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Evaluation of focused multipolar stimulation for cochlear implants in acutely deafened cats

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Abstract

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. *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.

Keywords: Cochlear implant; Electrical stimulation; Multipolar stimulation; Current focusing; Inferior colliculus

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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 neurones (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 is 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., 1983, 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 more 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 intracochlear electrodes while the remaining 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 and/or longer phase durations to achieve adequate loudness in implant users compared to MP stimulation (Litvak et al., 2007, 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 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 decide current weights for each electrode in such a way that an excitatory voltage is only delivered to the central electrode and null voltage to the other electrodes (figure 1).

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. However, the use of percutaneous connectors and related concerns about patient safety has 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.

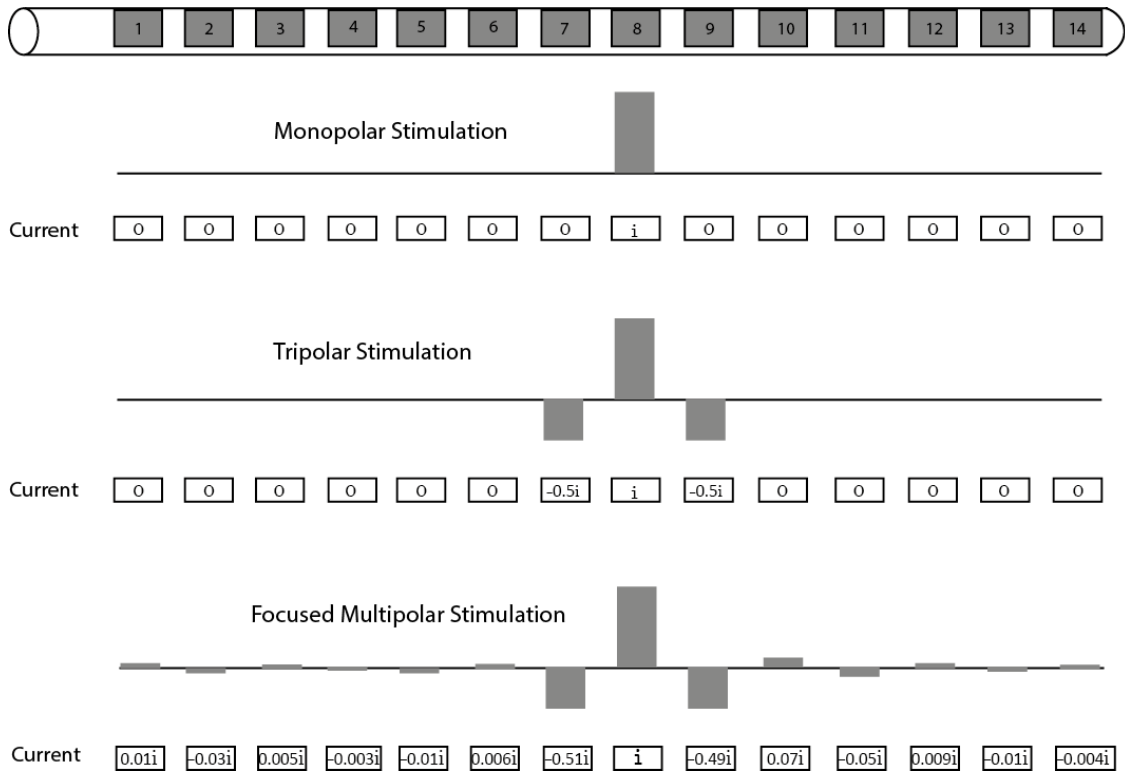


Figure 1: Schematic diagram illustrating monopolar (MP), tripolar (TP) and focused multipolar (FMP) stimulation centred on electrode 8. The amplitude only represents the anodic phase of a biphasic pulse.

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.

Methods

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).

Anaesthesia and surgery

Animals were anaesthetised using ketamine (intramuscular, 20 mg/kg) and xylazil (subcutaneous, 2 mg/kg), 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). An endotracheal tube was inserted at the beginning of the experiment to monitor respiration rate (normal levels: 10-20) and end-tidal CO₂ levels (normal levels: 3-5%). The core body temperature was maintained at $37.0 \pm 1^\circ\text{C}$.

