2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Filling in the Visual Gaps: Shifting Cortical Activity using Current Steering

Sabrina Jade Meikle, *Student Member, IEEE*, Maureen Ann Hagan, Nicholas Seow Chiang Price, Yan Tat Wong, *Senior Member, IEEE*

Abstract— **Cortical vision prostheses are being developed to restore sight in blind patients. Existing electrode arrays that electrically stimulate cortical tissue to artificially induce neural activity are difficult to position directly next to each other. Leaving space between implants creates gaps in the visual field where no visual percepts can be created. Here, we propose current steering as a solution to elicit a neural response between physical electrode locations. We assessed the centroid of neural activity produced by dual-electrode stimulation in the visual cortex of Sprague-Dawley rats. We determined that this centroid could be shifted between physical electrodes by altering the ratio of charge delivered to each electrode. This centroidal shift could enable better environmental perception for cortical implant patients by creating a complete visual field representation while maintaining safe array spacing.**

I. Introduction

Cortical vision prostheses use electrical stimulation of the primary visual cortex (V1) to elicit visual percepts in blind patients [1-4]. These visual percepts are termed phosphenes and commonly appear as white flashes of light within the visual field [5-7]. By combining patterns of phosphenes to emulate images, blind patients may have their visual capabilities restored [1-4].

To generate patterns of phosphenes across a subject's visual field requires multiple electrode arrays. One challenge in the development of intracortical vision systems is the spacing between the implanted arrays. When implanting multi-shank electrode arrays, pneumatic tools are used for rapid insertion into the brain to overcome the 'bed of nails' effect [1, 8]. The force and speed of implantation results in the displacement of the tissue [8], meaning implantation of adjacent arrays risks mechanical damage to both the brain and the arrays. Consequently, the implants require separation distances that interfere with the generation of images [1, 9]. Difficulties with environmental perception due to these visual field gaps decrease the usability of intracortical visual devices. Errors in implant placement can also cause electrodes to reside in cortical layers that require larger stimulation intensities for phosphene generation [10]. High stimulation intensities can cause tissue and electrolytic damage [11-13].

Current steering is a stimulation method that could mitigate these issues by creating virtual electrodes between physical electrode locations. Current steering requires the activation of two or more electrodes simultaneously where the stimulation interaction is proposed to elicit a centroid of neural activity between the two stimulating electrodes. This is known as a virtual electrode [14-19]. Previous current steering work only assessed either the neural activity response (retinal [15], optic nerve [16]) or the sensory output (cochlear [14, 18], cortical vision implant [17]). An understanding of both is required to determine the most efficacious stimulation paradigms. Current steering within the visual cortex was shown to produce phosphenes intermediately positioned to phosphenes created by single electrode stimulation in one patient [17]. The neural activation patterns in response to current steering were not assessed in this patient making it difficult to discern the mechanisms behind the behavioral response and if the optimal stimulation parameters were used.

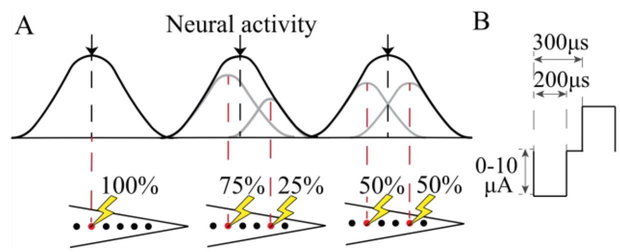

Fig. 1 **A)** By altering the percentage of charge delivered to the two stimulating electrodes, the neural activity response can be shifted across the cortex. **B)** The biphasic pulse delivered to each stimulating electrode had a 100µs interphase gap and 200µs pulse duration. The stimulus amplitude varied from 0-10µA.

As the neural activity of V1 correlates with the production of phosphenes [20], current steering within the visual cortex potentially produces a centroid of neural activity between physical electrodes. By altering the ratios of charge injected into the tissue between the two stimulating electrodes, we propose that the centroid of neural activity can be shifted i) **across cortex** parallel to the cortical surface thereby filling in the visual field gaps created by implant spacing and, ii) in a **laminar** direction perpendicular to the cortical surface enabling targeted activation of cortical layers despite inaccurate electrode placement (Fig. 1A).

