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Spatial and temporal characteristics of V1 microstimulation during chronic implantation of a microelectrode array in a behaving macaque

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Abstract

Objective—It has been hypothesized that a vision prosthesis capable of evoking useful visual percepts can be based upon electrically stimulating the primary visual cortex (V1) of a blind human subject via penetrating microelectrode arrays. As a continuation of earlier work, we examined several spatial and temporal characteristics of V1 microstimulation.

Approach—An array of 100 penetrating microelectrodes was chronically implanted in V1 of a behaving macaque monkey. Microstimulation thresholds were measured using a two-alternative forced choice detection task. Relative locations of electrically-evoked percepts were measured using a memory saccade-to-target task.

Main results—The principal finding was that two years after implantation we were able to evoke behavioural responses to electric stimulation across the spatial extent of the array using groups of contiguous electrodes. Consistent responses to stimulation were evoked at an average threshold current per electrode of $204 \pm 49 \mu\text{A}$ (mean $\pm$ std) for groups of four electrodes and $91 \pm 25 \mu\text{A}$ for groups of nine electrodes. Saccades to electrically-evoked percepts using groups of nine electrodes showed that the animal could discriminate spatially distinct percepts with groups having an average separation of $1.6 \pm 0.3 \text{ mm}$ (mean $\pm$ std) in cortex and 1.0 ± 0.2 degrees in visual space.

Significance—These results demonstrate chronic perceptual functionality and provide evidence for the feasibility of a cortically-based vision prosthesis for the blind using penetrating microelectrodes.

1. Introduction

Blindness is a prevalent cause of disability and poses extraordinary challenges to individuals in our society [1]. Although treatments exist for many causes of blindness, there is currently no effective treatment for those who are profoundly blind as a result of degeneration or damage to the retina and its connections to visual cortex.

Early studies have shown that surface stimulation of primary visual cortex (V1) in humans using an array of macroelectrodes ($1\text{--}9 \text{ mm}^2$) can evoke points of light called phosphenes, and that subjects could assimilate simple spatial patterns of phosphenes with simultaneous stimulation of groups of electrodes [2–4]. These studies, however, encountered limitations in resolution as a result of electrode size, placement, and the large currents required to generate

phosphenes. More recent studies in both humans and animals have shown that stimulation of V1 using penetrating microelectrodes resulted in improved resolution and a decreased amount of current needed to evoke phosphenes [5–7]. Several studies have explored the effectiveness of various stimulus parameters in evoking phosphenes using individual or pairs of microelectrodes in acute preparations [8–10]. Few studies, however, have looked at the performance and safety of microstimulation in V1 via chronically implanted arrays of microelectrodes.

To be useful, a visual prosthesis based on V1 microstimulation via an array of penetrating microelectrodes must provide reliable, targeted activation of the visual system over extended time periods. The array of implanted electrodes must retain the ability to evoke spatially distinct visual percepts, and the currents required to generate these percepts must remain stable and within a range that is safe to electrode and tissue throughout the life of the implant. Few studies have looked at the spatial and temporal characteristics of chronic V1 microstimulation. One study characterized the subjective perceptions of phosphenes evoked by stimulation of 38 microelectrodes in V1 of a blind human subject over a period of four months [6]. Initially, 34 of the 38 electrodes were found to evoke phosphenes using $\sim 20 \mu\text{A}$ currents and $\sim 2 \text{ mC cm}^{-2}$ charge densities. The threshold current for one electrode was monitored and found to be relatively stable over time. However, the parameters of stimulation for this electrode were adjusted throughout the study to maximize perception, making it difficult to quantify this result. Additionally, many of the implanted electrodes were not monitored for the duration of the study due to mechanical failure of the wire leads, and the long-term performance of the implant was not fully characterized. Another study looked at the performance of electrical stimulation of chronically implanted microelectrodes in V1 of a macaque monkey [5]. In this 16 month study, the animal was implanted with 152 microelectrodes and trained to saccade to the phosphenes evoked during stimulation of individual electrodes. Of the 152 electrodes that were implanted, 32 were selected for stimulation. The stimulation levels required to evoke saccades to phosphenes were $\sim 20 \mu\text{A}$ and $\sim 1 \text{ mC cm}^{-2}$. These stimulation levels did not damage the tissue based on histological analysis of the implant sites. The stability of these levels over time, however, was not quantified, and the functionality of the remaining 120 unstimulated electrodes was not discussed. Both of the above studies provided valuable insight into the feasibility of a visual prosthesis based on microstimulation of V1. However, several of the spatial and temporal characteristics of a chronic implant that are important to the future development of a prosthesis, such as the long-term reliability of all implanted electrodes, were not fully addressed.

