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Focused electrical stimulation using a single current source

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Abstract

Objective. Cochlear implants, while providing significant benefits to recipients, remain limited due to broad neural activation. Focussed multipolar stimulation (FMP) is an advanced stimulation strategy that uses multiple current sources to produce highly focussed patterns of neural excitation in order to overcome these shortcomings. *Approach*. This report presents single-source multipolar stimulation (SSMPS), a novel form of stimulation based on a single current source and a passive current divider. Compared to conventional FMP with multiple current sources, SSMPS can be implemented as a modular addition to conventional (i.e. single) current source stimulation systems facilitating charge balance within the cochlea. As with FMP, SSMPS requires the determination of a transimpedance matrix to allow focusing of the stimulation. The first part of this study therefore investigated the effects of varying the probe stimulus (e.g. current level and pulse width) on the measurement of the transimpedance matrix. SSMPS was then studied using *in vitro* based measurements of voltages at non-stimulated electrodes along an electrode array in normal saline. The voltage reduction with reference to monopolar stimulation was compared to tripolar and common ground stimulation, two clinically established stimulation modes. Finally, a proof of principle *in vivo* test of SSMPS in a feline model was performed. *Main results*. A probe stimulus of at least 40 nC is required to reliably measure the transimpedance matrix. *In vitro* stimulation using SSMPS resulted in a significantly greater voltage reduction compared to monopolar, tripolar and common ground stimulation. Interestingly, matching measurement and

stimulation parameters did not lead to an improved focussing performance. Compared to monopolar stimulation, SSMPS resulted in reduced spread of neural activity in the inferior colliculus, albeit with increased thresholds. *Significance*. The present study demonstrates that SSMPS successfully limits the broadening of the excitatory field along the electrode array and a subsequent reduction in the spread of neural excitation.

Keywords: cochlear implant, current focussing, phased array, spread of excitation, electrical stimulation

1. Introduction

A cochlear implant is the only treatment for severe to profound sensorineural hearing loss that is currently available in clinical practice. Modern cochlear implants generally stimulate auditory neurons using a monopolar (MP) stimulation mode where the intracochlear active electrode close to the targeted neural population is stimulated against a remote, extracochlear return electrode. While providing a significant benefit to speech understanding in low-complexity listening situations, recipients still experience difficulties in listening conditions with high background noise or with understanding of tonal languages and music perception (Fu et al., 1998, McDermott, 2012). Due to the spatial separation of the active and remote return electrodes and the highly conductive nature of the perilymph in which the electrode array is bathed, MP stimulation results in a broader spread of excitation of auditory neurons than occurs with acoustic stimulation (George et al., 2014a). In order to overcome this broad excitation, alternative approaches have been developed and tested clinically, including bipolar, tripolar (TP) and partial TP stimulation (Landsberger et al., 2012, Srinivasan et al., 2013). For TP stimulation, the electrodes adjacent to the stimulation electrode are used as the return electrodes. Partial TP is a combination of TP and MP stimulation where the return current is actively divided between the adjacent and remote return electrodes. While all these methods resulted in a decreased spread of excitation, they did not necessarily translate to clinical benefits in terms of improved speech perception (Srinivasan et al., 2013), potentially due to the speech encoding schemes used.

Focussed multipolar (FMP) stimulation (also known as phased array or all-polar stimulation) is an example of current focussing techniques and is designed to reduce the spread of neural excitation via the active cancellation of the voltages evoked at off-centre electrodes (van den Honert and Kelsall, 2007). In this approach multiple electrodes are simultaneously stimulated using multiple current sources with the aim that the superposition of currents will lead to a cancellation of the electrode potentials on all electrodes flanking the centre electrode (figure 1). The reliance of FMP on multiple

current sources contrasts to MP and BP stimulation which can be implemented with a single current source.

For FMP stimulation, interactions between electrodes are characterized by their transimpedance, i.e. the ratio between the measured voltage v_i at each non-stimulated electrode i and current i_j delivered at the stimulation electrode j:

$$z_{ij} = \frac{v_i}{i_j} \tag{1.1}$$

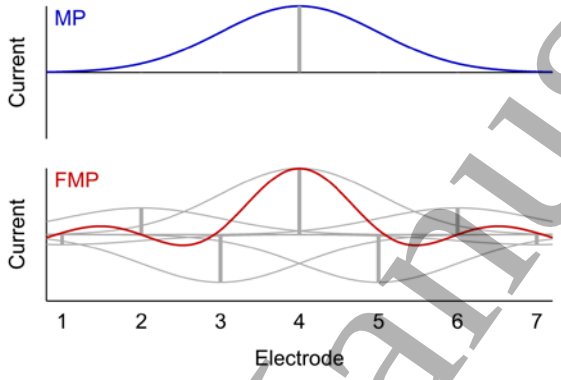

Figure 1: Current spread of monopolar (MP) and focussed multipolar (FMP) stimulation. The blue line indicates the overall voltage distribution for MP stimulation. The red line indicates the voltage distribution achieved via FMP stimulation if the effects of various electrode currents (grey lines) are superposed. The grey bars denote the magnitude and polarity of individual electrode currents. The figure shows a typical distribution of currents with alternating polarities. In both examples, electrode 4 was designated the centre electrode.

This allows the electrode array to be described as a linear system of stimulation currents and electrode potentials. Using this formalisation, a set of physical electrode currents $\boldsymbol{i}_\mathrm{e}$ are calculated that results in a virtual current at the focussed channel (FC) $\boldsymbol{i}_\mathrm{f}$ while all other electrode potentials are cancelled out. The required electrode currents are calculated from the FC currents via:

$$\boldsymbol{i}_\mathrm{e} = \boldsymbol{W}\boldsymbol{i}_\mathrm{f} \tag{1.2}$$

The dimensionless weights matrix $\boldsymbol{W}$ has the advantage that the set values of the FCs is expressed as a function of the current at the centre electrode.

Modelling studies predicted a reduced spread of activation (Frijns et al., 2011) which was subsequently confirmed in animal (George et al., 2014b, George et al., 2015b) and clinical studies (Long et al., 2014, Marozeau et al., 2015). Psychophysical studies in human subjects also indicated that current focussing can increase the spectral resolution of cochlear implants (Smith et al., 2013).