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 temporalis 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-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 on average 10 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.

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 (van den Honert and Kelsall, 2007) and Ross (Ross et al., 2003). 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 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 (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 μ s and an inter-phase gap of 50 μ s. For TP and FMP configurations, each pulse had a phase of 400 μ s and an inter-phase gap of 50 μ s. 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, current level (CL), as defined by Cochlear Ltd. (Australia), where,

$$\text{Current in } \mu\text{A} = 17.5 * (100 \wedge (\text{CL}/255))$$

The current was increased in discrete CL steps (10 repetitions for each level) up to a maximum stimulus level for each channel of either 255 CL, or the threshold for myogenic activity.

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 μ m intervals (centre to centre), each having a circular surface area of 413 μ m². 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"-tetramethylindocarbocyanine 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 μ m/s) 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 μ s 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 XT25TG30-04 speaker and a sound delivery vinyl tube. The whole system was calibrated over a frequency range of 0.5 – 40 kHz.

Data Analysis

Multi-unit activity was processed offline, using customised 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 4 times root mean square (RMS) 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 3-35ms post stimulus window (figure 2a, b). For each stimulus condition and CL, spike counts were averaged across 10 trials and normalised to the maximum spike rate at each recording site (Snyder et al., 2008). Normalised 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 2d). 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 2d), was determined for each stimulus condition (Landry et al., 2013). The recording site with the lowest threshold was defined as the best recording site.

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, 2004). A receiver operator characteristic curve was formed based on spike counts for 10 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 $\sqrt{2}$ 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 the compliance limit of the device, mainly 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' per dB) 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 2c (threshold level = 210 CL, level of cumulative d' of 1 from threshold level = 240 CL, Discrimination Slope = 0.86 d' per dB).