II. Methods

A. Animal preparation

Data were collected from five anesthetized Sprague-Dawley rats at 12 weeks (±5 days) of age. Animals were anesthetized using Halothane gas (5% induction, 1.5% maintenance). Animal temperature, heart rate, and anesthesia level were monitored. A custom-designed, four-shank, 64 channel Neuronexus Probe was inserted into the visual cortex (50µm electrode spacing, 200µm shank spacing). An estimate of array depth was obtained from the microdrive used for the insertion. A remote return electrode was also implanted. Data were collected from 1522 unique recording sites from seven penetrations with 43 unique stimulating pairs of electrodes.

S.J. Meikle, M.A. Hagan, N.S.C. Price and Y.T. Wong are with Department of Physiology, Monash University, Melbourne, VIC, Australia: (+61) 3 9905 1935; e-mail: yan.wong@monash.edu.

S.J. Meikle and Y.T. Wong are also with Department of Electrical and Computer Systems Engineering, Monash University, Melbourne, VIC, Australia.

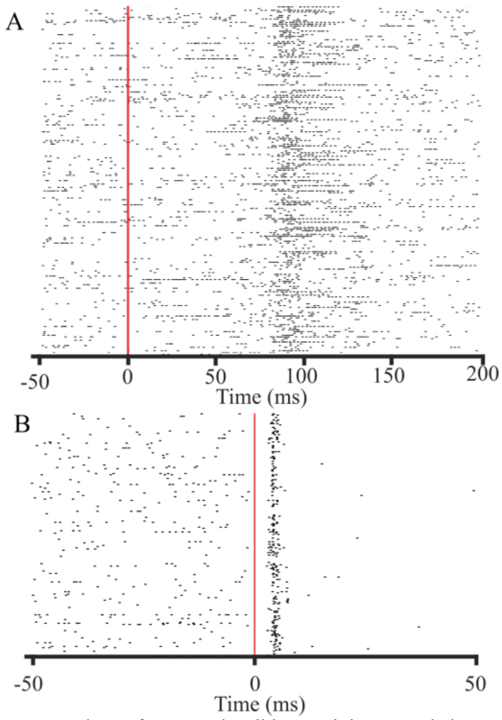

Fig. 2 Raster plots of neuronal spiking activity recorded at a single electrode. **A)** Response to flash stimuli at time zero. Clear increase in activity at 75ms indicating cells are responding to visual stimulus. N=200 trials. **B)** Response of the same cells shown in **A** to 6μA electrical stimulation at time 0. The stimulation pulse creates an artefact that was blanked (0-2ms). Action potentials were detected and concentrated immediately after the stimulation pulse (2-8ms) indicating the cells were responding to stimulation. N=200 trials.

These experiments were approved by the Monash Animal Ethics Committee.

B. *Electrophysiological recordings and stimulation*

An INTAN stim/recording controller (M4200) was used to electrically stimulate and record neural activity. Within a single stimulation block, the parameters were randomized (0 – 10μA total, 1-2 stimulating electrodes, 0-100% distribution of current between stimulating electrodes) and included control trials of 0μA (Fig. 1B). Stimulation blocks were completed with an interelectrode separation distance of 300-600μm between the two stimulating electrodes. Forty repetitions of each parameter combination were completed per stimulation block. Each trial lasted 0.5-0.8ms with random jitter added to prevent time-locking to noise frequencies. Placement of the array within the visual cortex was confirmed by visually evoked spiking responses (Fig. 2A).