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Aside from application for cochlear stimulation, current focussing is also a candidate for optimising deep brain stimulation (DBS) systems as suggested by modelling studies (Martens et al., 2011, Chaturvedi et al., 2012). Recently, focussed stimulation has been expanded to applications with two-dimensional, paddle-style electrode arrays for visual prosthesis. Using a modified approach of the FMP technique, it was shown that significant voltage reduction was achieved at electrodes surrounding the stimulation electrode compared to MP stimulation and subsequent, *in vivo* experiments showed an increased selectivity as determined by the spatial extent of cortical activation (Spencer et al., 2016). Finally, current focussing techniques have the potential to be applied to other areas of neuromodulation including spinal cord stimulators for the management of pain and peripheral nerve stimulation for a variety of bioelectronics applications (Shepherd, 2016).

While FMP stimulation has the potential to significantly reduce the spread of neural activation, it relies on multiple current sources compared to traditional stimulator designs that are typically based on a single current source and interleaved delivery of stimuli to multiple electrodes. Consequently, the power requirements of FMP stimulators pose challenges for mobile, battery-powered applications. Furthermore, the inherent balancing of charge delivered to the cochlea achievable with a single current source is not guaranteed if a combination of current sources and sinks is used for the stimulus generation. However, recent studies utilising chronic FMP reported there was no evidence of corrosion on any electrode, demonstrating its potential safety (Shepherd et al., 2017).

This report introduces a new, single-source multipolar stimulation (SSMPS) technique to deliver multipolar stimuli through conventional electrode arrays using a single current source with the addition of a variable impedance bank. The implementation of focused stimulation without the requirement for multiple current sources provides the advantage of using simpler charge balancing procedures. The passive division of currents can be compared to the clinically established common ground (CG) stimulation configuration, where all non-active electrodes are ganged together to act as a return electrode.

This report describes an investigation of the SSMPS strategy. First, the measurement conditions of the transimpedance matrix were examined in order to establish boundary conditions for a reliable parametrisation of a focussed stimulation system. We then examined the extent of focussing using SSMPS compared to the clinically established stimulation configuration of MP, TP and CG stimulation by measuring the voltage drop along the electrode array *in vitro*. Finally, we performed a proof-of-principle test of SSMPS in a feline cochlear implant model.

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2. Methods

2.1. Single-source multipolar stimulation

SSMPS is based on a passive current divider circuit consisting of a variable impedance connected in series with each electrode so that the resulting stimulation current is divided across all connected electrodes. The current division is based on the sum of the electrode/tissue impedance and the variable impedance as well as the connection to either the active or the return port of a single constant current stimulator (figure 2A).

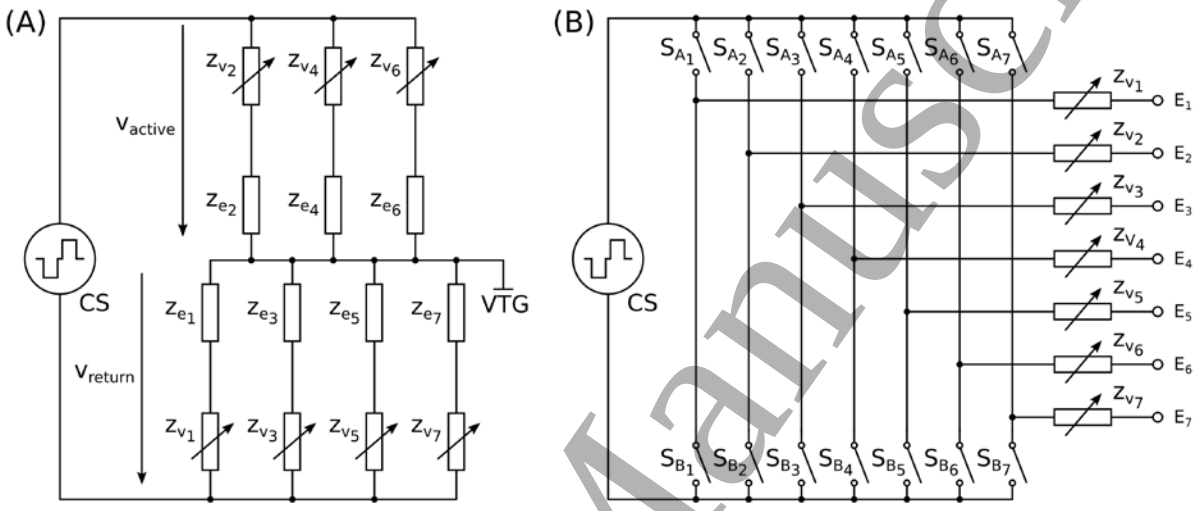

Figure 2: (A) Schematic illustration of a single-source multipolar stimulation system with 7 electrodes focussed at the centre electrode 4. Variable impedances ($\mathbf{z}_v$, implemented as a decade resistor bank) were used as a passive current divider to achieve the simultaneous delivery of focussing current to all electrodes based on a single current source (CS, implemented as a modified clinical cochlear implant stimulator (Irving et al., 2014)). The set values of the focussing currents were determined based on the electrode impedances ($\mathbf{z}_e$) and transimpedances between electrodes. Magnitude and polarity of the focussing currents determine the values of $\mathbf{z}_v$ and the connection to the active or return port of the CS. The off-centre currents typically have alternating polarities with increasing distance from the centre electrode. The virtual tissue ground (VTG) is not physically accessible via the electrode array. (B) Schematic illustration of the experimental setup including a switch matrix for the electrode channels to allow varying electrode current polarities. The switches S_{A_x} and S_{B_x} (implemented as an array of single-pole double-throw manual switches) connect electrode x (E_x) to the forward and return port of the CS, respectively.

For a practical implementation, the electrode impedances apparent to the stimulation system were approximated as solely resistive without any reactive components. As a consequence, the current divider of the SSMPS system was implemented using variable resistances only without any inductive

or capacitive elements based on a decade resistor bank and a switch matrix (figure 2B). The SSMPS system could generate a set of random stimulation currents through the active and return electrodes as long as the sum of all active currents matched the sum of all return currents which is also a requirement of conventional FMP stimulation.

