') to derive an ECAP to the last pulse in the train along with the stimulus artifact (B'-C'). Then the artifact template from single pulse recording was subtracted from to obtain the eCAP to the last pulse in the train [(B'-C') -(BC)], Zhang et al (2013).

Chapter 8: Conclusion

This work contributes to a small, but growing body of evidence on temporal processing abilities in CI users. Specifically, how individual differences in temporal processing and variations in neural health among CI users contributes to speech recognition. The results of this study demonstrate that the extent to which CI users are able to resolve gaps strongly predicts speech performance. The eCAP recovery function was not predictive of speech performance but the RGDT thresholds were in the same individuals across presentation levels. Individuals with post-lingual deafness and higher stimulation rates demonstrated shorter RGDT thresholds and better speech recognition scores, even when stimulation rates no higher than 900 pps/ch were used, which suggests in our small sample, the post-lingual group may have been able to reach partial stochastic independence which may explain some of the individual differences in performance. Furthermore, given the strong predictive power of RGDT thresholds its use more routinely in clinical practice should be considered. This study also demonstrated that the eCAP recovery function can be measured reliably and successfully in CI users without the need of any additional testing equipment in a routine clinical setting and was quick to administer.

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Appendix A:

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Sharmila Patel
St George's University Hospitals NHS Trust
Blackshaw Road
London
SW17 0QT

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

10 August 2018

Dear Miss Patel

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**The association between the temporal properties of the auditory nerve and its effects on auditory temporal processing and speech perception abilities in cochlear implant users**
IRAS project ID:	**244347**
Protocol number:	**n/a**
REC reference:	**18/LO/1241**
Sponsor	**University of Southampton**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Dr Ferdousi Chowdhury

Tel: 02380 595058

Email: rgoinfo@soton.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **244347**. Please quote this on all correspondence.

IRAS project ID	244347

Yours sincerely

Aliki Sifostratoudaki

Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Ferdousi Chowdhury, University of Southampton, Sponsor contact*
Dr Deborah McCartney, St George's University Hospitals NHS Foundation Trust, R&D Contact

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [Site Agreement]	1.0	01 June 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Certificate]		26 March 2018
GP/consultant information sheets or letters [GP Study Notification Letter]	1.0	01 February 2018
HRA Schedule of Events [244347_SOE_Research sites_Assessed by HRA.docx]	1	19 July 2018
HRA Statement of Activities [244347_SOA_Research sites_Assessed by HRA]	1	19 July 2018
IRAS Application Form [IRAS_Form_25062018]		25 June 2018
Letters of invitation to participant [Participant Invitation Letter]	1.0	29 June 2018
Participant consent form [Participant Consent Form]	1.0	01 February 2018
Participant information sheet (PIS) [Participant Information Sheet]	2	09 August 2018
Research protocol or project proposal [Research Proposal]	1.0	22 June 2018
Summary CV for Chief Investigator (CI) [CV]	1.0	22 June 2018
Summary CV for supervisor (student research) [Summary CV Supervisor]		

IRAS project ID	244347

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	For the purpose of HRA assessment revisions were necessary to the participant information sheet and consent form in order to bring them in line with HRA standards.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The Sponsor contact has confirmed that the model non-commercial agreement will be used with sites. The Sponsor has also provided a completed Statement of Activities and the Schedule of Events for information only.
4.2	Insurance/indemnity arrangements assessed	Yes	No comments
4.3	Financial arrangements assessed	Yes	This study is not receiving external funding.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	The Applicant confirmed that no personal identifiable information will leave the sites.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments

Section	Assessment Criteria	Compliant with Standards	Comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There is one site type in this study – research sites. Research sites will be responsible for all activity as listed in the Protocol. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator (PI) would be expected at this site type. The PI has been identified as the Chief Investigator. A Local Collaborator (LC) would not be expected at this site type as the CI is already employed by the Trust.

GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.