Investigating the effect of Focused Multipolar Stimulation for Cochlear Implants: Preclinical Studies

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Abstract

Multichannel cochlear implants have been well accepted as an effective and safe treatment for severe to profound sensorineural hearing loss through electrical stimulation of residual spiral ganglion neurons. However, speech intelligibility with existing cochlear implants is thought to be limited by poor spatial selectivity and interactions between channels caused by overlapping activation with contemporary stimulation strategies such as monopolar (MP) stimulation. Focused intracochlear stimulation, resulting in an increase in the number of truly independent stimulating channels available for simultaneous activation, may enable better speech and pitch recognition and also improve temporal resolution.

Various current focusing stimulation strategies such as tripolar (TP) stimulation have been reported to produce sharper excitation patterns and reduced channel interactions compared to MP stimulation at the cost of higher stimulation current levels. Focused multipolar (FMP) stimulation is another such focusing technique; utilizing simultaneous stimulation of multiple channels to create focused electrical fields. FMP stimulation has been validated in a small group of cochlear implant recipients showing that focusing can be achieved, however this was at the expense of higher stimulation currents compared to MP stimulation.

There have been no previous attempts to systematically compare the efficacy of FMP stimulation against TP stimulation or to determine whether factors such as neural survival and the electrode position within the cochlea would affect the performance of FMP stimulation. Controlled preclinical studies in experimental animals can reduce the possible confounding effects of neural survival in human studies. It is also important to test if FMP produces non-auditory sensations since the simultaneous nature of the stimuli would be expected to require greater charge to evoke neural responses.

The primary objectives of this thesis were to determine the efficacy of FMP stimulation, compared to both MP and TP stimulation, by evaluating a) the spatial extent of neural activation b) interactions between cochlear implant channels and c) modulation sensitivity to sinusoidal amplitude-modulated pulse trains. The effects of factors such as degeneration of spiral ganglion neurons, induced by long-term deafness, and the electrode position within the cochlea on the effectiveness of FMP, TP and MP stimulation were also examined. These objectives were achieved by implanting a multichannel cochlear implant into cats and guinea pigs, and recording the neural responses in the inferior colliculus in acute electrophysiological
experiments. Neural thresholds and the spread of activation along the tonotopic gradient were measured.

In summary, the main results of this thesis showed that FMP and TP stimulation resulted in more restricted neural activation and reduced channel interaction compared to MP stimulation and these advantages were maintained in cochleae with significant neural degeneration. Moreover, these effects were not adversely affected by the position of the electrode array within the scala tympani. Although greater charge was required to achieve threshold levels, no evidence of ectopic stimulation of non-auditory neurons was observed with FMP or TP stimulation. Systematically varying the degree of current focusing lowered threshold levels for FMP stimulation while still maintaining a selectivity advantage. Modulation detection of MP was found to be significantly better than FMP and TP stimulation at low stimulation levels, but similar at high stimulation levels. Importantly, there was no benefit in terms of restricted neural activation, reduced channel interaction or better modulation sensitivity for FMP compared to TP stimulation. The greater spatial selectivity, reduced channel interactions and the ability to convey modulation using FMP and TP stimulation would be expected to result in improved clinical performance. The insights into current focusing described in this thesis may also be helpful in other neural prostheses such as deep brain stimulation devices and visual prostheses, when more selective stimulation is desired.
Declaration

This is to certify that

i. the thesis comprises only my original work towards the PhD except where indicated in the Preface,

ii. due acknowledgement has been made in the text to all other material used,

iii. the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices

_____________________________
Shefin S. George
Preface

Work on this thesis would not have been possible without the valuable assistance provided by the following individuals.

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Poster


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# Table of Contents

Abstract ................................................................................................................................. i
Declaration .............................................................................................................................. iii
Preface ...................................................................................................................................... v
Journal Publications ............................................................................................................... vii
Conference Presentations .................................................................................................... ix
Acknowledgements ................................................................................................................ x
List of Figures ........................................................................................................................ xvii
Abbreviations ........................................................................................................................ xxi

## Chapter 1: Literature Review: Investigating the effect of focused multipolar stimulation for cochlear implants: preclinical studies ................................................................. 1

1.1 Introduction ..................................................................................................................... 3
1.2 The Auditory System ...................................................................................................... 6
  1.2.1 Cochlear anatomy .................................................................................................. 6
  1.2.2 Cochlear physiology ........................................................................................... 8
  1.2.3 Central anatomy and physiology of the auditory system ..................................... 9
  1.2.4 Inferior Colliculi ................................................................................................. 10
  1.2.5 Cochleotopic organisation ................................................................................ 12
1.3 Sensorineural Hearing Loss ......................................................................................... 13
1.4 Cochlear Implants ......................................................................................................... 15
1.5 Factors predicting cochlear implant success ................................................................... 17
1.6 Current Focusing .......................................................................................................... 22
1.7 Focused Multipolar Stimulation .................................................................................... 26
1.8 Research objectives of the thesis ................................................................................... 29
  1.8.1 Hypotheses ......................................................................................................... 29
  1.8.2 Organisation of thesis ......................................................................................... 30

## Chapter 2: Materials and Methods .................................................................................... 33

2.1 Experimental animals .................................................................................................... 35
2.2 Deafening procedure ...................................................................................................... 36
2.3 Acute Experiment .......................................................................................................... 36
  2.3.1 Cat anaesthesia and surgery ............................................................................... 36
  2.3.2 Guinea pig anaesthesia and surgery .................................................................... 37
  2.3.3 Inferior colliculus neural recording .................................................................. 38
Chapter 3: Evaluation of focused multipolar stimulation for cochlear implants in acutely deafened cats ................................................................. 41
3.1 Abstract................................................................. 43
3.2 Introduction........................................................... 44
3.3 Methods................................................................. 48
  3.3.1 Animals............................................................ 48
  3.3.2 Anaesthesia and surgery......................................... 48
  3.3.3 Electrical stimuli .................................................. 49
  3.3.4 Neural recording................................................... 51
  3.3.5 Data analysis ....................................................... 52
  3.3.6 Statistical analysis ............................................... 56
3.4 Results................................................................. 56
  3.4.1 Response images................................................... 56
  3.4.2 Threshold and discrimination slope ......................... 57
  3.4.3 Spread of activation in the IC ............................... 58
  3.4.4 Total neural response growth in the IC ..................... 60
  3.4.5 Spread of activation for end channels .................... 61
3.5 Discussion............................................................. 62

Chapter 4: Evaluation of focused multipolar stimulation for cochlear implants in long-term deafened cats ......................................................... 69
4.1 Abstract................................................................. 71
4.2 Introduction........................................................... 72
4.3 Methods................................................................. 76
  4.3.1 Experimental animals............................................ 76
  4.3.2 Deafening procedure ............................................ 77
  4.3.3 Physiological data collection .................................. 77
  4.3.4 Data analysis ....................................................... 80
  4.3.5 Cochlear histology................................................ 83
  4.3.6 Statistical analysis ............................................... 84
4.4 Results................................................................. 84
  4.4.1 Hearing status and cochlear histology ....................... 84
  4.4.2 Response images................................................... 86
  4.4.3 Effect of SGN degeneration and electrode configuration on spatial selectivity .................................................. 87
  4.4.4 Effect of pulse duration on spatial selectivity ............. 89
4.4.5 Effect of pFMP stimulation on spatial selectivity ...........................................89
4.4.6 Effect of electrode location on spatial selectivity ...........................................91
4.4.7 Comparison between normal hearing animals and long-term deafened animals ........................................................................................................................92
4.5 Discussion .........................................................................................................94

Chapter 5: Electrophysiological channel interactions using focused multipolar stimulation for cochlear implants ................................................................. 101
5.1 Abstract ........................................................................................................... 103
5.2 Introduction ..................................................................................................... 104
5.3 Methods .......................................................................................................... 107
  5.3.1 Experimental animals .............................................................................. 107
  5.3.2 Surgery and electrode insertion .............................................................. 108
  5.3.3 Cochlear electrical stimulation ............................................................... 109
  5.3.4 Multichannel recording .......................................................................... 111
  5.3.5 Data analysis .......................................................................................... 112
  5.3.6 Statistical Analysis .................................................................................. 115
5.4 Results ............................................................................................................ 115
  5.4.1 IC response images ................................................................................ 116
  5.4.2 Threshold interaction index ................................................................... 118
  5.4.3 Threshold shift ........................................................................................ 121
5.5 Discussion ....................................................................................................... 125

Chapter 6: Effect of current focusing on the sensitivity of inferior colliculus neurons to amplitude modulated stimulation ......................................................... 133
6.1 Abstract ........................................................................................................... 135
6.2 Introduction ..................................................................................................... 136
6.3 Methods .......................................................................................................... 138
  6.3.1 Experimental Animals .......................................................................... 138
  6.3.2 Anaesthesia, Surgery and Recording Procedure ................................. 139
  6.3.3 Stimulus Generation and Data Acquisition ....................................... 140
  6.3.4 Data Analysis ......................................................................................... 142
  6.3.5 Statistical Analysis ................................................................................ 145
6.4 Results ............................................................................................................ 145
  6.4.1 Average Spike Rate ............................................................................... 146
  6.4.2 Cycle Histograms ................................................................................... 147
  6.4.3 Peak Spike Rate ..................................................................................... 149
  6.4.4 Vector Strength ...................................................................................... 149
6.4.5 Modulation Detection Threshold ............................................ 152
6.4.6 Temporal Jitter ........................................................................ 153
6.4.7 Effect of stimulation level on MDT .......................................... 153
6.4.8 Effect of stimulation site on MDT ............................................. 154
6.5 Discussion .................................................................................... 155

Chapter 7: General Discussion .......................................................... 161
7.1 Overview of results ...................................................................... 163
7.2 Clinical implications ...................................................................... 164
  7.2.1 Extending experimental results to human speech perception ..... 164
  7.2.2 Clinical implementation of the FMP technique ....................... 168
  7.2.3 Applications to other neural prosthesis .................................. 169
7.3 Future Considerations ................................................................. 170
  7.3.1 Investigating the efficacy and safety of FMP following chronic
       intracochlear electrical stimulation ............................................ 170
  7.3.2 Identifying “dead” regions using FMP stimulation .................. 171
7.4 Conclusions .................................................................................. 172

Cited Literature .................................................................................. 173
List of figures

Figure 1.1 Diagram illustrating the anatomy of cochlea and the organ of Corti........8

Figure 1.2 Diagram illustrating the major ascending auditory pathway extending from the auditory nerve to the auditory cortex.........................................................10

Figure 1.3 Sagittal and coronal views of the inferior colliculus .....................11

Figure 1.4 Coronal section of the inferior colliculus showing cochleotopic organisation.................................................................13

Figure 1.5 Illustration of a cochlear implant with major components labelled .......16

Figure 1.6 Schematic diagrams illustrating different electrode configurations used in cochlear implants .................................................................23

Figure 3.1 Schematic diagrams illustrating monopolar (MP), tripolar (TP) and focused multipolar (FMP) stimulation centred on electrode 8. The amplitude only represents the anodic phase of a biphasic pulse.................................47

Figure 3.2 Overview of multichannel neural recording along the cochleotopic axis of the inferior colliculus (IC). .................................................................53

Figure 3.3 Response images across the cochleotopic axis of the IC to acoustic and electrical stimulations. a) pure tone at 12 kHz and electrical stimulation using b) FMP c) TP and d) MP electrode configuration. ........................................57

Figure 3.4 Group means for IC electrical thresholds and discrimination slopes (mean + SEM) measured for MP, FMP and TP stimulation configurations in acutely deafened cats ........................................................................................................58

Figure 3.5 STC Widths (mean + SEM) measured across MP, FMP and TP stimulation configurations a) at 1dB above threshold and b) at cumulative $d' = 1$ above threshold.........................................................................................59

Figure 3.6 Example of number of recording sites activated versus stimulating current level function for MP (closed circles), FMP (open squares) and TP (closed triangles) stimulation on a single cochlear channel........................................60

Figure 3.7 Example of normalised total neural response across the recording array versus stimulus intensity (expressed relative to threshold) for MP (closed circles), FMP (open squares) and TP (closed triangles) stimulation ..................61

Figure 3.8 STC Widths (mean + SEM) measured for end channels across MP and FMP configurations at 1dB above threshold.................................................62

Figure 4.1 Schematic diagram of a cross-section through a cochlea illustrating the degenerative changes that occur following sensorineural hearing loss........75
Figure 4.2 Schematic diagram showing an overview of the HL-14 stimulating electrode array implanted into the deafened cochlea and multichannel recording array...

Figure 4.3 Photomicrograph of a mid-modiolar section through a long-term deafened cat cochlea...

Figure 4.4 Response images across the cochleotopic axis of the IC to electrical stimulation using (a) FMP (b) TP and (c) MP electrode configurations in a long-term deafened cat...

Figure 4.5 Group means for IC thresholds, discrimination slopes, STC widths and growth function of total spike activity (mean + SEM) measured for MP, FMP and TP stimulation configurations in long-term deafened cats...

Figure 4.6 Group means for IC thresholds and STC widths (mean + SEM) measured for FMP stimulation using phase duration of 100 μs and 400 μs in long-term deafened cats...

Figure 4.7 Representative response images across the cochleotopic axis of the IC for pFMP stimulation of cochlear channel 12 using DF.

Figure 4.8 Group means (mean + SEM) for (a) threshold (b) STC width (c) discrimination slope and (d) increase in total neural spike activity measured for FMP stimulation with varying defocusing factor (DF).

Figure 4.9 Group means for IC thresholds and STC widths (mean + SEM) measured for MP, FMP and TP stimulation with normal and reverse positioning of the electrode array in long-term deafened cats.

Figure 4.10 Group means (mean + SEM) for a) IC thresholds (nC), (b) STC widths (mm) (c) discrimination slope and (d) growth function of total spike activity measured for MP, FMP and TP stimulation in acutely deafened cochleae.

Figure 5.1 Overview of how threshold interaction index and threshold shifts were calculated for two-channel stimulation.

Figure 5.2 Response images across the cochleotopic axis of the IC to two-channel electrical and acoustic stimulation.

Figure 5.3 a, b) Threshold interaction index (mean ± SEM) across the IC recording array obtained for different stimulation configurations versus inter-electrode spacing between two channels.

Figure 5.4 Normalized spike rate versus stimulus intensity plots for the best recording site of S2.

Figure 5.5 a, b) Threshold shift (mean ± SE) for different stimulation configurations in acutely deafened and long-term deafened cats.
Figure 6.1 Electrical stimulus waveforms and IC neural responses.....................143

Figure 6.2 Overview of the calculation of modulation detection thresholds (MDTs).. ........................................................................................................................................145

Figure 6.3 Spike rate (mean ± SEM) in the 50 to 1050 ms window after the onset of the pulse train, plotted as a function of modulation depth for various stimulation configurations ........................................................................................................................................147

Figure 6.4 Modulation cycle histograms of spikes across five trials measured at the best recording site to electrical stimulation of a CI channel in FMP, TP and MP stimulation configurations ........................................................................................................................................148

Figure 6.5 Mean spike rate for the peak modulation phase plotted as a function of modulation depth for various stimulation configurations..........................149

Figure 6.6 Distribution of vector strengths across the best recording sites from all the animalss. ........................................................................................................................................151

Figure 6.7 Modulation transfer functions (i.e., MDT (mean ± SEM) versus modulation frequency (Hz)) at 2 dB above threshold ........................................................................................................................................152

Figure 6.8 Modulation transfer functions (i.e., MDT (mean ± SEM) versus modulation frequency (Hz)) at 4 dB above threshold. ........................................................................................................................................154

Figure 6.9 Distribution of MDTs as a function of CI channel for various stimulation configurations........................................................................................................................................155
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ABR</td>
<td>auditory brainstem responses</td>
</tr>
<tr>
<td>AC</td>
<td>auditory cortex</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>BP</td>
<td>bipolar</td>
</tr>
<tr>
<td>CF</td>
<td>characteristic frequency</td>
</tr>
<tr>
<td>CG</td>
<td>common ground</td>
</tr>
<tr>
<td>CI</td>
<td>cochlear implant</td>
</tr>
<tr>
<td>CN</td>
<td>cochlear nucleus</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DF</td>
<td>defocusing factor</td>
</tr>
<tr>
<td>Dil</td>
<td>1,1-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate</td>
</tr>
<tr>
<td>EABR</td>
<td>electrically evoked auditory brainstem responses</td>
</tr>
<tr>
<td>eCAP</td>
<td>electrically evoked compound action potential</td>
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<tr>
<td>FMP</td>
<td>focused multipolar</td>
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<tr>
<td>H&amp;E</td>
<td>haematoxylin and eosin</td>
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<tr>
<td>IC</td>
<td>inferior colliculus</td>
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<td>ICC</td>
<td>central nucleus of the inferior colliculus</td>
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<td>ICD</td>
<td>dorsal nucleus of the inferior colliculus</td>
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<td>ICX</td>
<td>external nucleus of the inferior colliculus</td>
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<tr>
<td>IHC</td>
<td>inner hair cell</td>
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<tr>
<td>i.m.</td>
<td>intramuscular</td>
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<tr>
<td>i.p.</td>
<td>intraperitoneal</td>
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<tr>
<td>LL</td>
<td>lateral lemniscus</td>
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<td>MDT</td>
<td>modulation detection threshold</td>
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<tr>
<td>MGB</td>
<td>medial geniculate body</td>
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<td>MP</td>
<td>monopolar</td>
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<td>NSR</td>
<td>normalised spike rate</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>OHC</td>
<td>outer hair cell</td>
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<tr>
<td>PBS</td>
<td>phosphate buffered saline</td>
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<tr>
<td>p.e.</td>
<td>peak equivalent</td>
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<td>PFA</td>
<td>paraformaldehyde</td>
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<td>pFMP</td>
<td>partial focused multipolar</td>
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<tr>
<td>pps</td>
<td>pulses per second</td>
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<tr>
<td>s.c.</td>
<td>subcutaneous</td>
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<td>SEM</td>
<td>standard error of the mean</td>
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<td>SGN</td>
<td>spiral ganglion neuron</td>
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<td>SNHL</td>
<td>sensorineural hearing loss</td>
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<tr>
<td>SOC</td>
<td>superior olivary complex</td>
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<tr>
<td>SPL</td>
<td>sound pressure level</td>
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<td>STC</td>
<td>spatial tuning curve</td>
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<td>TP</td>
<td>tripolar</td>
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Chapter 1: Literature Review:
Investigating the effect of focused multipolar stimulation for cochlear implants: preclinical studies
1.1 Introduction

According to the World Health Organisation, over 360 million people worldwide suffer from disabling hearing loss. As a result of hearing impairment, adults have difficulty communicating and interacting with others affecting their social interaction and personal well-being (Dalton et al., 2003, Ciorba et al., 2012, Benova et al., 2015). Children experience delayed development of speech, language and cognitive skills that can adversely affect their learning progress (Culbertson and Gilbert, 1986, Hogan et al., 2011).

The damage to the auditory sensory epithelium in the inner ear causes sensorineural hearing loss, with widespread loss resulting in a permanent severe-to-profound hearing loss. The only therapeutic intervention for these patients is the use of a cochlear implant, a surgically implanted device designed to bypass the damaged or lost sensory receptors and electrically stimulate surviving auditory neurons in order to provide cues necessary for speech perception (Clark et al., 1984). Implant in approximately 324,000 individuals worldwide (FDA, 2012), the cochlear implant has been successful in restoring varying degrees of hearing to a significant number of deaf patients.

Speech and language outcomes with cochlear implants have improved remarkably in recent decades as a result of advances in implant technology and changes in the candidacy criteria (for review, see Waltzman and Roland (2014)). Considerable numbers of implant users are now able to obtain high levels of speech comprehension in favourable quiet listening conditions and can engage in conversational speech without visual cues, including speaking and listening on the telephone (Skinner et al., 1994, Bassim et al., 2005, Galvin et al., 2007, Moberly et al., 2016).

However, there is a large variability in performance across implant recipients (Blamey et al., 2013). Many implant users still poorly perceive speech in noise,
musical sounds and tonal languages (Fu et al., 1998, Barry et al., 2002, Leal et al., 2003, McDermott, 2004, Shannon et al., 2004, Gfeller et al., 2007). One factor affecting clinical outcomes is thought to be the efficacy of electrical stimulation in activating auditory nerve, which can be affected by the auditory nerve survival (Shepherd and Javel, 1997, Pfingst et al., 2015), location of the electrode in the cochlea (Shepherd et al., 1993, Holden et al., 2013) and the spread of neural activation associated with electrical stimulation (Black and Clark, 1980, van den Honert and Stypulkowski, 1987).

The highly conducting fluids and tissues of the cochlea lead to a very broad neural excitation using contemporary stimulation configurations such as monopolar (MP) stimulation (Bierer and Middlebrooks, 2002, Snyder et al., 2004). With MP stimulation, charge is applied to an active electrode within the cochlea with reference to an extracochlear return electrode. Additionally, the broad spread of current can cause interactions between channels during simultaneous MP stimulation (Shannon, 1983, Black et al., 1983b, Fu and Nogaki, 2005), often resulting in undesirable perceptual effects such as pain. Even though simultaneous channel interaction is reduced by using signal processing strategies based on sequential stimulation (McDermott, 1989, Wilson et al., 1991), interactions due to activation of overlapping neural populations are not eliminated. Moreover, the fine temporal patterns within channels are corrupted.

The focusing of current within the cochlea, resulting in an increase in the number of independent stimulating channels, is expected to improve the spectral and temporal information of speech transmitted by the implant, which in turn may enhance speech perception in background noise (Dorman et al., 1998, Fu et al., 1998, Friesen et al., 2001). Current focusing has the potential to evoke independent simultaneous channels of neural excitation at multiple sites along the auditory nerve that may convey more information within channels and preserve across-channel cues to improve pitch perception (Smith et al., 2002, Oxenham et al., 2004).
Psychophysical and physiological studies examining the spread of excitation in response to electrical stimulation have shown that tripolar (TP; see Section 1.6 for more details) stimulation produces a more focused spread of activation and reduces channel interactions compared to MP stimulation (Jolly et al., 1996, Miyoshi et al., 1999, Bierer and Middlebrooks, 2002, Snyder et al., 2004, Bierer and Middlebrooks, 2004, Snyder et al., 2008, Srinivasan et al., 2010). However, TP stimulation requires higher current levels and/or long phase durations to achieve adequate loudness in implant users compared to MP stimulation (Litvak et al., 2007a, Berenstein et al., 2008, Landsberger and Srinivasan, 2009).

Focused multipolar (FMP) stimulation (also referred to as phased array stimulation) is a current focusing technique, which operates by stimulating multiple electrodes simultaneously to create a sharpened electrical field. The method operates by stimulating multiple electrodes in a coordinated fashion with weighted positive and negative currents causing a superposition of current vectors (van den Honert and Kelsall, 2007) to attenuate the voltage around the intended area, predicting a more precise neural activation than TP stimulation. A few clinical studies in small groups of implant recipients have validated FMP stimulation showing that focusing can be achieved at the expense of higher stimulation currents compared to MP stimulation (van den Honert and Kelsall, 2007, Smith et al., 2013, Marozeau et al., 2015). However, there has been no previous direct comparison of FMP, TP and MP stimulation both in preclinical models and clinically. Moreover, little is known about the effect of factors such as neural survival and the electrode position within the cochlea on the performance of FMP stimulation.

Therefore, this thesis aims to investigate the efficacy of FMP stimulation, compared to both MP and TP stimulation, in an animal model by evaluating a) the spatial extent of neural activation; b) interactions between cochlear implant channels; and c) modulation sensitivity to sinusoidal amplitude-modulated pulse trains. The effects of factors such as degeneration of auditory neurons, induced by long-term deafness, and the electrode position within the cochlea on the effectiveness of FMP
stimulation are also examined. The efficacy of a stimulation mode that is referred to here as partial-FMP (pFMP) stimulation, to achieve lower stimulation thresholds compared to the standard FMP stimulation, is also explored. The remaining sections of this chapter will give a comprehensive overview of previous research leading to the research questions presented, and outline the potential clinical benefits of the research.

1.2 The Auditory System

The human sense of hearing is attributed to the auditory pathway that can be subdivided into two large subsystems, peripheral and central. The auditory periphery, comprising the outer ear (pinna and external auditory meatus), middle ear (tympanic membrane and ossicles) and inner ear (cochlea), is responsible for the collection and amplification of acoustic energy and transformation of these air-borne vibrations into neural impulses (Pickles, 1988). These neural codes are processed and interpreted by the central auditory pathway, which is composed of several complex sub-pathways and nuclei including the cochlear nuclei, the superior olivary complexes, the nuclei of the lateral lemniscus, the inferior colliculi, the medial geniculate bodies of the thalamus, and the auditory cortices (Ehret and Romand, 1997). This thesis will mainly focus on the cochleae and the inferior colliculi, which will be discussed in more detail in this chapter.

1.2.1 Cochlear anatomy

The human cochlea coils for about two and a half turns around a bony pillar called the modiolus and has the osseous spiral lamina as its structural base. It is about 10 mm wide with an uncoiled length of about 35 mm from base to apex (Maroonroge et al., 2009). Within the spiraled three-chambered cochlea, the endolymph-filled scala media (cochlear duct) separates the two perilymph-filled chambers: scala vestibuli and scala tympani (figure 1.1). The unique ionic composition of perilymph
and endolymph creates an electrochemical gradient between the cochlear compartments, which is essential for auditory transduction (Pickles, 1988, Wangemann, 2006, Johnstone and Sellick, 1972). The oval window is situated at the base of scala vestibuli and the round window is located at the base of scala tympani. Scala media is separated from the scala vestibuli by a relatively thin membrane called Reissner’s membrane or vestibular membrane (figure 1.1). The membrane that separates scala media and scala tympani is termed the basilar membrane.

The basilar membrane carries the specialised structure called the organ of Corti - the receptor organ of hearing. The organ of Corti is made up of sensory cells called the hair cells and several types of supporting cells (figure 1.1). The two types of hair cells – the inner hair cells (IHC) and the outer hair cells (OHC) – are arranged functionally in a series of longitudinal rows. In humans, there are approximately 16,000 hair cells within a cochlea (Ulehlova et al., 1987) with one row of IHC proximal to the modiolus, and three to five rows of OHC towards the lateral wall of the cochlea. The hair-like stereocilia at the tip of the hair cells are overlaid by a gelatinous structure called the tectorial membrane. The basal surfaces of the hair cells are innervated by the primary afferent, or spiral ganglion neurons (SGNs) all along the length of the basilar membrane (Zemlin, 1968).

The human organ of Corti is innervated by approximately 30,000 afferent or sensory neurons (Nadol, 1997, Harrison and Howe, 1974). The peripheral processes project through perforations in the osseous spiral lamina called habenula perforata and travel through the central part of the modiolus called Rosenthal’s canal to form the spiral ganglion (figure 1.1). About 90-95% of the SGNs, referred to as Type I cells project into the cochlear duct radially to the axis of the modiolus forming the radial bundle and innervate the nearest IHC (Spoendlin, 1972, Brown, 1987). Each IHC is innervated by approximately 10-30 Type I SGNs (Liberman et al., 1990). These nerve cells are myelinated (except their peripheral endings) bipolar neurons containing a large round nucleus. The remaining 5-10% of the SGNs course in an oblique fashion,
along the base of the organ of Corti, forming the outer spiral bundle, before synapsing with up to 10 OHCs (Spoendlin 1969).

![Diagram illustrating the anatomy of cochlea and the organ of Corti. The neural elements are highlighted in yellow and sensory hair cells are shown in purple. Modified from Marieb and Hoehn (2007).](image)

**Figure 1.1** Diagram illustrating the anatomy of cochlea and the organ of Corti. The neural elements are highlighted in yellow and sensory hair cells are shown in purple. Modified from Marieb and Hoehn (2007).

### 1.2.2 Cochlear physiology

The cochlea, acting as the mechanical frequency analyser, is responsible for exceptional sound analysis (Purves D, 2001). The cochlea specifically converts the mechanical vibrations of sound to neural impulses, which are transmitted to the parts of the brain involved in processing sound. The air-borne vibrations from the sound waves are transformed by the middle ear to generate a travelling wave in the fluid-filled cochlea via the oval window. The wave propagates from the basal to apical scala vestibuli and by doing so displaces the basilar membrane.

The basilar membrane is wider, thicker and more flexible at the apex and narrower, thinner and stiffer at the base. This variation in width, thickness and stiffness along its length restricts the entire basilar membrane from vibrating simultaneously to acoustic input (von Békésy and Wever, 1960). Instead, specific areas along the basilar membrane resonate in response to specific frequencies of sound. Lower frequencies
vibrate the basilar membrane maximally closer to the apex of the cochlea while higher frequencies produce maximum vibrations closer to the base (von Békésy and Wever, 1960, Rhode, 1971, Evans and Wilson, 1975, Khanna, 1982). The general mechanism of a spatial representation of frequency (referred to as tonotopic organisation), which first manifests in the displacement of the basilar membrane, is preserved throughout the entire auditory system. This topic will be revisited in §1.2.5.

Basilar membrane vibration causes a shearing motion of the tectorial membrane and differential displacement of stereocilia. This opens up mechanically sensitive ion channels in the hair cell membrane, leading to graded depolarization of the hair cell (Palmer and Russell, 1986). This subsequently opens calcium channels at the basal surface of the hair cell leading to the release of the excitatory neurotransmitter glutamate, initiating an action potential in the peripheral processes of the SGNs (Johnstone and Sellick, 1972), which carry auditory signals from the organ of Corti to the central nervous system.

1.2.3 Central anatomy and physiology of the auditory system

The ascending auditory pathway from the cochlea to the auditory cortex is illustrated in figure 1.2. The central axonal process originating from the cell body of SGNs form the auditory nerve before exiting the cochlea to join with the vestibular branch to form the vestibulocochlear nerve or the eighth cranial nerve. The axons of the auditory nerve enter the brainstem at the level of the lower pons and terminate in synapses with neurons in the ipsilateral cochlear nucleus (CN), the first relay in the central auditory pathway. Most central projections from neurons in the CN course upward to the contralateral superior olivary complex (SOC) or run directly to the contralateral inferior colliculus (IC), while the remaining neurons travel to the ipsilateral SOC. Each SOC sends projections to their ipsilateral inferior colliculus (IC) (Minifie, 1973). Fibres that project to the IC - originating from both CN and SOC - run
in a bundle known as lateral lemniscus (LL), consisting of both ipsilateral and the dominant contralateral projections associated with these pathways.

**Figure 1.2** Diagram illustrating the major ascending auditory pathway extending from the auditory nerve to the auditory cortex. Reprinted from Kandel et al. (2000).

