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Electrophysiological channel interactions using focused multipolar stimulation for cochlear implants

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Abstract

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. *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.

Keywords

Cochlear implant; Electrode configuration; Multipolar Stimulation; Current focusing; Channel Interaction; Inferior colliculus

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 non-simultaneous 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 intra-cochlear 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 (pTP) (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 of electrical stimulation and CI users generally prefer MP stimulation over BP/TP stimulation. The lower stimulation levels and better battery life explains the long-lasting use of MP instead of current focussing 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). 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, George et al., 2015). Moreover, Smith et al., (2013) used psychophysical tests to show that this multi-electrode 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 has been no direct comparison of channel interaction measures of FMP, TP and MP stimulation. In contrast to TP stimulation which uses three intracochlear electrodes, FMP stimulation employs all the intracochlear electrodes and, it is anticipated that FMP might be better than TP 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.

Methods

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 access 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, George et al., 2015).

Surgery and electrode insertion

Anaesthesia prior to surgery was induced by ketamine (intramuscular, 20 mg/kg) and xylazil (subcutaneous, 2 mg/kg), and maintained with a slow continuous intravenous infusion of sodium pentobarbital (3-8 mg/kg/hr). Core body temperature was maintained at 37.0 ± 1^{o}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) and end-tidal CO_2 levels (normal levels: 3-5%) throughout the duration of the experiment (2-3 days). Clavulox (subcutaneous, 10 mg/kg) as an antibiotic, and dexamethasone (intramuscular, 0.1 mg/kg) to minimize brain swelling were administered every 24 hours throughout the experiment.

All the four long-term deafened animals in cohort 1 were deafened, using procedures that have been described in detail elsewhere (Fallon et al., 2009, George et al., 2015). In brief, each animal neonatally received a daily injection of neomycin sulphate (subcutaneous, 60 mg/kg) until the animal was profoundly deaf (i.e. absence of a click-evoked auditory brainstem response at 100 dB peak equivalent (p.e) 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.

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 output of the stimulator delivered a single cathodic-first, charge balanced biphasic pulse. 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, current in μA = 17.5*(100 ^ (CL/255)).

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 same electrode and the current delivered to such electrodes was based on the summation of the weights of individual

channels. 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 current level on S1 was fixed at a level relative to its threshold when presented alone (i.e., sub-threshold, threshold or supra-threshold) while the current level 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 inter-electrode spacing) between the two channels. All combinations of inter-electrode spacing, stimulation configuration and current level were presented at random with each repeated 10 times.

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 μm^2. 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.

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 root mean square of the background activity for each recording channel in a 3–35 ms post-stimulus window. At each recording site, the spike counts were

averaged across 10 trials for each stimulating channel, stimulation configuration and current level. All responses showed a monotonic increase with stimulus level. To account for the variation in spike rate across the recording sites, each spike rate was normalized to the maximum spike rate at 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 1a). The data were smoothed with a 3 x 3 Gaussian function. The lowest current that elicited a normalized spike rate of 0.3 (indicated in figure 1a) 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.

Threshold Interaction Index

The difference between single-channel and two-channel neural responses was used as a measure to quantify channel interaction (figure 1d, e)

$$\text{Difference in neural response} = R_{S1+2} - (R_{S1} + R_{S2})$$

where, R_{S1+2} is the normalized neural response to simultaneous stimulation of S2 and fixed current S1and 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 1e) 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 1e). An interaction index greater than zero indicated a 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*.

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 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.