To achieve the desired current pattern, the resistor values of the variable impedance bank were calculated based on the electrode current vector $\boldsymbol{i}_{\mathrm{e}}$ and the vector of electrode impedances $\boldsymbol{z}_{\mathrm{e}} = \left(z_{\mathrm{e}_1}, z_{\mathrm{e}_2}, \ldots, z_{\mathrm{e}_k}\right)^T$, for an electrode array with *k* electrodes. The maximum voltage drop over an active electrode determined the total voltage drop between the active terminal of the stimulator and the virtual tissue ground (VTG):

$$v_{\mathrm{active}} = \max_p(i_{\mathrm{e}_p} z_{\mathrm{e}_p}) \tag{2.1}$$

Similarly, the voltage drop between the return terminal of the stimulator and the VTG was determined by the minimum voltage drop over any return electrode:

$$v_{return} = \min_p(i_{\mathrm{e}_p} z_{\mathrm{e}_p}) \tag{2.2}$$

With these two values, the variable impedance bank settings $\boldsymbol{z}_{\mathrm{v}} = \left(z_{\mathrm{v}_1}, z_{\mathrm{v}_2}, \ldots, z_{\mathrm{v}_k}\right)^T$ were calculated:

$$z_{\mathrm{v}_p} = \begin{cases} \dfrac{v_{\mathrm{active}}}{i_{\mathrm{e}_p}} - z_{\mathrm{e}_p}, & i_{\mathrm{e}_p} \geq 0 \\ \dfrac{v_{\mathrm{return}}}{i_{\mathrm{e}_p}} - z_{\mathrm{e}_p}, & i_{\mathrm{e}_p} < 0 \end{cases} \tag{2.3}$$

The sign of the element i_{e_p} of the electrode current vector determined whether the channel was connected in an active or a return configuration. The total stimulation current to be delivered by the current source was given by the sum of all positive elements of the electrode current vector $\boldsymbol{i}_{\mathrm{e}}$:

$$i_{\mathrm{total}} = \operatorname{sum}_p(i_{\mathrm{e}_p}), \qquad i_{\mathrm{e}_p} > 0 \tag{2.4}$$

As indicated above, SSMPS required the sum of the return currents to match the sum of the active currents.

2.1.1. SSMPS for focussed stimulation.

For the investigation of current focussing using SSMPS, the values of the variable impedance bank were calculated based on the electrode current vector $\boldsymbol{i}_{\mathrm{e}}$ as derived from the focussing technique reported by van den Honert and Kelsall (2007). Firstly, the maximum location *q* and the minimum location *r* of the weights vector $\boldsymbol{w}_f = \left(w_{1,f}, w_{2,f}, \ldots, w_{k,f}\right)^T$ of the desired FC *f* were determined, where $w_{1,2}$ is the current weight for electrode 1 when focussing electrode 2 which is derived from the inversion of the transimpedance matrix.

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$$q = i, \qquad w_{i,f} = \max_p(w_{p,f}) \tag{2.5}$$

$$r = i, \qquad w_{i,f} = \min_p(w_{p,f}) \tag{2.6}$$

The impedance bank settings $\boldsymbol{z}_{\mathrm{v}} = \left(z_{\mathrm{v}_1}, z_{\mathrm{v}_2}, \dots, z_{\mathrm{v}_k}\right)^T$ were then determined as a special case of the generic approach described in the previous section:

$$z_{\mathrm{v}_p} = \begin{cases} z_{\mathrm{e}_q}\dfrac{w_{q,f}}{w_{p,f}} - z_{\mathrm{e}_p}, & w_{p,f} \geq 0 \\ z_{\mathrm{e}_r}\dfrac{w_{r,f}}{w_{p,f}} - z_{\mathrm{e}_p}, & w_{p,f} < 0 \end{cases} \tag{2.7}$$

As for the generic case, the sign of the weight $w_{p,f}$ determined the active or return configuration of the respective channel.

To determine the total current that had to be delivered by the stimulator, the weights of the FC *f* were multiplied by the target current vector of the FC $\boldsymbol{i}_{\mathrm{f}} = \left(0, \dots, 0, i_{\mathrm{f}_f}, 0, \dots, 0\right)^T$, where i_{f_f} is a scalar value. The total current required was then given by

$$i_{\mathrm{total}} = \sum_p w_{p,f} i_{\mathrm{f}_f}, \qquad w_{p,f} > 0. \tag{2.8}$$

2.2. *In vitro* investigation of current focussing methods

In vitro measurements were performed using a HL14 cochlear electrode array (Cochlear Ltd., Australia) designed for use in the cat (Shepherd et al., 2011a). A Pt ball with a diameter of 1.5 mm was used as a return electrode and also served as a reference electrode for voltage measurements. The electrode array and the Pt ball electrode were immersed in 0.9 % (w/v) sodium chloride in deionized water (saline solution) to mimic the ionic concentration of a physiological electrolyte. Biphasic current pulses were delivered using an optically isolated benchtop laboratory stimulator manufactured in-house (Fallon et al., 2014).

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2.2.1. Transimpedance measurement. Impedances and transimpedances of stimulation electrodes were measured using the laboratory stimulator delivering a biphasic, constant current pulse to an electrode with a large platinum electrode used as the remote return electrode. Interleaved electrodes were used for recording but not for stimulation in the measurements. Electrode voltages and currents (sense resistor $R = 100\ \Omega \pm 1\ \%$) were continuously sampled at 1 MHz using a NI USB-6353 data acquisition interface (National Instruments Corp., USA). Five repetitions per voltage waveform were averaged in order to achieve a sufficiently high signal-to-noise ratio. The transimpedance was determined based on the end-of-phase voltage defined as the voltage sample at a time point of 1 µs before the trailing edge of the first stimulation phase (see figure 6).

2.2.2. Evaluation of focussed stimulation. The focussed stimulation using SSMPS was evaluated by accessing and recording the electrode potentials of interleaved electrodes on the array. Instead of stimulating consecutive electrodes, only every second electrode was used for stimulation so that the focussing effect could be assessed by analysing the electrode potentials at the interleaved locations (figure 3).

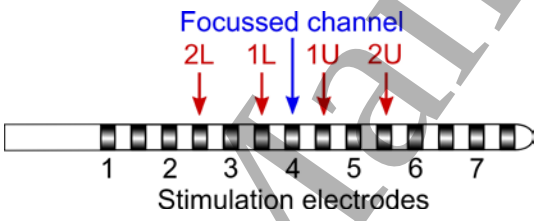

Figure 3: Seven electrodes of an array of 14 banded Pt electrodes were used for stimulation. The electrodes in between the stimulation electrodes were used as interleaved recording electrodes for the in vitro voltage measurements to assess the efficacy of the focussing.