The goal of the research reported herein is to develop a cortically-based neural prosthetic device that will restore functional vision to profoundly blind human individuals. This approach will work by electrically stimulating V1 via a number of Utah Electrode Arrays (UEAs) to produce useful visual percepts. During the first year of this study, we encountered a restricted ability to evoke percepts on many of the implanted electrodes [7]. Difficulty with reliably evoking percepts using arrays of microelectrodes implanted in cortex over extended time periods has been reported elsewhere [5, 6, 11]. Here, we present additional findings collected during the second year of implantation. We show that consistent visual percepts can be evoked via microstimulation of a UEA that has been implanted in V1 for two years. We found that we can evoke percepts for the majority of stimulated electrodes across the array by increasing the volume of stimulated cortical tissue through simultaneous stimulation of groups of electrodes. We also found that the threshold stimulus levels required to generate these percepts manifested a small, but significant increase with time. These levels, however, did not appear to cause any obvious damage to the system based on our ability to consistently evoke behavioural responses and the stability of the electrical properties of the implant over the course of experimentation. Two years after implantation,

we show that the animal can discriminate percepts evoked by stimulation of separate regions of the UEA, thus providing evidence of the functionality of an array of penetrating microelectrodes under chronic conditions for use as a visual prosthesis.

2. Methods

All surgical and experimental procedures were performed in accordance with the guidelines of the U. S. Department of Agriculture and were approved by the University of Utah's Institutional Animal Care and Use Committee.

2.1. Subject and surgery

In overview, two UEAs, a total of 192 electrodes, were implanted in V1 of a male rhesus macaque (*Macaca mulatta*) (figure 1). Early experiments involved mapping visually responsive regions for each electrode and determining the minimum currents required to evoke behavioural responses during single electrode stimulation [7]. One of the UEAs was lost due to a superficial infection at the connector approximately 18 months after implantation, so the data presented in this study were collected using the more posterior functional array from 19 to 24 months post-implantation.

We followed human protocols during the surgery and post-operative care. The UEAs were implanted in V1 of the animal using a pneumatic inserter [12]. Reference wires were used as the current return path during microstimulation and were placed in the subdural space. The arrays were implanted anterior to the calcarine sulcus and lateral to the sagittal fissure. This anatomical location was expected to represent the lower right visual quadrant at about eight degrees of eccentricity [13]. The orientation of the posterior array in cortex is identified using the wire bundle and remains consistent in subsequent figures. For a more detailed account of the surgery, see our companion work [7].

2.2. Microelectrode array

Fixed-geometry arrays of penetrating microelectrodes were used for neural recording and microstimulation (Cereport Array (UEA), Blackrock Microsystems, Salt Lake City, UT). These arrays were originally developed for a vision prosthesis [14, 15]. They have been successfully implanted in the motor cortex [16–19], the auditory cortex [20, 21], the auditory nerve [22, 23], the sciatic nerve [24], and the visual cortex [25, 26] of various animal models. Moreover, these electrodes have been acutely implanted in the middle temporal gyrus of epilepsy patients undergoing temporal lobectomy surgery [27–32] and chronically implanted in the motor cortex of paralyzed human patients [33–37]. Each array consisted of one hundred 1 mm long microelectrodes arranged in a 10×10 grid spaced 400 μm apart. The length of the electrode was chosen so that the electrode tip would reside approximately in layer 4 A/B of V1 [9, 38]. Each electrode base is electrically isolated from its neighbouring electrodes with glass, and the rest of the electrode, with the exception of the iridium-oxide tip, is insulated with a 2 μm coat of parylene-C. Each electrode tip is metalized with a sputtered iridium-oxide film (SIROF) for better charge injection capacity [39]. The electrodes have been manufactured to have an exposed tip length of $60 \pm 40 \mu\text{m}$, resulting in an active geometrical surface area of 500–4000 μm^2 . The electrode impedances ranged from 40 to 80 k Ω before implantation as measured with a 1 kHz sine-wave 10 nA constant current signal (Cerebus, Blackrock Microsystems, Salt Lake City, UT). Mean impedances were used for analysis after outliers (i.e. impedances greater than 2 M Ω) were discarded.