### 1.2.4 Inferior Colliculi

The IC is an obligatory relay nucleus receiving afferent inputs from nearly all the lower auditory nuclei such as the CN, the SOC and the LL (Beyerl, 1978, Moore, 1988,
Kudo, 1981, Shneiderman et al., 1988, Schofield and Cant, 1992, Aitkin et al., 1986, Stotler, 1953, Aitkin and Phillips, 1984, Semple and Aitkin, 1979) and thus, forming the primary integrative centre processing and encoding cues for sound localisation and sound identification (Semple and Aitkin, 1979, Delgutte et al., 1999, Devore et al., 2009). At this level, some axons decussate to the opposite IC via the commissure of the IC. Based on differences in the neuronal connections and architecture, the IC can be subdivided into three major sub-nuclei or subdivisions – the central nucleus (ICC), which forms the body of the IC, bordered dorsomedially by the dorsal nucleus (ICD) and surrounded laterally and rostrally by the external nucleus (ICX) (figure 1.3; Oliver and Morest, 1984, Malmierca et al., 1993, Faye-Lund and Osen, 1985, Stotler, 1953). The ICC is well-structured with neurons arranged in a laminar fashion (Oliver and Morest, 1984, Rockel and Jones, 1973, Morest and Oliver, 1984, Malmierca et al., 1995) reflecting a cochleotopic organisation (Merzenich and Reid, 1974, Rose et al., 1963, Syka et al., 2000). The lamination of the ICC is achieved by the parallel arrangement of the disk-shaped dendrites of the principal cells along with the axons of the LL and the multipolar cells (Rockel and Jones, 1973, Stotler, 1953).

![Figure 1.3 Sagittal and coronal views of the inferior colliculus. Modified from Oliver and Morest (1984).](image)

The ascending axons originating in the IC synapse in the auditory thalamus, mainly the medial geniculate body (MGB) (Aitkin and Phillips 1984). The ventral division of MGB receives input from the ipsilateral ICC and projects mainly to the ipsilateral
primary auditory cortex (Brodmann areas 41 and 42) while the medial and dorsal divisions receive input from multiple sites (including the ICD) and project to secondary auditory cortical areas. The human auditory cortex (AC) is situated at the upper surface of the temporal lobe embedded deep within the transverse temporal gyrus (Heschl’s gyrus) and the superior temporal gyrus. It is arranged into several columns of cells and subdivided into multiple areas, including primary auditory cortex surrounded by several secondary auditory areas. The AC plays an important role in sound localization, short-term auditory memory and speech analysis even though very little is known about its detailed role in speech perception and production.

1.2.5 Cochleotopic organisation

The synapsing of each SGN (Type I) to a single IHC reflect the existence of a cochleotopic organisation at the lowest level of ascending auditory pathway. Type I SGNs that innervate the IHCs at the apical region are maximally sensitive to low frequencies and those innervating the IHCs at more basal turns are sensitive to higher frequencies. This cochleotopicity is preserved throughout the ascending auditory pathway via connections between the organ of Corti and nuclei of higher auditory structures (Bourk et al., 1981, Moore, 1987). The spatial arrangement of neuronal cells at each level of the ascending auditory system makes them preferentially responsive to certain frequencies. Each neuron within the ascending auditory pathway is most sensitive to a specific or characteristic frequency (CF).

The ICC forms the basis for a systematic representation of the cochlea from apex to base along its dorsolateral to ventromedial axis (Rose et al., 1963, Merzenich and Reid, 1974, Aitkin et al., 1975, Malmierca et al., 1995) while ICX and ICD exhibit a broad and complex pattern of frequency organisation (Aitkin et al., 1986, Rose et al., 1963). The dorsolateral ICC is innervated mostly with fibres originating from lateral SOC representing low frequencies while the ventromedial ICC is radiated with fibres
from ventromedial SOC containing neurons with high CF (figure 1.4; Aitkin et al., 1986, Semple and Aitkin, 1979).

![Figure 1.4](image)

Figure 1.4 Coronal section of the inferior colliculus showing cochleotopic organisation along its dorsolateral-ventromedial axis. Modified from Oliver and Morest (1984).

The tonotopic organization of the cochlea is also represented in other auditory structures, including the CN (Rose et al., 1959, Sando, 1965, No and Lorente, 1933, Evans and Nelson, 1973, Sato et al., 1992), the SOC (Aitkin et al., 1970), the LL (Brugge and Geisler, 1978, Merchan and Berbel, 1996), the MGB (Moore and Goldberg, 1963, Oliver, 1984, Moore, 2000) and the primary auditory cortex (Rajan et al., 1990, Merzenich et al., 1975, Knight, 1977, Kudo and Niimi, 1980).

### 1.3 Sensorineural Hearing Loss

Damage to, or abnormality of, any structure in the auditory pathway can lead to a hearing impairment or hearing loss. Sensorineural hearing loss (SNHL) is the most common form of hearing loss and typically occurs following damage to, or complete destruction of, the delicate cochlear sensory hair cells or auditory nerve fibres. Damage or death of sensory hair cells can be caused by a variety of insults, including but not limited to chronic or acute exposure to excessive noise, ototoxic drugs, viral or bacterial infections, genetic defects and aging. Humans and other mammals lack the ability to spontaneously regenerate the sensory hair cells (Feghali et al., 1998,
Edge and Chen, 2008) and therefore damage to hair cells is permanent and typically gets progressively worse over time.

Following SNHL, the organ of Corti including the supporting structures undergo severe or total degeneration (Hinojosa and Marion, 1983). The alteration in the organ of Corti and lack of normal stimulation provided by the sensory hair cells leads to a number of degenerative and pathological changes to the peripheral processes and the SGNs that previously innervated the sensory hair cells (Spoendlin, 1984). This degeneration progresses over time and is characterised by swelling and demyelination of the peripheral processes followed by their retraction from the organ of Corti towards the SGN soma, and a more gradual shrinkage, demyelination and death of the cell bodies within Rosenthal’s canal (Nadol et al., 1989, Leake and Hradek, 1988, Hardie and Shepherd, 1999, Versnel et al., 2007).

SGN degeneration has been associated with disrupted neurotrophic support, a key for the development and survival of SGNs, from the sensory hair cells and the supporting cells (Ernfors et al., 1995, Gillespie and Shepherd, 2005, Zilberstein et al., 2012). Recent studies, however, have shown that SGN degeneration and neuronal death can occur even when the sensory hair cells are intact (Lin et al., 2011, Gannouni et al., 2015), suggesting that injury to SGNs can occur directly and there may be other factors that have an effect on the extent of SGN loss. Human temporal bone studies have shown a high degree of variability in the extent of degeneration of peripheral processes and SGNs associated with SNHL, and is attributed to a number of factors such as etiology, duration of deafness and age (Hinojosa and Marion, 1983, Nadol, 1997, Fayad and Linthicum, 2006). Long-term deprivation or lack of sensory activation at the auditory periphery can also affect the structure and function of the auditory system leading to extensive atrophic changes in the ascending auditory pathway (Kitzes and Semple, 1985, Kazee et al., 1995, Saada et al., 1996, Syka, 2002, Kral and Sharma, 2012, Lammers et al., 2015, Fallon et al., 2009).
When only some of the sensory hair cells are damaged, the SNHL is classified as mild to moderate. In these cases, a middle ear implant capable of vibrating the mobile structures of the inner ear or a conventional hearing aid may be a viable solution. When a large portion of the sensory hair cells are completely damaged/missing, severing the connections between the peripheral and central auditory systems, the person suffers from severe to profound hearing loss. Individuals with this condition gain little benefit from amplification; the only therapeutic intervention is the use of a cochlear implant that bypasses the damaged sensory hair cells to directly electrically stimulate the surviving SGNs.

1.4 Cochlear Implants

A cochlear implant (CI) is a neural prosthesis designed to directly electrically stimulate the surviving SGNs with current pulses and convey the pitch and temporal cues necessary for speech perception to the brain (Clark, 2003). Over the last five decades, CI devices have evolved; beginning with the attempts to electrically stimulate the auditory nerve to elicit hearing sensation (Gisselson, 1950, Djourno et al., 1957) to commercially viable multi-channel prostheses with sophisticated speech processing strategies (Simmons, 1966, Bilger et al., 1977, Clark et al., 1984, House, 1993, Niparko and Wilson, 2000, Mudry and Mills, 2013).

A typical modern CI system (figure 1.5) consists of an external component, which captures and processes sound signals and transmits the processed information to an implanted component via radio frequency link. Sound enters the microphone and travels to a sound processor where it is processed and divided into discrete frequency bands using a filter bank. The energy corresponding to each frequency band is then converted into a digital code specifying both the pattern of electrical stimuli and the electrode along the cochlea to be stimulated. The receiver/stimulator, which is fully implanted behind the ear, receives the stimulus parameters and conveys it to an array of electrode contacts on a silicon carrier
positioned within the scala tympani of the cochlea (i.e., intracochlear), locating individual electrodes at distinct sites along the length of the cochlea. The spatial location of the electric stimulus is designed to mimic the location-specific patterns of SGN excitation with varying acoustic frequency, and the stimulus charge encodes the loudness or acoustic intensity (Clark et al., 1978, Tong et al., 1982, Tong and Clark, 1985, McDermott et al., 1992, Townshend et al., 1987).

**Figure 1.5** Illustration of a cochlear implant with major components labelled. The external speech processor transmits speech information to an implanted stimulator, which sends current pulses to the electrodes placed within the scala tympani and stimulate surviving auditory neurons to convey speech information to the brain. Adapted from the Mayo Foundation for Medical Education and Research.

Charge balanced cathodic-first biphasic pulses (20-400 μsec/phase) instead of monophasic pulses are normally used as the stimulus waveform to avoid the risk of damage to the tissue (Loeb et al., 1982). Pulses are delivered at a rate of around 100 to 1000 pulses per second (pps) per electrode. These pulse trains are amplitude modulated based on the envelope energy of each frequency band, thereby conveying the temporal envelope information in the speech spectrum. In contemporary CIs, the electrodes are stimulated typically in a monopolar (MP) configuration, where the stimuli are presented to single intracochlear electrodes with reference to a remote extracochlear electrode usually placed under the
temporalis muscle or located on the case of the receiver-stimulator package. Substantially less stimulation levels and battery power are required to produce auditory percepts with MP stimulation (Pfingst et al., 2004).

1.5 Factors predicting cochlear implant success

A number of factors determine the success of a CI user in identifying and discriminating speech signals. Development of new and improved electrode array designs and more sophisticated speech processing strategies have considerably improved language and speech outcomes, with best performing subjects achieving near normal speech perception, at least in favourable listening conditions (for review, see Wilson and Dorman, 2008, Clark, 2013, Waltzman and Roland, 2014). Despite that, one of the most regular findings reported in the literature on CIs is the considerable variability in clinical performance of CI recipients, both in adults and children (Sarant et al., 2001, Gifford et al., 2008, Lazard et al., 2012, Moberly et al., 2016). Several recipient-dependent factors that predict success, including etiology, duration of hearing loss, age at onset of deafness and implantation, residual speech recognition, prelingual/postlingual status and rehabilitation services, have been identified (Gantz et al., 1993, Blamey et al., 1996, Rubinstein et al., 1999, Tyler et al., 2000, Svirsky et al., 2004, Holden et al., 2013, Blamey et al., 2013). The substantial variability in the functional integrity and structure of the cochlea and the auditory nerve across patients is expected to contribute to the considerable variability observed in patient outcomes. The effectiveness of SGN stimulation with intracochlear electrodes is thought to be constrained by two major factors that are intrinsic to the design of CIs: a) electrode-to-neuron interface, which is determined by the pattern of SGN survival along the length of the cochlea, the viability of stimulating those SGNs and peripheral processes, the proximity of the electrodes to the target neural structure, and bone and tissue growth within the scala tympani, and b) spread of neural activation associated with electrical stimulation.
SGNs are the target neural elements of a CI (Clopton et al., 1980, Linthicum et al., 1991). An ideal situation of excellent survival of SGNs along the length of the cochlea may support a good pitch representation via the use of multiple electrodes. However, following SNHL, a severe loss of sensory epithelia within the cochlea leads to secondary degeneration of SGNs and peripheral fibres, which gradually progresses over years in humans (see Section 1.3 for more details). The viability or status of the surviving SGNs and their physiological responsiveness to electrical stimulation is important for the effectiveness of an implant (Moxon, 1971, van den Honert and Stypulkowski, 1984, Coco et al., 2007, Pfingst et al., 2015).

The surviving SGNs remain capable of being depolarised and initiate the generation and propagation of action potentials via direct electrical stimulation using a CI. The general features of responses observed for SGNs in deafened cochleae, such as a monotonic increase in the discharge rate and reduction in the response latency and temporal jitter as a function of stimulus current, have been found to be similar to those recorded in normal cochleae (Shepherd et al., 2004). Nevertheless, a number of important functional changes in the response as a consequence of pathological changes in SGNs have been identified in studies in deafened animals. The demyelination and degeneration of the peripheral processes and the SGNs proximal to the stimulating electrode result in increased electrical thresholds i.e., the stimulus current level required to evoke the auditory system (Shepherd and Javel, 1997, Javel and Shepherd, 2000, Landry et al., 2011). An increase in threshold may lead to higher power consumption and result in a greater spread of activation as excitation current spreads within Rosenthal’s canal potentially exciting a spatially broad region of SGNs (Frijns et al., 1996, George et al., 2015a). Other characteristics of SGN responses identified in deafened cochleae include a significant increase in absolute refractory periods, reduction in response latencies and temporal jitter, and a reduction in the amplitude of electrically evoked compound action potentials (eCAP) and electrically evoked brainstem responses (EABR) (van den Honert and Stypulkowski, 1984, Shepherd and Javel, 1997, Shepherd et al., 2004, Ramekers et al., 2014).
A growing number of electrophysiological and clinical studies have examined the variability in performance with electrode arrays located in different anatomical locations e.g. scala tympani versus scala vestibule, medio-lateral position (i.e., position relative to the modiolar wall) and the depth of insertion. Various imaging techniques including conventional computed tomography (CT) (Harnsberger et al., 1987), multissection CT (Verbist et al., 2005), micro-CT (Postnov et al., 2006), cone-beam CT (Saeed et al., 2014), flat-detector CT (Struffert et al., 2010), spiral CT (Wang et al., 1998), rotational tomography (Aschendorff et al., 2007) and video-fluoroscopy (Roland et al., 2000) have been employed to determine the position of the electrode array within the cochlea. A major and consistent finding is that word recognition scores are generally lower when more electrodes are placed in the scala vestibuli compared to scala tympani (Skinner et al., 2007, Aschendorff et al., 2007, Finley et al., 2008, Holden et al., 2013), suggesting scala tympani as the favourable place to position the electrode array to achieve optimal outcomes while preserving intracochlear structures.

The past decade has seen the emergence of different peri-modiolar electrode designs aimed at placing the electrode contacts closer to the modiolus in an attempt to achieve lower thresholds and restrict current spread that may result in less channel interaction (Tykocinski et al., 2000, Parkinson et al., 2002, Richter et al., 2002, James et al., 2005). Detailed computational models (Frijns et al., 1995, Frijns et al., 1996), animal experiments (Shepherd et al., 1993, Xu et al., 1993) and human studies (Frijns et al., 2002, Saunders et al., 2002) have suggested beneficial influences of a medial position of the electrode array within the scala tympani. A closer apposition of the electrodes next to the inner wall of the scala tympani (i.e. adjacent to the modiolar wall) has been shown to reduce the psychophysical auditory thresholds, most comfortable loudness levels, eCAP thresholds and EABR thresholds in humans and animals, and increase dynamic range (Shepherd et al., 1993, Cords et al., 2000, Frijns et al., 2001, Donaldson et al., 2001, Saunders et al., 2002, Firszt et al., 2003, Long et al., 2014, Telmesani and Said, 2015). The peri-
modiolar electrode position has also been shown, in some cases, to produce an improvement in the spatial specificity of stimulation (Frijns et al., 2001, Cohen et al., 2003, Hughes and Abbas, 2006). Certain electrode designs show favourable influences on perception thresholds, spatial selectivity and dynamic range, mainly in the basal turn e.g., Clarion HiFocus (Wackym et al., 2004, Eisen and Franck, 2004) and Freedom Contour Advance (Telmesani and Said, 2015), while others show effects more apicalward e.g., Nucleus Contour (Cohen et al., 2001, Wackym et al., 2004). In human studies examining the medio-lateral position of the electrode array within the scala tympani, positioning closer to the modiolar wall has been related to better speech outcomes (van der Beek et al., 2005, Holden et al., 2013).

It has often been argued that a factor limiting performance after cochlear implantation is the widespread extent of the electric field within the cochlea when using MP stimulation. In principle, electrical stimulation of a single electrode site with a temporally modulated signal will excite a single cochlear place, giving rise to a unique pitch percept with the same temporal envelope as the electrical stimulus. In practice however, neural excitation via an electrode within the scala tympani is spatially broad due to the highly conductive fluid of the perilymph (Black and Clark, 1980, Black et al., 1981, Feigenbaum, 1987, van den Honert and Stypulkowski, 1987, Ifukube and White, 1987). The electrode configuration (i.e., the spatial arrangement of the electrodes) used to present the stimulus determines in part the shape and extent of the excitation pattern in the cochlea (Kral et al., 1998, van den Honert and Stypulkowski, 1984). As mentioned earlier, contemporary CI speech processors commonly use the MP electrode configuration. MP stimulation has been shown to produce very broad neural excitation patterns in the inferior colliculus and auditory cortex (Snyder et al., 2004, Bierer and Middlebrooks, 2002). This observation is not surprising; given that the active and return electrodes are widely separated resulting in broad electric fields.

Although a considerable number of CI users can engage in conversational speech in quiet conditions using MP stimulation (Skinner et al., 1994, Shannon et al., 1995,
Loizou et al., 1999), there is reduced performance when speech is presented in noise (Fu et al., 1998, Shannon et al., 2004). Many patients report difficulties discriminating speech in noise and poor perception of sounds such as music and tonal languages that are rich in temporal and spectral information (Skinner et al., 1994, Sucher and McDermott, 2007). The substantial overlap in current spread from adjacent channels may restrict most CI subjects from fully utilizing the spectral information provided by their implanta nd may cause increased sensitivity to noise (Fu and Nogaki, 2005, Dorman and Spahr, 2006). Present evidence suggests that even though there are up to 22 channels physically available in CI devices, no more than eight independent channels are available to convey useful speech information (Dorman et al., 1997, Fishman et al., 1997, Kiefer et al., 2000, Friesen et al., 2001, Garnham et al., 2002).

It has also been reported that simultaneous stimulation of multiple channels leads to channel interaction and spatial smearing (Boëx et al., 2003, Bierer and Middlebrooks, 2004, Stickney et al., 2006, Bierer, 2007, George et al., 2015b). Overlap of stimulating currents cause interactions between channels that can occur due to the summation of electric fields in the cochlea as well as overlapping neural excitation following stimulation (Shannon, 1983, Black et al., 1983b, Fu and Nogaki, 2005). Channel interaction is unpredictable, often resulting in undesirable perceptual effects (Hanekom and Shannon, 1998, Stickney et al., 2006).

In order to minimize channel interactions, traditional CIs use sequential stimulation where pulses delivered to each electrode are staggered such that only one channel is stimulated at any given instant (McDermott, 1989, Wilson et al., 1991). Even though simultaneous channel interaction is reduced by using signal processing strategies based on sequential stimulation, overlapping neural populations are still stimulated due to the broad current spread with MP stimulation. Moreover, the fine temporal patterns within channels are corrupted leading to poor temporal resolution. Thus, the loss of temporal and spectral information may limit the performance in noisy environments, appreciation of music and comprehension of tonal languages.
1.6 Current Focusing

During the past several years, increasing attention has been directed towards improving spatial selectivity by current focusing and increasing the number of distinct stimulation sites by current steering (Berenstein et al., 2008, Bonham and Litvak, 2008, van den Honert, 2010, Srinivasan et al., 2013, Smith et al., 2013). By adjusting currents applied simultaneously to multiple CI electrodes to control intracochlear electric fields, current focusing techniques may alleviate the issues associated with wide current spread and interaction between channels in the cochlea. It is widely anticipated that focused stimulation configurations that restrict the electric field in the cochlea may activate a more localised SGN population, and thus, provide better spectral perception than the traditional MP configuration.

Some anticipated improvements in implant performance using current focusing include: a) an increase in the number of independent channels of stimulation; b) minimise channel interactions and allow simultaneous stimulation of multiple channels to transmit fine temporal structure of sounds; and c) improve the amount of information conveyed within channels and preserve across-channel cues. An increase in the number of effective independent channels should improve the spectral information of speech transmitted by the implant, which in turn may enhance speech recognition in background noise (Dorman et al., 1998, Fu et al., 1998, Friesen et al., 2001). Preservation of fine temporal patterns and sufficient spatial resolution are important for pitch recognition and localization of sounds (Smith et al., 2002, Oxenham et al., 2004).

Several different electrode configurations have been proposed to achieve more focused stimulation than MP stimulation (figure 1.6): bipolar (BP), common ground (CG), tripolar (TP) and partial TP. With BP stimulation, stimuli are presented between two intracochlear electrodes and one or more inactive electrodes may separate the pair of electrodes. A CG configuration consists of a single intracochlear active electrode and a return that comprises of the remaining intracochlear electrodes. TP
stimulation delivers current pulses to a central active intracochlear electrode and uses two immediately adjacent intracochlear return electrodes. The partial TP configuration is a modification of TP stimulation where only a fraction of current from the centre active electrode is returned through two adjacent electrodes and the reminder through an extracochlear electrode.

*Figure 1.6* Schematic diagrams illustrating different electrode configurations used in cochlear implants. In a monopolar (MP) configuration, current flows between an intracochlear electrode and a remote large surface area electrode. In a bipolar (BP) configuration, current flows between two intracochlear electrodes. Common ground (CG) configuration consists of a single intracochlear active electrode and a return comprising the remaining intracochlear electrodes. In a tripolar (TP) configuration, the active electrode is a single intracochlear electrode, and the return consists of the two adjacent intracochlear electrodes. Adapted from Shepherd et al., (2013).

Studies using computational models of human and animal cochleae have demonstrated that TP stimulation can generate more spatially focused electric fields in the cochlea than BP and MP stimulation (Spelman et al., 1995, Frijns et al., 1996, Briaire and Frijns, 2000, Rattay et al., 2001, Frijns et al., 2011, Kalkman et al., 2015, Jolly et al., 1996, Kral et al., 1998, Litvak et al., 2007a, van den Honert and Kelsall, 2007). Electrophysiological research in animals examining the effects of current
focusing on the spread of neural excitation at different levels of the auditory pathway, such as the auditory nerve (van den Honert and Stypulkowski, 1987, Kral et al., 1998, Liang et al., 1999, Hartmann and Klinke, 1990), the IC (Snyder et al., 1990, Leake et al., 2000, Rebscher et al., 2001, Snyder et al., 2004, Snyder et al., 2008, Landry et al., 2013) and the auditory cortex (Raggio and Schreiner, 1999, Bierer and Middlebrooks, 2002, Middlebrooks and Bierer, 2002) are consistent with these predictions.

TP stimulation has been shown to produce a more spatially restricted neural activation pattern than BP stimulation, which in turn is more restricted than MP stimulation (see Bonham and Litvak (2008) for review). However, the charge required to achieve activation was the lowest for MP stimulation, while TP stimulation required the largest charge. Finer spatial selectivity with TP stimulation was also demonstrated by Bierer and Middlebrooks (2004) who examined interactions in the auditory cortex following two-channel stimulation. Channel interactions were greater with simultaneous MP stimulation than with BP stimulation, with the magnitude of threshold shifts with TP stimulation even smaller, indicating minimal current interaction. There have also been less direct measures of cochlear activity in humans and animals such as measurement of the auditory evoked potentials (Brown et al., 1996, Cohen et al., 2004, Miller et al., 2003); the findings of these studies indicating that MP evokes more widely distributed activity than BP stimulation.

Psychophysical studies of spatial and temporal interactions based on the human implant subjects’ estimates of loudness are consistent with the physiological findings (Shannon, 1983, White et al., 1984, Tong and Clark, 1986, McKay et al., 2001, Padilla and Landsberger, 2014). Loudness summation using MP summation was reported to be larger than for BP (McKay et al., 2001) or TP (Padilla and Landsberger, 2014) when low levels of stimulation were used. At higher levels, no significant difference was found between stimulation configurations. BP stimulation has also shown enhanced discrimination among channels stimulated sequentially (Busby et al., 1994). In
contrast to these, results of simultaneous and forward masking in humans have found mixed results in terms of spread of excitation by MP and BP stimulation. Most studies found that focused stimulation produces narrower spatiotemporal excitation patterns in human implant users (Chatterjee et al., 2006, Nelson et al., 2008, Bierer and Faulkner, 2010, Srinivasan et al., 2010, Shannon, 1983, Tong and Clark, 1986, Lim et al., 1989, Favre and Pelizzone, 1993, de Balthasar et al., 2003, Boëx et al., 2003, Bierer, 2007). Other studies showed little difference in the forward masking patterns created by MP and BP stimulation configurations (Cohen et al., 2001, Kwon and van den Honert, 2006), implying that the spatial extent of a BP current field is not consistently narrower than that of an equally loud MP stimulus.

Speech recognition performance of CI subjects has not been clearly and consistently correlated to spatial selectivity. Studies of speech perception have generally shown that patients perform at least as well with MP stimulation as with BP stimulation (Zwolan et al., 1996, Pfingst et al., 2001, Pfingst et al., 1997, Fu and Shannon, 1999) and most CI users can pitch-rank MP channels (Boëx et al., 2006). Speech perception is correlated with sensitivity to amplitude modulated pulse trains (Colletti and Shannon, 2005, Fu, 2002). Interestingly, Middlebrooks (2008a) has shown that BP stimulation has an elevated modulation detection threshold compared with MP stimulation, suggesting a possible reason for the lack of benefit of BP stimulation on speech perception. Nonetheless, it is important to recognize that channel interaction can affect the performance of CI subjects, especially in the presence of noise (Friesen et al., 2001, Fu and Nogaki, 2005). More recently, partial TP stimulation has been shown to significantly improve speech perception in noise (Srinivasan et al., 2013).

Townshend et al. (1987) examined the ability to discriminate stimulation of different electrodes on the basis of pitch (i.e., place-pitch sensitivity) and indicated that restricted current spread in the cochlea favoured more accurate discrimination of place-pitch percepts. However, a very recent study that evaluated the effect of electrode configuration in a group of CI listeners on a pitch ranking task observed no advantage for TP over MP stimulation (Fielden et al., 2015). This suggests that CI
users may have difficulty in accessing temporal pitch cues in either configuration. Several investigators have observed a positive correlation between CI subjects’ electrode discrimination ability and their speech recognition performance (Throckmorton and Collins, 1999, Nelson et al., 1995, Henry et al., 2000). Better pitch perception may be important to convey the rich aural texture of music or tonal language effectively (Wright et al., 2005, Xu and Pfingst, 2003). It is generally considered that new strategies based on improved spatial and temporal resolution of the electrical stimulus are required to achieve improvements in hearing via CIs.

### 1.7 Focused Multipolar Stimulation

Several investigators have proposed a method utilizing electrical field interactions between multiple electrodes to shape the stimulation of distinct neural populations. Van Compernolle (1985) described a method based on “current deconvolution” to solve the problem of current spread. This approach estimated a current spread function between a set of electrodes and the neural sites, mapping current levels at the electrodes to excitation levels at each neural site, using psychoacoustical experiments. This function is then inverted to give combinations of current patterns to produce excitation at only one site. Subsequently, Townshend and White (1987) extended this technique to calculate the current spread matrix using human subjects’ psychophysical thresholds. The current patterns computed to stimulate very precise neural sites was shown to produce reduced interaction and improve pitch ranking of stimuli for the subjects tested. Later, Rodenhiser and Spellman (1995) described a technique based on a least-squares approach, applied to a lumped-element model of an implanted cochlea of a guinea pig. The approach calculated the patterns of the necessary stimulating currents required to generate a focused electric field along the organ of Corti.
Building upon the “current deconvolution” technique, van den Honert and Kelsall (2007) described a method to shape the electric field potential based upon trans-impedance values measured by stimulating each electrode site. In this approach, current is applied to each intracochlear electrode in a MP configuration and a corresponding voltage is measured at all the other intracochlear electrodes. A trans-impedance matrix consisting of the ratio of the voltage to the current is generated, which represents the current spread functions for the stimulating electrode array. As the polarization effect precludes using the stimulating electrode to measure voltage, the diagonal values of the matrix are computed by simple linear extrapolation. A trans-admittance matrix is generated by inversing the matrix and each column in the inverse matrix constitutes a vector of numerical weights, which define the current from each electrode site to produce a stimulating voltage at one or multiple specific sites. This focusing process, described as “phased array”, “multipolar” or “all-polar”, is referred to as focused multipolar (FMP) stimulation in this thesis. FMP stimulation utilizes independent current sources to simultaneously stimulate all the adjacent, or “flanker”, electrodes with weighted positive and negative currents in order to restrict or “focus” the electric field produced by the central electrode.

van den Honert and Kelsall (2007) validated FMP stimulation with psychophysical data from three human subjects using percutaneous connectors i.e., connecters implanted in the skull to enable direct connection with an external bench top stimulator containing multiple current sources. Their results indicated that focusing could be achieved with FMP stimulation at the expense of higher stimulation currents than MP stimulation. They concluded their study stating that positioning of the electrode array within the cochlea may be important for minimizing stimulation current. As a means of potentially overcoming the issues of high current levels required to achieve threshold with standard FMP stimulation, a stimulation mode that is referred to here as ‘partial focused multipolar’ or partial-FMP (pFMP) has been investigated in this thesis. One of the purposes is to examine both the expected
reduction in threshold achieved with this approach as well as the spatial extent of the neural excitation (see Chapter 4 for details).

More recently, Smith et al (2013) investigated spectral resolution, comparing FMP stimulation with MP stimulation, using spectral ripple phase discrimination and ripple detection threshold measures on a small group of implant subjects with percutaneous connectors. This psychophysical test showed that the FMP stimulation improved the ability of CI users to discriminate spectral features in sound stimuli. The use of percutaneous connectors and related concerns about patient safety has limited the number of subjects involved in these studies. A recent investigation of several current focusing paradigms in a computational model of the human cochlea has also demonstrated the spatially restricted excitation patterns induced by FMP stimulation (Kalkman et al., 2015). These results indicate that FMP stimulation might be a promising tool for increasing the number of independent channels for stimulation along the cochlea. Recently, a clinical study on the potential benefits of FMP stimulation for reducing electrode interactions showed a significant reduction in interaction, mainly contributed by electric-field summation, between two spatially separated simultaneous stimuli compared to MP stimulation (Marozeau et al., 2015). However, there have been no direct comparisons of channel interaction measures using FMP, TP and MP stimulation.

FMP stimulation employs multiple current sources to deliver current pulses to all the intracochlear electrodes contrary to TP stimulation which uses three current sources to deliver current pulses to a central intracochlear electrode with two adjacent intracochlear return electrodes. Therefore, it has been hypothesized that FMP should produce a more focused region of activation than TP stimulation. The comparison of a range of TP alternatives with FMP channels by van den Honert and Kelsall (2007) suggested that most tripoles do not provide a close approximation of the corresponding FMP channel. Results from the modelling study conducted by Kalkman et al., (2015) showed that the excitation profiles produced by FMP and partial TP were similar, while TP resulted in different excitation profiles (with
pronounced side lobes), especially with lateral wall electrode arrays where higher stimulus intensities would be required to evoke neural activity.