C. *Artefact rejection and neuronal spike extraction*

Stimulation artefacts were independently rejected for each electrode by replacing data samples from 1ms before to 2ms after the stimulation time with a linear interpolation between the two endpoints. Following artefact rejection, the raw signals were bandpass filtered (0.3-7.7kHz) using multitapers (central frequency 4kHz, filter length 2ms). Neuronal spiking was extracted from electrode data using a threshold -4.5 times the signal standard deviation. Spikes were rejected if they exceeded ±500μV as this was likely to be caused by unwanted noise or artefact ringing. The baseline spike rate was calculated from a 60ms window immediately before the stimulation pulse. The baseline subtraction was confirmed to be accurate using the randomly dispersed 0μA control trials. An analysis window of 2-8ms was used to ensure the response was characterized before post-stimulation inhibition (Fig. 2B). The neural activity in the analysis window for each stimulation condition had to be at or above baseline levels for an electrode to be considered for further analysis.

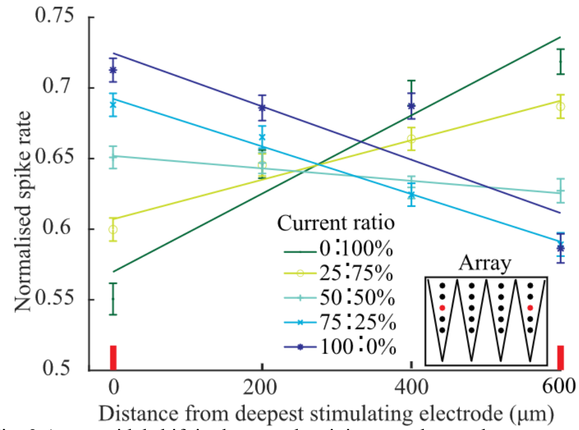

Fig. 3 A centroidal shift in the neural activity was observed across cortex as the current ratio shifted from 100% at the rightmost stimulating electrode to 100% at the leftmost stimulating electrode. This is represented by a clockwise rotation in the linear trendline. The stimulating electrode locations are represented by the red dashes at 0 and 600μm on the x-axis. Position of the stimulating electrodes relative to the array orientation is shown. Bars represent standard error. N=5 animals.

D. *Centroidal shift in neuronal activation*

The neural activity responses to current steering were assessed in two directions; i) across cortex and, ii) in a laminar direction. Five current ratios between two stimulating electrodes (0:100%, 25:75%, 50:50%, 75:25%, 100:0%) were tested to quantify whether a shift in neural activity occurred. For example, a total current of 10μA would correspond to the distributions of 0:10μA, 2.5:7.5μA, 5:5μA, 7.5:2.5μA, 10:0μA between the stimulating electrodes respectively based on the current ratios. The response at each recording electrode was normalized by the maximal firing rate observed across the five distributions for each total current. This created five normalized activity curves across each array shank for each total current. The area under each curve was calculated through integration. The position along the curve that corresponded with half of the area was used to identify the centroid. The change in centroid location per change in current distribution was recorded for all stimulating pairs of electrodes. For example, if the centroid on one shank of the array was found to be located 250μm, 200μm, 100μm, 75μm, 50μm from the deepest stimulating electrode for each change in current ratio respectively, the change in centroid location would be 50μm, 100μm, 25μm, 25μm. This is a relative change that can be averaged across total currents, stimulating electrode pairs, penetrations, and animals.

To visually assess the shift in the centroid, each pair of stimulating electrodes with the same separation distance were aligned. Sixty-five spike rate samples per electrode location were averaged in the laminar condition. Relative electrode locations with fewer than 65 aligned electrode samples were not included in the results. This prevented unreliable edge conditions with small sample numbers from affecting the result. The spike rates were normalized as above. The stimulating shanks were not included.

When the stimulating electrode pair were aligned in an across cortex condition, the electrode responses on each shank were normalized and averaged (50 electrode sites per electrode location, 13 sites per shank, 650 samples per shank were averaged altogether). Relative electrode locations with less than 50 samples were not included.

III. Results

A. *Shift in centroid across the cortex*

Using current steering across the visual cortex with a 600μm interelectrode distance creates a visually systematic shift in centroid as the current ratio applied to the two stimulating electrodes is manipulated (Fig. 3). These results indicate that electrodes positioned within the same layer at an interelectrode distance of 600μm or less should be able to generate and shift the virtual electrode. The exact centroid position was unable to be accurately determined with only 4 samples across cortex.