2.3. Instrumentation

The task control system, which handled the presentation of photic and electrical stimuli, consisted of custom software running on an embedded controller using a real-time operating system (National Instruments, Austin, TX). Visual stimuli were generated using a real-time visual stimulator (ViSaGe, Cambridge Research Systems, Rochester, Kent, England) and displayed on a CRT monitor (G90fb, ViewSonic, Walnut, CA). The animal was head-fixed using a minimally invasive technique [40] and eye positions were tracked with an infrared camera (1 kHz sampling rate, EyeLink 1000, SR Research, Mississauga, ON, Canada). Hand positions were monitored and behavioural responses registered with capacitive switches, which detected the presence of the animal's hand when it was within a few millimeters of the sensor. Physiological and behavioural data were recorded using a 128-channel data acquisition system (Cerebus, Blackrock Microsystems, Salt Lake City, UT). Data analysis was performed using Matlab technical computing software (MathWorks, Natick, MA).

2.4. Microstimulation

During the first year of experimentation, as reported in our previous work [7], we used a system that was capable of delivering a maximum of 100 μA to each electrode (RX7, Tucker-Davis Technologies, Alachua, FL). For microstimulation experiments reported here, we used a system that could deliver up to 300 μA across a 50 k Ω load to a total of 128 electrodes (IZ2, Tucker-Davis Technologies, Alachua, FL). The stimulator battery had a compliance voltage of ± 15 V (LZ48-400, Tucker-Davis Technologies, Alachua, FL). Constant-current pulses without anodic bias were delivered to V1 through the individual electrodes on the UEA. Each pulse consisted of a cathodic-first symmetric biphasic square wave with an interphase interval of 100 μs and a phase width of 200 μs . Pulses were delivered at 200 Hz for a duration of 200 ms. Current amplitudes were varied up to 300 μA . At these levels, up to 60 nC phase⁻¹ and 3 mC cm⁻² was delivered to the tissue through each electrode for a typical electrode tip geometrical surface area of 2000 μm^2 . Similar stimulation parameters evoked phosphenes in a human patient [6] and behavioural responses in a macaque monkey [5]. These parameters were used for all microstimulation experiments unless otherwise specified. For microstimulation experiments using groups of multiple contiguous electrodes, the reported currents were delivered to each of the individual electrodes of the group.

2.5. Threshold mapping

The animal's responses to stimuli of varying intensities were monitored to determine the minimum perceived intensity or threshold. The animal was placed in a primate chair inside a sound attenuated, dark chamber and was required to place each of its hands on a capacitance switch, one to its left and the other to its right. A small 0.1×0.1 visual degrees fixation point then appeared in the centre of a CRT screen 34 cm in front of the animal. Once the animal directed its gaze within 1 degree of the centre of the point, the trial would start. The animal had to maintain its gaze within this defined region, or the trial was aborted. For both photic and electric trials, stimuli were presented after fixation was maintained for a randomized duration of 500 to 1000 ms. Stimulus presentation was followed by a second randomized hold duration, and then an auditory cue was given indicating that the animal should make a response. The animal would then respond by removing its right hand to indicate that it did not perceive or its left hand to indicate that it did perceive a stimulus. Photic stimuli were round, monochromatic Gaussian shapes with diameters that varied from 0.25 to 0.5 visual degrees and locations that were presented randomly in the lower right quadrant of visual space where the UEA was previously determined to be located [7]. These stimuli were white against a dark background, and the luminance levels were kept in a range that was clearly visible to the animal. Electric stimuli consisted of the passage of current

simultaneously through one or more electrodes on the UEA using the parameters described in section 2.4. Microstimulation trials were sparsely introduced into an ongoing photic task and were rewarded with juice one hundred percent of the time regardless of the answer. Clearly visible photic trials and trials consisting of the absence of photic or electric stimuli were used as catch trials to ensure that the animal was responding truthfully. The animal was rewarded only if the correct response was made without any of the task constraints being violated. Using this forced-choice detection task, we were able to determine responses to electric stimulation at various amplitudes. Approximately five or more responses to electric stimuli presented at three or more current levels that spanned threshold (i.e. ~15 total responses) were considered to be a valid or consistent behavioural response. Psychometric data were fit using a Weibull cumulative distribution function, which was used to estimate response thresholds (current value at 50% probability of detection).