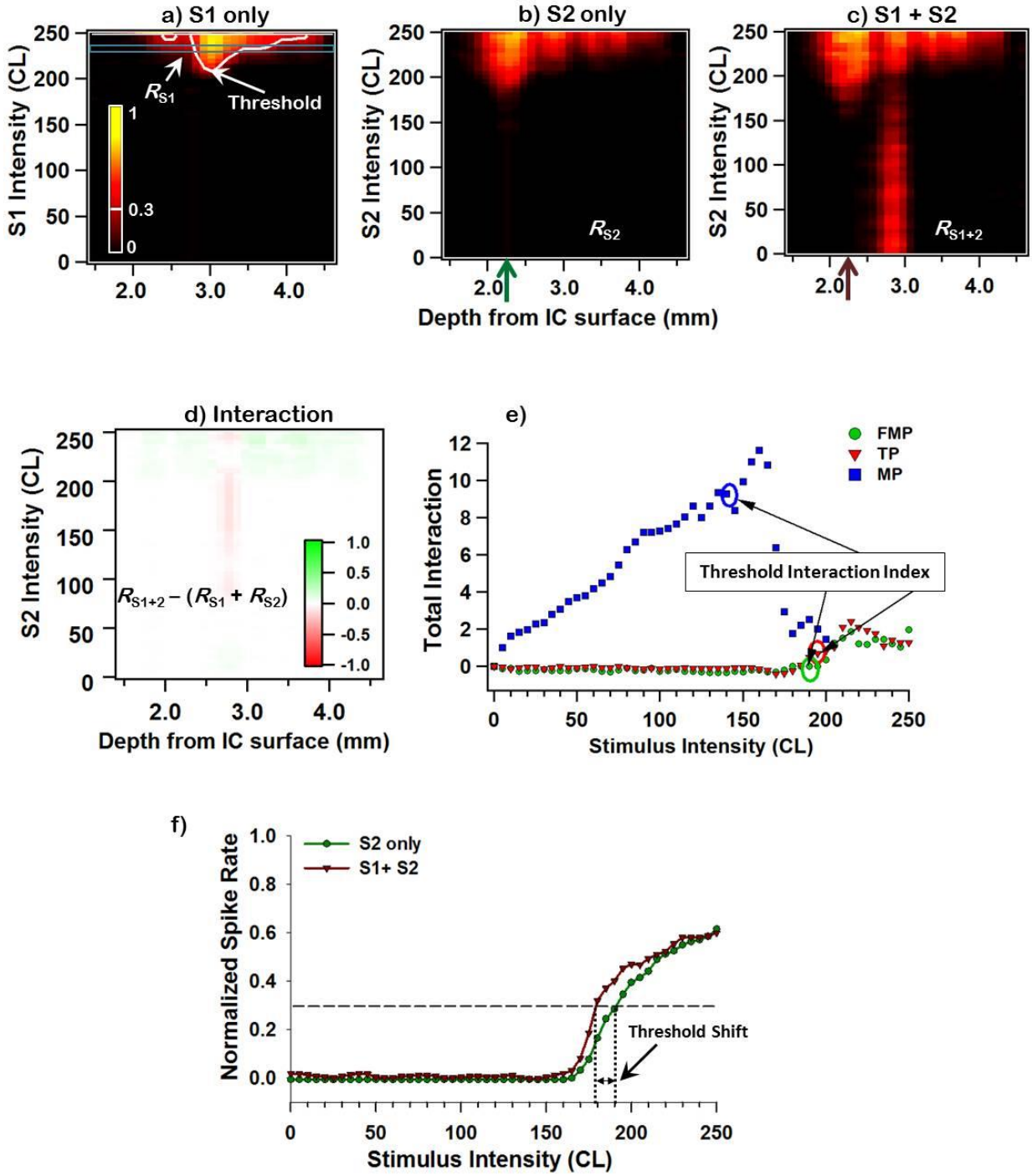

Figure 1: Overview of how threshold interaction index and threshold shifts were calculated for two-channel stimulation. Representative IC response images to electrical stimulation of a) S1 alone, b) S2 alone and c) S1 at 10 CL above its threshold and S2 simultaneously. Two-channel stimulation in FMP 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.

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.

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 spiral ganglion neuron (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.

IC Response Images

IC response images to electrical (seven animals) and acoustic (one animal) stimuli were generated. Figure 2 presents response images for a representative animal in the long-term deafened group following electrical stimulation in 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 current levels 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.

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.