The voltages were recorded with the identical setup used for transimpedance measurements except that interleaved electrodes were not connected to any stimulation circuitry. Five recordings were averaged for noise reduction. The end-of-phase voltage of the first, cathodic stimulation pulse was extracted and further analysed. Identical recording techniques were used to acquire data from MP, TP and CG stimulation. For these *in vitro* studies, a fixed pulse width of 200 µs was used for all configurations. MP stimulation as a common clinical stimulation method was used as a baseline, and a voltage reduction metric was defined referencing the voltage reduction of focussed stimulation using SSMPS, as well as TP and CG stimulation to the MP configuration. The voltage reduction η_v was defined as

$$\eta_v = 1 - \left| \frac{v_t}{v_{MP}} \right| \tag{2.9}$$

with the end-of-phase voltage under test v_t and the end-of-phase voltage of the MP recording v_{MP}.

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2.3. *In vivo* investigation of current focussing methods

All procedures were conducted with approval from the Bionics Institute 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. All experimental procedures were similar to (George et al., 2014a) and are only briefly described here. Data were collected from one adult cat with otoscopically normal tympanic membranes that was acutely deafened (10% w/v neomycin sulphate solution introduced into the round window and aspirated out the oval window (Hardie and Shepherd, 1999)) and bilaterally implanted with 14 contact intra-cochlear electrode arrays (Shepherd et al., 2011b) on the day of the experiment. Stimuli consisted of biphasic current pulses delivered in MP, TP and SSMPS configurations using a similar electrode selection technique as for the *in vitro* evaluation (i.e. only every 2nd electrode on the array was connected to the stimulator). Pulse width was fixed at either 100 μs for MP or 400 μs for TP and SSMPS stimulation, while the interphase gap was fixed at 50 μs for all configurations. Current was varied from below threshold to the maximum safe charge injection limit in pseudo-log steps by using the clinical current levels (CLs) as defined by Cochlear Corporation as.

$$i = 17.5 * 10^{-6} * 100^{\frac{CL}{255}} \quad (2.10)$$

Multi-unit neural activity was bilaterally recorded from both inferior colliculi (IC) using single shank silicon-substrate recording arrays (NeuroNexus Technologies, USA) and analysed using standard techniques to determine spatial tuning curve (STC) and quantify the spread of activation as the STC-width at 1 dB above threshold for different stimulus configurations (George et al., 2014a).

2.4. Experiment control, data analysis and presentation

The control of the stimulation and the recordings and the data analysis were performed using Igor Pro (Wavemetrics Inc., USA). SigmaPlot 12.0 (Systat Software Inc., USA) was used for statistical analyses. Normally distributed data is presented as means ± standard errors of the mean (SEMs). Paired t-tests, one-way analyses of variance (ANOVA), two-way ANOVA, one-way repeated measures (RM) ANOVA and two-way RM ANOVA were carried out. A Holm-Sidak test was used for post-hoc comparisons and Type I error (α) was set to 0.05 unless otherwise stated.

3. Results

3.1. Transimpedance measurements

As the underlying measurement for the parameterisation of a focussed stimulation system, the measurement of the transimpedance matrix and the resulting weights of a FC were investigated via the analysis of the electrode voltages at the end of the leading phase of stimuli delivered in MP mode. As previously reported (van den Honert and Kelsall, 2007), polarisation effects were observed for all voltages acquired and were responsible for an overestimation of the actual electrode impedance in the diagonal line of a measured transimpedance matrix. Therefore, the electrode impedances were approximated using linear extrapolation in order to determine the final transimpedance matrix used as a basis for the calculation of the weights of the FCs (van den Honert and Kelsall, 2007).. After normalisation to the value of the centre electrode of the FC, the resulting channel weights showed that the sign of the individual electrode currents was generally alternating (figure 4A). The largest components of the compensation currents were carried by the flanker electrodes proximal to the centre electrode of the FC regardless of whether a symmetric (equal number of compensation currents on either side of the FC) or an asymmetric flanker configuration was used. Due to the size of their contribution, the weight values of these electrodes were therefore analysed in order to determine the influence of the transimpedance measurement conditions on the focussing parameters. The weight value at the next higher electrode location is referred to as the upper flanker and the weight value at the next lower location is the lower flanker.

The influence of the parameters pulse width and current used for transimpedance measurements on the resulting weights were investigated and their effect on the upper and lower flankers analysed. The pulse width and current were varied in the range of 25 µs – 400 µs and 200 µA – 1.6 mA, respectively, which represents ranges of cochlear implant stimulus parameters typically used. Plotting the flanker values as a function of measurement current and pulse width indicated a charge-dependency (data not shown). Regrouped by charge, the flanker values asymptotically approached a stable value if measured with a higher charge (figure 4B). A one-way ANOVA of the flanker values measured with varying charges revealed that only flankers measured with a small charge showed significant differences to the maximum charge case of 640 nC (denoted with open symbols in figure 4B, $p < 0.05$, $n = 3 – 12$). Values for lower flankers were underestimated and values for upper flankers were overestimated compared to the asymptotically approached value. If short pulses of a pulse width of 25 µs were used, the lower charge limit that did not result in significant differences corresponded to a minimum measurement current of 1.6 mA while longer pulses required less current.