2.6. Memory saccade mapping

This task involved making saccades to the remembered spatial location of a previously presented photic or electric stimulus. The sequence of steps to complete a trial was similar to the threshold task described in section 2.5. To begin a trial, the animal was required to maintain fixation within 1 degree of a fixation point that was displayed at the centre of a CRT screen. After the start of the trial, a photic or electric stimulus was presented for 200 ms. The animal was required to maintain fixation during the presentation of the stimulus and for a random period of 500 to 1000 ms after the stimulus was removed. The animal was then required to saccade to the remembered location of the stimulus. For photic trials, round, monochromatic Gaussian shapes with a diameter of 0.25 visual degrees were presented, and the animal was required to saccade to within 1.5 degrees of the target location. Photic targets were distributed evenly across the lower right quadrant of visual space in the general location of the implanted electrodes. Targets that closely overlapped with the previously determined electrode locations were removed to avoid training the animal on photic saccade endpoints that closely resembled electric endpoints, making it difficult to distinguish the two types of saccades. For electric trials, a train of biphasic pulses (see section 2.4) were simultaneously delivered to one of three separate groups of nine contiguous electrodes. The animal was required to saccade to within a large region that encompassed the location of the implanted UEA in visual space. This region had a diameter of eight visual degrees and extended beyond the limits of the UEA location by at least two degrees on all sides.

2.7. Feline microstimulation

To confirm the results observed during microstimulation in the macaque, microstimulation was also performed via a chronically implanted UEA in feline motor cortex. For this experiment, the animal was anesthetized with Telazol administered intramuscularly at 0.01 mg/kg. Sterile, clinical fine-wire electrodes (Chalgren Enterprises, Inc., Gilroy, CA) were placed in the triceps or extensor carpi muscle. Reference electrodes were placed subcutaneously near the intramuscular electrode. Microstimulation was then applied using the parameters described in section 2.4. Electromyographic (EMG) signals to evoked muscle twitches were recorded at a sampling rate of 25 kHz using a data acquisition board (RHA2000-EVAL, Intan Technologies, Los Angeles, CA). To determine the amplitude of the evoked response, the recorded EMG was filtered with a 100–1500 Hz bandpass elliptic filter of order 10, rectified and then convolved with a Gaussian window of standard deviation 10 ms. The peak response was defined as the difference in the mean value of the convolved signal during the applied stimulus and a baseline value obtained prior to stimulus onset.

3. Results

We investigated several spatial and temporal characteristics of stimulation via a chronically implanted UEA in V1 for use as a visual prosthesis. Early experiments consisted of several months of periodic microstimulation at currents up to 96 μA [7]. Data shown here are from later experiments performed with a UEA that had been implanted for more than 18 months. These data consist of 83 stimulation sessions that span 8 months and include 81 of the 96 electrodes. Stimulus currents up to 300 μA were used.

3.1. Effect of simultaneous stimulation of multiple electrodes on response thresholds

Microstimulation was performed on individual electrodes and groups of two, four, and nine contiguous electrodes distributed evenly across the array to assess the functionality over the spatial extent of the array. Responses to systematic stimulation of individual electrodes across the array were tested. Microstimulation of 77 of the 96 electrodes at levels up to 200 μA , however, did not evoke consistent behavioural responses from the animal.

Following single electrode testing, stimulus levels were increased by increasing the number of electrodes that were simultaneously stimulated and the amount of current that was delivered to each of the electrodes of the group. Eight groups of two electrodes were tested and only two produced responses from which psychometric curves could be generated. The threshold currents per electrode for these groups were 268 and 300 μA . The six remaining groups did not evoke responses at levels up to 300 μA .