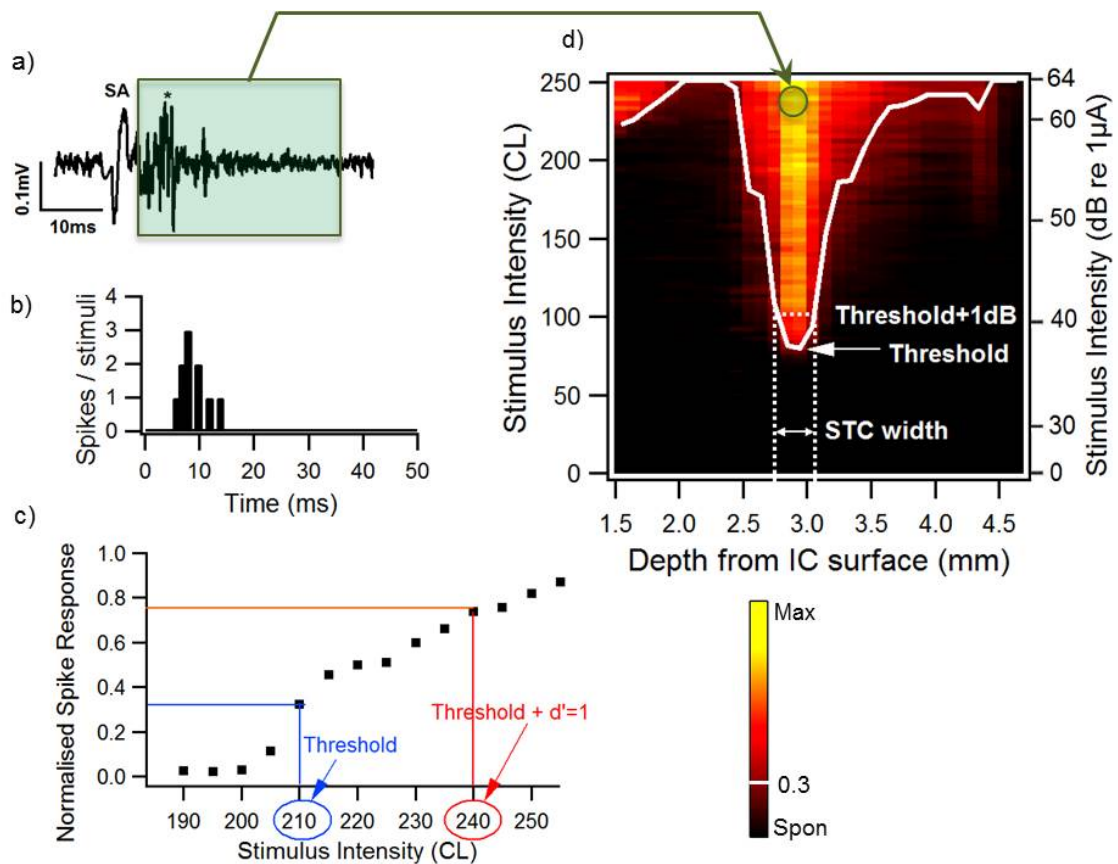


Figure 2: Overview of multichannel neural recording along the cochleotopic axis of the inferior colliculus (IC). a) A trace of multi-unit responses (*) and stimulus artefact (SA) from one IC recording site following electrical stimulation of a CI channel. The analysis window (3-35ms) used for spike counting 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).

Spread of activation in the Inferior Colliculus

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.

Spatial Tuning Curve Width: Spatial tuning curves (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 2d). 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 current level.

Measure of total neural response growth in the Inferior Colliculus

As reported by previous psychophysical studies (Litvak et al., 2007, 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 particular stimulus intensity. From these plots, the increases in neural response from 0 to 1dB above threshold as well as from threshold to the stimulus level yielding cumulative $d' = 1$ were computed and compared across the different stimulus configurations.

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.

Results

Across the 8 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 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.

Response Images

IC response images to electrical (six animals) and acoustic stimuli (one animal) were generated. Figure 3a presents an IC response image (and the STC) to a 12 kHz pure tone acoustic stimulus in one animal and figures 3b, c, 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. 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.

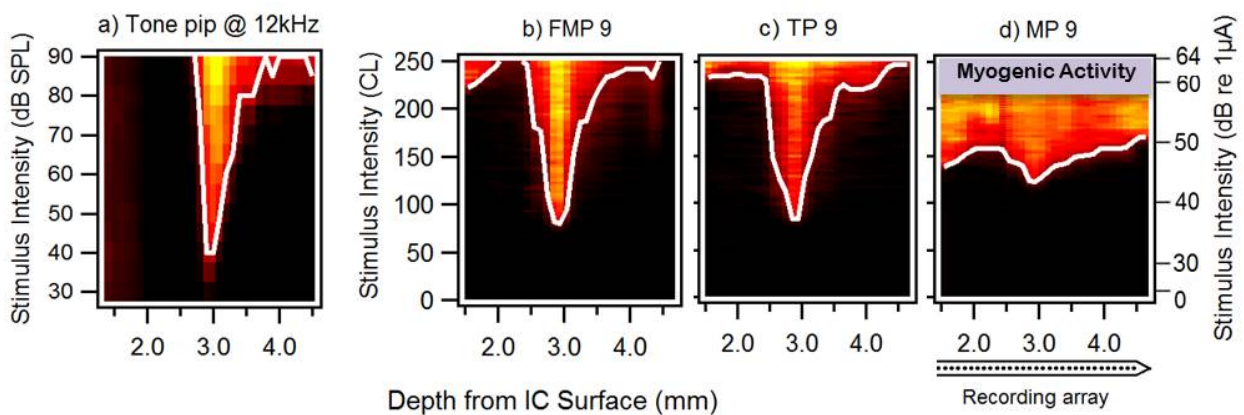


Figure 3: Response images across the cochleotopic axis of the IC to acoustic and electrical stimulations. a) pure tone at 12 kHz and electrical stimulation using b) FMP c) TP and d) MP electrode configuration. Each response image was generated by plotting depth of the IC recording site on the x-axis 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 μ s while TP and FMP configurations used pulses with 400 μ s 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.

Threshold and Discrimination slope

Minimum thresholds, converted to nC, for different stimulation configurations are shown in figure 4a. 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 ($p = 0.997$). 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 4b. Discrimination slopes averaged $1.93 (\pm 0.24)$ for MP, $1.14 (\pm 0.21)$ for FMP and $1.45 (\pm 0.25)$ 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 not significantly different from MP ($p = 0.201$) or FMP configurations ($p = 0.515$).