B. *Laminar shift in centroid*

As the injected current shifts from 100% at the stimulating electrode closest to the shank tip (left) to 100% towards the electrode at the top of the array (right) in Fig. 4, the linear slope alters in gradient illustrating an activation preference closest to the stimulating electrode with the most current. With a 300μm separation between the stimulating electrodes, the average shift per change in the distribution of current was 15.4μm with a standard error of 3.77μm. The shift with a 400μm separation was 10.8μm with a 9.8μm standard error. For a 500μm separation, the centroidal shift was larger at 16.75μm with a standard error of 10.32μm. There is a bias in the centroidal measurement towards the center of the measured slope since there is only a finite sampling area. This reduces the magnitude of the observed shift. However, these shifts in centroid were still determined to be significantly different from 0 using a t-test as these data were normally distributed. The p-values were 4.4×10^{-16}, 0.028, 0.0012 for the 300μm, 400μm and 500μm separation respectively. The 300μm spacing between electrodes had the largest and most visually consistent shift in centroid per change in the current distribution in a laminar direction (Fig. 4A). The 400μm trials followed the same trend but with less variation (Fig. 4B). The 500μm interelectrode distance exhibited no activity cross-over between the stimulating electrodes with the tip (leftmost) electrode eliciting the largest response (Fig. 4C).

IV. Discussion

Current steering across the cortex has immense implications in creating a complete picture for cortical implant patients. By using current steering paradigms to create virtual electrodes, common issues like physical electrode proximity could be overcome facilitating both safe electrode implantation and the perception of phosphenes across the visual cortex. As phosphene perception is thought to correlate with brain activity responses to stimulation, the current steering paradigm

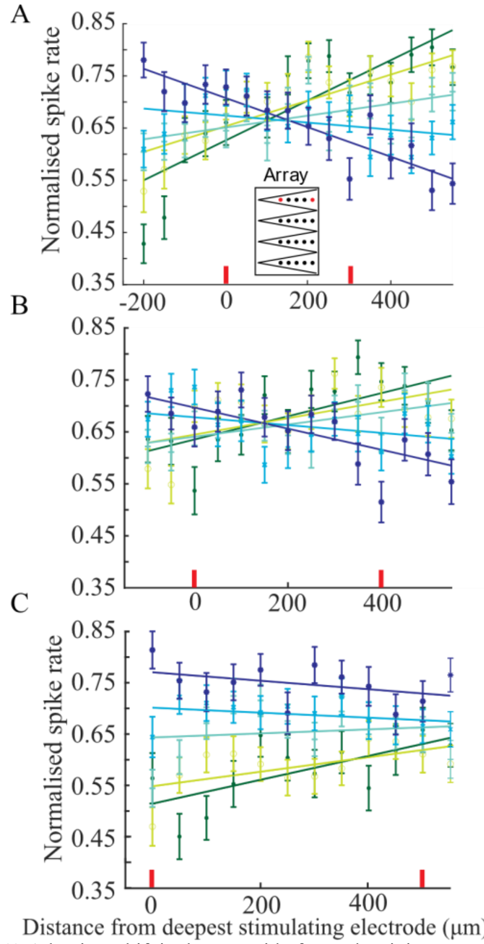

Fig. 4 **A)** A laminar shift in the centroid of neural activity occurred as the current ratio shifted from 100% at the rightmost stimulating electrode to 100% at the leftmost stimulating electrode. This is represented by a clockwise rotation in the linear trendline. Coloring is the same as Fig. 3. Bars represent standard error. There was a 300μm spacing between the stimulating electrodes. Relative orientation of the stimulating electrodes to the array is shown. N=5animals **B)** Same as **A** but with a 400μm interelectrode spacing. N=4 animals **C)** Same as **A** but with a 500μm interelectrode spacing N=4 animals