Stimulation of groups of four electrodes, in contrast, produced consistent behavioural responses across the spatial extent of the array. Thirty-two unique, overlapping groups were chosen for stimulation that tiled 75 percent of the array. Of the 32 stimulated groups, 26 produced consistent responses and psychometric curves were obtained. A total of 55 thresholds from the 32 unique groups were used to generate an average spatial threshold map (figure 2(a)). The average threshold current per electrode and standard deviation for all groups of four was $204 \pm 49 \mu\text{A}$.

Non-overlapping groups of nine contiguous electrodes were also tested. It was found that increasing the number of stimulated electrodes from four to nine led to a significant ($p < 0.05$, Kolmogorov–Smirnov) decrease in response threshold and a corresponding increase in the consistency of the responses across the spatial extent of the array. A total of 25 threshold values from 8 unique groups were used in the calculation of the spatial average (figure 2(b)). One hundred percent or 8 of the 8 unique groups produced consistent responses from which psychometric curves were obtained. The average threshold current per electrode and standard deviation for all groups of nine was $91 \pm 25 \mu\text{A}$. Nonlinear fits of the Weibull function to the raw psychometric data demonstrate that multiple electrode stimulation consistently evoked responses throughout the experiment (figure 2(c)).

To confirm that increasing the spatial extent of cortex being stimulated (i.e. increasing the number of electrodes) lowered the level of current per electrode needed to evoke a response, stimulation was also performed via a UEA in motor cortex of a feline. Data were collected 505 days post-implantation. Muscle twitches were recorded using EMG signals and the average rectified amplitude of the EMG was used as a response measure. An individual electrode and a group of four and nine contiguous electrodes were stimulated using the parameters described in section 2.4. The single electrode and the group of four were contained within the group of nine electrodes to minimize any variance in threshold based on spatial location. Stimulation was applied to each of the groups in a repetitive sequence over time to minimize the influence of anesthesia depth on the measured responses. Myometric curves were generated for each electrode group relating stimulus intensity to

response amplitude. The EMG responses showed a significant increase ($p < 0.05$) in amplitude as the number of electrodes per group increased for stimulus amplitudes of 200 and 250 μA (figure 2(d)). These results are similar to those observed in the macaque, and support the finding that simultaneous stimulation of groups of electrodes of a chronically implanted UEA decreases the amount of current required to generate robust physiological and behavioural responses.

3.2. Effect of pulse duration on response thresholds

A strength-duration curve was determined for one group of four contiguous electrodes to serve as a comparison with other studies and provide a metric for optimizing stimulation in terms of safety and efficacy. Threshold currents were measured at various pulse durations ranging from 0.15 to 0.8 ms (figure 3(a)). Other stimulation parameters were held constant at the values given in section 2.4. Chronaxie and rheobase were estimated by fitting the following hyperbolic function to the data:

$$I \cdot t = I_{rh} \cdot (t + \tau_{SD}) \quad (1)$$

where I = threshold current, I_{rh} = rheobase current, t = pulse duration, and τ_{SD} = chronaxie. This equation was found to provide the best fit for strength-duration data [41]. The chronaxie and rheobase estimated by the fit and the corresponding 95% confidence intervals were 0.16 ± 0.06 ms and 102 ± 13 μA , respectively. These values are comparable to those provided by other neural stimulation studies [3, 6, 8, 41–43] as shown in table 1. A linear trend ($R^2 = 0.97$) was observed between threshold charge density and pulse duration (figure 3(b)). Stimulation using a pulse duration of 0.2 ms resulted in a threshold charge density less than 2 mC cm^{-2} for this particular group of four contiguous electrodes. Throughout the study, 56 percent of all contiguous groups of four electrodes and 100 percent of all contiguous groups of nine electrodes had threshold charge densities below this value. Charge densities less than 2 mC cm^{-2} were determined to be safe to activated iridium microelectrodes and did not appear to decrease neuronal populations in the surrounding cortical tissue [44].

3.3. Stability of response thresholds over time

Thresholds were monitored over time from 566 to 789 days post-implantation for groups of four and nine electrodes (figure 4). Thresholds were measured 5 ± 2 times (mean $\pm$ std) for each of 11 groups spanning an average of 125 ± 78 days. Groups of four electrodes demonstrated a significant increase in threshold of $0.7 \pm 0.3 \mu\text{A day}^{-1}$ (weighted average $\pm$ 95% confidence interval). Groups of nine electrodes showed a smaller increase of $0.2 \pm 0.1 \mu\text{A day}^{-1}$. The root-mean-squared-error about the linear trend for groups of four and nine was 33 and 21 μA , respectively.