There has been no previous attempt to investigate FMP stimulation in controlled animal studies, which could reduce the possible confounding effects of neural survival in the human studies. By systematically controlling the extent of neural loss, animal experiments can enable the examination of the effects of neural degeneration. Animal experiments have the advantage of being able to evaluate the neural population directly from histological preparations of the cochlea. Current focusing modes have never been examined in animals with moderate or severe degeneration of SGNs; the previous experimental studies have used cochleae with near normal SGN populations. It is important to note that in human studies, the precise density of surviving SGNs is not known although the human temporal bone studies by Nadol et al., (1989) and others clearly demonstrate significant SGN loss in most adult patients suffering from sensorineural hearing loss.

1.8 Research objectives of the thesis

The research detailed in this thesis investigates the effectiveness of FMP stimulation using an intracochlear stimulating electrode in an adult animal model. Experiments were designed with the aim of providing fundamental knowledge essential to the clinical development of this novel stimulation technique designed to improve the spatial precision and temporal independence of cochlear activation.

1.8.1 Hypotheses

The specific hypotheses under investigation in this thesis are:

1. **FMP stimulation produces more spatially restricted patterns of neural excitation than MP and TP stimulation.**
2. **FMP stimulation reduces interactions between CI channels compared to MP and TP stimulation.**

3. **The advantages of FMP stimulation over MP and TP stimulation are maintained in cochleae with significant neural degeneration.**

4. **The efficacy of FMP stimulation is maintained when the electrode contacts are positioned distal to the SGNs.**

5. **FMP stimulation results in elevated modulation detection thresholds and thus, a decrease in modulation sensitivity compared with MP and TP stimulation.**

### 1.8.2 Organisation of thesis

Subsequent chapters will present four separate stand-alone studies investigating FMP stimulation with the aim of contributing to the clinical development of this novel stimulation strategy. Chapter 2 describes the common research methodology used throughout this thesis. Using an animal model with normal SGN survival, the efficacy of FMP stimulation, compared to MP and TP stimulation, to improve spatial selectivity following stimulation of a single CI channel was examined, and the results are presented in Chapter 3. The spread of neural activity across the IC, measured by recording the spatial tuning curve, was used as a measure of spatial selectivity. The purpose of the chapter is to answer the research question: *Does FMP stimulation produce more spatially restricted patterns of neural excitation than MP or TP stimulation?* The data presented represents the first time FMP stimulation has been used in animal studies.

In clinical situations, the effectiveness of CIs are thought to be influenced by a number of factors including: (a) the pattern of SGN survival along the length of the cochlea; and (b) the position of the electrode relative to the SGN population. The effects of widespread loss of SGNs and peripheral fibres following deafness and the position of the electrode array within the cochlea on stimulation modes (FMP, TP and MP stimulation) were evaluated and the results are reported in Chapter 4. Some of the questions this chapter address include: *Is the efficacy of FMP stimulation,
compared to MP and TP stimulation, maintained in cochleae with significant neural degeneration? Is FMP stimulation, compared to MP and TP stimulation, adversely affected by the position of the electrode relative to the neural elements? How does FMP stimulation threshold change with local neural survival compared with MP and TP stimulation? This chapter also describes a stimulation mode referred to as partial-FMP stimulation.

The interaction between CI channels in relation to their spatial separation along the array was explored using FMP, TP and MP stimulation. The extent of neural interaction in the IC produced by simultaneous stimulation of two CI channels (channel interaction) was measured over a range of stimulus intensities and the results are reported in Chapter 5. The research addresses the following question: Does FMP stimulation increase the number of independent CI channels compared to MP and TP stimulation?

Chapter 6 reports on the IC neural responses to amplitude-modulated electrical pulse trains examined to provide an insight on the modulation sensitivity using FMP stimulation compared to MP and TP stimulation. The research addresses the following question: Does FMP stimulation provide elevated modulation detection thresholds compared to MP and TP stimulation?

Finally, the findings from the four studies are summarized and their implications for clinical practice are discussed in chapter 7.
Chapter 2: Materials and Methods
This chapter will outline the general procedures and materials used throughout the experimental work conducted in this thesis, with study specific methods discussed in each individual chapter.

### 2.1 Experimental animals

Twelve healthy adult cats (N=12) and five young adult pigmented guinea pigs (N=5) were used to collect data for all studies included in this thesis. Six normally hearing adult cats, forming cohort 1, were used in the study described in chapter 3. Six adult cats that were neonatally deafened, forming cohort 2, were used in the study described in chapter 4. Eight adult cats (i.e., four cats from each previous cohort) were used in the study described in chapter 5. Five adult guinea pigs, forming cohort 3, were used in the study described in chapter 6. All procedures were in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and with the National Institutes of Health, USA guidelines regarding the care and use of animals for experimental procedures, and were approved by the Royal Victorian Eye and Ear Hospital Animal Research and Ethics Committee (Approval#12_250AB). All recordings were performed in a sound attenuated and electrically isolated Faraday room.

Prior to all experimentation, the hearing status of each otoscopically normal animal was examined by recording auditory brainstem responses (ABRs) to acoustic clicks (100 μsec square pulse; up to 100 dB peak equivalent sound pressure level (p. e. SPL)) and tone pips (5 msec total duration; 1 msec rise/fall; 1-32 kHz; up to 100 dB SPL) using standard techniques (Coco et al., 2007). Hypodermic needles placed at the skull vertex (positive), nape (negative) and the thorax (earth) were used as recording electrodes.
2.2 Deafening procedure

Normal hearing controls (cohort 1 and 3) were acutely deafened on the day of terminal experiment prior to cochlear implantation via direct administration of an ototoxic drug (10% neomycin sulphate in normal saline) into the round window, and aspirating the solution at the oval window to ensure access of the aminoglycoside to all regions of the cochlea (Hardie and Shepherd, 1999). This procedure produces a profoundly deaf animal model thereby eliminating the potential contamination of the neural recordings from electrophonic activity (Black et al., 1983a, Sato et al., 2016).

Each animal in cohort 2 (i.e., long-term deafened cats) was administered a daily injection of neomycin sulphate (60 mg kg\(^{-1}\); subcutaneously [s.c]) commencing the day after birth for approximately 20 days (Leake et al., 2000, Fallon et al., 2009). The hearing status of each animal was then measured by recording ABRs. If hearing persisted, neomycin injections were continued for three days before the next ABR recording. This procedure was repeated until the animal was profoundly deaf (i.e. absence of a click-evoked ABR at 100 dB p.e. SPL in both ears).

2.3 Acute Experiment

2.3.1 Cat anaesthesia and surgery

Cats were anaesthetized using ketamine (20 mg kg\(^{-1}\); intramuscular [i.m]) and xylazil (2 mg kg\(^{-1}\); s.c), and maintained over the duration of the experiment (2–3 days) with a slow continuous intravenous infusion of sodium pentobarbital (3–8 mg kg\(^{-1}\) h\(^{-1}\)). Hartmann’s solution (5 ml/h; s.c) was administered throughout to counteract fluid losses. Clavulox (10 mg kg\(^{-1}\); s.c) as an antibiotic and dexamethasone (0.1 mg kg\(^{-1}\); i.m) to minimize brain swelling were administered every 24 h throughout the experiment. An endotracheal tube was inserted at the beginning of the experiment.
to monitor respiration rate (normal levels: 10–20/min) and end-tidal CO₂ levels (normal levels: 3–5%). The core body temperature was maintained at 37.0 ± 1°C.

A post-auricular incision was made and the temporalis muscle retracted, exposing the tympanic bulla. The round and oval windows were exposed and gently punctured. Animals in cohort 1 were acutely deafened by introducing neomycin sulphate (10% w/v solution) into the scala tympani. Animals were implanted with a Hybrid-L 14 array (HL14), containing uniquely spaced 14 intracochlear platinum electrodes with an average electrode spacing of 0.35 mm over a 10.5 mm length (Shepherd et al., 2011). The electrode array was inserted from the round window into the scala tympani, placing typically 12–14 electrodes within the scala tympani. A platinum ball electrode was placed in the neck muscles to serve as the extracochlear return electrode. Following implantation, animals were placed in a stereotaxic frame (David Kopf Instruments, USA).

### 2.3.2 Guinea pig anaesthesia and surgery

Guinea pigs were premedicated with atropine sulphate (0.1 mg/kg; i.m). Anaesthesia was induced and maintained by administration (via face mask) of isoflurane (3% for induction and 1-1.5% for maintenance) with oxygen (1 L/min). A heating pad was used to maintain the core body temperature at 37.0 ± 1°C. The respiration rate (normal levels: 10-20/min) and end-tidal CO₂ (normal levels: 1-3%) were monitored over the duration of the experiment (15-17 h).

Prior to surgery, animals were placed in a stereotaxic frame (David Kopf Instruments, USA). Local anaesthesia (lignocaine, 20 mg/mL; s.c) was applied before making an incision above the left pinna. The temporalis muscle was retracted to expose the left tympanic bulla. The bulla was opened, the stapes was removed and the round and oval windows were punctured. The left cochlea was deafened using the procedure described earlier. Animals were implanted with a Hybrid-L 8 array (HL8), consisting of 8 intracochlear half-band platinum electrodes on a silicon carrier similar to the cat.
HL14 (Shepherd et al., 2011). The electrodes were 0.3 mm in length, spaced ~0.75 mm, centre to centre. The electrode array was inserted approximately 6.75 mm through the round window into the scala tympani (typically placing the eighth electrode at the round window) and fixed in place throughout the experiment.

### 2.3.3 Inferior colliculus neural recording

A craniotomy of the parietal bone was performed on the dorsolateral portion of the skull and the cerebral cortex was aspirated to expose the IC contralateral to the implanted cochlea. In cats, a portion of the tentorium was removed using a small diamond burr to expose the entire dorsolateral surface of the IC when required. Multi-unit neural activity was recorded using a single shank silicon-substrate recording array (NeuroNexus Technologies, USA) inserted along the cochleotopic axis of the central nucleus of the IC. The array consisted of 32 iridium recording sites spaced at intervals of 100 μm (centre to centre), each having a circular surface area of 413 μm². The array was mounted on a microdrive positioner (David Kopf Instruments, USA), positioned at the surface of the IC and advanced ~100 μm s⁻¹ along the dorsolateral to ventromedial extent of the IC, at a 45° angle from the sagittal plane, along the cochleotopic gradient of the IC (Snyder et al., 1990, Landry et al., 2013). The depth of penetration (~3.5 mm) was chosen by visually monitoring on an oscilloscope the neural activity at the tip recording site. The multi-channel array recorded spike activity from 32 IC sites simultaneously. Multi-unit spike activity from the recording sites was amplified, band-pass filtered (0.1 Hz - 7.5 kHz) and digitized at a sample rate of 30 kHz using a Cerebus data acquisition system (Blackrock Microsystems, USA).

Following the completion of all of the *in vivo* experimental protocols, the animal was euthanized with an overdose of sodium pentobarbital and transcardially perfused with 0.9% NaCl (37°C) followed by 4% paraformaldehyde (PFA; 4°C) in 0.1M phosphate buffered saline (PBS; pH = 7.35).
2.4 Cat cochlear histology

To evaluate the extent of SGN degeneration, cochleae of animals in cohort 2 were prepared for histological examination. Following sacrifice and overnight fixation at 4°C with 4% PFA, the cochleae were placed in 10% ethylenediamine tetraacetic acid in PBS at room temperature for decalcification. Decalcified cochleae were infiltrated with 30% sucrose in PBS for cryoprotection, then cryoembedded in Tissue-Tek O.C.T. cryosectioning compound (Sakura, Japan) using dry ice and ethanol. Prior to freezing, the cochleae were orientated with the modiolus parallel to the bottom surface of the embedding moulds. The frozen tissue blocks were serially sectioned in the modiolar plane at a thickness of 12 μm using a CM 1900 UV cryostat (Leica, Germany) at −20°C. Sections were stained with Mayer’s haematoxylin and Putt’s eosin (H&E) and coverslipped with distyrene/plasticiser/xylene (DPX) mountant (BDH Chemicals, UK). Sections were examined using an Axioplan inverted microscope (Zeiss, Germany). The status of cochlear pathology was determined by measuring the SGN density within the Rosenthal’s canal (Wise et al., 2011). In each section, different cochlear turns (basal, middle and apical) were identified. The area of the Rosenthal’s canal was measured using Carl Zeiss AxioVision LE 4.8.2.0 software and the SGNs in that area with a visible nucleus and nucleoli were counted to determine the density of the SGNs as cells per square millimetres for each cochlear turn.
Chapter 3: Evaluation of focused multipolar stimulation for cochlear implants in acutely deafened cats
EVALUATION OF FOCUSED MULTIPOLAR STIMULATION FOR COCHLEAR IMPLANTS IN ACUTELY DEAFENED CATS

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3.1 Abstract

\textbf{Objective}. The conductive nature of the fluids and tissues of the cochlea can lead to broad activation of spiral ganglion neurons using contemporary cochlear implant stimulation configurations such as monopolar (MP) stimulation. The relatively poor spatial selectivity is thought to limit implant performance, particularly in noisy environments. Several current focusing techniques have been proposed to reduce the spread of activation with the aim towards achieving improved clinical performance. \textbf{Approach}. The present research evaluated the efficacy of focused multipolar (FMP) stimulation, a relatively new focusing technique in the cochlea, and compared its efficacy to both MP stimulation and tripolar (TP) stimulation. The spread of neural activity across the inferior colliculus (IC), measured by recording the spatial tuning curve, was used as a measure of spatial selectivity. Adult cats ($n = 6$) were acutely deafened and implanted with an intracochlear electrode array before multi-unit responses were recorded across the cochleotopic gradient of the contralateral IC. Recordings were made in response to acoustic and electrical
stimulation using the MP, TP and FMP configurations. **Main results.** FMP and TP stimulation resulted in greater spatial selectivity than MP stimulation. However, thresholds were significantly higher ($p < 0.001$) for FMP and TP stimulation compared to MP stimulation. There were no differences found in spatial selectivity and threshold between FMP and TP stimulation. **Significance.** The greater spatial selectivity of FMP and TP stimulation would be expected to result in improved clinical performance. However, further research will be required to demonstrate the efficacy of these modes of stimulation after longer durations of deafness.

### 3.2 Introduction

Cochlear implants (CIs) have been well accepted as an effective and safe treatment for severe to profound sensorineural hearing loss through electrical stimulation of residual spiral ganglion neurons (SGN), and have now been implanted in over 300,000 individuals worldwide. The typical implanted device consists of an intracochlear array of electrodes, locating individual electrodes at distinct sites along the length of the cochlea, along with an implantable stimulator (Tong and Clark, 1985). The spatial location of the electric stimulus is designed to mimic the location-specific patterns of SGN excitation with varying acoustic frequency, and the stimulus current amplitude encodes the loudness or acoustic intensity. Conventional CIs stimulate the electrodes typically in a monopolar (MP) configuration, where current is injected between a single intracochlear electrode and a remote extracochlear return electrode.

While most CI subjects receive significant speech understanding in quiet listening conditions using MP stimulation (Tong and Clark, 1985, Skinner et al., 1994, Shannon et al., 1995, Loizou et al., 1999), performance of speech perception in noise, and musical appreciation are poor (Shannon et al., 2004). This is primarily thought to be because the electrical conductivity of the cochlear fluid (Feigenbaum, 1987) results in significant spread of current within the cochlea (Black and Clark, 1980, Ifukube and
White, 1987). This in turn results in broad neural activation patterns (van den Honert and Stypulkowski, 1987, Bierer and Middlebrooks, 2002), leading to poor spatial selectivity. As a result, although there are up to 22 channels physically available in CI devices, the number of independent channels is much less than this (Friesen et al., 2001).

It has also been reported that simultaneous stimulation of multiple MP channels leads to channel interaction and spatial smearing (Boëx et al., 2003, Bierer and Middlebrooks, 2004, Stickney et al., 2006, Bierer, 2007). Overlap of stimulating currents cause interactions between channels that can occur due to the summation of electric fields in the cochlea as well as overlapping neural excitation following stimulation (Shannon, 1983, Black et al., 1983b, Fu and Nogaki, 2005). Channel interaction is unpredictable, often resulting in undesirable perceptual effects (Hanekom and Shannon, 1998, Stickney et al., 2006). In order to minimize channel interactions, traditional CIs use sequential stimulation where pulses delivered to each electrode are staggered such that only one channel is stimulated at any given instant (McDermott, 1989, Wilson et al., 1991). Although there has been improvement in speech perception scores of CI subjects using signal processing strategies based on sequential stimulation, this clinical improvement has plateaued over the last decade (Seligman and Shepherd, 2004). Moreover, many patients report difficulties discriminating speech in noise and poor perception of sounds such as music and tonal languages that are rich in temporal and spectral information (Skinner et al., 1994, Sucher and McDermott, 2007). It is widely anticipated that improved spatially restricted intracochlear stimulation, resulting in an increase in the number of truly independent stimulating channels available for simultaneous activation, would lead to improved signal processing strategies.

Focusing of stimulation to achieve more spatially restricted patterns of excitation and reduced channel interactions may enable better speech and pitch recognition (Nelson et al., 1995, Henry et al., 2000, Bingabr et al., 2008) and also improve temporal resolution (Throckmorton and Collins, 1999). Current focusing techniques
such as bipolar (BP), partial tripolar (PTP) (also known as quadrupolar), and tripolar (TP) stimulation have been reported to produce sharper excitation patterns and reduced channel interactions compared to MP stimulation (Black and Clark, 1980, Jolly et al., 1996, Kral et al., 1998, Miyoshi et al., 1999, Bierer and Middlebrooks, 2002, Snyder et al., 2004, Srinivasan et al., 2010). With BP stimulation, current is delivered between two intracochlear electrodes while TP stimulation delivers current pulses to a central intracochlear electrode and uses two immediately adjacent intracochlear return electrodes. In PTP, only a portion of current is returned via the adjacent intra-cochlear electrodes while the remaining current is returned through an extracochlear electrode. TP stimulation has been shown to produce a narrower spread of excitation compared to MP, BP or PTP stimulation in computational modelling (Jolly et al., 1996, Kral et al., 1998), electrophysiological (Bierer and Middlebrooks, 2002, Snyder et al., 2004) and psychophysical studies (Bierer, 2007, Bierer and Faulkner, 2010). However, the increased selectivity comes at the cost of higher current levels (CLs) and/or longer phase durations required to achieve adequate loudness in implant users compared to MP stimulation (Litvak et al., 2007a, Berenstein et al., 2008, Landsberger and Srinivasan, 2009). Moreover, the efficacy of TP stimulation is limited when stimulating multiple channels simultaneously due to the interaction of electric fields in the cochlea.

Focused multipolar (FMP) stimulation is a current focusing technique, utilizing stimulation of multiple channels simultaneously to create a focused electrical field (also referred to as phased array stimulation, van den Honert and Kelsall, 2007). FMP stimulation uses independent current sources to simultaneously stimulate all electrodes on the array with weighted positive or negative currents in order to restrict or ‘focus’ the electric field. This stimulation technique involves the measurement of trans-impedances between all electrodes. The trans-impedance matrix is then used to determine current weights for each electrode in such a way that an excitatory current is only delivered to the central electrode and return current to the other electrodes (figure 3.1).
Figure 3.1 Schematic diagrams illustrating monopolar (MP), tripolar (TP) and focused multipolar (FMP) stimulation centred on electrode 8. The amplitude only represents the anodic phase of a biphasic pulse.

A clinical study conducted on a small group of implant recipients using percutaneous connectors (van den Honert and Kelsall, 2007) has validated FMP stimulation showing that focusing can be achieved at the expense of higher stimulation currents than MP stimulation. Recently, FMP stimulation has also been shown to increase spectral resolution (Smith et al., 2013). However, the use of percutaneous connectors and related concerns about patient safety have limited the number of subjects involved in this study. Moreover, the efficacy of FMP stimulation has not been previously examined relative to TP stimulation. Thus, using an animal model with normal auditory neural survival, we measured the efficacy of FMP stimulation in the cochlea by measuring neural activation in the inferior colliculus (IC) based on previous studies (Shepherd, 1999, Snyder et al., 2004, Bierer et al., 2010). These controlled animal studies also reduced the possible confounding effects of neural survival in the human studies.

In the present study, we evaluated the efficacy of FMP stimulation in producing more
focused activation when compared to MP and TP electrode configurations. In order to quantify the spread of activation, IC spatial tuning curves (STCs) were generated. We also measured the total neural response in the IC as a metric to evaluate the loudness growth. For each stimulation configuration, we compared the threshold to elicit IC neural activation, spread of activation, and total neural response growth in the IC.

3.3 Methods

3.3.1 Animals

Six normally hearing adult cats were used in this study. Four animals were implanted unilaterally while two were implanted bilaterally, providing a total of eight implanted cochleae. All procedures were in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and with the National Institutes of Health, USA guidelines regarding the care and use of animals for experimental procedures, and were approved by the Royal Victorian Eye and Ear Hospital Animal Research and Ethics Committee. All recordings were performed in a sound attenuated and electrically isolated Faraday room. Prior to deafening and implantation, the normal hearing status of each animal was confirmed by recording the auditory brainstem response to acoustic stimuli using standard techniques (Coco et al., 2007, Fallon et al., 2009).

3.3.2 Anaesthesia and surgery

Animals were anaesthetized using ketamine (intramuscular, 20 mg kg\(^{-1}\)) and xylazil (subcutaneous, 2 mg kg\(^{-1}\)), and maintained over the duration of the experiment (2–3 days) with a slow continuous intravenous infusion of sodium pentobarbital (3–8 mg kg\(^{-1}\) h\(^{-1}\)). An endotracheal tube was inserted at the beginning of the experiment to monitor respiration rate (normal levels: 10–20/min) and end-tidal CO\(_2\) levels.
normal levels: 3–5%). The core body temperature was maintained at 37.0 ± 1°C.

In one animal, deafening and cochlear implantation procedures were performed following IC exposure and recording of IC responses to acoustic stimulation, and in the remaining five animals, the deafening and cochlear implantation was performed prior to exposure of the IC.

A post-auricular incision was made and the temporals muscle retracted, exposing the tympanic bulla. The round and oval windows were exposed and gently punctured. The animals were acutely deafened by introducing neomycin sulphate (10% w/v solution) into the round window, and aspirating the solution at the oval window to ensure access of the aminoglycoside to all regions of the cochlea (Hardie and Shepherd, 1999). Following deafening, animals were implanted with a Hybrid-L14 array (HL14), containing uniquely spaced 14 intracochlear platinum electrodes with an average electrode spacing of 0.35 mm over a 10.5 mm length (Shepherd et al., 2011). The electrode array was inserted from the round window into the scala tympani, placing typically 10–12 electrodes within the scala tympani. A platinum ball electrode was placed in the neck muscles to serve as the extracochlear return electrode. Following implantation, animals were placed in a stereotaxic frame (David Kopf Instruments, USA).

A craniotomy was performed through the parietal bone on the dorsolateral portion of the skull contralateral to the implanted cochlea and the cerebral cortex was removed to reveal the dorsal surface of the IC. If required, a portion of the tentorium was removed using a small diamond burr to expose the entire dorsolateral surface of the IC.

### 3.3.3 Electrical stimuli

All electrical stimuli were generated by an in-house purpose built multi-channel stimulator, consisting of 14 Howland current sources with a topology based on previous designs described by van den Honert and Kelsall (2007) and Ross et al
The stimulator was controlled using custom software implemented in Igor Pro (Wavemetrics, USA). Electrical stimuli consisted of cathodic-first, charge balanced single biphasic pulses presented at rate of 4 Hz. The term ‘channel’ was used to address a set of electrodes used to deliver current in a particular stimulation configuration. The channels were numbered increasing from base to apex, in accordance with the convention used for the clinical CI (figure 3.1). The number of its centre electrode indicated each FMP and TP channel. It was possible to only stimulate channels that had at least one adjacent or ‘flanker’ on each side using both FMP and TP—these channels were referred to as ‘internal’ channels and used for with all three electrode configurations. For the channels without flankers on both sides, only MP and FMP stimulation were performed—these channels were referred to as ‘end’ channels. For each FMP channel, the weight vector was constructed based on the strategy adapted from van den Honert and Kelsall (2007). The trans-impedance matrix was measured for all intracochlear electrodes, with each column of the inverse of this matrix used to determine the numerical weights that determined the current from each electrode to produce a single FMP stimulation channel.

For MP stimulation, each pulse had a phase of 100 μs and an inter-phase gap of 50 μs. For TP and FMP configurations, each pulse had a phase of 400 μs and an inter-phase gap of 50 μs. The differences in pulse durations were a result of the greater charge required using FMP and TP configuration to evoke neural activity. The stimulator was limited to a maximum current of 1.75 mA to ensure that charge density did not exceed safe levels (Brummer and Turner, 1977). Electrode shorting and capacitive coupling were used to achieve net zero direct current (Huang et al., 1999). The electrical current was programmed in clinical units, CL, as defined by Cochlear (Australia), where,

\[
\text{Current in } \mu\text{A} = 17.5 \times (100 \frac{\text{CL}}{255})
\]

The current was increased in discrete CL steps (ten repetitions for each level) up to
a maximum stimulus level for each channel of either 255 CL, or the threshold for myogenic activity.

### 3.3.4 Neural recording

A multi-channel silicon substrate recording array (NeuroNexus Technologies, USA) was inserted along the cochleotopic axis of the central nucleus of the IC (ICC), contralateral to the implanted cochlea, to record multi-unit neural activity (Landry et al., 2013). The recording array consisted of a single shank with 32 iridium recording sites spaced at 100 μm intervals (centre to centre), each having a circular surface area of 413 μm². In order to histologically confirm the location of the recording array in the IC, the array was coated in a fluorescent stain (3% 1,1′′-dioctadecyl-3,3, 3′′,3′′-tetra- methylindocarbocyanine perchlorate (DiI) in absolute ethanol (Dicarlo et al (1996)). The array was mounted on a microdrive positioner (David Kopf Instruments, USA), positioned at the surface of the IC and advanced slowly (~100 μm s⁻¹) along the dorsolateral to ventromedial extent of the IC, at a 45° angle from sagittal plane, along the cochleotopic gradient of the ICC (Snyder et al., 1990). The depth of penetration (~4.2 mm) was chosen by visually monitoring the responses of neurons at the tip recording site to electrical stimulation (or acoustic stimulation in one animal). The array recorded neural activity over approximately 3.2 mm of the IC. Multi-unit spike activity from the 32 recording sites was amplified, filtered and digitized at a sample rate of 30 kHz using a Cerebus data acquisition system (Blackrock Microsystems, USA). Multi-unit recordings to electrical stimulation were made over a range of CLs and different stimulation configurations (MP, FMP and TP). At the conclusion of the experiment, the animal was sacrificed with an overdose of sodium pentobarbital. Histological analysis confirmed that all recording arrays were located within the ICC.

In one animal, IC responses to acoustic stimulation were recorded prior to deafening and cochlear implantation in order to facilitate direct comparison between acoustic and electrical (MP and FMP) neural responses. Acoustic stimuli consisted of tone
bursts (100 ms duration, 5 ms linear rise/fall, 1–32 kHz, 0–90 dB SPL) and clicks (100 μs duration, 0–90 dB SPL), generated using custom designed software. The stimuli were delivered closed-field using a Tucker Davis Technologies SA1 Stereo Power Amp (TDT, USA), a 4’ Vifa XT2STG30-04 speaker and a sound delivery vinyl tube. The whole system was calibrated over a frequency range of 0.5–40 kHz.

### 3.3.5 Data analysis

Multi-unit activity was processed offline, using customized spike detection scripts in IgorPro (Wavemetrics, USA). Stimulus artefacts were removed using the techniques detailed in Heffer and Fallon (2008). Spikes were detected when the signal exceeded four times root mean square for each recording channel (Fallon et al., 2009). Based on first-spike latencies and the early onset response of IC neurons, spikes were counted in a 3–35 ms post-stimulus window (figures 3.2(a), (b)). For each stimulus condition and CL, spike counts were averaged across ten trials and normalized to the maximum spike rate at each recording site (Snyder et al., 2008). Normalized spike rates (NSRs) recorded across the array were displayed as ‘response images’ with the stimulus intensity on the y-axis and the depth of the recording site on the x-axis (figure 3.2(d)). Each response image illustrated the spread of activation across the recording array for a given stimulating channel and stimulus configuration. Threshold, defined as the lowest current that elicited a NSR of 0.3 (indicated by the white line in figure 3.2(d)), was determined for each stimulus condition (Landry et al., 2013). The recording site with the lowest threshold was defined as the best recording site.
Figure 3.2 Overview of multichannel neural recording along the cochleotopic axis of the inferior colliculus (IC). a) A trace of multi-unit responses (*) and stimulus artefact (SA) from one IC recording site following electrical stimulation of a CI channel. The analysis window (3-35ms) used for spike counting is shown in the shaded box. b) post-stimulus time histogram (PSTH) of spikes for stimulation of a CI channel, showing early onset response of IC neurons from 5-15 ms post-stimulus. c) Normalised spike rate versus stimulus intensity function of the best recording site. Threshold level and level of level of cumulative $d'$ of 1 from threshold level are indicated d) IC response image illustrating the spatial extent of evoked multi-unit activity recorded across the recording array. Each point on the response image was normalised between the spontaneous activity rate and maximum response. Normalised spike rates (NSR) were represented by colours from yellow to black as shown in this scale with yellow representing the highest activity. Moreover, the data was smoothed with a 3x3 Gaussian function. A spatial tuning curve (STC) was constructed by connecting the stimulus levels that elicited 0.3 normalised responses on each IC recording site (shown by the white line). The tip of the STC corresponds to the IC minimum threshold. STC width was derived at 1dB above IC minimum threshold (illustrated by dashed white lines).

The growth in neural response with increasing stimulus intensity at each recording site was quantified by the discrimination index, $d'$, computed by a procedure derived from signal detection theory (Green and Swets, 1966, Macmillan and Creelman,
A receiver operator characteristic curve was formed based on spike counts for ten trials of each of two different stimulus levels. The area under the receiver operator characteristic curve was expressed as a standard deviate and the resulting z-score was multiplied by √2 to obtain $d'$. Thus, the value of $d'$ gave an indication of whether two different stimulus levels can produce discriminable spike responses and possibly, two perceptually discriminable loudness levels.

For the best recording site of each response image, the value of $d'$ was cumulated across increasing stimulus levels above IC threshold (i.e. NSR of 0.3). The lowest stimulus level that yielded a cumulative $d'$ of 1 from the threshold level was chosen to measure spread of activation and total neural response growth in the IC. This method of using cumulative $d'$ to measure different features of neural response was adapted from previous studies (Middlebrooks and Bierer, 2002, Middlebrooks and Snyder, 2007).

In 70.5% cases of FMP and TP stimulation, we were unable to achieve saturating levels of stimulation within our predefined safety limits because of elevated threshold. For that reason, it was impractical to use the standard method to quantify complete dynamic ranges (i.e. range of currents eliciting NSR of 10–90% of the saturating spike rate). Hence, in the present study, we measured the ‘discrimination slope’ as an indication of dynamic range, adapted from Middlebrooks and Snyder (2007). The discrimination slope of each stimulating channel was measured (expressed in units of $d'\text{dB}^{-1}$) from the difference in stimulus intensities between the threshold level and the level that resulted in cumulative $d' = 1$ above the threshold level at the best recording site, as illustrated in figure 3.2(c) (threshold level = 210 CL, level of cumulative $d'$ of 1 from threshold level = 240 CL, Discrimination Slope = 0.86 $d'\text{dB}^{-1}$).