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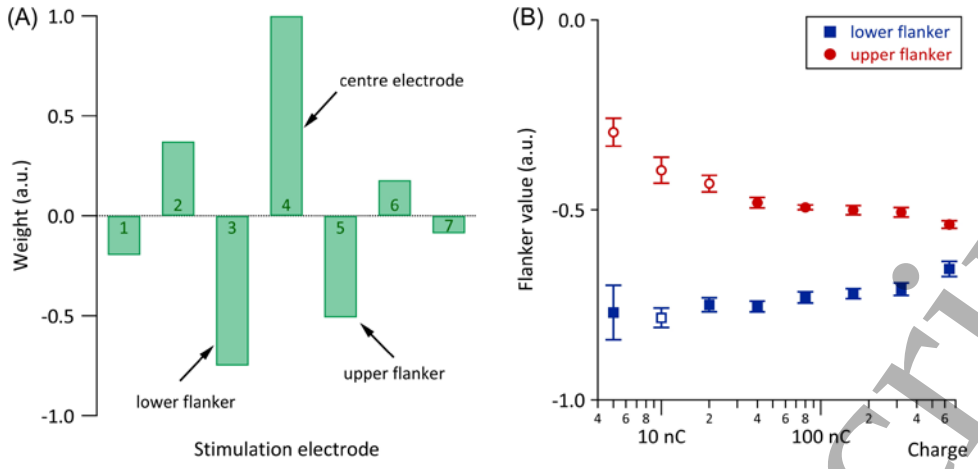

Figure 4: (A) Based on the transimpedance matrix for a particular electrode array, the weights of the stimulation current distribution were calculated and specified in arbitrary units (a.u.). The flanker values on electrodes proximal to the centre electrode of the focussed channel carried the largest contribution of off-centre currents and were therefore used to assess the quality of the transimpedance measurements. (B) An asymptotic approximation to a final value was observed with increasing charge of the transimpedance measurement pulse. A minimum charge was required to achieve values not significantly different from the data point with the highest measurement charge. Open symbols denote values significantly different from this point (one-way ANOVA, $p < 0.05$, $n = 3 – 12$).

3.2. Current focussing via single-source multipolar stimulation

3.2.1. Return current mismatch. The balance of active and return stimulation currents is a prerequisite for the SSMPS technique due to the absence of a separate return electrode. For FMP stimulation, this balance is directly dependent on the weights matrix and the resulting currents for a FC. The relative current mismatch e_c for FC c was calculated as $e_c = \sum_p w_{p,c}$ (3.1)

with the electrode current weight $w_{p,c}$. The current mismatch was calculated as 1 ± 0.2 % (mean ± SEM, $n = 81$) and was deemed negligible with regard to the tolerance of current measurement resistors of 1 %. It was also in good agreement with previously published findings (van den Honert and Kelsall, 2007).

3.2.2. Electrode currents generated by single-source multipolar stimulation

SSMPS was developed as a method to deliver stimulation currents via multiple electrodes of an electrode array simultaneously based on a passive current divider. In an ideal case, constant currents are delivered through each electrode; however, non-resistive components of the electrode-tissue interface resulted in distorted current waveforms. In order to evaluate the current division, five recordings of the currents delivered were averaged for noise reduction, integrated over the first phase

and compared with the set charges as defined by the product of the set currents and pulse widths. The noise level was determined by delivering a current pulse with an amplitude of zero. After integration, the noise level measurement was 40 ± 6 pC (mean ± SEM, n = 3). The noise floor for charge measurements was defined as the mean plus two standard deviations of the recorded charge noise in order to present charge measurements with a confidence level of 95 %. The delivered charges differed from the set charges with a trend towards delivered charges exceeding the set values, particularly for small charges (figure 5). The average error in charge delivery was 56 ± 1 % (n = 19384); however, even though the charge delivery was error prone, coarse shaping of the stimulation currents was achieved and SSMPS was implemented.

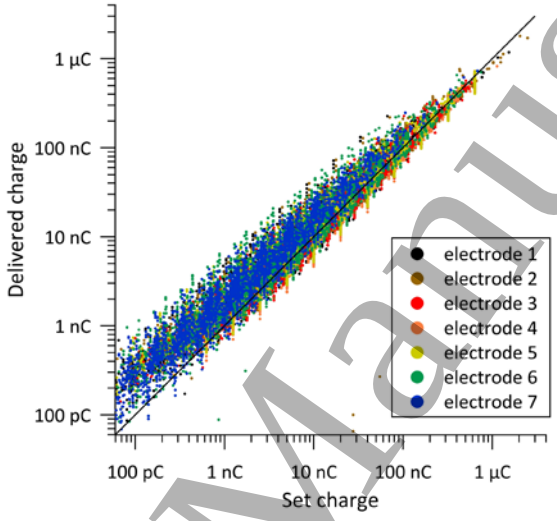

Figure 5: Set and delivered charge per physical electrode for SSMPS. With the black line denoting the ideal case of a delivered charge matching the set value, a mismatch between the set and the delivered charge values are evident. Charges below the noise floor level are not shown.

3.2.3. Voltage reduction at interleaved recording sites.

The extent of focussing was investigated by analysing the voltages (figure 6) at interleaved electrodes on the array (see figure 3) when FC 4, a symmetric (equal number of compensation currents on either side of the FC) focussed channel. The end-of-phase voltage was determined for the recording electrodes 1U, 2U, 1L and 2L and the voltage reduction with reference to MP stimulation was calculated. A value of 1 represents the ideal case of a reduction of 100 % while a value of zero indicates no reduction compared to MP stimulation.

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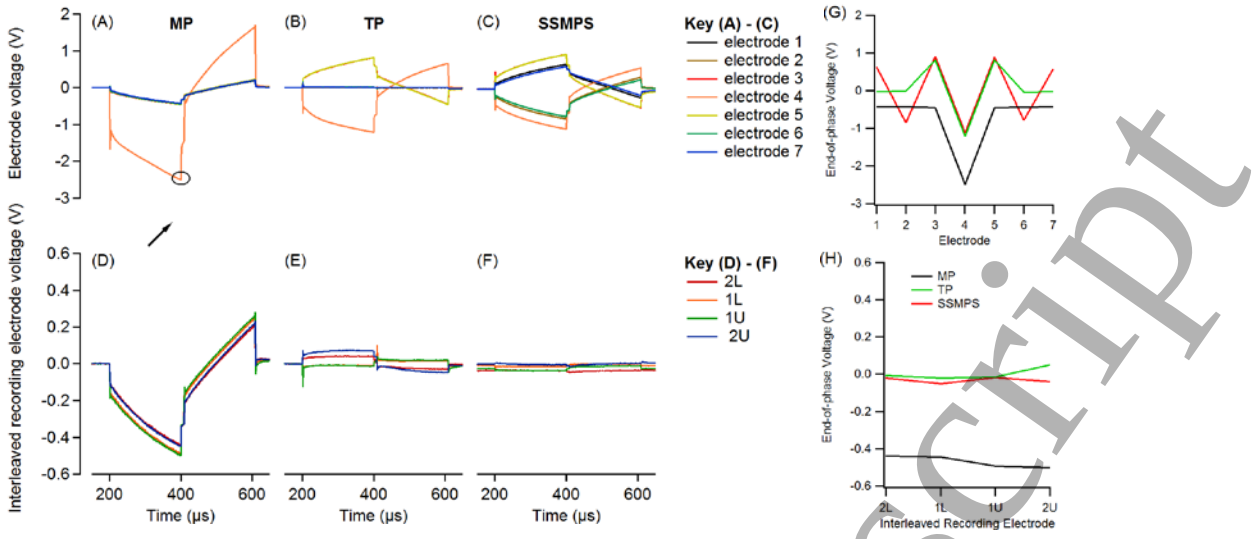