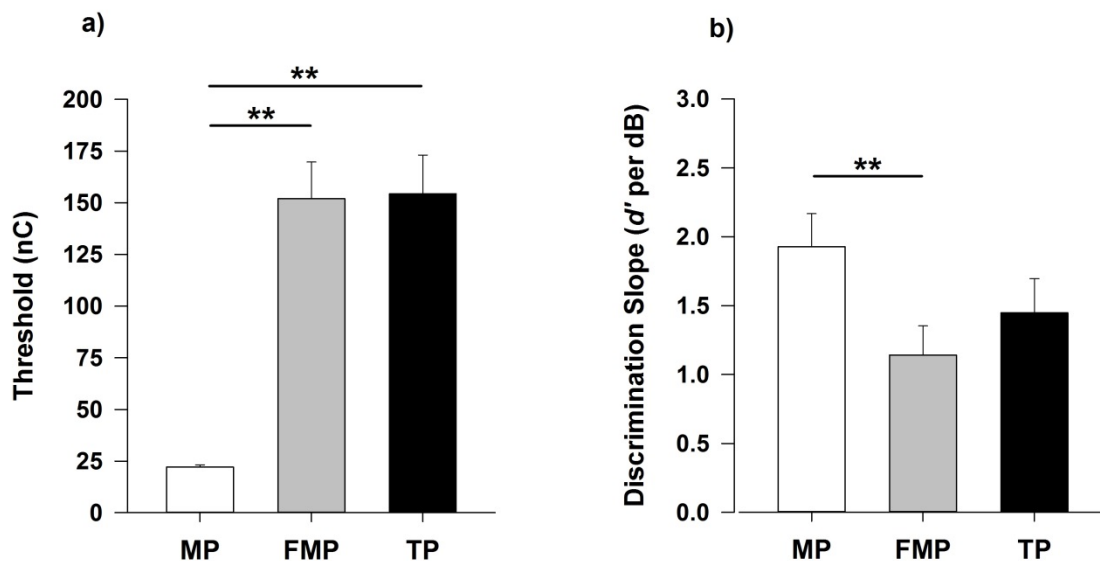


Figure 4: Group means for IC electrical thresholds and discrimination slopes (mean + SEM) measured for MP, FMP and TP stimulation configurations. a) Threshold levels are expressed in charge (nC). b) Discrimination slopes measured at the best recording sites are expressed as d' per dB. ** $p < 0.050$, $N = 51$ channels.

Spread of activation in the Inferior Colliculus

Spatial Tuning Curve Width

STC widths at both 1 dB and $d' = 1$ above threshold (figure 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 5b).

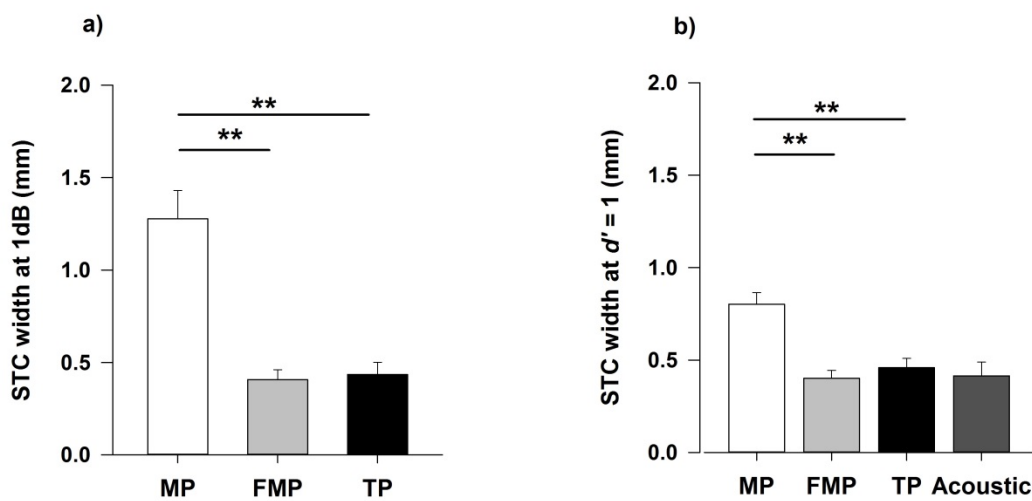


Figure 5: STC Widths (mean + SEM) measured across MP, FMP and TP stimulation configurations a) at 1dB above threshold and b) at cumulative $d' = 1$ above threshold. Means of STC widths for acoustic stimulation measured at cumulative $d' = 1$ above threshold is shown only for the purpose of comparison and were not included in the statistics. ** $p < 0.001$.