**3.3.5.1 Spread of activation in the IC**

The spread of neural activity in the IC was used to compare the selectivity of responses between the different stimulation configurations. To quantify the spread
of activation, different features of IC activity were analysed.

**STC width.** STCs were generated for each response image by joining the stimulus intensities that yielded 0.3 NSR on each recording site (Landry et al., 2013). The widths of STCs were measured at cumulative $d' = 1$ as well as 1 dB above minimum threshold and compared between the MP, TP and FMP stimulation configurations.

**Number of active recording sites.** For each IC response image, the total number of active recording sites was computed at different stimulus intensity levels. A recording site was considered active if the spike activity was at least 0.3 NSR (figure 3.2(d)). A plot with the total number of active recording sites versus stimulus intensity expressed in charge (nC) was obtained for each cochlear stimulating channel. The stimulus intensity was expressed in charge to account for the difference in phase durations used with different stimulation configurations. The slope of the rising component of the plot was calculated as another measure of the spread of IC activation, with steeper slopes corresponding to a more rapid spread of activation. Moreover, the number of active recording sites at a stimulus level of cumulative $d' = 1$ above threshold was computed and compared between MP, FMP and TP stimulations, to indicate the spatial selectivity at a discriminable CL.

### 3.3.5.2 Measure of total neural response growth in the IC

As reported by previous psychophysical studies (Litvak et al., 2007a, Landsberger and Srinivasan, 2009), it is important to evaluate if sufficient loudness can be achieved using current focusing within the safe charge limits of implant electrodes as well as within the compliance limits of the device. For this reason, we used the total neural response as a correlate for loudness (McCreery et al., 2010). For each cochlear channel stimulated, plots of total neural response across the recording array versus stimulus intensity (expressed in dB re. threshold) were derived. Total neural response was calculated by summing up the NSR on each active recording site at each stimulus intensity. From these plots, the increases in neural response from 0 to 1 dB above thresholds as well as from threshold to the stimulus level yielding cumulative $d' = 1$ were computed and compared across the different stimulus
configurations.

3.3.6 Statistical analysis

All statistical analyses were performed using SigmaPlot Version 12.5 (Systat, USA). Comparisons of IC minimum threshold, discrimination slope, spread of activation and total neural response growth between MP, TP and FMP stimulation were performed using one-way repeated measures ANOVAs, with Tukey corrected post-hoc testing of individual comparisons where appropriate. Comparison of spread of activation for MP and FMP stimulation at the end channels was performed using a paired t-test.

3.4 Results

Across the eight cochleae, 51 internal CI channels were stimulated using MP, FMP and TP configurations and 16 end channels were stimulated using MP and FMP configurations. The main analyses were done for internal channels only. For end channels, only the width of STC was measured and compared between MP and FMP stimulation. The number of contralateral IC recording sites that responded to electrical stimulation of internal channels was 233 for MP, 159 for FMP and 162 for TP out of a total of 256 implanted recording sites in the IC.

3.4.1 Response images

IC response images to electrical (six animals) and acoustic stimuli (one animal) were generated. Figure 3.3(a) presents an IC response image (and the STC) to a 12 kHz pure tone acoustic stimulus in one animal and figures 3.3(b)-(d) illustrate IC response images from another animal to stimulating cochlear channel 9 (in the apical fifth of the array) in three different stimulation configurations.
Figure 3.3 Response images across the cochleotopic axis of the IC to acoustic and electrical stimulations. a) pure tone at 12 kHz and electrical stimulation using b) FMP c) TP and d) MP electrode configuration. Each response image was generated by plotting depth of the IC recording site on the x-axis and stimulus intensity on the y-axis. The tip of each response image corresponded to the recording site that is most sensitive to that particular stimulus. In this example, the location of most sensitive recording site corresponded to ~2.9 mm from the IC surface. Each response image for electrical stimulation was labelled according to configuration and channel number (shown for stimulating channel 9). Note that for MP stimulation, each pulse had a phase of 100 μs while TP and FMP configurations used pulses with 400 μs phase duration, so the difference in electrical threshold between stimulation configurations are not evident in this figure. Representative acoustic and electrical data shown here are from different animals.

For both acoustic and electrical stimulation, the width of the STC increased with increasing stimulus intensity above threshold. FMP and TP STCs were similar to those with acoustic stimulation but resulted in widespread IC activation at higher intensities. MP stimulation generally resulted in very broad STCs even at low intensities and significant myogenic activity at higher intensities.

3.4.2 Threshold and discrimination slope

Minimum thresholds, converted to nC, for different stimulation configurations are shown in figure 3.4(a). Thresholds were significantly different between stimulation configurations (one-way RM ANOVA, $p < 0.001$); with post-hoc tests indicating that MP stimulation had a significantly lower threshold than FMP or TP stimulation ($p'$s < 0.001). The thresholds for FMP and TP stimulation were not significantly different ($p = 0.997$). However, regardless of the stimulation configuration, charge per phase and charge densities required to reach threshold were below the maximum safe stimulus.
levels for platinum electrodes used in our study.

Discrimination slopes for the best recording sites (IC sites with the lowest thresholds) were computed for MP, FMP and TP stimulation configurations and are presented in figure 3.4(b). Discrimination slopes averaged 1.93 (± 0.24) for MP, 1.14 (± 0.21) for FMP and 1.45 (± 0.25) for TP stimulation. Significantly different discrimination slopes were found for different stimulations configurations (one-way RM ANOVA, $p = 0.020$) with post-hoc testing indicating FMP stimulation had significantly lower discrimination slope compared to MP ($p = 0.016$) and TP stimulation was not significantly different from MP ($p = 0.201$) or FMP stimulation ($p = 0.515$).

### 3.4.3 Spread of activation in the IC

#### 3.4.3.1 STC width

STC widths at both 1 dB and $d' = 1$ above threshold (figure 3.5) were significantly different between stimulation configurations (one-way RM ANOVA, $p < 0.001$). The STC width was significantly higher for MP than both FMP and TP stimulation configurations ($p's < 0.001$). There was no significant difference in the STC widths
between FMP and TP configurations ($p = 0.967$ for 1 dB above threshold and $p = 0.639$ for $d' = 1$ above threshold). As a comparison, the STC width for acoustic stimulation at $d' = 1$ above threshold was similar to that found with FMP and TP stimulation (figure 3.5(b)).

![Figure 3.5 STC Widths (mean + SEM) measured across MP, FMP and TP stimulation configurations a) at 1dB above threshold and b) at cumulative $d' = 1$ above threshold. Means of STC widths for acoustic stimulation measured at cumulative $d' = 1$ above threshold is shown only for the purpose of comparison and were not included in the statistics. ** $p < 0.001$.](image)

### 3.4.3.2 Number of active recording sites

As another measure of the spread of activation, the number of recording sites activated in the IC was plotted against stimulus intensity for each cochlear stimulation channel as shown in figure 3.6(a). As the stimulus intensity increased, the number of activated recording sites monotonically increased. The rate of increase of active sites with stimulus intensity is presented in figure 3.6(b) and was significantly dependent on the stimulation configuration (one-way RM ANOVA, $p < 0.001$). MP stimulation activated significantly greater number of recording sites per stimulus intensity (nC) compared to that of FMP and TP configurations ($p < 0.001$) while there was no significant difference between FMP and TP configurations ($p = 1$).
Figure 3.6 a) Example of number of recording sites activated versus stimulating current level function for MP (closed circles), FMP (open squares) and TP (closed triangles) stimulation on a single cochlear channel (shown only for charge levels up to 400 nC). Fitted linear function for the rising component is also shown. Group data for the slope of growth in active recording sites (mean + SEM) expressed as b) increase in active recording sites per nC for MP, FMP and TP stimulation and c) number of active recording sites at $d' = 1$ for the MP, FMP, TP and acoustic stimulations. Means for acoustic stimulation is shown only for the purpose of comparison and were not included in the statistics. ** $p < 0.001$.

The number of recording sites activated at the CL that resulted in a cumulative $d' = 1$ for all the stimulation configurations is shown in figure 3.6(c), along with representative data for acoustic stimulation. Although the difference was smaller using this metric, MP stimulation still resulted in activation of a significantly greater number of recording sites at $d' = 1$ compared to FMP and TP configurations (one-way RM ANOVA, $p < 0.001$). There was no significant difference between FMP and TP configurations ($p = 0.998$) and both of these modes resulted in a similar spread of activation to that found with acoustic stimulation (figure 3.6(c)).

3.4.4 Total neural response growth in the IC

Given the different spread of activation in the IC with different stimulation configurations, we also measured the total neural response summed across the IC. There was a monotonic increase in neural response with increasing stimulus intensity. The growth functions were approximately linear as stimulation increased from threshold to 2 dB above threshold (figure 3.7(a)). The increase in total neural
response was dependent on stimulus configuration (figure 3.7(b); one-way RM ANOVA, \( p < 0.001 \)) with FMP and TP electrode configurations having a significantly lower rate of growth compared to the MP configuration (\( p < 0.001 \)). There was no significant difference between FMP and TP configurations (\( p = 0.996 \)). The rate of growth in total neural response from threshold to cumulative \( d' = 1 \) was also different for different configurations (figure 3.7(c); one-way RM ANOVA, \( p < 0.001 \)). While no significant difference was observed between FMP and TP configurations (\( p = 0.963 \)), FMP and TP configurations showed a slower growth compared to MP configuration (\( p's < 0.001 \)). The total neural response growth measured at \( d' = 1 \) for acoustic stimulation was more similar to that found with FMP and TP stimulation (figure 3.7(c)).

![Figure 3.7](image)

**Figure 3.7** a) Example of normalised total neural response across the recording array versus stimulus intensity (expressed relative to threshold) for MP (closed circles), FMP (open squares) and TP (closed triangles) stimulation. The total neural response at threshold, 1dB above threshold and cumulative \( d' = 1 \) above threshold were utilised to compute the increase in total neural response. Group data for the growth function of total spike activity (mean + SEM) expressed as b) increase in normalised neural response at 1 dB for MP, FMP and TP stimulation and c) increase in normalised neural response at \( d' = 1 \) for the MP, FMP, TP and acoustic stimulation. Data for acoustic stimulation are shown only for the purpose of comparison and were not included in the statistics. ** \( p < 0.001 \).

3.4.5 Spread of activation for end channels

It has been reported that FMP stimulation of end channels resulted in substantial stimulus spread beyond the ends of the array compared to the internal channels (van
den Honert and Kelsall, 2007). To analyse this effect, the STC widths of MP and FMP end channels were evaluated and compared (figure 3.8). In contrast to internal channels, there was no significant difference in STC width between MP and FMP at 1 dB above threshold (paired t-test, \( p = 0.637 \)) as well as at cumulative \( d' = 1 \) (paired t-test, \( p = 0.410 \)) for end channels indicating that there is greater spread for the end channels.

![Figure 3.8](image)

**Figure 3.8** STC Widths (mean + SEM) measured for end channels across MP and FMP configurations at 1 dB above threshold. No significant difference was found in the STC width of MP and FMP end channels. N=16 channels.

### 3.5 Discussion

The present study evaluated the efficacy of FMP stimulation in producing restricted neural activation when compared to other stimulation configurations based on simultaneous multi-unit recordings from the IC. The data presented in this paper represents the first time FMP stimulation has been used in animal studies. The results showed that a significantly narrower spread of neural activation was achieved with FMP and TP stimulation compared to MP stimulation, although greater charge was required to achieve equivalent neural excitation using the FMP and TP current focusing techniques. In addition, MP stimulation was found to have a greater total neural response growth compared to FMP and TP stimulation. Importantly, there
was no benefit in terms of restricted neural activation for FMP compared to TP stimulation.

Several previous studies have demonstrated that thresholds increase systematically with decreasing extent of cochlear activation in both animal neurophysiological (Black and Clark, 1980, Kral et al., 1998, Rebscher et al., 2001, Snyder et al., 2004, Snyder et al., 2008) and human psychophysical (Busby et al., 1994, Pfingst et al., 1997, Bierer, 2007) studies. Consistent with these and previous reports of FMP stimulation (van den Honert and Kelsall, 2007, Long et al., 2014), MP stimulation had significantly lower thresholds than FMP and TP stimulation. Nevertheless, the stimulus levels required to evoke neural activity at threshold level using these current focusing techniques were below the safe charge limits for platinum electrodes as well as within the compliance limits of the device.

In clinical studies, dynamic range is usually defined as the range of CLs from the threshold level to the maximum comfortable loudness level (Nelson et al., 1996, McKay et al., 1999) while in animal studies, it is usually defined as the range of CLs eliciting normalized spike rate of 10–90% of maximum response (Shepherd and Javel, 1997, Fallon et al., 2009). In our study, we seldom saw saturated responses using current focusing techniques within the predefined safety limits of the device. Hence, we calculated discrimination slope (expressed in units of $d'$ dB$^{-1}$) as a measure of dynamic range, at least for the initial slope of the suprathreshold stimulus-response function. Despite the slight difference in definition, we found that the discrimination slope of the most sensitive IC site using MP stimulation in this study of 1.93 was similar to that reported by Middlebrooks and Snyder (2007) of 1.98. The discrimination slope was significantly lower for FMP stimulation than for MP stimulation, indicating a greater dynamic range for FMP stimulation. This result agrees with the general trend reported by previous animal studies that dynamic ranges tend to become more narrow when moving from the most spatially focused configuration to the most diffused configuration (Marsh et al., 1980, Bierer and Middlebrooks, 2002, Middlebrooks and Bierer, 2002).
Our results showed that TP stimulation reduced the extent of cochlear stimulation and produced narrower neural activation in the IC compared to MP stimulation. This result is consistent with previous studies on the effect of TP stimulation on spread of excitation, based on neural recordings from the auditory nerve (Kral et al., 1998), the IC (Snyder et al., 2004, Bonham and Litvak, 2008) and the primary auditory cortex (Bierer and Middlebrooks, 2002, Middlebrooks and Bierer, 2002). Similar to our study, Snyder et al (Snyder et al., 2004) showed that TP stimuli produce more restricted neural IC activation compared to MP stimulation, in acutely deafened guinea pigs.

We found more restricted activation (narrower STC widths) in the IC in response to FMP stimulation compared to MP stimulation. At all CLs relative to threshold (1dB or $d' = 1$), the STC widths for FMP stimulation were narrower than MP stimulation. Moreover, in most cases, at high stimulus levels, FMP response images remained relatively narrow, where MP response images tended to extend across the entire recording array. We also observed that the measures of spread of activation (STC width and number of active recording sites) with FMP stimulation were generally similar to that of acoustic stimulation. FMP stimulation has been validated in a small group of implant recipients using percutaneous connectors where it was referred to as phased array stimulation (van den Honert and Kelsall, 2007). Psychophysical results from these recipients showed restricted excitation and reduced spread of masking of FMP compared to MP stimulation.

Our experimental data showed no significant difference in the spread of activation between FMP and MP stimulations at the end channels. This result agrees with the clinical findings of van den Honert and Kelsall (2007) that the current focusing at the end channels is reduced by un-cancelled voltage beyond the ends of the array, resulting in substantial stimulus spread. Our result implies that FMP stimulation is more effective for channels with at least one flanker on both sides. Although, the efficacy of FMP stimulation was degraded when moving to end channels, importantly it was not found to be inferior to MP channels.
It is assumed that loudness corresponds to total neural activity (Litvak et al., 2007a, McCreery et al., 2010). We compared total neural activity elicited by the different stimulation configurations in order to compare stimulus ‘loudness’. Our results showed that FMP and TP stimulation have a slower growth of total neural response compared to MP stimulation. On comparing electric and acoustic stimuli at a discriminable CL above threshold \(d' = 1\), the total neural response elicited by FMP and TP stimulation appeared to be lower than that of acoustic stimuli, while MP stimulation resulted in a faster growth compared to acoustic stimulation. However, one must bear in mind the limitations in considering total neural response as an accurate measure of loudness (Relkin and Doucet, 1997, McKay et al., 2001).

It has been shown that BP stimulation produces more spatially restricted excitation patterns than MP stimulation (Black and Clark, 1980, van den Honert and Stypulkowski, 1987, Bierer and Middlebrooks, 2002). Moreover, BP stimulation has shown to provide better discrimination among sequentially stimulated channels (Busby et al., 1994, Middlebrooks and Bierer, 2002), and thus suggesting more precise transmission of spectral information with BP stimulation compared to MP stimulation. Contrary to the physiological findings, psychophysical tests of speech recognition have not reported any significant improvement in speech understanding with BP stimulation compared to MP stimulation (von Wallenberg et al., 1995, Zwolan et al., 1996, Pfingst et al., 1997). While this may suggest that restricted neural activation by cochlear channels is not necessarily advantageous, it is anticipated that more localized and spatially precise activation of different cochlear regions may reduce channel interaction when stimulating multiple channels simultaneously. This can improve the temporal fine structure of speech across a number of temporally independent stimulating channels. This can potentially improve speech recognition in noise and appreciation of music and comprehension of tonal languages. Further studies of the efficacy of FMP stimulation to increase the number of temporally independent CI channels are warranted. While TP stimulation was found to be equally effective to FMP stimulation in this study, it may result in increased
interference when stimulating adjacent channels.

While this study has shown that FMP stimulation can produce a narrow spread of activation in the IC in animals without deafness-induced loss of SGNs, we intend to proceed to further studies to determine the relationship between threshold, local neural survival and electrode position. It is critical for FMP stimulation to demonstrate its efficacy over a wide range of SGN survival that reflects the clinical situation, without increasing the incidence of non-auditory neuronal (facial or vestibular nerve) activation, and without exceeding the maximum current supported by the device.

In conclusion, the present study indicated that FMP stimulation resulted in more restricted neural activation than MP stimulation, except at the end channels. Reducing the number of flanker electrodes to two (i.e. TP stimulation) did not result in a significant change in the spread of excitation. These results suggest that current focusing has the potential to not only improve spectral resolution but to also increase the number of temporally independent channels. Future work is needed to further investigate the efficacy of FMP stimulation and to test the hypothesis that finer spectral and temporal resolution will improve speech understanding in noise and convey the rich aural texture of music or tonal languages effectively.

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Chapter 4: Evaluation of focused multipolar stimulation for cochlear implants in long-term deafened cats
The work contained in this Chapter has been published in its entirety (George et al., 2015a)

EVALUATION OF FOCUSED MULTIPOLAR STIMULATION FOR COCHLEAR IMPLANTS IN LONG-TERM DEAFENED CATS

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4.1 Abstract

\textit{Objective.} Focused multipolar (FMP) stimulation has been shown to produce restricted neural activation using intracochlear stimulation in animals with a normal population of spiral ganglion neurons (SGNs). However, in a clinical setting, the widespread loss of SGNs and peripheral fibres following deafness is expected to influence the effectiveness of FMP. \textit{Approach.} We compared the efficacy of FMP stimulation to both monopolar (MP) and tripolar (TP) stimulation in long-term deafened cat cochleae (n=8). Unlike our previous study, these cochleae contained <10\% of the normal SGN population adjacent to the electrode array. We also evaluated the effect of electrode position on stimulation modes by using either modiolar facing or lateral wall facing half-band electrodes. The spread of neural activity across the inferior colliculus, a major nucleus within the central auditory pathway, was used as a measure of spatial selectivity. \textit{Main results.} In cochleae with significant SGN degeneration, we observed that FMP and TP stimulation resulted in greater spatial selectivity than MP stimulation (p < 0.001). However, thresholds were
significantly higher for FMP and TP stimulation compared to MP stimulation ($p < 0.001$). No difference between FMP and TP stimulation was found in any measures. The high threshold level for FMP stimulation was significantly reduced without compromising spatial selectivity by varying the degree of current focusing (referred as ‘partial-FMP’ stimulation). Spatial selectivity of all stimulation modes was unaffected by the electrode position. Finally, spatial selectivity in long-term deafened cochleae was significantly less than that of cochleae with normal SGN population (George et al., 2014). *Significance*. The present results indicate that the greater spatial selectivity of FMP and TP stimulation over MP stimulation is maintained in cochleae with significant neural degeneration and is not adversely affected by electrode position. The greater spatial selectivity of FMP and TP stimulation would be expected to result in improved clinical performance.

### 4.2 Introduction

Cochlear implants (CIs) electrically stimulate spiral ganglion neurons (SGNs) in order to restore functional hearing in severe-to-profoundly deaf patients. CIs take advantage of the known tonotopic organization of the inner ear by dividing speech into discrete frequency bands that are mapped to specific electrodes along the electrode array. Conventional CIs typically stimulate the electrodes in a monopolar (MP) configuration, where current is injected between a single intracochlear electrode and a remote extracochlear return electrode. However, the conductive nature of the cochlea leads to spatially broad neural excitation (van den Honert and Stypulkowski, 1987, Bierer and Middlebrooks, 2002); resulting in a limited number of independent stimulation sites (Friesen et al., 2001) and interactions between channels (Bierer and Middlebrooks, 2004, Stickney et al., 2006). While most CI subjects typically receive significant benefit in speech understanding in quiet listening conditions using MP stimulation, their performance diminishes in more difficult listening conditions such as speech in noisy environments and musical
perception (Friesen et al., 2001, Shannon et al., 2004). This is likely to be due to limited spatial resolution provided by the implant (McDermott and McKay, 1997, Fu et al., 1998). It is widely anticipated that focusing of stimulation to achieve more spatially restricted patterns of excitation and reduced channel interactions may improve speech and pitch recognition (Nelson et al., 1995, Henry et al., 2000, Bingabr et al., 2008, Srinivasan et al., 2013).

Focused multipolar (FMP) stimulation has been proposed as a method to create focused electrical fields in the cochlea and thus produce a more restricted spread of neural activation compared to conventional MP stimulation. FMP uses multiple independent current sources to simultaneously stimulate all electrodes on the intracochlear electrode array with weighted anodic or cathodic currents in order to restrict or ‘focus’ the electric field. A clinical study conducted on a small group of implant recipients using percutaneous connectors (van den Honert and Kelsall, 2007) has validated FMP stimulation showing that focusing can be achieved, although at the expense of higher stimulation currents required to evoke auditory percepts compared to MP stimulation. This spatial restriction is consistent with the findings of a recent study (Kalkman et al., 2015), which investigated several current focusing paradigms in a computational model of the human cochlea. Psychophysical investigation of FMP stimulation has shown to significantly improve patients ability to discriminate spectral features and dynamic ripple stimuli, suggesting an increase in spectral resolution (Smith et al., 2013). Recently, a clinical study on potential benefits of FMP stimulation for reducing electrode interactions showed a significant reduction in interaction, mainly contributed by electric-field summation, between two spatially separated simultaneous stimuli compared to MP stimulation (Marozeau et al., 2015). Consistent with these clinical and modelling studies, we have previously shown that FMP stimulation can produce a narrower spread of activation in the inferior colliculus (IC) compared to MP stimulation in acutely deafened animals, i.e. animals without loss of SGNs or peripheral fibers (George et al., 2014); although again at the expense of an increase in threshold.
Another promising current focusing technique is tripolar (TP) stimulation, where current is delivered to a central intracochlear electrode utilizing two adjacent intracochlear return electrodes. TP stimulation has been reported to produce sharper excitation patterns compared to MP stimulation (Bierer and Middlebrooks, 2002, Snyder et al., 2008, Fielden et al., 2013). However, as with FMP, the increased selectivity comes at the cost of higher current levels (CLs) to achieve adequate loudness in implant users compared to MP stimulation (Litvak et al., 2007a, Berenstein et al., 2008, Landsberger and Srinivasan, 2009). In order to provide greater loudness at the same CL as TP stimuli, partial tripolar (PTP) stimulation has been proposed (Mens and Berenstein, 2005, Litvak et al., 2007a, Srinivasan et al., 2013). In PTP, only a portion of current is returned via the adjacent intracochlear electrodes while the remaining current is returned through an extracochlear electrode. Closely analogous to the PTP stimulation, in the present study, we explore the efficacy of a stimulation mode that is referred to here as ‘partial focused multipolar’ or partial-FMP (pFMP) to achieve lower stimulation thresholds compared to the standard focusing FMP stimulation we have used previously (George et al., 2014). The technique involves varying the degree of current focusing by changing the level of compensation current (see Methods section for details).

As outlined above, current focusing techniques typically require high CLs to achieve threshold activation (Bierer and Faulkner, 2010, Zhu et al., 2012). In clinical situations, threshold levels are thought to be influenced by both: (a) the pattern of neural survival along the length of the cochlea; and (b) the position of the electrode relative to the neural population (Shepherd et al., 1993, Xu et al., 1993, Bierer, 2010, Long et al., 2014). Following sensorineural hearing loss, sensory hair cell loss leads to a number of degenerative and pathological changes to the peripheral processes and the SGNs that are the target neurons of CIs (figure 4.1). Degeneration is characterized by the retraction of the peripheral processes towards the SGN soma and a more gradual degeneration of the cell bodies within the Rosenthal canal (Nadol et al., 1989, Wise et al., 2005). The degeneration, which is progressive over time,
affects SGN responses to an electrical stimulus. Extensive loss of peripheral process and ongoing degeneration of SGNs can result in increased electrical thresholds (Shepherd and Javel, 1997, Landry et al., 2011). An increase in threshold would lead to higher power consumption and result in a greater spread of activation as excitation current spreads within Rosenthal’s canal potentially exciting a spatially broad region of SGNs (Frijns et al., 1996).

Figure 4.1 Schematic diagram of a cross-section through a cochlea illustrating the degenerative changes that occur following sensorineural hearing loss (Shepherd et al., 2013). (a) Normal cochlea showing the three fluid filled compartments (scala tympani, scala media and scala vestibuli), the organ of corti (OC) with sensory hair cells and the cell bodies of the spiral ganglion neurons (SGNs) within the Rosenthal’s canal. The peripheral process of the SGNs innervate the sensory hair cells (b) In a deaf cochlea, the sensory hair cells of the OC is severely damaged which results in the gradual degeneration of the OC. This was the typical status of the SGNs of acutely deafened cochleae in which we conducted our previous study (George et al., 2014) on FMP stimulation (note that the OC would be intact with degenerated sensory hair cells). (c) In a long-term deafened cochlea, more gradual degenerative changes such as extensive loss or retraction of peripheral processes and ongoing death of SGNs occur. This is the typical condition of clinically implanted cochleae.

Another factor that determines the effectiveness of CIs is the radial distance between the electrode and the neural population. There have been several previous studies conducted to investigate the effect of location of the electrode array within the scala tympani on neural excitation. Both electrophysiological (Shepherd et al., 1993, Xu et al., 1993) and psychophysical (Saunders et al., 2002, Long et al., 2014) studies have shown a significant correlation of threshold (electrical/ perceptual) CLs with electrode distance from the modiolus. In addition, electrodes in close proximity to SGNs (i.e. adjacent to the modiolar wall) have been shown to produce more
restricted neural activation in human cochleae (Cohen et al., 2003) as well as contribute to higher word recognition scores (Holden et al., 2013). It is worth noting that these studies came to a similar conclusion, using a variety of stimulation electrode geometries, that electrodes placed closer to the SGNs are beneficial.

Consequently, in the present study, we examine the efficacy of FMP stimulation compared to MP and TP stimulation in cochleae with significant SGN degeneration, induced by long-term deafness in experimental animals. These data will provide evidence of the efficacy of FMP across clinically relevant populations of SGN survival (Nadol et al., 1989). In addition, pFMP stimulation was investigated to examine the level at which threshold CL can be lowered without compromising spatial selectivity. Finally, we evaluated the influence of electrode position within the scala tympani on spatial selectivity and threshold of FMP stimulation to determine the optimum electrode array placement.

### 4.3 Methods

#### 4.3.1 Experimental animals

Data were collected from six adult cats that were chronically deaf for a duration of 10 to 12 months. Four animals were implanted unilaterally while two were implanted bilaterally, providing a total of eight implanted cochleae (n=8). Apart from the deafening, the experimental methodology and data analysis reported here are identical to that described in our previous study (George et al., 2014). Therefore, only essential elements of surgical, electrical stimulation and neural recording procedures are outlined here. All procedures were in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and with the National Institutes of Health, USA guidelines regarding the care and use of animals for experimental procedures, and were approved by the Royal Victorian Eye and Ear Hospital Animal Research and Ethics Committee.
4.3.2 Deafening procedure

Each animal was administered a daily injection of neomycin sulphate (60 mg kg\(^{-1}\); subcutaneously [s.c]) commencing the day after birth for approximately 20 days (Leake et al., 2000, Fallon et al., 2009). The hearing status of each animal was then measured by recording the auditory brainstem response (ABR) to acoustic stimuli using standard techniques (Coco et al., 2007). If hearing persisted, neomycin injections were continued for three days before the next ABR. This procedure was repeated until the animal was profoundly deaf (i.e. absence of a click-evoked ABR at 100 dB peak equivalent sound pressure level (p.e. SPL) in both ears).

4.3.3 Physiological data collection

Animals were anaesthetized using ketamine (intramuscular, 20 mg kg\(^{-1}\)) and xylazil (subcutaneous, 2 mg kg\(^{-1}\)), and maintained over the duration of the experiment (2–3 days) with a slow continuous intravenous infusion of sodium pentobarbital (3–8 mg kg hr\(^{-1}\)). An endotracheal tube was inserted at the beginning of the experiment to monitor respiration rate (normal levels: 10–20) and end-tidal CO\(_2\) levels (normal levels: 3–5%). The core body temperature was maintained at 37.0 ± 1°C. Animals were implanted with a Hybrid-L 14 array (HL14), consisting of 14 half-band platinum electrodes, inserted approximately 10.5 mm through the round window into the scala tympani (Shepherd et al., 2011). A platinum ball electrode was placed in the neck muscles to serve as the extracochlear return electrode. Following implantation, animals were placed in a stereotaxic frame.

An in-house designed multi-channel stimulator generated all electrical stimuli. Electrical stimuli were cathodic-first, charge balanced single biphasic pulses presented at rate of 4 Hz. The current amplitude was programmed in clinical CL units defined by Cochlear Ltd., ranging between 0 and 255, where, current in μA = \(17.5 \times (100^{CL/255})\). With MP stimulation, current pulses with phase duration of 100 μs and inter-phase gap of 50 μs were delivered to an intracochlear electrode and the
extracochlear return electrode. In the TP stimulation configuration, current pulses with 400 μs phase and 50 μs inter-phase gap were delivered to a central intracochlear electrode with two adjacent intracochlear return electrodes, each carrying half the current in opposite phase. In FMP stimulation mode, weighted positive and negative current pulses, with phase durations of either a 100 or 400 μs with a 50 μs inter-phase gap, were delivered simultaneously to multiple electrodes. The differences in pulse durations were a result of the greater charge required using FMP and TP configurations to evoke neural activity. The term ‘channel’ was used to address a set of electrodes used to deliver current in a particular stimulation configuration. The channels were numbered increasing from base to apex, in accordance with the convention used for the clinical CI (figure 4.2(a)). The number of its centre electrode indicated each FMP and TP channel. For each FMP channel, the weight vector was constructed based on the strategy adapted from (van den Honert and Kelsall, 2007). The trans-impedance matrix was measured for all intracochlear electrodes, with each column of the inverse of this matrix used to calculate the numerical weights that determined the current from each electrode to produce a single FMP stimulation channel.
As described in George et al. (2014), a craniotomy was performed to expose the entire dorsolateral surface of the contralateral IC. Multi-unit recordings to electrical stimulation were made over a range of CLs and different stimulation configurations (MP, FMP and TP). Multi-unit neural activity was recorded using a 32-channel silicon substrate recording array (NeuroNexus Technologies, USA) inserted along the...
The array recorded neural activity over approximately 3.2 mm of the IC. Neural spike activity from the 32 recording sites was amplified, band-pass-filtered (0.3–5 kHz) and digitized at a sample rate of 30 kHz using a Cerebus data acquisition system (Blackrock Microsystems, USA). At the conclusion of the experiment, the animal was euthanized and the cochleae were collected for histological analysis.