Figure 6: Voltage recordings at stimulated and interleaved recording electrodes for different stimulation modes when stimulating FC 4. Monopolar (MP: A, D), tripolar (TP: B, E) and single-source multipolar (SSMPS: C, F) were compared. End-of-phase voltages (circled in (A)) were measured for stimulated electrodes (G) and interleaved recording electrodes (H). The stimulation current was set to 800 µA for MP and TP. SSMPS parameters were calculated based on the same target current on the centre electrode of the focussed channel.

The influence of the transimpedance measurement parameters on the voltage reduction was analysed for the FC 4. The transimpedance matrix was measured at the current levels 100 µA, 400 µA and 1600 µA using pulse widths of 25 µs, 100 µs and 400 µs. The weights matrix was calculated and used as a basis for actual stimulus delivery with different stimulation pulse widths and currents. The effects of the transimpedance measurement conditions were assessed by a two-way RM ANOVA of the measurement current and the measurement pulse width. A significant effect on the voltage reduction could be determined for the transimpedance measurement current at all the interleaved recording electrodes ($p < 0.001$, $n = 105$). For the transimpedance measurement pulse width, there was also a highly significant effect for the electrodes 2U, 1L and 2L ($p < 0.001$, $n = 105$).

Based on the significant influence of the transimpedance measurement condition, it was hypothesized that the maximum voltage reduction, and therefore the most effective current focussing, would be achieved if the same stimulus current and pulse width were used to measure the transimpedance and delivery the focused stimulation. This hypothesis implied that when the transimpedance matrix was measured with a high charge pulse, optimal voltage reduction would be achieved if a high charge stimulus was delivered. Similarly, if the transimpedance matrix was measured with a low charge pulse, the maximum voltage reduction was achieved in case of stimuli with low charges. For the nine transimpedance measurement conditions only two instances were found that showed the maximum reduction when the transimpedance measurement parameters matched the stimulation parameters. The

resulting distribution was clearly distinct from the expected distribution (as derived from H_0) and no further statistical testing was performed. It was concluded that the voltage reduction was not improved if the transimpedance measurement parameters matched the stimulation parameters.

Consequently, two sets of transimpedance measurement parameters were selected and used for further investigation where the effects of the stimulation parameters were studied. The first set comprised a transimpedance measurement current of 1600 µA and a pulse width of 400 µs which represents the maximum charge case ('SSMPS-max'). While the best focussing success was expected for this case, the charge levels would be expected to exceed typical perceptual limits for cochlear implants. A second case was therefore chosen using a measurement pulse expected to be subthreshold clinically for most cochlear implant users (current of 400 µA, pulse width of 25 µs, 'SSMPS-clinical').

Table 1: Effect of stimulation parameters on the focussing. The table shows the effects of the stimulation parameters pulse width and current on the voltage reduction at electrodes 2L, 1L, 1U and 2U when using the stimulation strategies SSMPS-max, SSMPS-clinical, TP and CG. The significance of the effects was determined via a two-way ANOVA with factors pulse width and the current (* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, n = 3).

Stimulation strategy	**Test parameter**	**2L**	**1L**	**1U**	**2U**
SSMPS-max	Pulse width	**	-	***	*
	Current	-	*	-	-
SSMPS-clinical	Pulse width	**	***	***	-
	Current	-	-	-	-
TP	Pulse width	***	***	***	*
	Current	-	-	-	-
CG	Pulse width	*	***	***	-
	Current	-	-	-	-

Using these transimpedance measurements conditions, the effects of the stimulation parameters on the voltage reduction were analysed via a two-way ANOVA with factors current and pulse width. Table 1 illustrates the significance levels of the detected effects for the two test cases (SSMPS-max and SSMPS-clinical) and TP and CG stimulation for comparison. Overall, a significant effect of the pulse width on the voltage reduction was found for all tested stimulation strategies at most of the tested electrodes where a longer pulse width led to a higher voltage reduction. In contrast, the stimulation current had only a minor effect on the voltage reduction and therefore the focussing success. Holm-Sidak post-hoc tests further corroborated these trends and statistically significant effects were identified for the comparisons between the shorter pulses (lower voltage reductions) and longer pulses (higher voltage reductions).

Focused electrical stimulation using a single current source

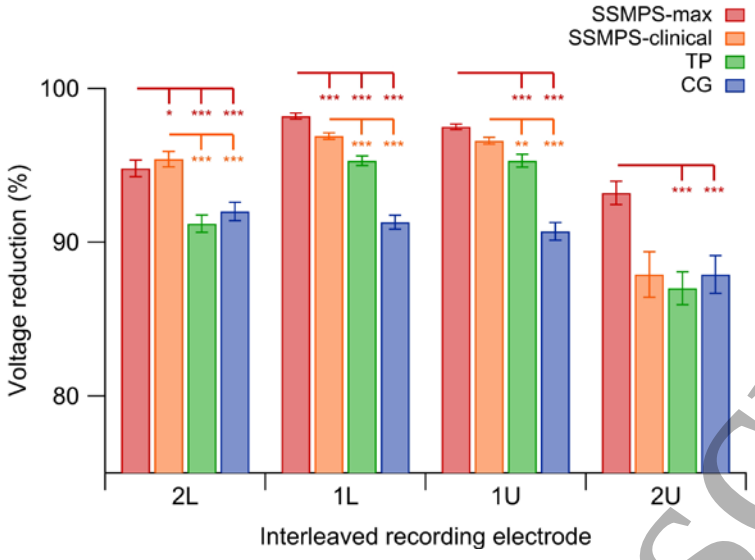

Figure 7: Voltage reduction at interleaved recording electrodes compared to MP stimulation. All tested modes showed voltage reductions in excess of 85 % compared to MP mode. For the SSMPS mode, significantly higher voltage reductions compared to TP and CG were found for both tested transimpedance measurement conditions (one-way RM ANOVA, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, $n = 105$).