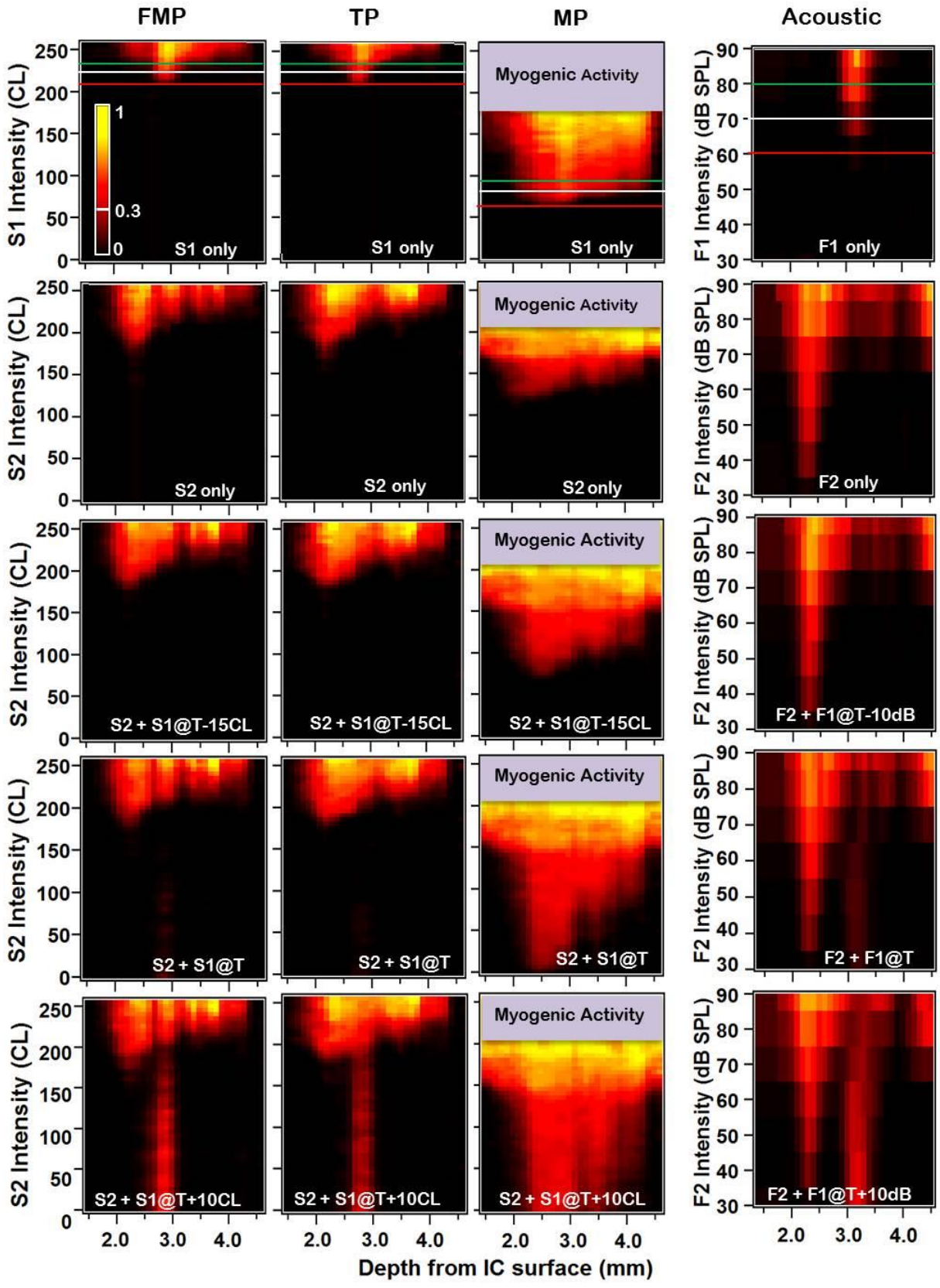

Figure 2: Response images across the cochleotopic axis of the IC to electrical and acoustic stimulation. Columns 1, 2 and 3 represent the response images generated for FMP, TP and MP stimulation configurations, respectively in a long-term deafened cat while column 4 presents the response images for acoustic 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-15CL or T-10dB), threshold (T) and supra-threshold (T+15CL or T+10dB) levels, respectively. Data are from animals 12_306 and 12_307.

Threshold interaction index

Figure 3a, 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 figure 3a and 3b, we observed a general trend of reduction in threshold interaction index with increased inter-electrode spacing in the case of MP stimulation.