4.3.4 Data analysis

Multi-unit activity was processed offline, using customized spike detection scripts in IgorPro (Wavemetrics, USA). Stimulus artefacts were removed using the techniques detailed in Heffer and Fallon (2008). Spike detection threshold was set at four times root mean square for each recording channel (Fallon et al., 2009). Spikes in a 3–35 ms post stimulus window were used in the analysis. The window parameters were based on first-spike latencies and the early onset response of IC neurons to the electrical stimulation (figure 4.2(a)). At each recording site, the spike counts were averaged across 10 trials for each stimulus channel, stimulation configuration and CL and normalized to the maximum spike rate.

4.3.4.1 Response images

Normalized spike rates (NSRs) recorded across the array were displayed as ‘response images’ with the stimulus intensity on the y-axis and the depth of the recording site on the x-axis (figure 4.4). Each response image illustrated the spatial extent of evoked multi-unit neural activity across the recording array for a given stimulating channel and stimulus configuration. With each response image, the lowest CL that elicited a NSR of 0.3 was taken as the threshold for that stimulus condition (Landry et al., 2013). The recording site with the lowest threshold was defined as the best recording site.

As the stimulus intensity increased, there was a monotonic increase in neural response. To quantify the growth in neural response with increase in stimulus level
at each recording site, the discrimination index, $d'$, was computed using a procedure derived from signal detection theory (Macmillan and Creelman, 2005). The area under the receiver operator curve, formed for each pair of CLs (threshold CL and a supra-threshold CL), was expressed as a standard deviate and the resulting $z$-score was multiplied by $\sqrt{2}$ to obtain $d'$.

The value of $d'$ was computed across increasing stimulus levels above the threshold level (i.e. NSR = 0.3) for the best recording site of each stimulating channel. The supra-threshold CL that resulted in a significant increase in the neural response (i.e., the CL that yielded a $d'$ of 1 above the threshold response) was defined as the distinguishable level (figure 4.2(c)) and this level was chosen to measure spread of activation and total neural response growth in the IC. This distinguishable level was also used to measure the ‘discrimination slope’ of the best recording site (expressed in units of $d'$ per dB; calculated from the difference between the threshold and the distinguishable level) as an indication of dynamic range for the initial slope of the supra-threshold stimulus-response function (Middlebrooks and Snyder, 2007, George et al., 2014). This slope was used as a measure of dynamic range because we seldom saw saturated responses using current focusing techniques within the predefined clinical safety limits of the device.

### 4.3.4.2 Effect of SGN degeneration and configuration on spatial selectivity

To study the effect of SGN degeneration and stimulation configuration on the IC neural response, minimum threshold, discrimination slope, spread of activation and the total neural response growth in the IC were measured for each response image and compared between the MP, FMP and TP stimulation configurations.

**Spread of activation in the IC**

To quantify the spread of activation, a spatial tuning curve (STC) was constructed for each IC response image by connecting the stimulus levels that elicited threshold response (NSR = 0.3) at each IC recording site (figure 4.4). The widths of STCs were measured at the distinguishable level and compared between the MP, TP and FMP
stimulation configurations.

Measure of total neural response growth in the IC

We measured the total neural response across the recoding array as a correlate for loudness (Litvak et al., 2007a, McCreery et al., 2010). We calculated the total neural response for each channel stimulated by summing the NSR on each active recording site at a particular CL. The increases in neural response from threshold level to the distinguishable level were computed and compared across the different stimulus configurations.

4.3.4.3 Effect of pulse duration on spatial selectivity

With FMP and TP stimulation, high threshold levels and widespread SGN degeneration associated with long-term deafness resulted in requiring longer pulse durations for electrical stimulation. In order to confirm that different pulse durations (100 μs and 400 μs) used in our study did not have a confounding effect on spatial selectivity, sixteen FMP channels with low IC threshold using 400 μs phase duration pulses were also stimulated using 100 μs phase duration. We compared the STC widths and thresholds measured for longer pulses with that of shorter pulses.

4.3.4.4 Effect of pFMP on spatial selectivity

FMP stimulation involved the measurement of trans-impedances between all electrodes. The trans-impedance matrix was then used to determine current weights for each electrode in such a way that an excitatory voltage was only delivered to the central electrode and null voltage to the other electrodes (van den Honert and Kelsall, 2007). The technique that we have used to vary the degree of focusing was to simply multiply the diagonal terms (calculated by linear extrapolation) of the trans-impedance matrix by a factor called the ‘peak multiplier’. Since the effects of the peak multiplier were non-linear, we developed a focusing variable called the defocusing factor (DF) that varied between 0 and 1, where peak multiplier is $1/(1−DF)$. DF of 0 corresponded to the most focusing or standard FMP stimulation and DF of 1 corresponded to the least focusing or standard MP stimulation (see
figure 4.7 for example). Data was collected from three cochleae for this purpose. Twenty-one FMP channels (i.e., channels with at least two flanker electrodes on each side) were stimulated at DF of 0.0, 0.1, 0.2, 0.4, 0.6 and 0.8.

4.3.4.5 Effect of electrode location on spatial selectivity
We implanted two animals bilaterally; in one ear the electrode array was positioned normally (i.e., half band electrodes facing the modiolus) while the electrode array in the other ear was deliberately positioned with the half band electrodes facing the lateral wall (figure 4.2(b)). In the remaining four unilaterally implanted animals, the electrode array was positioned normally. This provided a total of 50 channels with the electrode placed normally and 15 channels with the electrode placed in reverse position in order to evaluate the efficacy of stimulation configuration as a function of electrode position within the scala tympani.

4.3.4.6 Comparison between normal hearing and long-term deafened animals
In order to determine whether significant reductions in SGN population will reduce the advantage of FMP stimulation in producing focused neural activation, we compared the STC width and threshold measured for long-term deafened animals with our previous study (George et al., 2014) using acutely deafened animals (i.e., cochleae with normal SGN populations).

4.3.5 Cochlear histology
To evaluate the extent of SGN degeneration, cochleae of all animals were prepared for histological examination. The implanted cochleae were removed, decalcified, trimmed, embedded in cryosectioning compound and serially sectioned in the modiolar plane at a thickness of 12 μm using a cryostat at −20 °C. Sections were stained with haematoxylin and eosin and examined under the light microscope. The status of cochlear pathology was determined by measuring the SGN density within the Rosenthal’s canal (Wise et al., 2011). In each section, different cochlear turns (basal, middle and apical) were identified. The area of the Rosenthal’s canal was
measured using Carl Zeiss AxioVision LE 4.8.2.0 software and the SGNs in that area with a visible nucleus and nucleoli were counted to determine the density of the SGNs as cells per square millimetres for each cochlear turn.

4.3.6 Statistical analysis

All statistical analyses were performed using SigmaPlot Version 12.5 (Systat, USA). Comparisons of IC threshold, discrimination slope, STC width and total neural response growth between MP, TP and FMP stimulation were performed using one-way repeated measures ANOVAs, with Tukey corrected post-hoc testing of individual comparisons where appropriate. Comparisons of threshold and STC width measured at 100 μs and 400 μs phase durations with FMP stimulation were performed using a paired t-test. Comparisons of threshold and STC width measured for different DFs were performed using one-way repeated measures ANOVAs, with Tukey corrected post-hoc testing of individual comparisons. Comparisons of threshold and STC width measured at two different electrode locations were performed by pooled t-test. Where two animal groups (acute and long-term deafened) were compared, a pooled t-test was used.

4.4 Results

4.4.1 Hearing status and cochlear histology

Following deafening, all the animals had click thresholds ≥100 dB p. e. SPL and were therefore confirmed to be profoundly deaf. The cochlear sections were used to examine the status of the organ of corti and to quantify SGN survival. Figure 4.3(a) shows a representative mid-modiolar section illustrating the typical cochlear pathology observed in this study. Analysis of the cochlear histology indicated a total loss of the organ of corti in all cochlear turns, with reduced SGNs within the Rosenthal’s canal and loss of peripheral processes within the osseous spiral lamina.
The mean SGN density within the Rosenthal’s canal at different cochlear regions measured in this study was compared to the mean SGN density within normal hearing cat cochleae from a previous study (Wise et al., 2011). We observed a significant loss of SGNs in all the cochlear regions (figure 4.3(b)), with the basal and middle regions exhibiting around 6–10% SGN survival compared to normal cochleae.

Figure 4.3 Photomicrograph of a mid-modiolar section through a long-term deafened cat cochlea (a) illustrating the cochlear regions examined i.e. lower basal (LB), upper basal (UB), lower middle (LM), upper middle (UM) and apical (A) regions. The right panels show higher magnification images of lower basal cochlear region illustrating the reduced SGN population. (b) Mean % of SGN survival within Rosenthal’s canal at different cochlear regions in long-term deafened cochleae (n = 6). Mean SGN density measured in the present study is expressed relative to the data from normal hearing cat cochleae i.e., an average SGN density (expressed in cells per square millimetres) of 1146.1 for LB, 1202.08 for UB, 1289.73 for LM, 1331.36 for UM and 1101.8 for A regions (Wise et al., 2011). Error bar = Standard error of the mean (SEM).
4.4.2 Response images

IC response images were generated for electrical stimulation with MP, FMP and TP stimulus configurations. Figure 4.4 presents IC response images from one animal following electrical stimulation of cochlear channel 8 (in the apical sixth of the array) in three different stimulation configurations. In each panel, an STC was plotted by connecting threshold at each IC recording site (shown by the white line). Increases in stimulus intensity above threshold resulted in increasing spread of activation along the recording array and thus, increasing width of the STC. The STCs of FMP and TP stimulation were similarly narrow at low intensities while MP STCs were very broad, generally spreading across the entire recording array and resulting in significant myogenic activity at high intensities (figure 4.4(c)).

![Figure 4.4](image)

**Figure 4.4** Response images across the cochleotopic axis of the IC to electrical stimulation using (a) FMP (b) TP and (c) MP electrode configurations in a long-term deafened cat. Normalized spike rates (NSR) were represented by colours from yellow to black with yellow representing the highest activity. A spatial tuning curve (STC) was constructed by connecting the stimulus levels that elicited 0.3 NSR on each IC recording site (shown by the white line). The tip of each STC corresponded to the recording site that was most sensitive to that particular electrical stimulus. In this example, the location of the most sensitive recording site corresponded to ~1.9 mm from the IC surface. Each response image was labelled according to configuration and channel number (shown for stimulating channel 8). Note that for MP stimulation, each pulse had a phase of 100 μs while TP and FMP configurations used pulses with 400 μs phase duration, so the differences in electrical threshold between stimulation configurations are not evident in this figure.
4.4.3 Effect of SGN degeneration and electrode configuration on spatial selectivity

Across the six long-term deafened animals, 65 CI channels were stimulated using MP, FMP and TP configurations. Figure 4.5 shows minimum threshold, discrimination slope, STC width and growth function of the total spike activity for MP, FMP and TP stimulation in long-term deafened cats.

4.4.3.1 Threshold and discrimination slope

Minimum thresholds, converted to nC per phase, are shown in figure 4.5(a). Mean thresholds were significantly different between stimulation configurations (one-way RM ANOVA, \( p < 0.001 \)); with post-hoc tests indicating that MP stimulation had a significantly lower threshold than FMP or TP stimulation (\( p' s < 0.001 \)) and the thresholds for FMP and TP stimulation were not significantly different (\( p = 0.938 \)). Discrimination slopes for the best recording sites (IC sites with the lowest thresholds) were computed for MP, FMP and TP stimulation configurations and are presented in figure 4.5(b). There was no significant difference in the discrimination slopes between MP, FMP and TP stimulation configurations (one-way RM ANOVA, \( p = 0.827 \)).

4.4.3.2 Spread of activation in the IC

A repeated measure ANOVA revealed a significant difference among the STC widths measured using different stimulation configurations (figure 4.5(c), \( p < 0.001 \)) and Tukey post hoc analysis confirmed that the STC width was significantly higher for MP than both FMP and TP stimulation configurations (\( p' s < 0.001 \)). There was no significant difference in the STC widths between FMP and TP configurations (\( p = 0.346 \)).
**Figure 4.5** Group means for IC thresholds, discrimination slopes, STC widths and growth function of total spike activity (mean + SEM) measured for MP, FMP and TP stimulation configurations in long-term deafened cats. (a) Threshold levels are expressed in charge (nC). (b) Discrimination slope ($d'$ per dB) was calculated from the threshold level and the level that resulted in $d' = 1$ above the threshold level (i.e., the distinguishable level) on the best recording site. (c) STC widths (mm) measured at the distinguishable level. (d) Increase in total spike activity. ** $p < 0.001$, N = 65 channels.

### 4.4.3.3 Measure of total neural response growth in the IC

There was a monotonic increase in neural response with increasing stimulus intensity associated with each electrode configuration. The increase in total neural response from the threshold to the distinguishable level was dependent on stimulus configuration (figure 4.5(d); one-way RM ANOVA, $p < 0.001$); with post-hoc tests confirming that FMP and TP electrode configurations have significantly lower rate of growth compared to the MP configuration ($p < 0.001$). There was no significant difference between FMP and TP configurations ($p = 1$).
4.4.4 Effect of pulse duration on spatial selectivity

Figure 4.6 shows the mean threshold and STC width measured for FMP channels stimulated at 100 μs and 400 μs phase duration. As expected, there was a significant difference in the threshold expressed in charge/phase between 100 μs and 400 μs phase duration (figure 4.6(a); paired t-test, \( p < 0.001 \)). However, no difference was found between the STC widths (figure 4.6(b); paired t-test, \( p = 0.625 \)) at these two pulse durations pooled across 16 FMP channels.

![Figure 4.6](image)

**Figure 4.6** Group means for IC thresholds and STC widths (mean + SEM) measured for FMP stimulation using phase duration of 100 μs and 400 μs in long-term deafened cats. (a) Threshold levels expressed in charge (nC). (b) STC widths (mm). ** \( p < 0.001 \), N = 16 channels.

4.4.5 Effect of pFMP stimulation on spatial selectivity

IC response images were plotted for FMP channels at DF of 0, 0.1, 0.2, 0.4, 0.6 and 0.8. Representative response images generated from one animal by stimulating cochlear channel 12 and the corresponding FMP weights on each electrode with DF of 0, 0.2, 0.4 and 0.8 are illustrated in figure 4.7.
Figure 4.7 Representative response images across the cochleotopic axis of the IC for pFMP stimulation of cochlear channel 12 using DF of 0.0, 0.2, 0.4 and 0.8. As the DF is increased from 0 to 0.8, the IC threshold (minima of STC) decreased, spread of neural activity increased and the myogenic threshold also decreased. The panel above each response image shows the corresponding weighting of stimulation current for pFMP stimulation of channel 12.

The mean threshold, STC width, discrimination slope and growth rate of total neural spike activity measured with various DFs are shown in figure 4.8. As expected, the threshold decreased monotonically and the spread of activation increased as DF increased from 0 to 0.8. Threshold at DF of 0 was significantly greater (figure 4.8(a); one-way RM ANOVA) than the threshold at DF of 0.1 ($p < 0.05$), DF of 0.2 ($p < 0.001$), DF of 0.4 ($p < 0.001$), DF of 0.6 ($p < 0.001$) and DF of 0.8 ($p < 0.001$). With STC width, no significant difference was observed on increasing the DF from 0 to 0.6 (figure 4.8(b); one-way RM ANOVA, $p$'s $> 0.05$) while the widths measured at DF of 0.8 were significantly greater than that measured at DF of 0 ($p < 0.05$). We also performed analyses for STC width measured at a higher supra-threshold level (i.e., the stimulus level that elicited a NSR of 0.7), which exhibited a similar trend as the STC width measured at the distinguishable level (data not shown). One way RM ANOVAs performed on the mean discrimination slopes for different defocusing factors revealed that only the discrimination slope for DF of 0.8 was significantly higher than that for DF of 0 (figure 4.8(c); $p < 0.05$), indicating a reduced dynamic range for the least-focused FMP compared to standard FMP. Moreover, we observed a significant
increase in growth rate of total neural response only for DF of 0.8 compared with DF of 0 (figure 4.8(d); one-way RM ANOVA, p < 0.05).

**Figure 4.8** Group means (mean + SEM) for (a) threshold (b) STC width (c) discrimination slope and (d) increase in total neural spike activity measured for FMP stimulation with varying defocusing factor (DF) without adjusting the total net current delivered to the intracochlear electrodes. DF of 0 is the most focused stimulus while DF of 0.8 is the least focused. * p < 0.05, ** p < 0.001, N = 21 channels.

### 4.4.6 Effect of electrode location on spatial selectivity

Figure 4.9 shows different features measured to evaluate the efficacy of current focusing with different electrode locations within the cochlea. As expected, there was a small but significant difference in the MP thresholds for the two electrode
locations within the scala tympani (figure 4.9(a); t-test); thresholds measured with
the electrode array in the reverse position were significantly greater than the normal
position ($p = 0.002$). However, there was no significant difference in the threshold
measured for normal and reverse electrode positioning using FMP (figure 4.9(a); t-

threshold, $p = 0.691$) or TP stimulation configurations (t-test, $p = 0.782$). No significant
difference in the STC width was observed (t-test, $p = 0.493$ for MP stimulation, $p =
0.197$ for FMP stimulation and $p = 0.440$ for TP stimulation; figure 4.9(b)) for the
different electrode array locations.

![Figure 4.9](image.png)

**Figure 4.9** Group means for IC thresholds and STC widths (mean + SEM) measured for MP, FMP
and TP stimulation with normal and reverse positioning of the electrode array in long-term
deafened cats. (a) Threshold levels (nC) (b) STC widths (mm). ** $p < 0.001$, N = 50 (normal
position) and 15 (reverse position) channels.

### 4.4.7 Comparison between normal hearing animals and long-term
deafened animals

Figure 4.10 shows pooled data from acutely deafened cochleae data taken from our
previous study (George et al., 2014) in comparison with data from long-term
deafened cochleae obtained from the present study. A comparison of IC thresholds
from MP stimulation revealed no significant difference between acutely deafened
and long-term deafened animals (figure 4.10(a); t-test, $p > 0.05$). However, there was
a significant difference in FMP and TP thresholds when these two groups were
compared; thresholds from long-term deafened cochleae were significantly higher than the acutely deafened cochleae (figure 4.10(a); t-test, p’s < 0.01).

Figure 4.10 Group means (mean + SEM) for a) IC thresholds (nC), (b) STC widths (mm) (c) discrimination slope and (d) growth function of total spike activity measured for MP, FMP and TP stimulation in acutely deafened cochleae (normal SGN population; from George et al. (2014); N = 8) and long-term deafened cochleae (N = 8). * p < 0.01, ** p < 0.001.

A comparison of STC widths measured for different stimulation configurations revealed a significant difference between the two groups (figure 4.10(b)). STC widths obtained from acutely deafened animals were significantly narrower than those from long-term deafened animals (t-test, p’s < 0.001). There was no significant difference in discrimination slope between the acutely deafened cochleae and the long-term deafened cochleae in any stimulation configuration, indicating that chronic deafness did not affect the dynamic range of each stimulation configuration
significantly (figure 4.10(c); t-test, \( p's > 0.05 \)). There was a significant effect of chronic deafness on the growth of total neural response for all stimulation configurations, with rate of growth higher in long-term deafened cochleae compared to acute deafened cochleae (figure 4.10(d); t-test, \( p's < 0.01 \)).

### 4.5 Discussion

In the present study, we investigated the effects of SGN degeneration and electrode placement on spatial spread of neural activation using intracochlear FMP stimulation compared to MP and TP stimulation. We also investigated the effects of pulse duration and varying levels of compensation current on spatial selectivity of FMP stimulation.

The main finding of this study was that, in animals with severe SGN degeneration, FMP and TP stimulation produced significantly narrower spatial spread of neural activity in the IC than MP stimulation; although greater current was required to achieve threshold level using FMP and TP stimulation. We found no significant difference in the discrimination slope measured for MP, FMP and TP stimulation, indicating little difference in the dynamic range for different stimulation configurations. In addition, MP stimulation was found to have a rapid growth in total neural response compared to TP and FMP stimulation. However, there was no significant difference between FMP and TP stimulation in any of the measures. In comparison with our previous study (George et al., 2014) that evaluated the efficacy of FMP stimulation in acutely deafened cats with normal SGN survival, the present data from long-term deafened animals demonstrated an elevated IC threshold for FMP and TP stimulation. There was no significant difference in MP threshold between the long-term deafened and acute cochleae, despite the difference in SGN survival. There was a noticeable increase in the width of the STC measured for all the three stimulation configurations in long-term deafened cochleae compared to acute deafened cochleae, suggesting degradation in the stimulation performance with SGN
degeneration. However, it should be noted that the spatial extent of neural activation remained significantly smaller with FMP and TP stimulation compared to MP stimulation in long-term deafened cochleae with severe SGN degeneration.

Longer pulse widths were employed with FMP and TP stimulation compared to MP stimulation, as FMP and TP required a greater charge per phase to evoke neural activity than MP. In clinical stimulation strategies, stimulus amplitude and pulse duration are used to modulate the loudness percept. Previous studies have shown that longer pulse durations result in a greater spread of neural activation than stimuli with equal charge/phase or equal loudness using shorter pulse durations (Shannon, 1985, McKay and McDermott, 1999). Consequently, in the present study, it was important to justify the comparison of spread of neural activation produced by FMP stimulation using 400 μs and MP stimulation using 100 μs. Our data indicated that the spatial selectivity of FMP stimulation is not influenced by the phase duration of the electrical stimuli.

Using pFMP stimulation strategy, the present study illustrated a general decrease in the threshold in the IC as the DF was varied from 0 to 0.8. However, there was no significant increase in the STC width on increasing the DF from 0 to 0.6 and a significant increase was observed only on increasing the DF to 0.8. Thus, the present study showed that it is possible to significantly lower the FMP threshold level without a significant increase in the spread of neural activation by raising the DF from 0 up to 0.6. This would be roughly analogous to PTP, a configuration similar to TP (Kral et al., 1998, Litvak et al., 2007a, Landsberger et al., 2012). This configuration has been shown to provide the benefits of both TP and MP stimulation by preserving restricted neural activation while lowering the threshold CL (Mens and Berenstein, 2005, Srinivasan et al., 2013). The present study also showed a gradual increase in the discrimination slope of the best recording site on moving from the standard FMP (DF=0) to the least-focused FMP (DF=0.8) with a significant difference observed between DF of 0 and 0.8. This indicates a reduced dynamic range for the less-focused FMP, at least for the initial slope of the supra-threshold stimulus-response function.
Even though our analysis focused on the responses at a near-threshold level, we observed a similar trend with the spread of activation when measured at a higher stimulus level (i.e., at the level that elicited a NSR of 0.7).

In the present study, we observed significant increases in MP threshold levels when the electrode array was implanted in the reverse position. This observation is consistent with a number of previous studies that reported that an electrode array placed closer to the modiolar wall results in lower threshold levels (Shepherd et al., 1993, Xu et al., 1993, Saunders et al., 2002). However, in a somewhat surprising result, we observed that the position of the electrode array did not appear to affect FMP and TP threshold levels. Additionally, the spatial selectivity during MP, FMP and TP stimulation was unaffected by electrode position. This suggests that the efficacy of current focusing techniques to produce restricted neural activation is not compromised with electrode position within the scala tympani. This is in contrast to a clinical study (Cohen et al., 2003) in which the effect of electrode type on the spatial extent of electrically evoked compound action potential (ECAP), estimating the peripheral spread of neural excitation, was investigated using MP stimulation. The mean width was found to be significantly smaller for the half-banded modiolar hugging Contour array compared to a straight-banded array, indicating a positive correlation between the spread of neural excitation and the radial distance of the electrode from the modiolus. The discrepancy between the results of the present study and the Cohen et al study is likely to be related to a number of factors. Firstly, the different distances between the electrode and the target SGNs; the two electrode positions (normal and reverse) tested in the present study would have resulted in less variation in the radial distance of the electrode from the modiolus than in the Cohen et al study. Secondly, the change in selectively observed by Cohen et al may also have resulted from changes in the geometry of the electrode (half-band compared to full-band). Thirdly, it is likely that the ECAP results of Cohen et al are influenced by the effect of electrode position on recordings as well as any effect on the stimulation itself. Finally, Saunders et al. (2002) has suggested that several
factors such as the etiology of the hearing loss and pattern of fibrous tissue growth can influence the correlation between the psychophysical measures and electrode distance, so it is worth noting that all electrodes were acutely implanted in the current study, so there would have been no fibrous tissue capsule.

In the present study, the results indicate that current focusing is not highly dependent on distance from the SGNs, at least within the confines of the dimensions of the cat cochlea. In a recent modelling study, Kalkman et al. (2015) showed that current focusing using FMP was not diminished using electrodes positioned along the lateral wall of the cochlea. Indeed, Kalkman demonstrated improved focusing using this electrode position compared to electrodes placed close to the SGNs. The finding that spatial selectivity for all stimulation modes was unaffected by the electrode position could be interpreted as the site of stimulation in these experiments had spread centrally to the auditory nerve or the auditory brainstem. However, we observed a systemic shift in the location of the most sensitive IC recording site to more ventromedial locations when moving the electrical stimuli from an apical cochlear channel to a more basal channel, consistent with the fact that were selectively stimulating SGNs within the cochlea.

In short, the present study has indicated that the high degree of spatial selectivity achieved using FMP stimulation compared to MP stimulation is maintained in cochleae with low SGN survival and in situations when the electrodes are positioned proximal to the lateral wall. Moreover, the spatial selectivity measures of FMP stimulation remained unchanged across phase durations of 100–400 μs. The study also illustrates how threshold level can systematically decrease as the degree of ‘focusing’ is varied from the most focused (DF=0) to the least focused (DF=0.8). Importantly, on comparing long-term deafened cochleae with cochleae having normal SGN and peripheral fiber populations, we saw a significant increase in STC width for MP, FMP and TP stimulation and a significant increase in FMP and TP thresholds.
Clinical significance

The difference in SGN survival patterns across different listeners is likely to contribute to the variability in CI performance from listener to listener. Recently, Seyyedi et al. (2014) reported a positive correlation between speech perception scores using conventional stimulation strategies and overall SGN count. Technologies designed to improve the electrode–neural interface may be important in optimizing the effectiveness of new stimulation strategies for improved CI performance. In the present study, the performance of current focusing techniques was associated with the SGN survival. Significantly higher stimulation currents were required to achieve threshold activation in cochleae with extensive SGN loss. Biological interventions aimed at preserving SGNs and their peripheral process and promoting their regrowth, such as the administration of exogenous neurotrophins (Wise and Lisa, 2012), may play an important role in concert with current focusing techniques in enhancing CI function.

Importantly, FMP stimulation has the potential to provide benefit for other neural prostheses such as deep brain stimulation to treat movement disorders and spinal cord stimulation to manage chronic pain, where excitation of non-target neurons could cause adverse side effects. Techniques that effectively focus electrical stimulation will provide a benefit for these systems by ensuring a more precise and controlled form of neural activation.

We have shown that FMP stimulation produces highly spatially restricted excitation in cochleae with normal and severe SGN loss. Future experimental work is required to investigate whether FMP stimulation can increase the number of temporally independent channels and to examine the long-term safety of FMP stimulation.
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Chapter 5: Electrophysiological channel interactions using focused multipolar stimulation for cochlear implants
ELECTROPHYSIOLOGICAL CHANNEL INTERACTIONS USING FOCUSED MULTIPOLAR STIMULATION FOR COCHLEAR IMPLANTS

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5.1 Abstract

\textit{Objective.} Speech intelligibility with existing multichannel cochlear implants (CIs) is thought to be limited by poor spatial selectivity and interactions between CI channels caused by overlapping activation with monopolar (MP) stimulation. Our previous studies have shown that focused multipolar (FMP) and tripolar (TP) stimulation produce more restricted neural activation in the inferior colliculus (IC), compared to MP stimulation. \textit{Approach.} This study explored interactions in the IC produced by simultaneous stimulation of two CI channels. We recorded multi-unit neural activity in the IC of anaesthetized cats with normal and severely degenerated spiral ganglion neuron populations in response to FMP, TP and MP stimulation from a 14 channel CI. Stimuli were applied to a ‘fixed’ CI channel, chosen toward the middle of the cochlear electrode array, and the effects of simultaneously stimulating a more apical ‘test’ CI channel were measured as a function of spatial separation between the two stimulation channels and stimulus level of the fixed channel. Channel interactions
were quantified by changes in neural responses and IC threshold (i.e., threshold shift) elicited by simultaneous stimulation of two CI channels, compared to stimulation of the test channel alone. **Main results.** Channel interactions were significantly lower for FMP and TP than for MP stimulation \((p < 0.001)\), whereas no significant difference was observed between FMP and TP stimulation. With MP stimulation, threshold shifts increased with decreased inter-electrode spacing and increased stimulus levels of the fixed channel. For FMP and TP stimulation, channel interactions were found to be similar for different inter-electrode spacing and stimulus levels of the fixed channel. **Significance.** The present study demonstrates how the degree of channel interactions in a CI can be controlled using stimulation configurations such as FMP and TP; such knowledge is essential in enhancing CI function in complex acoustic environments.

### 5.2 Introduction

Modern cochlear implants (CIs) employ multiple stimulating channels to convey complex speech information, where a channel refers to a combination of one or more active and return electrodes used to deliver electrical stimuli. Speech perception with multi-channel CIs has greatly improved over the years, to the level that most subjects receive very good speech understanding in quiet listening conditions. However, psychophysical studies suggest that when multiple channels are stimulated simultaneously, overlap of stimulating currents cause interactions between channels with a high degree of spectral smearing (Boëx et al., 2003, Bierer, 2007). Channel interactions along with limited spatial selectivity are believed to saturate the performance of CI users when more channels are activated (Friesen et al., 2001, Fu and Nogaki, 2005, Başkent, 2006). Moreover, some of the variability in speech understanding abilities found across CI users is thought to be associated with the degree of channel interactions (Hanekom and Shannon, 1998, Stickney et al., 2006).
Channel interactions can result from the vector summation of electric current fields in the cochlea as well as overlapping neural excitation at the periphery, or at a more central level following stimulation (Shannon, 1983, de Balthasar et al., 2003). A single neuron or neural population can be affected by stimuli from several stimulation channels, leading to these stimuli being perceptually indistinguishable or confused. The interaction can also be unpredictable (Stickney et al., 2006), often resulting in uncontrolled loudness. Many CI users report difficulties discriminating speech in noise and poor perception of sounds such as music that are rich in temporal and spectral information (Skinner et al., 1994, Sucher and McDermott, 2007). Several psychophysical experiments have demonstrated changes in behavioural responses (i.e., threshold and loudness measures), speech recognition scores and the quality of the sound, consistent with the degree of channel interaction associated with simultaneous and nonsimultaneous stimulation (White et al., 1984, Favre and Pelizzone, 1993, McKay et al., 2001, Tang et al., 2011, Snel-Bongers et al., 2012, Padilla and Landsberger, 2014).