One group of four electrodes was stimulated 7.5 times more frequently and at higher levels than the other groups of four (figure 4, solid line). This group was stimulated using an average charge density of 2.9 mC cm^{-2} and a maximum of 7 mC cm^{-2} . The remaining groups of four electrodes were stimulated using a combined average charge density of 1.9 mC cm^{-2} and a maximum of 2.9 mC cm^{-2} . Groups of nine electrodes were stimulated with a combined average charge density of 0.9 mC cm^{-2} and a maximum of 1.5 mC cm^{-2} . The increase in threshold for the high stimulation group of four was not found to be significantly different from the other groups of four ($p = 0.6$, ANOVA).

3.4. Functional status of the electrodes and implant sites

Electrode impedances before each stimulation session, electrode voltage-time traces during stimulation sessions, and behavioural visual thresholds to photic stimuli that excited regions

of V1 where the UEAs were implanted were monitored to verify functionality and help identify damage to electrodes or tissue.

The mean impedance of the electrodes, as measured using a 1 kHz sine-wave 10 nA constant current signal, showed an initial increase above pre-implantation values from approximately 2 to 12 weeks after implantation. The combined average impedance during this period was 492 ± 46 k Ω (mean $\pm$ SEM). This increase was followed by a gradual decrease towards pre-implantation values (figure 5(a)). A similar pattern was observed in chronic UEA implants in feline cortex [45]. The mean impedance and standard error of the electrodes at the start of the current study 562 days after implantation was 57 ± 2 k Ω . No significant changes from this value were observed for the remainder of the study ($p = 0.4$, ANOVA).

Effective stimulation currents for some groups of four electrodes produced a maximum cathodic voltage excursion (E_{mc}) that exceeded the generally regarded safe limit of -0.6 V [39, 44]. It was possible, however, to reduce these voltages to safe levels by increasing the number of electrodes to nine. Voltage traces in response to biphasic current pulses of 100 and 200 μ A for two electrodes are shown in figure 5(b). The upper traces are from an electrode that was stimulated using high charge density levels as described in section 3.3. Impedances measured using a small-signal 1 kHz sine-wave for these two electrodes were 59 and 79 k Ω for the upper and lower traces, respectively. E_{mc} can be approximated with the voltage during the inter-phase interval of each trace. This value exceeds the safety limit for both electrodes when using a 200 μ A stimulus and is within this limit for a 100 μ A stimulus. Both electrodes were in groups of four and nine that provided consistent behavioural responses to stimulation throughout the course of the study.

Before implantation, dark-adapted thresholds to photic stimuli were measured in the approximate location of visual space representing the region of cortex where the UEA was implanted and were found to range from 250 to 550 μ cd m $^{-2}$. Ten months after implantation, thresholds for the visual field locations represented by the cortex where the array was implanted were measured and ranged from 420 to 490 μ cd m $^{-2}$. Twenty-five months after implantation and following stimulation at levels up to 300 μ A, thresholds for stimuli presented at the same locations ranged from 370 to 470 μ cd m $^{-2}$. These values are similar to human thresholds [7] and indicate that cortical function was not impaired by the implantation and chronic presence of the UEA. Further, no behavioural evidence of epileptiform activity occurred in response to electric stimulation, and the animal never exhibited signs of neurological deficiencies or other behavioural abnormalities throughout the course of experimentation.

3.5. Spatial discrimination of phosphenes

Data were collected for saccades made to electrical stimulation of three groups of nine contiguous non-overlapping electrodes. These data were obtained to confirm that electrical stimulation was producing visual percepts that the animal could spatially discriminate. Data from this task were collected 790 to 804 days post-implantation and show saccades to both photic and electric stimuli (figure 6).