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 3c 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.

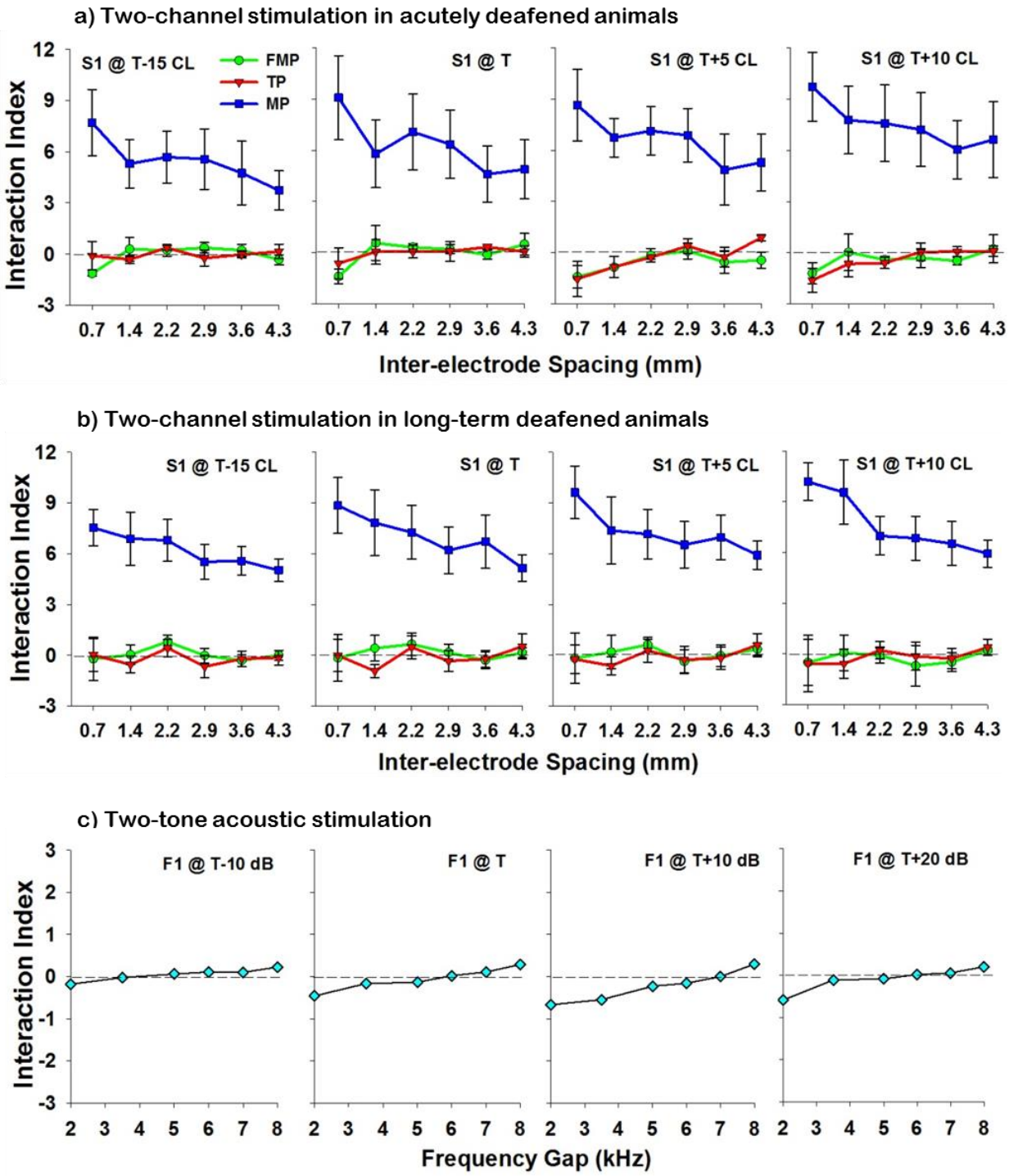

Figure 3: a, b) Threshold interaction index (mean ± SEM) across the IC recording array obtained for different stimulation configurations versus inter-electrode spacing between two channels (S1 and S2) stimulated simultaneously in a) acutely deafened (N = 4 pairs of CI channels tested at each inter-electrode 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.