It has been postulated that spatially restricting intracochlear electrical stimulation by focusing of current may maximize the number of truly independent channels that would lead to a more natural sound perception. Current focusing stimulation modes such as bipolar (BP) stimulation (van den Honert and Stypulkowski, 1987, Rebscher et al., 2001), tripolar (TP) (Jolly et al., 1996, Snyder et al., 2004) and quadrupolar or partial tripolar stimulation (Landsberger and Srinivasan, 2009, Bierer et al., 2010) have been reported to activate restricted population of neurons compared to monopolar (MP) stimulation (which is used in most contemporary CIs), however at the expense of higher stimulation current. Both psychophysical measures (Boëx et al., 2003, Stickney et al., 2006, Bierer, 2007) and electrophysiological studies (Bierer and Middlebrooks, 2004) of channel interaction have revealed that current focusing modes result in reduced channel interaction. Despite this, MP is the most commonly used configuration for CIs and CI users generally prefer MP stimulation over BP/TP stimulation. Studies of speech perception have generally shown that patients
perform at least as well with MP stimulation as with BP stimulation (Zwolan et al., 1996, Pfingst et al., 2001) and many CI users can pitch-rank MP electrodes (Boëx et al., 2006). Moreover, the lower stimulation levels for MP stimulation often result in better battery life than current focusing strategies.

Focused multipolar (FMP) stimulation (also referred to as phased array or multipolar stimulation), has also been proposed as a method to spatially restrict neural activation in the cochlea (van den Honert and Kelsall, 2007). In contrast to TP stimulation which uses three intracochlear electrodes, FMP stimulation employs all the intracochlear electrodes and it has been hypothesized, therefore, to produce a more focused region of activation than TP stimulation. Our previous electrophysiology studies on acutely deafened and long-term deafened cats showed that single channel FMP stimulation can produce a narrower spread of activation in the inferior colliculus (IC) compared to MP stimulation, with no significant difference observed between FMP and TP stimulation (George et al., 2014, 2015a). Moreover, Smith et al (2013) used psychophysical tests to show that this multielectrode stimulation mode improved the ability of CI users to discriminate spectral features in sound stimuli. These results indicate that FMP stimulation might be a promising tool for increasing the number of independent channels for stimulation along the cochlea. Recently, a clinical study conducted by Marozeau et al (2015) reported a significant reduction in channel interactions with FMP compared to MP stimulation in a psychophysical task. However, there have been no direct comparisons of channel interaction measures using FMP, TP and MP stimulation.

The primary goal of the present study was therefore to evaluate IC neural responses to simultaneous two-channel stimulation in the cochlea using FMP compared to both MP and TP stimulation. We conducted the study in both acutely deafened (i.e., cochleae with normal spiral ganglion neuron (SGN) populations) and long-term deafened (i.e., cochleae with severe SGN degeneration) cats to also evaluate any effects of chronic deafness/SGN degeneration on channel interactions. We chose to study the simultaneous condition because it results in the highest degree of channel
interactions (Favre and Pelizzone, 1993, Boëx et al., 2003). Measures of channel interactions while varying the spatial separation of the channels (inter-electrode spacing) across the cochlear electrode array were also compared across stimulation configurations. Finally, we also tested the influence of stimulus level on channel interactions.

5.3 Methods

5.3.1 Experimental animals

All procedures were conducted with approval from the Royal Victorian Eye and Ear Hospital Animal Research and Ethics Committee, and were in accordance with the Australian Code of Practice for the Care and Use of Animals for scientific purposes and with the National Institutes of Health, USA guidelines regarding the care and use of animals for experimental procedures. Data were collected from eight adult cats with otoscopically normal tympanic membranes, divided into two experimental groups. One cohort was chronically deaf for approximately one year, and consisted of two animals that were implanted unilaterally and two animals that were implanted bilaterally, providing a total of six long-term deafened acutely implanted cochleae (n = 6). The second cohort had three acutely deafened normal hearing cats; two implanted unilaterally and one implanted bilaterally, providing a total of four acutely deafened and acutely implanted cochleae (n = 4). Finally, in one normal hearing animal, only acoustic stimulation was performed to assess interactions between acoustic tones. The basic procedures for deafening, cochlear implantation and multichannel recording were similar to those described in our previous studies (George et al., 2014, 2015a).
5.3.2 Surgery and electrode insertion

Anaesthesia prior to surgery was induced by ketamine (intramuscular, 20 mg kg\(^{-1}\)) and xylazil (subcutaneous, 2 mg kg\(^{-1}\)), and maintained with a slow continuous intravenous infusion of sodium pentobarbital (3–8 mg kg h\(^{-1}\)). Core body temperature was maintained at 37.0±1°C using a thermostatically controlled heating pad. An endotracheal tube was inserted at the beginning of the experiment to monitor respiration rate (normal levels: 10–20/min) and end-tidal CO\(_2\) levels (normal levels: 3–5%) throughout the duration of the experiment (2–3 days). Clavulox (subcutaneous, 10 mg kg\(^{-1}\)) as an antibiotic, and dexamethasone (intramuscular, 0.1 mg kg\(^{-1}\)) to minimize brain swelling were administered every 24 h throughout the experiment.

All the four long-term deafened animals in cohort 1 were deafened using procedures that have been described in detail elsewhere (Leake et al., 2000, Fallon et al., 2009). In brief, each animal received a daily injection of neomycin sulphate (subcutaneous, 60 mg kg\(^{-1}\)) from one day after birth until the animal was profoundly deaf (i.e. absence of a click-evoked auditory brainstem response at 100 dB peak equivalent sound pressure level (SPL) in both ears). In three normal hearing animals from cohort 2, acute deafening was performed prior to cochlear implantation by introducing neomycin sulphate (10% w/v solution) into the round window, and aspirating the solution at the oval window to ensure access of the aminoglycoside to all regions of the cochlea (Hardie and Shepherd, 1999).

A post-auricular incision was made and the temporalis muscle retracted, exposing the tympanic bulla. The round window was exposed and gently punctured. Animals were implanted with a Hybrid-L 14 array (HL14), consisting of 14 intracochlear half-band platinum electrodes with an average inter-electrode spacing of ~0.72 mm (centre to centre), inserted approximately 10.5 mm through the round window into the middle turn of the scala tympani (Shepherd et al., 2011). A platinum ball electrode was placed in the neck muscle to serve as the extracochlear return
electrode. Following implantation, animals were placed in a stereotaxic frame (David Kopf Instruments, USA).

A craniotomy was performed through the parietal bone on the dorsolateral portion of the skull contralateral to the implanted cochlea and the cerebral cortex was removed to reveal the dorsal surface of the IC. If required, a portion of the tentorium was removed using a small diamond burr to expose the entire dorsolateral surface of the IC. A multi-channel recording array (NeuroNexus Technologies, USA) was inserted along the cochleotopic axis of the central nucleus of the IC. At the conclusion of the experiment, the animal was euthanized and the cochleae were collected for histological analysis.

5.3.3 Cochlear electrical stimulation

An in-house purpose built multi-channel stimulator, consisting of 14 Howland current sources, generated all electrical stimuli. The stimulator was controlled using custom software implemented in Igor Pro (Wavemetrics, USA). The stimulator delivered single cathodic-first, charge-balanced biphasic pulses. The stimulus repetition rate was 4 Hz. The amplitude of the stimulus waveform was programmed in clinical current levels (CLs) units defined by Cochlear Corporation, ranging between 0 and 255, where, \( \text{current in } \mu\text{A} = 17.5 \times \left(100^{\text{CL}/255}\right) \).

With MP stimulation, using only one current source, current pulses were delivered to a single intracochlear electrode and the extracochlear return electrode. In TP stimulation, three current sources were used and current pulses were delivered to a central intracochlear electrode with two adjacent intracochlear return electrodes, each carrying half the current in opposite phase. In FMP stimulation, weighted positive and negative current pulses were delivered simultaneously to multiple electrodes. Phase durations were 100 μs/phase for MP stimulation, while FMP and TP stimulation had phase durations of 400 μs/phase. The differences in phase durations were a result of the greater charge required using FMP and TP
configurations to evoke neural activity (George et al 2014). Interphase gaps were 50 μs for all stimulation configurations.

A ‘channel’ in this study referred to a set of electrodes (active and return) used to deliver current in a particular stimulation configuration. The channels were numbered increasing from base to apex, in accordance with the convention used for the clinical CI. The number of its centre electrode indicated each FMP and TP channel. For each FMP channel, the weight vector was constructed based on the strategy adapted from van den Honert and Kelsall (2007). The trans-impedance matrix was measured for all intracochlear electrodes, with each column of the inverse of this matrix used to calculate the numerical weights that determined the current from each electrode to produce a single FMP stimulation channel.

All the CI channels were individually stimulated in FMP, TP and MP stimulation configuration before protocols for two-channel stimulation were executed. During two-channel stimulation, two CI channels were stimulated simultaneously using the same stimulation configuration i.e., FMP, TP or MP. Note that, for all FMP channel pairs and a few TP channel pairs, this involved using overlapping flanker electrodes and therefore current delivered to these electrodes was based on the summation of the weights of individual channels, determined using trans-impedance measurements. The two channels consisted of a ‘fixed’ channel (S1) chosen towards the middle of the cochlear array (i.e. a channel with approximately equal number of flanker electrodes on both sides in the FMP configuration) and a more apical ‘test’ channel (S2). The CL on S1 was fixed at a level relative to its threshold when presented alone (i.e., sub-threshold, threshold or suprathreshold) while the CL on S2 was increased from 0 up to a maximum stimulus level of either 255 CL or the threshold for myogenic activity in 5 CL steps. Channel interactions were studied as a function of spatial separation (5/6 levels of interelectrode spacing) between the two channels. All combinations of inter-electrode spacing, stimulation configuration and CL were presented at random with each repeated 10 times.
5.3.4 Multichannel recording

Multi-unit neural activity was recorded using a single shank silicon-substrate recording array (NeuroNexus Technologies, USA). The array consisted of 32 iridium recording sites spaced at intervals of 100 μm (centre to centre), each having a circular profile with a surface area of 413 μm². The array was mounted on a microdrive positioner (David Kopf Instruments, USA), positioned at the surface of the IC and advanced at ~100 μm s⁻¹ along the dorsolateral to ventromedial extent of the IC, at a 45° angle from the sagittal plane, along the cochleotopic gradient of the IC (Snyder et al., 1990). The depth of penetration (~4.2 mm) was chosen by visually monitoring the responses of neurons at the tip recording site to stimulation. Multi-unit spike activity from each recording site was amplified, filtered and digitized at a sample rate of 30 kHz using a Cerebus data acquisition system (Blackrock Microsystems, USA).

In one normal hearing animal, IC responses to acoustic stimulation (i.e., two tones presented simultaneously) were recorded. The head was secured with hollow ear bars to allow closed-field acoustic stimulation. The stimuli were delivered using a Tucker Davis Technologies SA1 Stereo Power Amp (TDT, USA) and two 4’ Vifa XT25TG30-04 speakers (Speakerbits, Australia). The whole system was calibrated over a frequency range of 0.5–40 kHz. Acoustic stimuli consisted of pure tone bursts (100 ms duration, 5 ms linear rise/fall), generated using custom designed software. On a given trial, the first tone (F1; 13.5 kHz) was fixed at a stimulus level relative to its threshold while the second tone (F2) was varied in stimulus intensity or frequency (11.5, 10, 8.5, 7.5, 6.5 or 5.5 kHz, 30–90 dB SPL in 10 dB steps). We chose to present these particular tone frequencies as these frequencies corresponded approximately to the cochlear position of electrically stimulated channels used in the two-channel stimulation (Greenwood, 1990). Each combination of frequency and stimulus intensity of tones were presented in a random order with 10 repetitions.
5.3.5 Data analysis

Multi-unit spiking activity was processed offline, using customized spike detection scripts in IgorPro (Wavemetrics, USA). Electrical stimulus artefacts were removed using the techniques detailed in Heffer and Fallon (2008). Based on first-spike latencies and the early onset response of IC neurons, spikes were counted when the signal exceeded four times the root mean square of the background activity for each recording channel in a 3–35 ms post-stimulus window. At each recording site, spike counts were averaged across 10 trials for each stimulating channel, stimulation configuration and CL. All responses showed a monotonic increase in activity with increasing stimulus levels. To account for the variation in absolute spike rate across recording sites, each response was normalized to the maximum spike rate of each recording site for any stimulus. The normalized spike rates were displayed as ‘response images’ with the stimulus intensity on the y-axis and the depth of the recording site on the x-axis (figure 5.1(a)). The data were smoothed with a 3 × 3 Gaussian function. The lowest current that elicited a normalized spike rate of 0.3 (indicated in figure 5.1(a)) was defined as the threshold (Landry et al., 2013, George et al., 2014) and the recording site that yielded the threshold was defined as the best recording site. To quantify the interaction between channels, different features of IC activity were analysed.

5.3.5.1 Threshold interaction index

The difference between single-channel and two-channel neural responses was used as a measure to quantify channel interaction (figures 5.1(d) and (e))

\[
\text{Difference in neural response} = R_{S1+S2} - (R_{S1} + R_{S2})
\]

where, \(R_{S1+S2}\) is the normalized neural response to simultaneous stimulation of S2 and fixed current S1 and \(R_{S1}\) and \(R_{S2}\) are the individually normalized neural responses to single channel stimulation of fixed current S1 and S2, respectively. The neural response difference calculated for each recording site was then summed across all the 32 recording sites at each stimulus level to calculate the total interaction across the recording array. A total interaction versus S2 stimulus level curve (figure 5.1(e))
was obtained for each combination of inter-electrode spacing, stimulation configuration and S1 stimulus level. From these curves, the total interaction calculated at the threshold of S2 alone was chosen as the threshold interaction index (coloured circles in figure 5.1(e)). An interaction index greater than zero indicated facilitation across the recording array caused by the stimulation of two channels, while an interaction index less than zero indicated a suppression or masking of the neural response across the recording array following two-channel stimulation.

A similar method was followed to calculate threshold interaction index for two-tone acoustic stimulation. In brief, for each recording site, the responses generated when the two tones (F1 and F2) were presented separately were subtracted from the response resulting from presenting the two tones simultaneously i.e., \( R_{F1+2} - (R_{F1} + R_{F2}) \). The difference in response was then summed across the IC recording array and plotted against the stimulus intensity of F2. The response difference calculated at the threshold of F2 alone was chosen as the acoustic threshold interaction index.

### 5.3.5.2 Threshold shift

Channel interactions were also quantified by threshold shifts on the best recording site (i.e., the recording site that yielded the lowest threshold to single-channel stimulation). This measure of channel interaction is based on methods used previously, both in animals and in humans (Bierer and Middlebrooks, 2004, Bierer, 2007). The single-channel thresholds were first measured, followed by the two-channel thresholds. Threshold shift was computed as the difference between single-channel and two-channel thresholds (figure 5.1f) i.e.,

\[
\text{Threshold shift} = T_{S1+2} - T_{S2}
\]

where, \( T_{S1+2} \) is the threshold of the best recording site of S2 when stimulated along with S1 and \( T_{S2} \) is the threshold of S2 when stimulated alone. Positive threshold shifts indicated increases in threshold of S2 in the presence of S1 while negative threshold shifts indicated reduction in threshold of S2 when stimulated along with S1. A larger threshold shift was interpreted as an indication of greater channel interaction.
Figure 5.1 Overview of how threshold interaction index and threshold shifts were calculated for two-channel stimulation. Representative IC response images to electrical stimulation of a) S1 alone, b) S2 alone and c) S1 at 10 CL above its threshold and S2 simultaneously. Two-channel stimulation in FMP stimulation configuration with an inter-electrode spacing of 5 was used in this particular example. Each response image was generated by plotting depth of the IC recording site on the x-axis and stimulus level on the y-axis. The normalized spike rates were represented by colours from yellow to black with yellow representing the strongest activity. A spatial tuning curve was constructed by connecting the stimulus levels that elicited a normalized spike rate 0.3 on each IC recording site (shown by the white line in the top-left panel). The tip of the spatial tuning curve corresponded to the threshold and the best recording site (i.e., the recording site that was most sensitive to that particular electrical stimulus). d) The panel reveals the difference between the responses generated when fixed current S1 and S2 were stimulated together and the responses generated for each channel alone i.e., $R_{S1+2} - (R_{S1} + R_{S2})$. The interactions were represented by colours from red to green with white representing no...
interaction. e) Example of total interaction across the IC recording array versus stimulus intensity curve for MP (blue squares), FMP (green circles) and TP (red triangles) stimulation. The threshold interaction index was chosen based on the threshold level of S2 alone for each stimulation configuration. For the example above, threshold interaction index for FMP = 0.3145, TP = 0.5327 and MP = 9.4856 (indicated by coloured circles). f) Example of normalized spike rate versus stimulus intensity plots for the best recording site of S2 (indicated by green and dark red arrows in b) and c) respectively). The data represented by green circles illustrate the spike rate obtained for stimulation of S2 alone while the red triangles represent spike rates for stimulating S2 and S1 simultaneously. Threshold shift was computed by subtracting the single-channel threshold from the two-channel threshold. The threshold shift observed in this particular example is -10 CL.

5.3.6 Statistical Analysis

All statistical analyses were performed using SigmaPlot Version 12.5 (Systat, USA). Comparisons of interaction indices and threshold shifts between stimulation configurations and inter-electrode spacings at each stimulus level on S1 were made using two-way ANOVAs, with Tukey corrected post-hoc testing of individual comparisons where appropriate. Long-term deafened and acutely deafened animals were treated separately. To determine the effect of a single factor on threshold interaction index or threshold shift for each stimulation configuration, one-way ANOVAs were performed.

5.4 Results

Across the eight animals, we obtained detailed measurements of IC neural responses to electrical and acoustic stimulation (192 recording sites from six recording array placements in the long-term deafened cats, 128 recording sites from four recording array placements in the acutely-deafened cats and 32 recording sites from the normal hearing cat in which we performed only acoustic stimulation). We tested a total of 54 pairs of CI channels (8 pairs with inter-electrode spacing of 1, 2 and 6; 10 pairs with inter-electrode spacing of 3, 4 and 5).
The histological findings in long-term deafened animals have been presented previously (George et al 2015). In brief, the analysis of the mid-modiolar sections indicated a total loss of the organ of Corti in all cochlear turns, with reduced SGN survival within the Rosenthal’s canal and widespread loss of peripheral processes within the osseous spiral lamina. The basal and the middle turns exhibited around 6–10% SGN survival while the apical turn exhibited ~30% SGN survival, compared to normal cochleae.

5.4.1 IC response images

IC response images to electrical (seven animals) and acoustic (one animal) stimuli were generated. Figure 5.2 presents examples of response images recorded in one animal from the long-term deafened group following electrical stimulation with different stimulation configurations (columns 1, 2 and 3), and a normal hearing animal following acoustic stimulation (column 4).

In this particular example, the two CI channels electrically stimulated are channel 7 (S1) and channel 12 (S2) resulting in an inter-electrode spacing of five. The vertical columns represent the response images for different stimulation configurations and horizontal rows of images represent the responses to single-channel stimulation of S1 (row 1) and S2 (row 2) and two-channel stimulation of S1 and S2 at different S1 stimulus levels (rows 3 to 5), as indicated. Increases in stimulus level resulted in increasing spread of neural activation along the recording array and MP stimulation at high CLs resulted in significant myogenic activity (column 3). Simultaneous stimulation of S1 and S2 evoked neural responses even at very low S2 current levels on the recording sites that were most sensitive to stimulation of S1 alone (rows 4 and 5), with MP stimulation evoking stronger and wider responses compared to FMP and TP stimulation.
Figure 5.2 Response images across the cochleotopic axis of the IC to electrical and acoustic stimulation. Columns 1, 2 and 3 represent the response images generated for FMP, TP and MP stimulation configurations, respectively in a long-term deafened cat while column 4 presents the response images for acoustic stimulation in a normal hearing animal. In this figure, the two CI channels electrically stimulated are channel 7 (S1) and channel 12 (S2) resulting in an inter-electrode spacing of five (i.e., ~3.6 mm). In the first three columns, rows of images represent
responses to stimulation of channel 7 (S1) alone (row 1), channel 12 (S2) alone (row 2) and simultaneous stimulation of S1 and S2 with current level on S1 constant at 15 CL below threshold (T) (row 3), at T (row 4) and at 10 CL above T (row 5). In column 4, rows represent neural responses to 13.5 kHz (F1) and 5.5 kHz (F2) pure tones presented either alone (rows 1 and 2) or simultaneously with stimulus intensity of F1 held at 10 dB below (row 3), at its T (row 4) or 10 dB above (row 5). In the first row of panels, horizontal lines with different colours highlight the different stimulus levels applied to S1/F1 during two-channel/two-tone stimulation, with red, white and green indicating sub-threshold (T-15 CL or T-10 dB), threshold (T) and supra-threshold (T+15 CL or T+10 dB) levels, respectively. Data are from animals 12_306 and 12_307.

Column 4 represents IC response images to a 13.5 kHz (F1; row 1) and 5.5 kHz (F2; row 2) pure tones presented alone and when presented simultaneously with stimulus intensity of F1 held constant at 10 dB below its threshold (row 3), at threshold (row 4) and at 10 dB above threshold (row 5). We chose to present 13.5 kHz and 5.5 kHz in this example as these frequencies corresponded approximately to the cochlear position of electrically stimulated channel 7 and channel 12, respectively. As with electrical stimulation, neural spikes were seen at low stimulus intensities for F2 following two-tone stimulation (rows 4 and 5) and the number of recording sites evoked at very low stimulus intensities was similar to that of FMP and TP stimulation configurations.

5.4.2 Threshold interaction index

Figures 5.3 (a) and (b) shows the average threshold interaction index at S2 threshold for two-channel electrical stimulation of 54 electrode pairs as a function of inter-electrode spacing for acutely deafened and long-term deafened animals and for different stimulation configurations. Note that the inter-electrode spacing is expressed in mm considering the average spacing between electrodes (centre-to-centre) of ~0.72 mm in the HL14 electrode array. A two-way ANOVA (stimulation configuration and inter-electrode spacing as factors) showed that interaction indices were significantly different between stimulation configurations (p-values < 0.001) at all stimulus levels on S1 and in both acutely deafened and long-term deafened animals; with post-hoc tests indicating that MP stimulation had a higher threshold
interaction index than FMP or TP stimulation ($p$-values < 0.001) and no significant difference between FMP and TP stimulation ($p$-values > 0.05). Moreover, no significant difference was observed between different inter-electrode spacings ($p$-values > 0.05) and no significant interaction between stimulation configuration and inter-electrode spacing ($p$-values > 0.05). However, as illustrated in figures 5.3(a) and (b), we observed a general trend of reduction in threshold interaction index with increased inter-electrode spacing in the case of MP stimulation.
**Figure 5.3** a, b) Threshold interaction index (mean ± SEM) across the IC recording array obtained for different stimulation configurations versus inter-electrode spacing between two channels (S1 and S2) stimulated simultaneously in a) acutely deafened (N = 4 pairs of CI channels tested at each inter-electrode spacing across 4 cochleae) and b) long-term deafened animals (N= 4 pairs of CI channels tested at inter-electrode spacing of 0.7, 1.4 and 4.3 mm and 6 pairs tested at inter-electrode spacing of 2.2, 2.9 and 3.6 mm across 6 cochleae). Different symbol shapes and colours represent different stimulation configurations. Each column of panels represents the threshold interaction index in the condition in which the current on S1 was fixed at a level relative to its threshold (T) (i.e., T-15 CL (column 1), T (column 2), T+5 CL (column 3) and T+10 CL (column 4)). c) Threshold interaction index across the IC recording array measured for two-tone acoustic stimulation. The difference in frequency (frequency gap) between the two tones presented...
expressed in kHz is plotted on the x-axis. Points falling below the black dashed line indicate a suppressed interaction while those above the dashed line indicate those conditions that exhibited facilitation.

To determine the effect of stimulus level of S1 (i.e., T-15, T, T+5 and T+10 CL) on threshold interaction index for each stimulation configuration, independent one-way ANOVAs were performed. In acutely deafened animals, no significant difference was observed between interaction indices measured at different S1 stimulus levels for each stimulation configuration (p-values > 0.05). The same pattern of results was observed in long-term deafened animals (p-values > 0.05).

Figure 5.3(c) demonstrates the effect of stimulus intensity of F1 (13.5 kHz) on the strength of interactions when presented along with F2 (11.5, 10, 8.5, 7.5, 6.5 or 5.5 kHz). The threshold interaction index with two-tone stimulation was considerably smaller than those found with electrical stimulation (i.e., close to zero) for all frequency pairs at all stimulus intensities of F1. There was a slight change in the threshold interaction index with increasing frequency gap (i.e., the frequency difference between F1 and F2), and a trend towards a small amount of suppression with closely spaced tones. Acoustic data are shown only for the purpose of comparison and were not included in the statistics.

5.4.3 Threshold shift

For each CI channel assigned as S2, a normalized spike rate versus stimulus intensity plot was derived for the best recording site. Figure 5.4 presents examples of normalized spike rate versus stimulus intensity plots, with each of the first three panels representing an electrical stimulation configuration and the last panel representing acoustic stimulation. In every panel, there was a monotonic increase in spike rate with increasing stimulus intensity. In this particular example, on increasing the current level on S1, the rate-intensity plots were shifted to the left indicating a reduction in the threshold (0.3 normalized spike rate; shown by the dotted line) of the best recording site of S2 in the presence of S1. Greater shifts in the rate-intensity
plots were observed with MP stimulation configuration (figure 5.4(c)) indicating a larger reduction in MP thresholds compared to FMP and TP stimulation. As a comparison, shifts in the rate-intensity plots for acoustic stimulation was similar to that found with FMP and TP stimulation (figure 5.4(d)).

**Figure 5.4** Normalized spike rate versus stimulus intensity plots for the best recording site of S2. Each panel represents neural spikes obtained in response to electrical stimulation using a) FMP b) TP c) MP stimulation configuration and to d) acoustic stimulation. The stimulus level delivered to S2/F2 is plotted on the x-axis and the normalized spike rate of the best recording site of S2/F2 is plotted on the y-axis. In each panel, lines marked with yellow circles represent rate-intensity plots obtained for stimulation of S2/F2 alone while lines marked with blue triangles, pink squares and green diamonds indicate rate-intensity plots derived for stimulating S2/F2 and S1/F1 simultaneously while the stimulus level on S1/F1 was at sub-threshold (T-15 CL/T-10 dB), threshold and supra-threshold (T+10 CL/T+10 dB), respectively. The insets in a) and b) highlights the slight variation in threshold crossings of the rate-intensity plots. This particular example is shown for an inter-electrode spacing of five and for 13.5-11.5 kHz frequency pair. Data are from animal 13_219 and 12_307.

Threshold shifts, expressed in CL, measured for three stimulation configurations in acutely deafened and long-term deafened animals are shown in figures 5.5(a) and (b). The plotted threshold shifts were measured at the best recording site of S2. Columns of panels represent conditions in which the S1 current was held constant at a level relative to its threshold. The mean threshold shift measured for most cases was negative indicating that the threshold of S2 was reduced when stimulated along with S1.
A two way ANOVA (stimulation configuration, inter-electrode spacing as factors) showed significantly different threshold shifts for different stimulation configurations ($p$-values < 0.001) in both acutely deafened and long-term deafened animals and for all the tested stimulus levels on S1.

**Figure 5.5 a, b)** Threshold shift (mean ± SE) for different stimulation configurations in acutely deafened (N = 4 pairs of CI channels tested at each inter-electrode spacing across 4 cochleae) and long-term deafened cats (N= 4 pairs of CI channels tested at inter-electrode spacing of 0.7, 1.4 and 4.3 mm and 6 pairs tested at inter-electrode spacing of 2.2, 2.9 and 3.6 mm across 6
For each panel, the x-axis and y-axis are inter-electrode spacing between the channels stimulated simultaneously (i.e., S1 and S2) and threshold shift of the best recording site of S2, indicating the threshold when stimulated along with S1 relative to the threshold when stimulated alone, respectively. In each panel, threshold shifts are plotted for MP (blue squares), FMP (green circles) and TP (red triangles) stimulation. Columns 1, 2, 3 and 4 represent simultaneous stimulation of S1 and S2 with the current on S1 held constant at 15 CL below its threshold (T – 15 CL), at its threshold (T) and at 5 and 10 CL above its threshold (T+5 CL, T+10 CL), respectively. c) Threshold shift, expressed in dB, measured for two-tone acoustic stimulation at different stimulus intensities of F1 and for various frequency gaps between F1 and F2.

In both experimental groups, threshold shifts in the IC were significantly larger for MP compared to both FMP and TP stimulation configurations (p-values < 0.001), while threshold shifts for FMP and TP stimulation configurations were not found to differ (p-values > 0.05). A significant interaction was observed between stimulation configuration and inter-electrode spacing (p-values < 0.05) for all S1 stimulus levels tested. With MP stimulation, threshold shifts measured for adjacent stimulated channels, i.e., an inter-electrode spacing of 0.7 mm, were significantly larger than those measured for an inter-electrode spacing of 3.6 mm (p-values < 0.01) and 4.3 mm (p-values < 0.001) in both normal-hearing and long-term deafened groups. With FMP and TP stimulation, there was no significant difference between threshold shifts measured for different inter-electrode spacing (p-values > 0.05). A one-way ANOVA was performed to see the effect of stimulus level of S1 on threshold shifts for each stimulation configuration. Both experimental groups showed a significant increase in MP threshold shifts as the stimulus on S1 was increased from sub-threshold (T-15 CL) to supra-threshold (T+10 CL) (all p-values < 0.001).

Figure 5.5(c) demonstrates the threshold shift measured for two-tone acoustic stimulation as a function of frequency gap between the two tones presented simultaneously. The data points represent shifts in the threshold of best recording site of F2 (11.5, 10, 8.5, 7.5, 6.5 or 5.5 kHz) when presented along with F1 (13.5 kHz) at its threshold (T), sub-threshold (T-10 dB) and supra-threshold (T+10 dB and T+20 dB) levels. Note that we have used interpolation in obtaining a finer measure of acoustic threshold shift. The magnitudes of threshold shifts tended to vary among frequency pairs. A negative shift in the threshold was observed only for the closest
frequency pair (i.e., 13.5–11.5 kHz), which increased as the stimulus intensity of 13.5 kHz was increased. With 13.5–10 kHz and 13.5–8.5 kHz pairs, no threshold shift was observed at all stimulus levels of 13.5 kHz. However, with the farthest frequency pairs, thresholds were found to increase in the presence of 13.5 kHz. Acoustic data are shown only for the purpose of comparison and were not included in the statistics.