Finally, the different stimulation modes were compared to each other in order to establish if an improved current focussing effect was achieved by using SSMPS (figure 7). Therefore, a one-way RM ANOVA was performed of the stimulation strategies SSMPS-max, SSMPS-clinical, TP and CG. All methods showed a mean voltage reduction compared to MP stimulation in excess of 85 % ($n = 105$). For SSMPS-max, a significantly greater voltage reduction was achieved compared to TP and CG stimulation ($p < 0.001$). In the case of a clinically more viable set of transimpedance measurement parameters (SSMPS-clinical), a significant reduction could be shown for all interleaved recording electrodes except 2U.

All results presented above were obtained from the analysis of the FC 4, a symmetric (equal number of compensation currents on either side of the FC) focussed channel. Identical analyses were performed for FCs 3 and 5, asymmetric (non-equal number of compensation current on either side of the FC) focussed channels, for which the findings were in good agreement with the outcomes of the analysis of FC 4 (data not shown).

3.2.4. In vivo results

The extent of focussing was investigated by analysing the spread of activation along the tonotopic axis of the IC (Figure 8). For SSMPS the transimpedance was measured at maximum charge (SSMPS-max). Similar to previous reports (George et al., 2016, George et al., 2015b, George et al., 2014a), MP stimulation had a significantly lower threshold (one-way RM ANOVA, $p < 0.001$; $n = 6$)

and broader activation (one-way RM ANOVA, p = 0.009; n = 6) than focused stimulation. SSMP-max was not significantly different from TP on either measure.

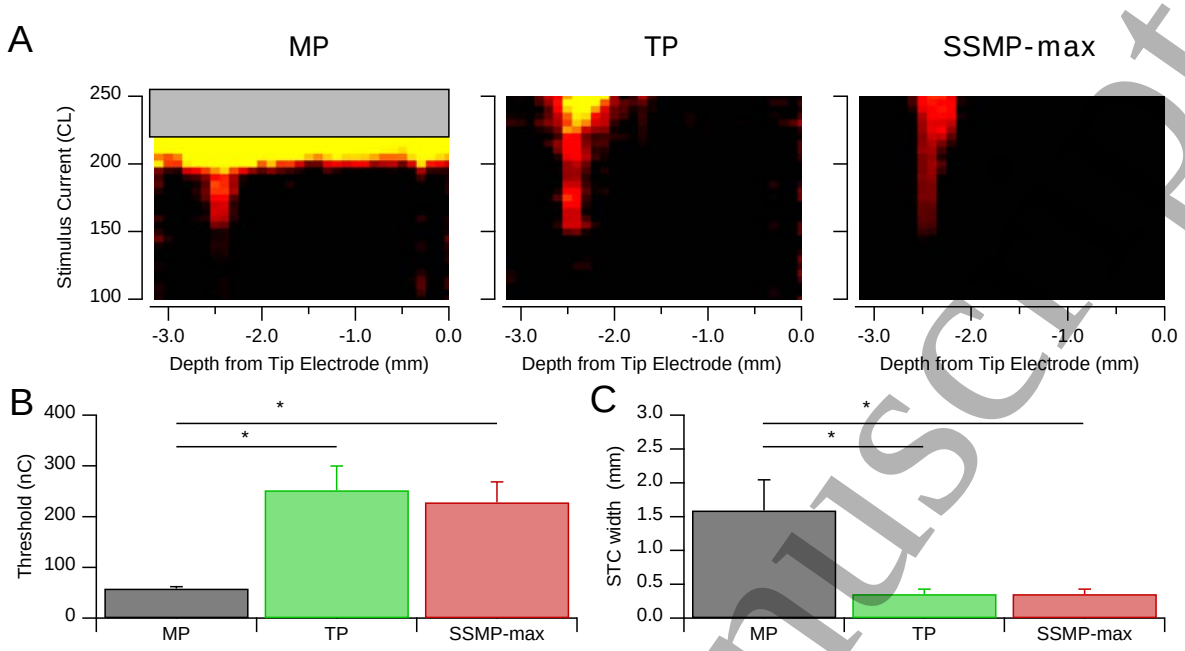

Figure 8: (A) Response images across the cochleotopic axis of the inferior colliculus (IC) to electrical stimulation using monopolar (MP), tripolar (TP) and single source multipolar (SSMP) configurations. Each response image was generated by plotting depth of the IC recording site on the x-axis and stimulus intensity on the y-axis with colour representing normalised spike rate from black (spontaneous) to maximum response (yellow). Note that for MP stimulation, each pulse had a phase of 100 µs while TP and SSMP configurations used pulses with 400 µs phase duration, so the difference in electrical threshold between stimulation configurations are not evident in this figure. (B) For MP mode, significantly lower thresholds compared to TP and SSMP were found (one-way RM ANOVA, * $p < 0.05$). (C) For MP mode, significantly wider spreads of activation (quantified as the spatial tuning curve (STC) width at 1 dB above threshold) compared to TP and SSMP were found (one-way RM ANOVA, * $p < 0.05$). Grey bar indicates stimulation that produced unwanted muscle activation.

4. Discussion

SSMPS is a method to deliver multipolar electrical stimulation based on the principle of passive current division thereby removing the need for multiple current sources for multipolar stimulation. While the passive impedance divider adds a degree of complexity in terms of practical implementation, the single current source required has the potential to simplify the overall complexity of the stimulation circuitry. Depending on the technology chosen and system design of the current source and impedance divider, this scheme has the potential to reduce the overall power requirements for highly focussed stimulation. The concept of SSMPS guarantees an overall charge balance within the scope of the stimulation electrode array at a theoretical level. Further investigations into the safety

due to the lack of control over the charge injection at the level of individual electrodes will be required. However, the concept is comparable to CG stimulation, a clinically accepted stimulation mode, where the return current is distributed over the non-active electrodes without control over the currents at the level of individual electrodes (Seligman and Shepherd, 2004). In the presented form, the measurement of the transimpedance matrix relies on an external return electrode not required for the actual neural stimulation. Additional investigation is needed to evaluate whether an electrode (or electrodes) that is part of the stimulation array could be used as the return path for the transimpedance measurements, thereby eliminating the need for an external return electrode.