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 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 4c) 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 4d).

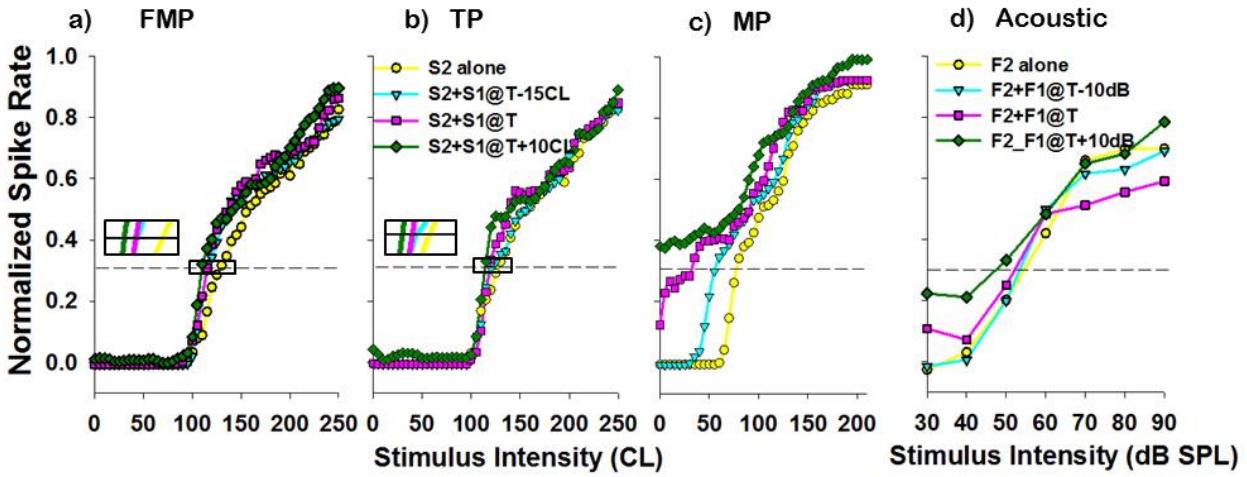

Figure 4: Normalized spike rate versus stimulus intensity plots for the best recording site of S2. Each panel represents neural spikes obtained in response to electrical stimulation using a) FMP b) TP c) MP stimulation configuration and to d) acoustic stimulation. The stimulus level delivered to S2/F2 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 figure 5a,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. 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 5c 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.