Number of active recording sites

As another measure of the spread of activation, for each cochlear stimulation channel the number of recording sites in the IC activated was plotted against stimulus intensity as shown in figure 6a. 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 6b and was significantly dependent on 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 ($p = 1$). The number of recording sites activated at current level that resulted in a cumulative $d' = 1$ for all the stimulation configurations is shown in figure 6c, along with representative data for acoustic stimulation. Although the difference was smaller using this metric, MP stimulation still resulted in activation of 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 these modes resulted in similar spread of activation to that found with acoustic stimulation (figure 6c).

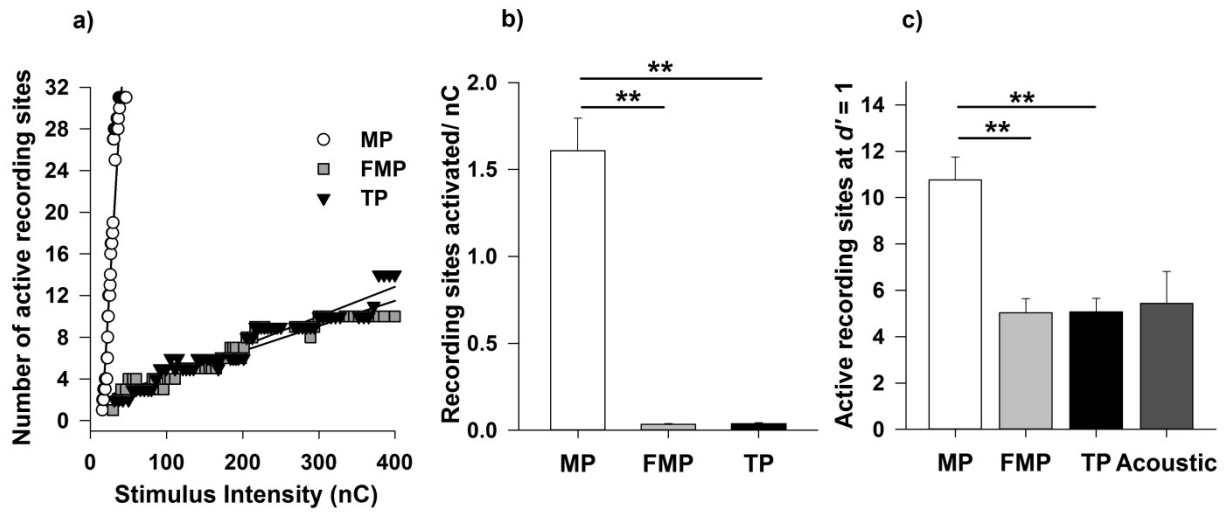


Figure 6: a) Example of number of recording sites activated versus stimulating current level function for MP (closed circles), FMP (open squares) and TP (closed triangles) stimulation on a single cochlear channel (shown only for charge levels up to 400 nC). Fitted linear function for the rising component 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. ** $p < 0.001$.

Total neural response growth in the Inferior Colliculus

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 7a). The increase in total neural response was dependent on stimulus configuration (figure 7b; 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 7c; 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 7c).