Careful consideration is required if SSMPS is to be implemented for clinical application. Impedance changes caused by tissue growth or failure modes associated with the leadwire or electrode array affect the current divider and as a consequence the resulting electrode currents. If the changing electrode currents suddenly exceed the safe charge injection limit, non-reversible electrochemical reactions can occur at the electrode-tissue interface generating potentially harmful reaction products in the tissue surrounding the electrode interface (Cogan, 2008). The lack of control over the currents in general, and potentially aggravated by a changing electrode impedance, can also affect the charge balance per electrode, resulting in a net DC injection at individual electrodes posing an additional safety concern (Huang et al., 1999). However, as noted above, this also applies to CG stimulation that has a good clinical safety record.

SSMPS for FMP stimulation was investigated in several stages. First, the measurement conditions of the transimpedance matrix were evaluated by measuring the transimpedances, calculating the weights matrix and analysing the resulting upper and lower flankers. While it was assumed that the upper and lower flankers represented a valid measure for the assessment of the transimpedance matrix measurement, the analysis could be further refined by developing a metric taking into account all the weights of a FC. The development of this metric would need to allow for the spatial location of the electrode associated with a weight value in order to adjust its contribution to the overall focussing performance. With the upper and lower flankers as a measure, the transimpedance measurement conditions were analysed. It was found that the flanker values approached a stable value with increasing measurement charges and a minimum charge of 40 nC was determined for transimpedance measurements. The stabilisation of the flanker values with increasing charge was in good agreement with the findings of van den Honert and Kelsall (2007) who selected measurement parameters so that the electrode voltage plateaued in order to get stable measurements. Although these experiments determined a range of measurement parameters, care must be taken when translating them to an *in vivo* scenario. The measurement in conductive saline solution resulted in small voltages. Performing the measurements in a biological environment with different electrical conductivity distributions could lead to increased voltages measured which could further reduce the amount of charge needed to measure transimpedance values. Further investigations will be required in order to determine the

minimum charge required, aiming at measuring below perceptual thresholds for the optimisation of clinical protocols.

Although measured in the context of a detailed investigation of SSMPS, these results also translate to FMP stimulation based on multiple current sources (van den Honert and Kelsall, 2007). The findings offer insight into the measurement of the transimpedance matrix with regards to the design of stimulation protocols for preclinical (George et al., 2014b, George et al., 2015b) and clinical applications (Smith et al., 2013, Long et al., 2014, Marozeau et al., 2015) of focussed stimulation and may go some way to explain the lack of benefit of FMP over TP often observed. In particular, it may be that the transimpedance matrices used have not provided the optimal focusing, and if transimpedance matrices were measured at higher charge levels benefits of FMP over TP might be observed.

The second part of the investigation examined the characteristics of SSMPS as a method to perform FMP stimulation. When analysing the electrode currents generated by SSMPS, changes of the individual electrode currents over the pulse duration were noticed in the form of deviations from the ideal constant currents. It was assumed that they were caused by polarisation effects associated with the non-linear nature of the electrode interface which the resistive current divider – implemented based on a real approximation of the electrode impedances – did not allow for. Even though current shaping was achieved, a future improvement of the current divider could include capacitive elements compensating the reactive components of the electrode impedances. However, the shortcomings of the presented implementation of SSMPS were acceptable for this study with regard to the main aim of the study – current focussing. The analysis of the focussing success was based on the measured voltage at interleaved recording electrodes and the reduction thereof compared to the effects of a MP stimulus. While this approach yielded a quantitative result, possible clinical outcomes have to be assessed with the consideration that the voltage reduction was determined at an electrode site rather than the location of neural activation which was supposed to be limited.

When the influence of the transimpedance measurement parameters on the voltage reduction was analysed, both current and pulse width affected the focussing success significantly. However, the maximum voltage reduction, i.e. the best focussing, was not achieved with matching transimpedance measurement pulse and stimulation pulse parameters. Hypothesising that the focussing success might be dependent on the quality of the transimpedance measurement as determined in a previous step, it was concluded that a fixed set of transimpedance measurement parameters could be chosen for all stimulation parameters. Using two sets of transimpedance measurement parameters reflecting the presumed ideal scenario and a scenario that was deemed clinically viable, focussing was assessed and the results compared with TP and CG stimulation, as clinically established stimulation configurations. For SSMPS, the pulse width of the test stimulus had a significant effect on the voltage reduction while

the current had only a marginal influence. Polarisation effects of the stimulation electrodes were potentially responsible for this difference. While changing stimulation currents led to a mostly linear scaling of the voltage profiles and therefore had only minor effect on the focussing success, a change of the pulse width significantly affected the voltage distributions at the end of the first stimulation phase due to the exponential temporal dependency at the capacitive tissue interface. This changed distribution altered the properties of the superposed voltages and hence the overall cancellation effect. Compared with TP and CG stimulation, current focussing using SSMPS exhibited improved performance in terms of voltage reduction. The difference that was observed between the focussing results when using the two different transimpedance measurement parameter sets was potentially linked to the quality of the transimpedance measurement.

In terms of a clinical implementation, it can be concluded that a stimulation protocol with set transimpedance measurement conditions and a fixed pulse width is a suitable candidate for future research and potentially resulting in clinical application.

When used for cochlear implant stimulation, SSMPS resulted in significantly narrow regions of excitation than MP, but was not different to TP. These results are similar to the results using standard FMP (George et al., 2016, George et al., 2015a, George et al., 2015b, George et al., 2014a), whereby FMP did not result in any advantage of TP using similar techniques. However, the long-term benefits of the different focusing strategies are yet to be tested in a clinical setting where the improved voltage reductions demonstrated in vitro may translate to improved outcomes.

5. Conclusions

A novel method for implementing multipolar stimulation using a single current source was described and its performance when utilized for current focussing was investigated *in vitro* and *in vivo*. A minimum charge per phase of 40 nC was identified in order to obtain a reliable measurement of the transimpedance matrix. Current focussing using SSMPS was then demonstrated and improved focussing performance could be shown compared to TP or CG stimulation *in vitro*. SSMPS results in decreased spread of activation *in vivo*, albeit at the expense of increased thresholds compared to MP stimulation.

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