5.5 Discussion

In the present study, we evaluated the interactions between electrical stimuli presented simultaneously to two CI channels using FMP, MP and TP stimulation, based on simultaneous multi-unit spike activity recorded from the IC in acutely and long-term deafened cats. We tested pairs of stimulating channels that varied in spatial separation from 0.7 (i.e., adjacent channels) to 4.3 mm. We also examined the effect of varying stimulus level on the degree of channel interactions. The threshold shift and threshold interaction index measurements of the present study showed that MP stimulation produced significantly stronger channel interactions than FMP and TP stimulation. With MP stimulation, the magnitude of threshold shift was dependent on (a) the spatial separation between the stimulated channels, and (b) the stimulus level on the fixed channel. On the contrary, with FMP and TP stimulation, we observed only a weak dependence on these factors. Importantly, we observed no benefit in terms of reduced channel interaction for FMP compared to TP stimulation. Finally, we observed similar effects in acutely deafened cochleae and cochleae with very poor SGN survival.

Relation to other electrophysiological studies

Simultaneous stimulation of two CI channels generally resulted in interaction indices greater than zero and negative threshold shifts, which both indicated a facilitatory interaction. This effect was more prominent with MP stimulation, which corroborates the hypothesis of electric current field summation within the
conducting tissues of the cochlea. As also expected with direct electric field summation, we observed that the negative threshold shifts were greatest for adjacent MP channels and progressively decreased as the spatial separation between the channels was increased although the threshold interaction index did not change significantly with spatial separation. This suggests that the spread of current in the cochlea from individual MP channels may have excited a similar or overlapping population of SGNs to some extent even when the stimulated channels were separated by up to 4 mm in the cochlea. Even though the facilitatory interactions observed in the present study are most likely due to direct electric field summation in the cochlea, they may also be a consequence of overlapping neural populations activated by the two channels (Moore, 1978) at the periphery, or at more central structures resulting from the broad spread of activation in the auditory nerve.

The significantly smaller interactions measured with FMP and TP stimulation are consistent with reduced overlap of stimulating current, resulting from restricted electric current fields in the cochlea. In particular, it was observed that spatial separation between the two stimulated channels had little effect on channel interactions for FMP and TP stimulation. This is consistent with previous electrophysiological findings of restricted multi-neuronal activity in the IC (Snyder et al., 2004, George et al., 2014) and auditory cortex (Bierer and Middlebrooks, 2002) with single-pulse FMP and/ or TP stimulation, indicating reduced current spread in the cochlea using these current focusing techniques. In clinical use, speech processors stimulate implants with electrical pulse trains. Although the effects of current focusing on temporal integration among successive pulses is less clear, our findings suggest significantly more interactions with MP stimulation compared to TP/FMP stimulation in the sustained responses to pulse trains. Note that MP and BP stimulation has been shown to produce significantly narrower spatial profiles during sustained responses to pulse trains compared to the onset response (Schoenecker et al., 2012).
The present results can be compared with the neurophysiological study conducted by Bierer and Middlebrooks (2004) in guinea pigs examining the interactions between two CI channels, based on multi-unit spike activity recorded from the auditory cortex. Channel interactions were quantified by the change in the cortical response threshold of a CI channel resulting from a stimulus presented on another CI channel. They reported similar negative threshold shifts as seen in this study, which varied strongly with stimulation configuration. Consistent with the present results, they found that threshold shifts were greater with simultaneous MP stimulation than with TP stimulation, and the magnitude of threshold shifts seen with TP stimulation was negligible in most cases but rather variable across animals. Similar to the stronger and wider IC responses to two-channel stimulation seen in the present study (e.g., figure 5.2), Bierer and Middlebrooks observed that two-channel stimulation increased the extent of cortical responses and shifted the cortical centroid of activity compared to that of single channel stimulation. Note, that in addition to testing the effect of a sub-threshold pulse as performed by Bierer and Middlebrooks, our analyses also included the effect of a supra-threshold pulse on one channel on the neural responses of another channel. Most clinical stimulation strategies involve presenting supra-threshold stimulus to multiple channels.

Negative threshold shifts were observed for two-tone acoustic stimulation using smaller frequency gaps especially at higher stimulus intensities, consistent with integration of energy within a critical band. However, for the same tone pairs, two-tone acoustic stimulation also resulted in negative interaction indices indicating suppression or masking effects. The discrepancy between these results is likely to be related to differences in the channel interaction measures used in the present study i.e., threshold shift is a single channel measure while threshold interaction index is a full array measure. While these results may seemingly contradict each other, both of them are consistent with previous electrophysiological studies examining the effects of two-tone stimulation on neural responses at different levels of the auditory pathway, and highlight the complex interactions that are possible with simultaneous

In the present study, a few interesting observations were also made when comparing data from electrical stimulation in acutely deafened and long-term deafened animals, and acoustic stimulation in normal hearing animals. Although not significant, the acutely deafened animals showed a trend towards a small amount of suppression with FMP and TP stimulation of closely spaced channel pairs (figure 5.3(a)), similar to that seen in the normal hearing animals with small frequency gaps (figure 5.3(c)). However, this trend was not observed in long-term deafened animals and with MP stimulation. These observations are consistent with previous studies that suggest that current focusing techniques can be more sensitive to factors that can degrade the stimulation performance, such as the degree of neural degeneration within the cochlea (Bierer, 2007, George et al., 2015a). While the mechanisms underlying these observations are not clear, they are likely an indication of how duration of deafness could be a predictor of CI outcomes.

Relation to human psychophysics studies

Our results are in agreement with psychophysical measures conducted in CI users to estimate the degree of channel interaction produced by two channels stimulated simultaneously (Tong et al., 1982, Shannon, 1983, White et al., 1984, Favre and Pelizzone, 1993, Boëx et al., 2003, de Balthasar et al., 2003, Stickney et al., 2006, Bierer, 2007). These psychophysical studies computed the channel interaction by measuring the behavioural threshold following stimulation of a single channel and comparing that with the threshold measured with simultaneous stimulation of two channels (simultaneous masking). Thus, in these experiments, channel interaction was measured at the threshold level and the amount of change in threshold reflected the extent of overlap between the stimulating current pulses. In accordance with the present study, channel interactions measured with MP stimulation were found to decline with increasing spacing between the channels (White et al., 1984, Favre and
Importantly, simultaneous MP stimulation was observed to produce larger threshold shifts compared to BP stimulation, suggesting reduced channel interaction with current focusing (White et al., 1984, Boëx et al., 2003, Stickney et al., 2006). Further support for this hypothesis comes from the work of Bierer (2007), who evaluated two-channel responses using different stimulation configurations in nine CI users. Their findings are consistent with the present results in that both studies demonstrated that the largest threshold shifts occurred with MP stimulation compared to TP stimulation during simultaneous stimulation and that the threshold shifts observed for current focusing techniques were generally smaller and more variable across channels.

Another psychophysical technique used to assess channel interaction has been the degree of loudness summation. It is considered that the degree of loudness summation is dependent on the degree of channel interaction i.e., the smaller the channel interaction, the smaller the loudness summation. Several psychophysical studies have compared loudness summation of MP with BP (McKay et al., 2001) and TP stimulation (Padilla and Landsberger, 2014). McKay et al (2001) found that at lower levels (50% of the dynamic range), loudness summation was greater for MP than BP stimulation. However, at high levels, loudness summation was similar for both stimulation configurations. These results are consistent with Padilla and Landsberger (2014) who demonstrated that loudness summation is similar for MP and TP stimulation at a medium, comfortable level while MP loudness summation was larger than TP loudness summation at softer levels of stimulation. These results would effectively mean that focused stimulation provides a greater reduction in channel interaction and spread of excitation compared to unfocused stimulation, at least at quieter levels. Our present results for threshold interaction index are consistent with these conclusions.

The interactions between multiple CI channels that occur at the periphery or at more central structures are expected to contribute to the perception of a CI user. Previous studies on CI users have found a strong relationship between the level of interactions
using speech processing strategies based on simultaneous stimulation and their speech recognition scores (Stickney et al., 2006) as well as their spectral-ripple discrimination ability (Jones et al., 2013). Thus, one can infer from these studies that speech recognition abilities can be improved by reducing/avoiding electric-field interactions (Zwolan et al., 2005) and by increasing the number of independent channels available to effectively transmit the spectro-temporal cues. Our results show that interactions between two simultaneously stimulated channels are significantly less for FMP and TP stimulation than MP stimulation. This suggests that speech-processing strategies based on simultaneous stimulation of multiple channels to convey speech information, would benefit from these current focusing stimulation techniques. Furthermore, even though we studied only interactions between two CI channels, the little or no threshold shifts observed for adjacent FMP and TP channels may suggest the feasibility of stimulating multiple (i.e., three or more) independent channels to transmit enhanced speech information with these stimulation configurations. Indeed, experimental partial TP strategy has been shown to significantly improve speech perception in noise (Srinivasan et al., 2013).

It was anticipated that FMP stimulation would result in reduced interaction when stimulating adjacent channels, compared to TP stimulation. However, no difference between FMP and TP stimulation was found in any of the measures of channel interaction in the present study. This suggests that both the stimulation modes produce similar patterns of current spread at the targeted SGN population. Note that the current implementation of FMP stimulation is designed to minimize the voltage at the electrode site rather than at the neural elements, which may contribute to this finding.

In conclusion, the present study demonstrated that a sub-threshold or supra-threshold stimulus presented on one CI channel elicited a small/negligible influence on the threshold and neural response evoked on a second channel using FMP and TP stimulation compared to MP stimulation. Importantly, TP stimulation was found to be equally effective to FMP stimulation in this study. Along with our previous studies
that demonstrated restricted neural activation with FMP and TP stimulation, the present study suggests that current focusing has the potential to improve spectral resolution and increase the number of temporally independent channels.

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Chapter 6: Effect of current focusing on the sensitivity of inferior colliculus neurons to amplitude modulated stimulation
EFFECT OF CURRENT FOCUSING ON THE SENSITIVITY OF INFERIOR COLICULUS NEURONS TO AMPLITUDE MODULATED STIMULATION

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6.1 Abstract

In multichannel cochlear implants (CIs), current is delivered to specific electrodes along the cochlea in the form of amplitude-modulated pulse trains, to convey temporal and spectral cues. Our previous studies have shown that focused multipolar (FMP) and tripolar (TP) stimulation produce more restricted neural activation and reduced channel interactions in the inferior colliculus (IC), compared to traditional monopolar (MP) stimulation, suggesting that focusing of stimulation could produce better transmission of spectral information. The present study explored the capability of IC neurons to detect modulated CI stimulation with FMP and TP stimulation, compared to MP stimulation. The study examined multiunit responses of IC neurons in acutely deafened guinea pigs by systematically varying the stimulation configuration, modulation depth and stimulation level. Stimuli were sinusoidal amplitude-modulated pulse trains (carrier rate of 120 pulses/sec). Modulation sensitivity was quantified by measuring modulation detection thresholds (MDTs), defined as the lowest modulation depth required to differentiate the response of a modulated stimulus from an unmodulated one. While MP stimulation showed significantly lower MDTs than FMP and TP stimulation (\(p\)-values \(< 0.05\)) at stimulation \(\leq 2\) dB above threshold, all stimulation configurations were found to have similar modulation sensitivities at 4 dB above threshold. There was no difference found in modulation sensitivity between FMP and TP stimulation. The present study demonstrates that current focusing techniques such as FMP and TP...
can adequately convey amplitude modulation, and are comparable to MP stimulation especially at higher stimulation levels, although there may be some trade-off between spectral/temporal fidelity with current focusing stimulation.

6.2 Introduction

Along with improved speech processor hardware and electrode designs, developments in stimulation strategies, such as the use of amplitude-modulated interleaved electrical pulse trains, have resulted in remarkable speech understanding in multichannel cochlear implant (CI) users (Wilson et al., 1991, Skinner et al., 1994, McDermott et al., 1992, Dorman, 1993). In most modern stimulation strategies, the slow varying temporal envelopes of band-pass filtered components of sound are conveyed in the modulation waveforms and the spectral information is transmitted by activation of electrodes at appropriate cochlear places. The electrodes are stimulated typically in a monopolar (MP) configuration, where stimuli are presented to single intracochlear electrodes with reference to a remote extra-cochlear electrode. In contrast to the generally good speech comprehension in most CI users in quiet conditions, there is a great deal of difficulty when speech is presented in noise (Fu et al., 1998). Many patients report poor perception of sounds such as music and tonal languages that are rich in temporal and spectral information (Skinner et al., 1994, Sucher and McDermott, 2007).

There are two schools of thought as to why this maybe the case. Firstly, CI users are generally provided with limited spectral and temporal information compared to normal hearing listeners (Friesen et al., 2001, Won et al., 2015). The importance of both temporal and spectral resolution for good speech reception has been reported in normal hearing listeners (Xu et al., 2005, Xu and Pfingst, 2008, Souza et al., 2015) and in recipients of auditory prostheses (Shannon, 1992, Cazals et al., 1994, Donaldson and Nelson, 2000, Fu, 2002, 2004, Colletti and Shannon, 2005, Nie et al., 2006). For example, higher speech perception scores are correlated to better
temporal processing capabilities, as measured by amplitude modulation detection thresholds (MDTs) (Cazals et al., 1994, Fu, 2002, Won et al., 2011, Gnansia et al., 2014, De Ruiter et al., 2015).

Secondly, due to the large current spread from MP stimulation, methods to increase the number of truly independent channels available for stimulation and improve spectral resolution by current focusing have become of great interest in CI research. Psychophysical and electrophysiological studies have shown that bipolar (BP) and tripolar (TP) stimulation produce sharper excitation patterns and decreased perceptual interactions among simultaneously stimulated channels compared to MP stimulation (van den Honert and Stypulkowski, 1987, Snyder et al., 1990, Kral et al., 1998, Bierer and Middlebrooks, 2002, Bierer and Middlebrooks, 2004, Chatterjee et al., 2006, Srinivasan et al., 2010). However, studies of speech perception have generally shown that CI users tend to perform as well with MP stimulation as with BP and TP stimulation (Zwolan et al., 1996, Pfingst et al., 1997, 2001, Mens and Berenstein, 2005, Berenstein et al., 2008, Fielden et al., 2015). An electrophysiological study by Middlebrooks (2008a) reported that narrow BP stimulation resulted in higher MDT compared with MP stimulation, suggesting a possible reason for the lack of speech perception benefit with BP stimulation over MP stimulation. A factor hypothesized to account for the increase in MDTs obtained with BP stimulation is that responses to narrow BP stimuli tend to show increased trial-by-trial variations in first-spike latencies (i.e., temporal jitter) and thus a more temporally dispersed pattern of ascending drive with BP stimulation compared to MP stimulation (Middlebrooks, 2008a).

Focused multipolar (FMP) stimulation (also referred to as phased array stimulation), has also been used as a method to spatially restrict neural activation in CIs (van den Honert and Kelsall, 2007, Smith et al., 2013, Marozeau et al., 2015). Our previous electrophysiological studies in both acute and long-term deafened animals showed that FMP stimulation can produce a narrower spread of activation in the inferior colliculus (IC) and reduced channel interactions compared to MP stimulation, with
no significant differences observed between FMP and TP stimulation (George et al., 2014, 2015a, 2015b). These results indicate that current focusing stimulation can improve spectral resolution. An important question then arises as to how current focusing stimulation would compare against traditional MP stimulation when conveying amplitude modulation information.

The present study examined IC neural responses to amplitude-modulated electrical pulse trains using FMP and TP stimulation compared to MP stimulation, in acutely deafened guinea pigs. We tested modulation depths from -42 dB (i.e., 0.78% modulation) up to 0 dB (i.e., 100% modulation) and compared responses to unmodulated pulse trains. Measures of modulation sensitivity based on phase locking (vector strengths) and spike count of IC neurons while varying the modulation frequency and stimulus level were compared across stimulation configurations.

6.3 Methods

6.3.1 Experimental Animals

Data were obtained from five young adult pigmented guinea pigs (300 to 600 g) of either sex. All procedures were in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes and with the National Institutes of Health, USA guidelines regarding the care and use of animals for experimental procedures, and were approved by the Bionics Institute Animal Research Ethics Committee. The hearing status of each animal was pre-assessed on the day of the experiment by measuring the auditory brainstem response (ABR) to acoustic stimuli delivered to each ear using standard techniques (Coco et al., 2007).
6.3.2 Anaesthesia, Surgery and Recording Procedure

Animals were pre-medicated with atropine sulphate (0.1 mg/kg, intramuscular). Anaesthesia was induced and maintained by administration (via face mask) of isoflurane (3% for induction and 1-1.5% for maintenance) with oxygen (1 L/min). A heating pad was used to maintain the core body temperature at 37.0 ± 1°C. The respiration rate (normal levels: 10-20/min) and end-tidal CO₂ (normal levels: 1-3%) were monitored over the duration of the experiment (15-17 hours).

Prior to the surgery, animals were placed in a stereotaxic frame (David Kopf Instruments, USA). Local anaesthesia using lignocaine (20 mg/mL, subcutaneous) was applied before making an incision above the left pinna. The temporalis muscle was retracted to expose the left tympanic bulla. The bulla was opened, malleoincudal ossicle was removed and the round and oval windows were punctured. The left cochlea was deafened by infusing neomycin sulphate (10% w/v solution) into the round window, and aspirating the solution at the oval window to ensure the access of the drug to all regions of the cochlea (Hardie and Shepherd, 1999). This was done in order to ensure that the electrophysiological responses were not contaminated by electrophonic activity arising from stimulation of hair cells (Black et al., 1983a, Sato et al., 2016). Animals were implanted with a Hybrid-L 8 array (HL8), consisting of 8 intracochlear half-band platinum electrodes on a silicon carrier (Shepherd et al., 2011). The electrodes were 0.3 mm in length, spaced ~0.75 mm, center to center. The electrode array was inserted approximately 6.75 mm through the round window into the scala tympani and fixed in place throughout the experiment. Note that the uncoiled length of a guinea pig cochlea is ~18-19 mm (Fernandez, 1952).

A craniotomy of the parietal bone was performed on the right dorsolateral portion of the skull and the cerebral cortex was aspirated to expose the IC contralateral to the implanted cochlea. Multi-unit neural activity was recorded using a single shank silicon-substrate recording array (NeuroNexus Technologies, USA) inserted along the cochleotopic axis of the central nucleus of the IC. The array consisted of 32 iridium recording sites spaced at intervals of 100 μm (centre to centre), each having a
circular surface area of 413 μm². The array was mounted on a microdrive positioner (David Kopf Instruments, USA), positioned at the surface of the IC and advanced ~100 μm s⁻¹ along the dorsolateral to ventromedial extent of the IC, at a 45° angle from the sagittal plane, along the main cochleotopic gradient of the IC (Snyder et al., 1990). The depth of penetration (~3.5 mm) was chosen by visually monitoring responses of neurons at the tip recording site to electrical stimulation. Multi-unit spike activity from the recording sites was amplified, filtered and digitized at a sampling rate of 30 kHz using a Cerebus data acquisition system (Blackrock Microsystems, USA). At the conclusion of the experiment, the animal was euthanized with an intraperitoneal injection of lethabarb (0.5 mg/kg).

6.3.3 Stimulus Generation and Data Acquisition

Stimulus waveforms were generated by an in-house purpose built multi-channel stimulator, consisting of multiple Howland current sources. The stimulator was controlled using custom software implemented in Igor Pro (Wavemetrics, USA). Electrical stimuli consisted of 1 sec modulated/unmodulated trains of biphasic pulses. Individual pulses were charge balanced, cathodic first, 400 μs per phase, with an interphase gap of 50 μs. A long phase duration was used due to the greater charge required for FMP and TP configurations to evoke neural activity (George et al., 2014). The carrier pulse rate was 120 pps and pulse trains were presented at a repetition rate of 0.5 Hz. While clinical CIs stimulate at higher rates, the carrier pulse rate in this study was limited to 120 pps to ensure that stimulus artefacts did not contaminate the multiunit recordings. The peak amplitude of the stimulus waveform was limited to 1.75 mA.

Stimuli were presented in MP, TP and FMP stimulation configurations. With MP stimulation, using only one current source, current pulses were delivered to a single intracochlear electrode. With TP stimulation, three current sources were used and current pulses were delivered to a central intracochlear electrode with two adjacent intracochlear electrodes, each carrying half the current in the opposite phase. With FMP stimulation, weighted positive and negative current pulses were delivered
simultaneously to all intracochlear electrodes (van den Honert and Kelsall, 2007, George et al., 2014).

A “channel” in this study refers to a set of cochlear electrodes used to deliver current in a particular stimulation configuration. Channels were numbered increasing from base to apex, in accordance with the convention used in clinical CIs. The number of its centre electrode indicated each FMP and TP channel. For each FMP channel, the weight vector was constructed based on the strategy adapted from van den Honert and Kelsall (2007). A trans-impedance matrix was measured for all intracochlear electrodes, with each column of the inverse of this matrix used to calculate the numerical weights that determined the current from each electrode to produce a single FMP stimulation channel.

All cochlear channels were stimulated with unmodulated and modulated pulse trains using FMP, TP and MP stimulation. Amplitude modulated stimuli were sinusoidal modulated pulse trains (figure 6.1). Pulse trains were modulated by the function

\[ 1 + \frac{mcos(2\pi f_m(t))}{2} - \frac{m}{2} \]

where \( m \) is the modulation depth (defined as the ratio between the minimum and peak current levels, adapted from (Perry, 2012)) and \( f_m \) is the modulation frequency (in Hz). Modulation frequencies used were 10, 20, 30 and 40 Hz. Modulation depths when represented in decibels as \( 20 \log_{10}(m) \) ranged from 0 to -42 dB in 6 dB steps (i.e., 100, 50, 25, 12.5, 6.25, 3.125, 1.5625, 0.78125% modulation; figure 6.1). The peak current level of the modulated pulse train was fixed at 2 dB above the threshold of the unmodulated pulse train. A subset of CI channels were also tested at 1 and 4 dB above the threshold. Combinations of stimulation configuration, modulation frequency, modulation depth and peak current level were presented at random with each repeated 5 times.
6.3.4 Data Analysis

Multi-unit activity was processed offline, using customized spike detection scripts in IgorPro (Wavemetrics, USA). The signal was band-pass filtered (0.3-5 kHz) and stimulus artefacts were removed using techniques detailed in Heffer and Fallon (2008). Spikes were detected when the signal exceeded four times root mean square for each recording channel (Fallon et al., 2009). Analysis was performed on a 50 to 1050 ms window after onset of the pulse train (figure 6.1); responses prior to 50 ms were excluded to avoid the effects that may have occurred due to the onset response, if any. For each stimulus condition, spike counts were averaged across five trials and normalized between the spontaneous activity rate (average spike rate in 33–3 ms pre-stimulus window prior to all stimuli) and maximum response for any stimulating electrode as detailed in (Landry et al., 2013).

Thresholds were estimated from “IC response images” in which normalized spike rates were displayed with the stimulus intensity on the y-axis and the depth of the recording site on the x-axis; this analysis is detailed in our previous study (George et al., 2014). The lowest current that elicited a normalized spike rate of 0.3 was defined as the IC threshold (Landry et al., 2013). The response amplitude of 0.30 was chosen for threshold because lower response amplitudes such as 0.20 at recording electrodes near the lowest threshold site tended to be within 2 s.d. of the I/O baseline mean while higher response amplitudes, such as 0.50, were often very jagged (i.e. highly variable between adjacent recording sites). IC threshold and the best recording site (i.e., the recording site that yielded the lowest threshold) were computed for each CI channel when presented with unmodulated pulse trains. We also calculated the standard deviation of the first spike latency across trials (i.e., temporal jitter) for each best recording site.
Figure 6.1 Electrical stimulus waveforms and IC neural responses. Amplitude vs. time plots of a) unmodulated biphasic pulse train, and pulse trains modulated at b) -12 dB and c) 0 dB. Individual pulses were charge balanced, cathodic-first, 400 μs per phase, with an interphase gap of 50 μs (shown in the inset in (a)). Carrier pulse rate is 120 pps, modulation frequency is 10 Hz and the stimulus duration is 1 sec. Panels d-f) Traces of multi-unit responses (including 200 ms pre-stimulus) from a recording site in the IC following electrical stimulation of a CI channel using FMP stimulation at the modulation depths shown in panels a-c. Each panel of spike responses demonstrate locking to the envelope of the stimulus depicted in the panel above. Dotted red lines indicate the start of the stimulus. Data presented here are after stimulus artefact removal. Panels g-i) Peri-stimulus time histogram (binwidth = 8.3 ms) for the responses to unmodulated and modulated pulse trains (shown in the panel above) including pre-stimulus activity. Analysis was performed in a 50-1050 ms post-stimulus window (shown in shaded rectangle). Panels j-k) Modulation cycle histograms (binwidth = π/6) generated from the spike responses across five trials of the stimuli shown in panels a-c, demonstrating the extent of phase locking of IC spike activity. The mean vector strength (VS) computed for different modulation depths are indicated in the corresponding panel.
IC neural responses to a modulated stimulus were characterized by a) averaged spike rate across the duration of stimulation and b) the vector strength of IC neuronal phase locking at the modulation frequency. The extent of phase locking of IC spikes to the modulator waveform was quantified by computing the vector strength (Goldberg and Brown, 1969, Middlebrooks, 2008b, Krishna and Semple, 2000). Each spike was expressed as a unit vector, with the phase (θ) obtained by expressing the spike time relative to the stimulus period. The mean vector strength was determined by averaging the resulting vector (across n spikes over the duration of stimulation). Vector strength could vary from a minimum of 0 (no phase locking) to a maximum of 1 (all spikes occur at the same unique phase). Vector strength was calculated only for trials that resulted in activity of more than four spikes over the 1s recording period (Middlebrooks, 2008a). The statistical significance of the vector strength was assessed by applying the Rayleigh’s test of circular uniformity at the level of p < 0.01 (Stephens, 1969).

The change in vector strength with modulation depth (figure 6.2a) at each recording site was quantified by the discrimination index, d’, computed by a procedure derived from signal detection theory (Green and Swets, 1966, Macmillan and Creelman, 2005). A receiver operator characteristic curve was formed based on vector strengths elicited for five trials when the stimulus was modulated and unmodulated, by varying the vector strength criterion from 0 to 1. The area under the receiver operator characteristic curve was expressed as a standard deviate and the resulting z-score was multiplied by √2 to obtain d’. For the best recording site (i.e., the recording site that was most sensitive) of each stimulating channel, the value of d’ was computed across modulation depths of -42 to 0 dB, in steps of 6 dB. The lowest interpolated modulation depth that yielded a d’ of 1 was chosen as the MDT (figure 6.2b), an adaption of the methodology described by Middlebrooks (2008a).
Figure 6.2 Overview of the calculation of modulation detection thresholds (MDTs). a) Vector strength (mean ± SEM) for an individual IC site across five trials versus modulation depth plots are shown for FMP, TP and MP stimulation configurations demonstrating the trend of vector strength to with modulation depth. The vector strength computed for unmodulated stimulation in each configuration is also shown. b) Values of $d'$ are plotted as a function of modulation depth for the 3 stimulation configurations. Each value of $d'$ was computed from the area of the receiver operator characteristics curve formed based on vector strengths calculated for five trials when the stimulus was unmodulated and modulated at a particular depth. The modulation depth when each interpolated plot crosses $d'$ of 1 was chosen as the MDT (arrows in b).

6.3.5 Statistical Analysis

All statistical analyses were performed using SigmaPlot Version 13.5 (Systat, USA). Comparisons of IC threshold, spike rate and temporal jitter between MP, TP and FMP stimulation were performed using one-way RM ANOVAs, with Tukey corrected post-hoc testing of individual comparisons where appropriate. A two-way RM ANOVA was performed to compare the effects of two stimulus parameters on MDTs. Simple linear regression was used as a measure of correlation between two variables.

6.4 Results

Across five animals, we tested four cochlear channels each in four animals and one cochlear channel in the final animal, thus totalling 17 channels. We obtained
measurements of IC neural responses from 160 recording sites based on five recording array placements. However, the main analyses were done on 17 recording sites (i.e., the best recording site that was most sensitive to each CI channel). The best recording sites for FMP, TP and MP stimulation of a particular CI channel were not always the same, as observed in our previous studies.

Consistent with our previous animal studies using single pulses (George et al., 2014, 2015a), thresholds for IC activation using single pulses and unmodulated pulse trains were significantly higher (one-way RM ANOVAs, \( p < 0.001 \)) for FMP and TP than for the MP configuration. Using single pulses, IC thresholds averaged 37.6 ± 3.4 dB (re 1 µA; mean ± SEM) for MP, 50.3 ± 7.2 dB for FMP and 51.9 ± 8.2 dB for TP stimulation. IC thresholds using unmodulated pulse trains averaged 40.1 ± 4.6 dB (re 1 µA; mean ± SEM) for MP, 52.7 ± 8.7 dB for FMP and 53.8 ± 8.5 dB for TP stimulation.

**6.4.1 Average Spike Rate**

For each cochlear channel, the spike rate in the 50 to 1050 ms window after the onset of the pulse train was derived for the best recording site. Figure 6.3 shows the mean spike rate measured for FMP (circles), TP (triangles) and MP (squares) stimulation as a function of modulation depth for various modulation frequencies. Note that the mean spike rate measured for stimulation using an unmodulated pulse train is also shown in each plot.

We observed a general trend of reduction in the overall spike rate with increased modulation depths. In the case of MP stimulation, a significant reduction in the spike rate was observed from -18 dB onwards (compared to the unmodulated stimulus) at all modulation frequencies (one-way RM ANOVA, \( p < 0.05 \)). For FMP and TP stimulation, spike rate was significantly reduced at -6 dB and at 0 dB (one-way RM ANOVA, \( p < 0.05 \)).
Figure 6.3 Spike rate (mean ± SEM) in the 50 to 1050 ms window after the onset of the pulse train, plotted as a function of modulation depth for various stimulation configurations. Each panel represents a particular modulation frequency, as indicated. Spike rate corresponding to the unmodulated pulse train is also included in each panel. The modulated and unmodulated pulse trains are presented at 2 dB above the threshold of an unmodulated pulse train. n = 17 channels.

6.4.2 Cycle Histograms

Modulation cycle histograms, which show the distribution of spikes over the phase of the modulating waveform, demonstrated the temporal patterning of IC activity across various stimulation configurations and various modulation depths (figure 6.4). In each panel, the associated vector strength, which quantifies the phase locked firing of spikes i.e., the tendency of spikes to occur over a range of phases of the stimulating waveform, is indicated. The top row of panels shows the spike patterns to unmodulated pulse trains and lower values of vector strength indicate the absence of/weaker phase locking. For all stimulation configurations, phase locking was weak at very low modulation depths, and strengthened with increasing with modulation depth. At all modulation depths, MP stimulation resulted in stronger phase locking/larger vector strengths compared to FMP and TP stimulation.
Figure 6.4 Modulation cycle histograms of spikes across five trials measured at the best recording site to electrical stimulation of a CI channel in FMP, TP and MP stimulation configurations. Each column of panels show responses to pulse trains sinusoidally modulated at 10 Hz and at various depths, as indicated. The modulated/unmodulated pulse trains were presented at 2dB above the threshold of the unmodulated pulse train. Spike times occurring 50 to 1050 ms after onset of the pulse train are binned according to modulator phase, $\pi/6$. Total spike rate (TSR) and vector strength (VS; averaged across five trials) are indicated in each panel.
* indicates significant vector strength (Rayleigh’s test; \( p < 0.01 \)). Data is shown for the best recording site of each stimulation configuration.