may provide a method to fill in the gaps of the visual field corresponding to the gaps between implants. A smooth transition of virtual electrodes across the visual cortex, as was demonstrated here, will also likely result in a much more natural perception of motion with a reduction in pixilation. This will enable better environmental perception for cortical implant users. The mechanisms underlying these effects are potentially related to the horizontal connections across cortex rather than the interacting electric fields. According to the threshold equation for action potential initiation [21, 22], the theoretical voltage 200μm away from the stimulating electrodes during dual-electrode sitmulation of the across condition was less than the minimum to induce an action potential. However, a normalized spike rate above 0 occurred for all conditions. One explanation for this is the horizontal connections across cortex are likely to propagate action potentials within the same layer which aids the likelihood of activity summation. This indicates that larger interelectrode distances may be implemented than the exponential decay of the initial injected charge would allow.

Current steering in a laminar direction may be beneficial in targeting feedforward layers of the cortex that are more likely to propagate the signal thereby creating a phosphene at lower sitmulation intensities. The reduction in the ability of the electrodes at a 500µm spacing to create a similar neural activity response could be attributed to the activation of electrodes in different layers of the visual cortex. The lower layers of cortex are feedback layers that are more likely to inhibit cortical activity responses. To achieve the 500µm interelectrode spacing, the leftmost electrode was estimated to be positioned within the lower layers using the pneumatic microdrive. However, histological analysis of the layering was not completed making this indefinite. The optimal stimulation target is at the layer III/IV boundary [12, 23]. This implies that positioning the electrodes within layers I to IV will summate while positioning within V or VI will inhibit the signal. Ensuring both electrodes are within the first four layers and subsequently steering the activation towards the boundary of III/IV is much easier than targeting that location directly with a single electrode. These results also imply that the cortical connections will substantially affect the observed summation associated with current steering in addition to the traditional electric field overlap [17].

V. Conclusion

Current steering has the potential to improve environmental perception for blind individuals with cortical vision implants. Both a complete visual field view without gaps and smooth motion perception could be achieved while maintaining safe implant spacing. This work illustrated that a virtual electrode can be created and shifted in both the laminar and across cortex conditions. Additionally, it is possibly the communicative neural networks partially driving the summation response that creates the virtual electrode. This is evidenced by the decrease in the effectiveness of centroidal shift as the electrodes are spaced further apart in the laminar condition; however, in the across cortex condition with even larger spacing, a consistent shift in centroid can still be seen that is qualitatively similar to the smallest spacing option of the laminar condition.

Acknowledgment

We acknowledge the Australian Research Council (DE180100344, DP200100179) and the National Health and Medical Research Council (APP1185442) for financial support. We also thank Timothy Allison-Walker for his help during data collection.

References

[1] J. V. Rosenfeld *et al.*, "Tissue response to a chronically implantable wireless intracortical visual prosthesis (Gennaris array)," *Journal of Neural Engineering,* Article vol. 17, no. 4, 2020, Art no. 046001

[2] Y. T. Wong *et al.*, "CMOS stimulating chips capable of wirelessly driving 473 electrodes for a cortical vision prosthesis," *Journal of Neural Engineering,* Article vol. 16, no. 2, 2019, Art no. 026025

[3] P. R. Troyk, "The Intracortical Visual Prosthesis Project," in *Artificial Vision: A Clinical Guide*, V. P. Gabel Ed. Cham: Springer International Publishing, 2017, pp. 203-214.

[4] E. Fernández and R. A. Normann, "CORTIVIS Approach for an Intracortical Visual Prostheses," in *Artificial Vision: A Clinical Guide*, V. P. Gabel Ed. Cham: Springer International Publishing, 2017, pp. 191-201.