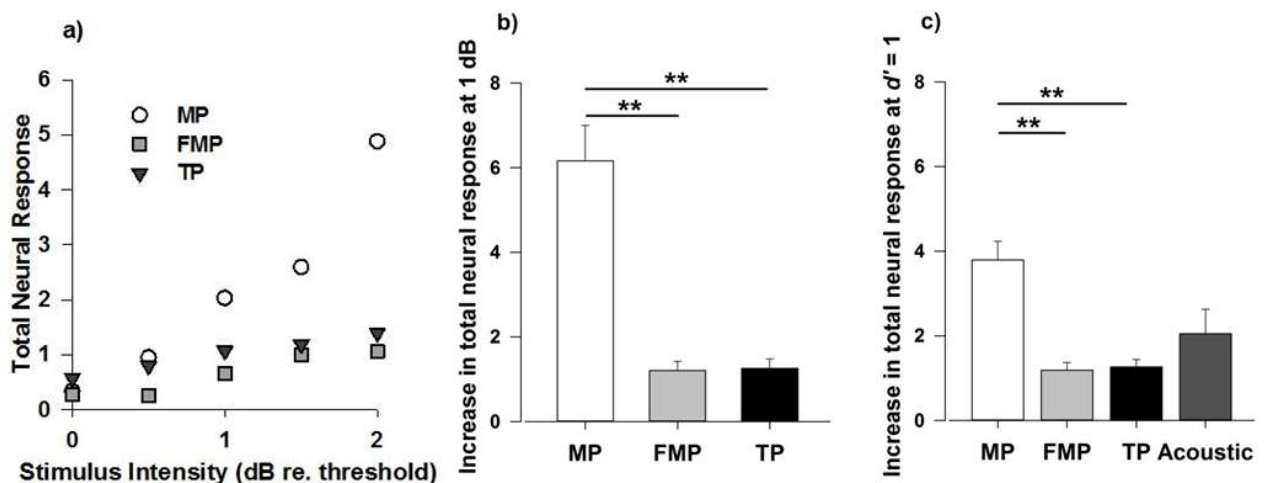


Figure 7: a) Example of normalised total neural response across the recording array versus stimulus intensity (expressed relative to threshold) for MP (closed circles), FMP (open squares) and TP (closed triangles) stimulation. The total neural response at threshold, 1dB above threshold and cumulative $d' = 1$ 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. ** $p < 0.001$.

Spread of activation for end channels

It has been reported that FMP stimulation of end channels results 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 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.

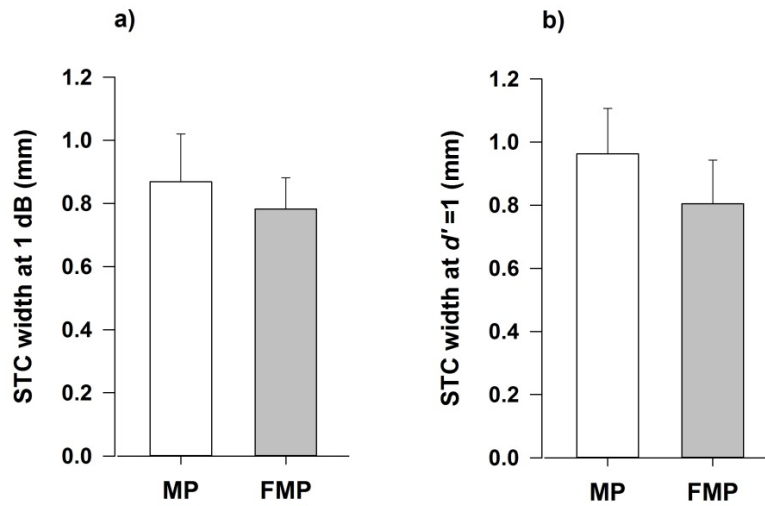


Figure 8: STC Widths (mean + SEM) measured for end channels across MP and FMP configurations at 1dB above threshold. No significant difference was found in the STC width of MP and FMP end channels. N=16 channels.

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 could be 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 more rapid 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 the previous report of FMP stimulation (van den Honert and Kelsall, 2007), 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 current levels 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 current levels eliciting normalised 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 compliance limit of the device. Hence, we calculated discrimination slope (expressed in units of d' per dB) as a measure of dynamic range, at least for the initial slope of the suprathreshold stimulus-response function. We found that the discrimination slope of the most sensitive site of each IC response image was significantly higher 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). The study by Middlebrooks and Snyder (2007) reported discrimination slope of 1.98 for MP scala tympani stimulation and this value is comparable to the mean discrimination slope of 1.93 obtained with MP stimulation in this study.

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* (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 current levels relative to threshold (1 dB 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 restricted, whereas MP response images tended to extent 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 patients 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.*, 2007, 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 current level 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 localised and spatially precise activation of cochlear

region 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 superior 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 spiral ganglion neurons, 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 results 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 not only to improve spectral resolution but can 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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