### 6.4.3 Peak Spike Rate

In contrast to the mean spike rate, the peak spike rate (i.e. the maximum of the cycle histogram) showed an increasing trend with increased modulation depths in all three stimulation strategies (figure 6.4). These data are summarised in Figure 6.5 and demonstrated that MP stimulation showed significant increase (compared to the unmodulated stimulus) from -12 dB onwards, while FMP and TP stimulation showed significant increase at 0 dB (one-way RM ANOVAs, \( p \)-values < 0.05).

![Figure 6.5 Mean spike rate for the peak modulation phase plotted as a function of modulation depth for various stimulation configurations. Spike rate corresponding to the unmodulated pulse train is also included. The modulated pulse trains were presented at 2dB above the threshold of an unmodulated pulse train and were modulated at 10 Hz. n =17 channels.](image)

### 6.4.4 Vector Strength

The distributions of vector strength across all best recording sites for FMP, TP and MP stimulation configurations and for modulation frequencies of 10, 20, 30 and 40 Hz are shown in figure 6.6. These distributions include vector strengths of best recording sites from all animals, represented by different symbols, with closed symbols representing vector strengths that were statistically significant (Rayleigh
test, \( p < 0.01 \) and open symbols indicating vector strengths that were not significant. The vector strengths computed for IC responses to unmodulated pulse trains presented in three different stimulation configurations are also shown (dotted lines). In every panel, vector strengths increased monotonically with increasing modulation depth. Vector strengths varied amongst stimulation configurations, with 50% of sites showing significant vector strengths with MP stimulation at modulation depths greater than or equal to -24dB, and with FMP and TP stimulation at modulation depths greater than or equal to -12dB.
Figure 6.6 Distribution of vector strengths across the best recording sites from all the animals. Each row represents vector strengths for modulation frequencies of 10, 20, 30 and 40 Hz and columns represent various stimulation configurations, as indicated. Each individual animal’s data are represented with a different symbol. Every vector strength is shown, with closed symbols indicating statistically significant vector strengths ($p < 0.01$, Rayleigh test) and open symbols indicating those that failed to produce significant phase locking. In each panel, dotted lines indicate the average vector strength computed across the best recording sites when stimulated with unmodulated pulse trains in a particular stimulation configuration. The modulated pulse trains are presented at 2dB above the threshold of an unmodulated pulse train. n=17 channels across 5 animals.
6.4.5 Modulation Detection Threshold

Figure 6.7 shows MDTs based on vector strength for the best recording sites to electrical stimulation of cochlear channels in different stimulation configurations. A two-way RM ANOVA (stimulation configuration and modulation frequency as factors) showed that MDTs were significantly different between stimulation configurations \((p < 0.001)\) and not between different modulation frequencies \((p > 0.05)\), with no significant interaction between stimulation configuration and modulation frequency \((p > 0.05)\). Post-hoc tests indicated that MP stimulation exhibited lower MDTs than FMP and TP stimulation \((p\text{-values} < 0.001)\), and no significant difference was observed between FMP and TP stimulation \((p > 0.05)\). The MDTs measured across all modulation frequencies averaged \(-18.08 \pm 0.87 \text{ dB}\) for FMP, \(-17.62 \pm 0.82 \text{ dB}\) for TP and \(-26.47 \pm 1.08 \text{ dB}\) for MP stimulation.

![Figure 6.7](image_url)

**Figure 6.7** Modulation transfer functions (i.e., MDT (mean ± SEM) versus modulation frequency (Hz)) based on vector strength of the best recording sites shown for FMP (circle), TP (triangle) and MP (square) stimulation configurations. The modulated pulse trains are presented at 2 dB above the threshold of an unmodulated pulse train. \(n = 17\) channels across 5 animals.
6.4.6 Temporal Jitter

An independent measure of the temporal characteristics of responses to each stimulation configuration was provided by the temporal jitter calculated as the standard deviation of first spike latency. Temporal jitter generally decreased monotonically with increasing current level. The jitter values measured at 2 dB above threshold averaged $0.73 \pm 0.35$ ms, $0.69 \pm 0.29$ ms and $0.54 \pm 0.26$ ms for FMP, TP and MP stimulation respectively. However, the difference was not significant between different stimulation configurations (one-way RM ANOVA, $p > 0.05$, n=17).

6.4.7 Effect of stimulation level on MDT

To study the effects of overall stimulation level on MDTs, a subset of CI channels (n=9 channels across 3 animals) were stimulated at lower (1 dB above the threshold) and higher (4 dB above the threshold) stimulation levels. At 1 dB above the threshold, configuration effects on MDTs was similar to that observed at 2 dB above the threshold i.e., MP stimulation exhibited lower MDTs than FMP and TP stimulation (one-way RM ANOVA, $p$-values < 0.05) with no significant difference between FMP and TP stimulation ($p > 0.05$) (data not shown). However, at 4 dB above the threshold, no significant difference was observed between the different stimulation configurations (figure 6.8; one-way RM ANOVA, $p$-values > 0.05).

To determine the effect of stimulation level on MDTs for each stimulation configuration, independent one-way RM ANOVAs were performed. In the case of MP stimulation, MDTs measured at higher stimulation level (i.e., at 4 dB) were significantly higher than that measured at lower stimulation levels ($p$-values < 0.05). With FMP and TP stimulation, no significant difference was observed between MDTs measured at different stimulation levels.
Figure 6.8 Modulation transfer functions (i.e., MDT (mean ± SEM) versus modulation frequency (Hz)) based on vector strength of the best recording sites shown for FMP (circle), TP (triangle) and MP (square) stimulation configurations. Note that the modulated pulse trains are presented at 4 dB above the threshold of an unmodulated pulse train. n=9 channels across 3 animals.

6.4.8 Effect of stimulation site on MDT

The modulation sensitivity or the strength of phase locking varied according to the site of the CI channel. Figure 6.9 shows the distribution of MDTs as a function of CI channel number measured across all modulation frequencies for different stimulation configurations. For each stimulation configuration, MDTs exhibited a significant correlation with the stimulation site (p-values < 0.001). Highest MDTs were recorded for the basal CI channels. This dependency is likely to be the major factor contributing to the wide variations observed in vector strengths in figure 6.6.
Figure 6.9 Distribution of MDTs as a function of CI channel for various stimulation configurations. Data is shown for channels stimulated with modulated pulse trains with peak current at 2 dB above the threshold. Data across all tested modulation frequencies is grouped together.

6.5 Discussion

In the present study, we evaluated the responses of IC neurons to sinusoidal amplitude-modulated pulse trains using FMP and TP stimulation, and compared these to responses obtained with MP stimulation. We also examined the effects of stimulation level and modulation frequency on modulation sensitivity for the different stimulation configurations. The sensitivity of IC neurons to amplitude modulation was characterized based on the average spike rate over the duration of the stimulus and the strength of phase locking, represented by the vector strength. To the best of our knowledge, the data presented in this paper represents the first report of electrophysiological modulation detection using FMP and TP stimulation.

The main finding of this study was that at lower stimulation levels (1 and 2 dB above threshold), MP stimulation had lower MDTs than FMP or TP stimulation, while no significant difference was observed between FMP and TP stimulation. However, at 4 dB above threshold MDTs did not differ significantly between stimulation configurations, as a result of increased MDTs at higher stimulation levels with MP
stimulation. Moreover, we observed a reduction in spike rate with increased modulation depths, with MP stimulation resulting in a significant reduction in spike rate at shallower modulation depths than FMP and TP stimulation. We did not observe any difference between different modulation frequencies tested. Finally, modulation sensitivity was generally poorer when stimulating more basal CI channels.

It is worth noting that in the present study comparisons of stimulation configuration at particular stimulation levels expressed in dB re threshold may be confounded by the fact that we might have operated at different levels of dynamic range given the previous reports of different dynamic ranges for MP, TP and FMP (George et al., 2014, 2015a). For example, 2 dB above the threshold might be at different loudness level i.e., a softer level for FMP and TP stimulation compared to MP stimulation (see top panel of figure 6.4, where MP stimulation has resulted in higher spike rate compared to FMP and TP stimulation). However, given that MDT is similar across all stimulation levels (i.e., 1, 2 and 4 dB above threshold) for FMP and TP stimulation, this difference in dynamic range between the stimulation configurations should not affect the main findings.

Relation to other animal studies
The present study can be compared with the electrophysiological study conducted by Middlebrooks (2008a) in acutely deafened guinea pigs. That study examined phase locking of neurons in the auditory cortex to the envelope of modulated electric pulse trains presented in MP and narrow BP (i.e., adjacent active and return electrodes) stimulation configurations, with both configurations using the next-to-most apical intracochlear electrode as the active electrode. Middlebrooks reported that modulation detection of MP stimulation was significantly better than narrow BP stimulation for the 254 and 4096 pps carrier rates. Similarly, the present study showed that MP stimulation tended to enhance modulation sensitivity compared to FMP and TP stimulation at lower stimulation levels. However, the advantage in
modulation sensitivity with MP over FMP and TP stimulation was only observed at low stimulation levels. Even though the stimulation levels in Middlebrooks’ study were set to 2, 4 and 6 dB above threshold, data was reported only for the stimulation level that produced the lowest MDT when comparing MP with BP stimulation. Therefore it is possible that a similar level effect may have been present in the Middlebrooks study but it was not evident due to the collapsing across stimulation level.

Middlebrooks proposed that the better modulation sensitivity seen with MP stimulation was due to the widespread and synchronous neural activation that typically occurs with MP stimulation. This hypothesis was supported by the significantly lower temporal jitter observed in response to MP stimulation compared to BP stimulation. In contrast, there was no significant difference in temporal jitter at 2 dB above threshold in the present study between all three stimulation configurations tested. While the present study observed a reduction in IC spike rate with increased modulation depth, Middlebrooks’ study reported that the spike rate typically increased with modulation depth. The discrepancy between these two results is likely to be related to differences in the modulation waveforms used. The present study used modulated waveforms with the peak amplitude fixed (i.e., maximum down modulation) at a level above the nominal carrier level; thereby, greater modulation depths resulting in reduced number of points where current level exceeds neural threshold (refer figure 6.1c). In contrast, the Middlebrooks’ study used modulated waveforms with current levels ranging above and below (i.e., mean up and down modulation) the mean current in modulated waveform, such that the peak amplitude increased with increase in modulation depth and typically resulting in increased spike rates. Finally, Middlebrooks’ data showed a considerable increase in the percentage of units that showed no phase locking at any modulation depth with BP stimulation. This effect was, however, not evident with TP or FMP stimulation in the present study. A likely explanation for the failure to find this effect is that the present study analysed only the best recording sites or the most sensitive
units while Middlebrooks reported every unit that was recorded. Moreover, some of the differences found between the two studies might be a consequence of the difference in recorded structure i.e., IC versus auditory cortex.

In the cat, Middlebrooks and Snyder (2010) calculated the highest pulse rate to which IC unit significantly phase locked to investigate temporal processing capabilities of electrical stimulation. In the cat, 50\% of units were shown to have limiting rates of 120 Hz for MP stimulation independent of their characteristic frequency (CF), while low CF neurons had even higher limiting rates. In the present study, even though we excluded responses prior to 50 ms to avoid onset response, we observed that 100\% of best recording sites displayed a significant phase locking (ranging from 0.46 to 0.99 on including first 50 ms and 0.48 to 0.99 on excluding response prior to 50 ms) to the carrier pulse rate employed i.e., 120 Hz.

**Relation to human studies**

The ability to detect amplitude modulation has been widely used to measure the temporal-envelope processing capability in CI users. Modulation transfer functions, defined as the plot of MDTs as a function of modulation frequency, measured in CI subjects generally show low pass characteristics with a 100-150 Hz cut-off frequency (Shannon, 1992, Busby et al., 1993). Similarly, for the low modulation rates used in this study (10 – 40 Hz), there was no change in the modulation sensitivity with modulation frequencies.

Consistent with several reports on the significant variability in MDTs across listeners and also across stimulation sites within listeners (Fu, 2002, Colletti and Shannon, 2005, Pfingst et al., 2008), we observed that vector strengths and MDTs varied widely among stimulation sites for all stimulation configurations. There have been reports of systematic variation in MDTs along the cochlear length in some CI users (Pfingst, 2011, Garadat et al., 2012). Consistent with these reports, the current study showed a clear tendency for more apical channels to have enhanced modulation sensitivity. This could be related to the systematic anatomical differences along the cochlear
spiral, such as wider cross-sectional diameter of the scala at more basal locations, resulting in current to flow along different pathways. It is also possible that these variations could be induced by differences in the location of the stimulating electrodes relative to the modiolus as a function of cochlear length. This also consistent with the results of Middlebrooks and Snyder (2010) which indicated that low frequency IC sites have better temporal acuity than high frequency sites.

There are several caveats to note when comparing the present animal study with human psychophysical data. Among these are a range of species-dependent factors and differences in the experimental methodology including duration of deafness and electrical stimulation parameters. Additionally, psychophysical (or perceptual) MDTs differ methodologically from the electrophysiologically determined (neural) MDTs in the midbrain described in the present study. Stimulation levels in human psychophysical studies are normally set at levels within the dynamic range from threshold to most comfortable level whereas, the present study tested modulation sensitivity at stimulation levels relative to the lowest IC activation threshold. Most human psychophysical studies have found that MDTs generally improve as the stimulation level is increased (though some CI users were reported to show no effect above 30% of their dynamic range (Shannon, 1992, Fu, 2002, Galvin and Fu, 2009)). In contrast, we observed that modulation sensitivity of MP stimulation reduced at higher stimulation levels. A similar trend of decrease in modulation sensitivity with increased stimulation level was reported by Middlebrooks (2008a). In 77.7% cases of MP stimulation and 24.6% and 22.5% cases of FMP and TP respectively, we observed that IC neurons were driven to saturation at 4 dB above threshold. This might have contributed to the impairment of modulation sensitivity of MP stimulation at high stimulation levels. However, modulation sensitivities of FMP and TP stimulation showed no stimulation level effect, demonstrating the adequate modulation detection capability of FMP and TP stimulation even at high stimulation levels. Moreover, FMP and TP stimulation were found to have similar modulation sensitivity. This is consistent with our previous electrophysiological studies that
showed similar performance in spatial selectivity and channel interactions with FMP and TP stimulation (George et al., 2014, 2015a, 2015b).

In summary, the results from the present study demonstrated elevated MDTs using FMP and TP stimulation, compared to MP stimulation, at low stimulation levels. However, the current focusing techniques such as FMP and TP stimulation remain capable of conveying amplitude modulation at high stimulation levels, at least within the confines of the present study, which to our knowledge has not been demonstrated previously. Previous results from our laboratory have shown significant improvements in spatial selectivity as well as reduced channel interactions with FMP and TP stimulation compared to MP stimulation, even in cochleae with significant neural degeneration. Associating the present data to our previous studies highlights the possible trade-off between spectral and temporal fidelity with these current focusing techniques. The exact phenomenon that limits the modulation sensitivity of more restricted stimulation techniques is still not clear. Future work needs to be done to explore the mechanism by which phase locking to focused stimulation might impair transmission of modulating waveforms. In addition, the performance of FMP stimulation in relation to speech recognition should be examined in future studies.

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Chapter 7: General Discussion
The research presented in this thesis aimed to evaluate the efficacy of FMP stimulation, compared to MP and TP stimulation, in an animal model. Specifically, experiments were designed with the aim of providing fundamental knowledge essential to the clinical development of this novel stimulation technique for CI implants. The efficacy of FMP stimulation to improve spatial selectivity following stimulation of a single CI channel, compared to MP and TP stimulation, was examined by measuring neural activation in the IC. These responses were examined in animals with normal SGN survival (Chapter 3) and, in long-term deafened animals with severely degenerated SGNs (Chapter 4) to study the effects of long-term deafness on the effectiveness of FMP stimulation. The extent of interactions in the IC produced by simultaneous stimulation of two CI channels (channel interaction) was also explored using FMP, TP and MP stimulation (Chapter 5). Finally, IC responses to amplitude-modulated electrical pulse trains were examined to provide an insight on modulation sensitivity using FMP stimulation compared to MP and TP stimulation (Chapter 6).

7.1 Overview of results

The data presented in Chapter 3 represents the first time FMP stimulation has been used in animal studies. It was found that better spatial selectivity is achieved with FMP and TP stimulation compared to MP stimulation in animals with normal auditory nerve survival, although thresholds were significantly higher for FMP and TP stimulation. The results presented in Chapter 4 indicated that the greater spatial selectivity of FMP and TP stimulation over MP stimulation was maintained in cochleae with significant SGN degeneration and was not adversely affected by electrode position within the scala tympani. In addition, no evidence of ectopic stimulation of non-auditory neurons was observed with FMP and TP stimulation even in long-term deafened animals where greater current levels are required. However, an increase in the spread of neural activation and electrical threshold
associated with long-term deafness indicated degradation in the stimulation performance with chronic deafness compared to the results obtained in acutely deaf animals. There was no benefit in terms of restricted neural activation for FMP compared to TP stimulation.

The threshold shift and threshold interaction index measurements reported in Chapter 5 indicated that MP stimulation produced significantly stronger channel interactions than FMP and TP stimulation. With MP stimulation, the magnitude of threshold shift was dependent on (a) the spatial separation between the stimulated channels, and (b) the stimulation level. In terms of reduced channel interactions, there was no benefit of FMP compared to TP stimulation. The results presented in Chapter 6 demonstrate better modulation detection with MP stimulation, compared to FMP and TP stimulation, at low stimulation levels. However, the current focusing techniques such as FMP and TP stimulation remain capable of conveying amplitude modulation at high stimulation levels, at least within the confines of the present study, which to our knowledge has not been demonstrated previously. Importantly, none of the above measures showed a difference between FMP and TP stimulation. Therefore, the remaining part of this discussion will address FMP and TP stimulation strategies as focused stimulation.

7.2 Clinical implications

7.2.1 Extending experimental results to human speech perception

The electrophysiological results presented in this thesis provide evidence that intracochlear stimulation using focused stimulation can reliably produce neural activation patterns that are more spatially restricted than those produced by MP stimulation. While the work reported in this thesis was being conducted, Smith et al. (2013) performed psychophysical experiments in nine CI subjects with percutaneous connectors to test the hypothesis that narrower excitation patterns
using FMP stimulation would increase spectral resolution, including the
discrimination of spectral ripple phase and dynamic ripple detection. FMP
stimulation was shown to significantly improve subjects’ ability to discriminate
spectral features and detect dynamic modulations in sound stimuli. Previous clinical
studies have shown that the spectral resolving power of CI users is correlated with
their speech perception, especially in noise (Fu et al., 1998, Friesen et al., 2001, Fu
and Nogaki, 2005, Henry et al., 2005, Hong and Turner, 2006, Won et al., 2007, Litvak
et al., 2007b). However, further psychophysical and speech perception studies will
have to determine whether this effect holds for FMP stimulation.

The little or no interaction between two focused channels, especially with adjacent
ones, as seen in the present study suggests the feasibility of stimulating multiple (i.e.,
three or more) independent channels simultaneously to provide fine across-channel
timing information with simultaneous or overlapping pulses. Similarly, in a recent
psychophysical study performed on five participants at the Bionics Institute, FMP
stimulation resulted in less current summation for simultaneously activated FMP
channels compared to MP channels (Marozeau et al., 2015). In a clinical application,
the ability to activate different cochlear places independently with simultaneous
pulses, or pulses overlapping in time may allow higher stimulation rates and
consequently lower current levels to be used.

The present study suggests that a potential limitation of focused stimulation is that
it requires greater charge to evoke a neural response due to the shunting of current
through the conductive perilymph in the scala tympani. Moreover, the slower
increase in excitation spread with current level for focused stimulation, as
demonstrated in the present study, might lead to insufficient loudness perceived
with FMP stimulation, as reported with TP stimulation (Mens and Berenstein, 2005).
In order to achieve sufficient loudness, focused stimulation will require pulses of
longer duration and correspondingly will require lower stimulation rates. This could
mean that some focused channels may not achieve a comfortably loud level
(Marozeau et al., 2015), particularly in cochlear regions with poor neural survival.
Additionally, this could significantly decrease the life of the batteries that power an implant. Nevertheless, in the present study, we were able to significantly lower the FMP threshold levels without a significant increase in the spread of neural activation by varying the degree of current focusing i.e., partial FMP.

Speech perception studies have observed that certain individuals show improved speech perception with focused stimulation while others perform best with MP stimulation (Mens and Berenstein, 2005, Berenstein et al., 2008). Mens and Berenstein (2005) found no significant benefit with flat TP +2 stimulation (which used two intracochlear return electrodes on each side of the active electrode) on monosyllabic word perception in quiet or in noise, although there was a trend of subjects preferring and performing better with the partial TP strategy. A follow-up study by Berenstein et al. (2008) reported that subjects appreciated voice quality best with MP, perception of environmental sounds best with TP, and music experience best with current steering (virtual channels). The vowel perception test conducted at the Bionics Institute using multi-electrode real-vowel stimuli, comparing FMP and MP stimulation, showed that two participants out of three identified vowels more accurately in a simultaneous FMP mode compared to a sequential MP mode (Jeremy Marozeau 2016; personal communication). These results suggest that focused stimulation might only be beneficial for some participants.

It must be acknowledged that while the spread of neural activation almost certainly influences the evoked perception from the CI, several other factors contribute to the inter-individual variability in CI performance. The results presented in this thesis suggest that auditory nerve survival has a significant influence on CI performance. A recent clinical study has shown a positive correlation between speech perception scores using conventional stimulation strategies and overall SGN count (Seyyedi et al., 2014). Based on the findings of the present study, one might expect that SGN survival would have more of an effect on performance if focused stimulation strategies are used.
Better modulation sensitivity of MP stimulation, as demonstrated in this present study, might explain why some users perform at least as well with MP stimulation as with focused stimulation. As discussed previously, the temporal modulation sensitivity is correlated with speech recognition ability in CI users (vowel and consonant identification: (Cazals et al., 1994, Fu, 2002); phoneme recognition: (Xu et al., 2005, Gnansia et al., 2014); word identification: (Won et al., 2011, De Ruiter et al., 2015)). Relating the results presented in Chapter 6 to these previous speech perception studies suggests that there may not be substantial speech perception benefits with CI stimulation strategies based on current focusing techniques in quiet listening conditions; though, these current focusing techniques may enable more reliable performance in a noisy environment. Indeed, Srinivasan et al. (2013) showed significantly improved speech perception in noise with experimental partial TP stimulation compared to the experimental MP stimulation for all six participants. They also observed that the results for experimental conditions were significantly poorer than the result with their clinical map. This suggests that difference in performance of participants in experimental studies could be attributed to the short time given to them to adapt to the tested experimental focused stimulation strategies. MP stimuli may be very similar to (or the same as) what subjects would perceive in real life with their clinical program. Certainly, greater time may be necessary for subjects to adjust to the new experimental stimulation strategies. Finally, it is also possible that the existing speech processing strategies based on sequential stimulation may not be capable of utilizing the benefits of restricted activation patterns created by current focusing. Novel speech processing strategies capable of taking advantage of focused stimulation may need to be developed.

An important finding presented in this thesis is the similarity observed between TP and FMP stimulation in terms of spatial selectivity, channel interactions and modulation sensitivity. This is consistent with a recent modelling study using a computational model of the human cochlea (Kalkman et al., 2015), which predicted similar excitation patterns for FMP and TP/pTP stimulation. While this observation
was surprising at first; given that the compensating current on the adjacent flankers (i.e., electrodes adjacent to the centre electrode) were almost always similar in both modes may provide an explanation for the observed indifference. We observed that the weights for adjacent flankers for FMP stimulation were consistently negative and fell in the range of -0.609 to -0.446 with mean of -0.5229, similar to that of -0.5 with TP stimulation, with the weights for the remaining flankers ranging between -0.17 and 0.22. Furthermore, the current implementation of FMP stimulation (based on a trans-impedance measurement) is designed to minimize the voltage at the electrode site rather than at the neural elements, which may also contribute to this finding. Our findings suggest that both stimulation modes produce similar patterns of current spread at the targeted SGN population. As a result, the perceptual consequences of these current focusing techniques might be similar. The benefits shown by FMP and TP in acutely stimulated cochleae warrant further investigation of these modes of stimulation in humans following chronic intracochlear electrical stimulation. Multiple current sources, required for implementing these techniques, are available in some present-day CIs. It would be interesting to see if speech perception using FMP and TP would be different in take-home CI experiments with more complex listening tasks, such as listening to speech in background noise.

### 7.2.2 Clinical implementation of the FMP technique

As previously discussed, FMP stimulation in its present form involves the measurement of trans-impedances between all intracochlear electrodes to determine current weights for each electrode to produce individual stimulating channels. Transimpedance values take into account the state of the electrode-neuron interface as well as subject specific anatomical and physiological factors at the time of measurement. In the present study, the transimpedance values measured generally exhibited good stability over the duration of the experiment. However, in the clinical situation, the transimpedance values would be expected to undergo change due to fibrous tissue encapsulation of the electrode array or related changes in the cochlea with time. Subsequent reduction in longitudinal shunting can
result in gradual sharpening of the current spread functions, as observed by van den Honert and Kelsall (2007). Therefore, it may be necessary to revise the transimpedance matrix from time to time to account for these changes. Based on experience while undertaking the work reported in this thesis, the transimpedance matrix for a 22 channel clinical CI could be generated in less than a minute, and therefore, updating the transimpedance matrix each time the speech processor is turned-on would be technically achievable.

The method for estimating the diagonal, i.e. the electrode impedances that cannot be measured due to polarization effects, also influences the calculation of current weights, which in turn affects the potential fields generated during FMP stimulation. For the present study, the linear estimator as presented by van den Honert and Kelsall (2007) was used. As it is clinically impossible to measure the cochlear tissue potential using the electrode that is delivering current during trans-impedance measurements, the weight on each point of the diagonal was linearly extrapolated from its neighbouring electrodes. However, it is unclear whether this method is optimal. A modified estimation method taking into account the physiological environment and longitudinal asymmetries in electrode position due to tapering of the scala tympani might improve the focusing outcome. Other methods have been proposed based on a computational model (Frijns et al., 2011, Kalkman et al., 2015) or by iteratively adjusting the channel weights in systematic ways, referred to as optimized multipolar stimulation (Smith et al., 2009, 2013). It may be important to test these optimized methods in future electrophysiological or clinical studies.

### 7.2.3 Applications to other neural prosthesis

Research outcomes from this thesis provide an important platform for the development of similar techniques in other prostheses such as visual prosthesis, deep brain stimulation (DBS) and spinal cord stimulation. Excitation of non-target neurons could cause adverse side effects when using DBS to treat movement disorders associated with Parkinson’s disease, essential tremor and dystonia (Kringelbach et al., 2007) and spinal cord stimulation to manage chronic neurological
pain (Panescu, 2008). For example, adverse side effects associated with inappropriate DBS stimulation include tetanic muscle contraction, speech disturbance, ocular deviation and psychological disorders. Factors such as imprecise electrode placement and tissue growth can reduce the therapeutic effectiveness of electrical stimulation (McIntyre et al., 2004). Therefore, techniques that effectively focus electrical stimulation will provide a benefit for these systems by ensuring a more precise and controlled form of neural activation, and can lead to improvements in therapeutic efficacy.

FMP stimulation is being currently investigated at the Bionics Institute in retinal implants, which aims to restore vision to people who lost their sight to degenerative retinal diseases, with the aim of increasing spatial resolution in implanted patients (Spencer et al., 2015).

7.3 Future Considerations

7.3.1 Investigating the efficacy and safety of FMP following chronic intracochlear electrical stimulation

The studies carried out within this thesis improve our understanding of efficacy of FMP stimulation in acutely implanted cochleae. However, little is known about the effect of the biological response associated with chronic FMP stimulation. The fibrous tissue encapsulation around chronic implants and bony growth can alter the electrode impedance (Newbold et al., 2004) as well as the electrical stimulation current distributions. An increase in the spread of neural activation has been previously reported at different levels of the auditory pathway in animals following chronic electrical stimulation (Leake et al., 2000, Vollmer et al., 2007, Landry et al., 2013), suggestive of reduced spatial selectivity with chronic implantation and stimulation. Even though the mechanisms responsible for this increase are less clear, the effect could be the result of anatomical or physiological changes in the auditory
pathway following chronic intracochlear electrical stimulation. Therefore, it is important to investigate the changes at the electrode-tissue interface in response to chronic FMP stimulation, especially when it requires higher charge to evoke a response. Our lab has begun to evaluate whether FMP stimulation using platinum electrodes can be performed safely and effectively in an animal model of profound deafness; this will provide insights into the likely effects of chronic intracochlear electrical stimulation using FMP technique.

### 7.3.2 Identifying “dead” regions using focused stimulation

The results presented within this thesis provide evidence that long-term deafened cochleae (i.e., cochleae with significantly degenerated SGNs) exhibit an elevated threshold for focused stimulation. This result along with the clinical finding of larger channel-to-channel variability in focused threshold as compared to MP stimulation (Marozeau et al., 2015) suggest that focused stimulation may be sensitive to changes in neural survival along the cochlea. Thus, focused stimulation may reveal neural “dead regions”, which are regions where there is locally poor neural survival compared to surrounding regions. The large channel-to-channel variability in thresholds and comfortable levels have also been observed with BP and TP stimulation both psychophysically (Pfingst and Xu, 2004, Bierer, 2007) and physiologically (Rebscher et al., 2001, Snyder et al., 2004). Neural “dead regions” are thought to impair speech perception, as implant channels situated near them are essentially activating the same neural population as neighbouring ‘good’ channels, thus reducing the channel independence in that region. Long et al. (2014) has shown a significant correlation between the variability of FMP thresholds across the electrode array and speech understanding with ten participants. Work has recently begun in our laboratory using an animal model with well-defined neural “dead regions” to better understand the relationship between the electrical hearing threshold profile in focused stimulation and neural survival. In future, this may allow focused thresholds be used as a tool to identify channels with a poor electrode-neuron interface, and a measure of CI effectiveness in activating the auditory system.
7.4 Conclusions

The studies described within this thesis have demonstrated that FMP and TP stimulation result in more restricted neural activation and reduced channel interactions compared to MP stimulation using intracochlear stimulation in an animal model. The results also demonstrated that this advantage of FMP and TP is maintained in cochleae with significant neural degeneration more reflective of the clinical situation and is not adversely affected by electrode position. Modulation detection of MP stimulation is significantly better than FMP and TP stimulation at low stimulation levels, though; current focusing techniques such as FMP and TP stimulation remain capable of conveying amplitude modulation even at high stimulation levels. Importantly, there is no benefit in terms of restricted neural activation, reduced channel interaction and better modulation sensitivity for FMP compared to TP stimulation. With the illustrated benefits of better spatial selectivity, reduced channel interactions and being able to encode amplitude modulation, our data warrant the further development of implants that can stimulate the auditory nerve with all the electrodes in the array simultaneously with sufficient accuracy of the current levels, in order to safely apply FMP stimulation.
Cited Literature


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Author/s:
Sam George, Shefin

Title:
Investigating the effect of focused multipolar stimulation for cochlear implants: preclinical studies

Date:
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