[5] G. S. Brindley and W. S. Lewin, "The sensations produced by electrical stimulation of the visual cortex," *The Journal of Physiology,* vol. 196, no. 2, pp. 479-493, 1968

[6] W. H. Dobelle and M. G. Mladejovsky, "Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind," *The Journal of Physiology,* Article vol. 243, no. 2, pp. 553-576, 1974

[7] N. R. Srivastava *et al.*, "Estimating Phosphene Maps for Psychophysical Experiments used in Testing a Cortical Visual Prosthesis Device," in *2007 3rd International IEEE/EMBS Conference on Neural Engineering*, 2-5 May 2007, pp. 130-133

[8] P. A. House, J. D. MacDonald, P. A. Tresco, and R. A. Normann, "Acute microelectrode array implantation into human neocortex: preliminary technique and histological considerations," *Neurosurgical focus,* Article vol. 20, no. 5, 2006

[9] A. Campbell and C. Wu, "Chronically Implanted Intracranial Electrodes: Tissue Reaction and Electrical Changes," (in eng), *Micromachines (Basel),* vol. 9, no. 9, p. 430, 2018

[10] B. Király *et al.*, "In vivo localization of chronically implanted electrodes and optic fibers in mice," *Nature Communications,* vol. 11, no. 1, p. 4686, 2020

[11] K. Torab, T. S. Davis, D. J. Warren, P. A. House, R. A. Normann, and B. Greger, "Multiple factors may influence the performance of a visual prosthesis based on intracortical microstimulation: nonhuman primate behavioural experimentation," *Journal of Neural Engineering,* vol. 8, no. 3, p. 035001, 2011

[12] E. A. DeYoe, J. D. Lewine, and R. W. Doty, "Laminar Variation in Threshold for Detection of Electrical Excitation of Striate Cortex by Macaques," *Journal of Neurophysiology,* vol. 94, no. 5, pp. 3443-3450, 2005

[13] T. J. Allison-Walker, M. A. Hagan, N. S. C. Price, and Y. T. Wong, "Local field potential phase modulates neural responses to intracortical electrical stimulation," in *2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, 20-24 July 2020, pp. 3521-3524

[14] J. B. Firszt, D. B. Koch, M. Downing, and L. Litvak, "Current Steering Creates Additional Pitch Percepts in Adult Cochlear Implant Recipients," *Otology & Neurotology,* vol. 28, no. 5, 2007

[15] G. Dumm, J. B. Fallon, C. E. Williams, and M. N. Shivdasani, "Virtual electrodes by current steering in retinal prostheses," *Investigative Ophthalmology and Visual Science,* Article vol. 55, no. 12, pp. 8077-8085, 2014

[16] Y. Yan *et al.*, "Electrically Evoked Responses in the Rabbit Cortex Induced by Current Steering With Penetrating Optic Nerve Electrodes," *Investigative Ophthalmology & Visual Science,* vol. 57, no. 14, pp. 6327-6338, 2016

[17] M. S. Beauchamp *et al.*, "Dynamic Stimulation of Visual Cortex Produces Form Vision in Sighted and Blind Humans," *Cell,* vol. 181, no. 4, pp. 774-783.e5, 2020

[18] D. M. Landsberger and A. G. Srinivasan, "Virtual channel discrimination is improved by current focusing in cochlear implant recipients," *Hearing Research,* vol. 254, no. 1, pp. 34-41, 2009

[19] P. Rebelo *et al.*, "Thalamic Directional Deep Brain Stimulation for tremor: Spend less, get more," *Brain Stimulation,* vol. 11, no. 3, pp. 600-606, 2018

[20] W. H. Bosking, M. S. Beauchamp, and D. Yoshor, "Electrical Stimulation of Visual Cortex: Relevance for the Development of Visual Cortical Prosthetics," (in eng), *Annu Rev Vis Sci,* vol. 3, pp. 141-166, 2017

[21] J. Platkiewicz and R. Brette, "A threshold equation for action potential initiation," *PLoS Computational Biology,* Article vol. 6, no. 7, p. 25, 2010, Art no. e1000850

[22] B. H. Brown, R. H. Smallwood, D. C. Barber, P. V. Lawford, and D. R. Hose, *Medical physics and biomedical engineering*. Taylor & Francis, 2017.

[23] T. Allison-Walker, M. A. Hagan, N. S. C. Price, and Y. T. Wong, "Microstimulation-evoked neural responses in visual cortex are depth dependent," *Brain Stimulation,* Article vol. 14, no. 4, pp. 741-750, 2021.