These data demonstrate that the animal was able to discriminate the location of three separate visual percepts produced by electrical stimulation of three groups of nine contiguous electrodes. The distance between these groups of electrodes was 1.6 ± 0.3 mm (mean $\pm$ std) on the array, and the corresponding separation in visual space, based on the measured receptive field locations, was 1.0 ± 0.2 degrees. The mean electric saccade centres showed a significant separation ($p < 0.05$, MANOVA), and the locations in visual space corresponded with the locations where the visual percepts would be expected to appear

based on the map of receptive fields. The average distance to target for the photic saccades was 0.6 degrees, and the average standard deviation of the scatter of saccade endpoints was 0.5 degrees. For electric saccades, the average distance to target was 2.9 degrees, and the average standard deviation of the scatter was 1.0 degree. The scatter of endpoints for electric saccades was 2.0 times greater than for photic saccades. This decrease in electric saccade precision was also observed in a related study [5].

4. Discussion

In this work, we investigated several spatial and temporal characteristics of V1 microstimulation using a chronically implanted UEA in a behaving macaque monkey. After 2 years of implantation, consistent behavioural responses to microstimulation were obtained over the spatial extent of the array by activating larger volumes of cortical tissue through stimulation of groups of contiguous electrodes. It was found that increasing the size of the contiguous groups reduced the threshold current and charge density delivered through each electrode to levels generally considered safe [44]. In addition, no behavioural signs of epileptiform activity occurred in response to multiple electrode stimulation, and neither stimulation nor the presence of the UEA in V1 impacted the behavioural photic thresholds to light stimuli that excited regions of V1 where the UEA was implanted.

4.1. Stimulation thresholds in a chronically implanted UEA

Early microstimulation experiments performed approximately three months after the implantation of the UEA yielded behavioural responses to stimulation of individual electrodes with threshold currents ranging from 18 to 76 μA [7]. More than a year after these experiments, we show that simultaneous stimulation of groups of electrodes using currents ranging from 57 to 300 μA was required to produce consistent behavioural responses. Additionally, threshold currents for several electrode groups were found to increase with time. Other chronic microstimulation studies have reported increases in thresholds or a loss of functional electrodes with time [8, 11]. Many V1 microstimulation studies have not reported an increase, but these studies were performed with either acute electrode placement or with chronic implantation of no more than 4 months [6, 9, 10, 46, 47]. This observed increase in stimulation thresholds over the course of the study may have resulted from alteration of the implanted tissue or the electrode array.

Studies have shown that a glial sheath develops around chronically implanted penetrating microelectrodes and that this sheath may serve as a resistive barrier to the flow of current [48, 49]. Contraction of this sheath as it ages, as well as, movement of the tissue in relation to the rigid array of electrodes might lead to extrusion of the array or the formation of a fluid barrier between the electrode surface and tissue. This fluid layer could provide a low impedance return path for injected current during stimulation, effectively shunting current away from the target tissue and causing an increase in stimulation thresholds. Microstimulation itself can affect the surrounding tissue, which might also lead to an increase in thresholds. Levels used to evoke behavioural responses during V1 microstimulation have ranged from 2 to 200 μA [6–10, 46, 47] with charge densities as high as 7.7 mC cm^{-2} [6]. Continuous stimulation as low as 0.2 mC cm^{-2} was found to induce a loss of cortical neurons from within a radius of 150 μm of the electrode tips [50]. It is unknown if or how this neuronal loss would affect stimulation-evoked percepts. Many V1 microstimulation studies have exceeded this level of stimulation [5–7, 46]. The total duration of stimulation applied in these studies, however, was typically much less than the continuous stimulation paradigms that are found in studies assessing tissue safety. We applied up to 300 μA and 3 mC cm^{-2} on some of our electrodes to evoke responses. One group of four electrodes was repeatedly stimulated with an average charge density of 2.9 mC

cm^{-2} . This group did not show a significantly larger increase or demonstrate a larger variation in threshold with time when compared with other groups of electrodes.