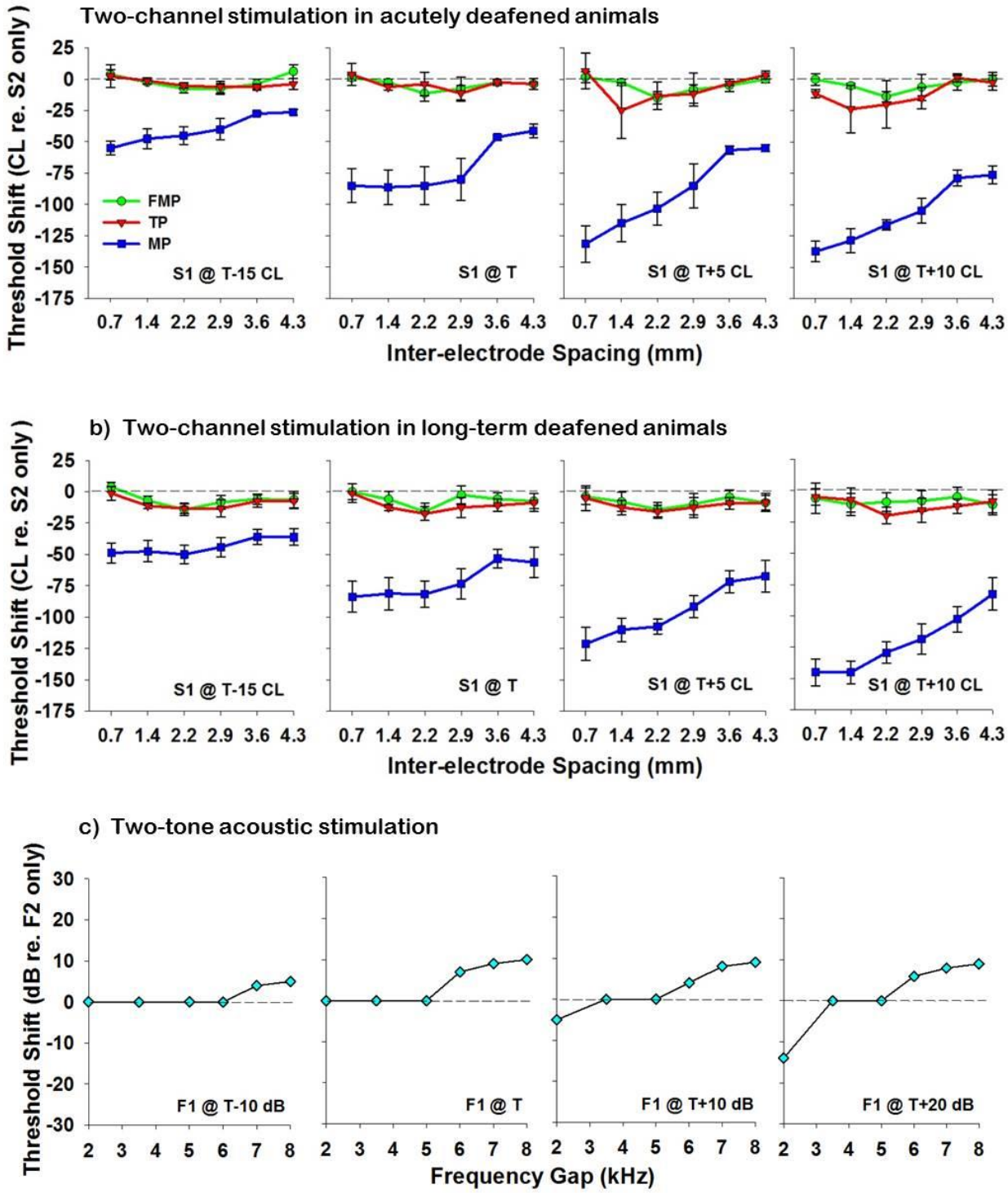

Figure 5: a, b) Threshold shift (mean ± SE) for different stimulation configurations in acutely deafened (N = 4 pairs of CI channels tested at each inter-electrode spacing across 4 cochleae) and long-term deafened cats (N= 4 pairs of CI channels tested at inter-electrode spacing of 0.7, 1.4 and 4.3 mm and 6 pairs tested at inter-electrode spacing of 2.2, 2.9 and 3.6 mm across 6 cochleae). 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.

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, it 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 interaction for FMP and TP stimulation. This is consistent with previous electrophysiological findings of restricted multi-neuronal activity in the IC (George et al., 2014, Snyder et al., 2004) 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. However, the effect of current focusing on spread of neural activation during sustained responses to pulse trains is less clear (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 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.

Two-tone acoustic stimulation resulted in negative interaction indices for closely spaced tones, indicating a suppression effect. This is consistent with previous electrophysiological studies on the effect of a tone when sounded in the presence of another tone on the neural responses at different levels of the auditory pathway (Galambos, 1944, Ehret and Merzenich, 1988, Calford and Semple, 1995, Kadia and Wang, 2003). However, negative threshold shifts were observed for closely spaced tones, especially at higher stimulus intensities indicating the integration of energy within a critical band. Considering what is known about two-tone stimulation and the difference between the two interaction measures used in the present study, this observation is not all that surprising.

In the present study, a few interesting observations were made on comparing data from acutely deafened, long-term deafened and normal animals. Even though not significant, the acutely deafened animals showed a trend towards a small amount of suppression with closed spaced channel pairs (figure 3a) similar to the normal hearing animals (figure 3c). However, this trend was not observed in long-term deafened animals. This could imply an effect of duration of deafness on the auditory processing and thus, translating to the variability in the performance of CI users.

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 Pelizzone, 1993). Importantly, simultaneous MP stimulation was observed to produce larger threshold shifts compared to bipolar (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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