A SIROF UEA implanted in cat sensorimotor cortex for over 300 days exhibited decreased impedances and an increased charge storage capacity with implant time [51]. It was suggested that these changes might be caused by leakage of electrolyte under the parylene insulation of the electrodes, leading to an overall increase in surface area and thus an overestimation of charge density during microstimulation. The surface area of SIROF UEA electrodes can vary significantly from 500 to 4000 μm^2 , adding another component of uncertainty to the estimation of charge density. The maximum safe charge density during stimulation of iridium microelectrodes can range from 0.4 to 4 mC cm^{-2} [44, 51–53]. The variance in this value can be attributed to differences in the electrode fabrication, the parameters of stimulation used in testing, and the conditions under which the stimulation was applied. Seven hours of intracortical microstimulation in feline sensorimotor cortex was shown to damage the electrodes at levels above 2 mC cm^{-2} [44]. These electrodes were constructed from iridium microwire, the tips were composed of activated iridium oxide film, and anodically biased biphasic pulses with a width of 400 μs were used for stimulation. With the same parameters of stimulation that were used in our experiments, but under acute conditions in physiological phosphate buffered saline, the maximum safe charge density for a SIROF UEA was estimated to be 2 mC cm^{-2} [52]. Levels that exceeded this value were needed to evoke percepts on some of our electrodes. The impedances and the voltage traces during stimulation of these electrodes, however, did not exhibit any obvious changes over time.

It is likely that the observed increase in stimulation thresholds over the course of the study is related to the chronic presence of the UEA in tissue or to changes that resulted at the electrode-tissue interface due to microstimulation. Even when stimulating at high current levels, we did not observe any catastrophic failures in the ability to evoke visual percepts. However, continuous chronic stimulation at these levels might eventually result in a failure to evoke percepts through alterations to the implanted tissue or the electrode array. One way to minimize these alterations might be to increase the surface area of the electrodes by exposing more of the electrode tip during the manufacturing process. This would likely degrade spatial resolution acutely, but it would also decrease charge density and might improve chronic performance. In spite of the increasing thresholds, we show that every group of electrodes that evoked behavioural responses initially was able to evoke consistent responses throughout the duration of the study at levels that are unlikely to cause device failure. Further, repeated stimulation and the chronic presence of the UEA in tissue have not adversely affected the animal's vision or overall health.

4.2. Microstimulation using multiple electrodes

In this study, we showed that simultaneous stimulation of contiguous groups of microelectrodes was needed to produce consistent primate behavioural and feline motor responses and that the threshold level of stimulation per electrode decreased as electrode number increased. It appears, therefore, that a tradeoff between resolution and safety exists for this device under chronic conditions for use as a visual prosthesis. The question arises: What are the features of the percepts produced during multiple electrode stimulation using a chronically implanted UEA? Few studies have attempted to characterize the percepts evoked during stimulation of multiple microelectrodes in V1. One study in a human patient showed that two distinct phosphenes could be generated by simultaneously stimulating two nearby electrodes with a separation of 500 μm or more using currents near 50 μA [6]. This study also showed that simultaneous stimulation of multiple electrodes could be used to form simple visual patterns, such as a vertical line of phosphenes, and that less current was required to produce a visual percept when compared to stimulation of the individual

constituent electrodes. Studies have looked at the effective spread of current during microstimulation and found that the radius of activated tissue is proportional to the square root of the total current applied during stimulation [54]. At currents less than 100 μA , such as those used in many acute microstimulation experiments, the radius of activated tissue is predicted to be less than 500 μm and confined to a hypercolumn in V1. For our study, the average threshold for stimulation of groups of four and nine contiguous electrodes was 204 and 91 μA , respectively. Using these thresholds, the estimated current spread would be near or greater than the inter-electrode separation of 400 μm of the UEA. Due to the overlap in effective current between stimulated electrodes, the individual percepts during multiple electrode stimulation are likely to combine to form a single larger and possibly amorphous percept. In addition to the passive spread of current, the complex neuronal structure of V1 may introduce even more complexity to the resulting percept when stimulating multiple electrodes. Our results from the memory saccade experiment support the idea of a spatially diffuse and amorphous percept. We found that the scatter of saccades to electric targets during stimulation of nine contiguous electrodes was 2.0 times greater than that for photic targets. In a related chronic study, the scatter of electrically-evoked saccades during single electrode stimulation was found to be 2.5 times greater than for photic saccades [5]. One explanation for this difference may be that electrically-evoked saccades are inherently more imprecise than saccades to photic stimuli. It may also be that electrically-evoked percepts are more amorphous and spatially diffuse than the punctate photic stimuli used to guide saccades. In spite of the decreased saccade precision to electrically-evoked percepts, we were still able to show discrimination when stimulating separate groups of nine contiguous electrodes using a chronically implanted UEA. The complex spatio-temporal nature of the percepts generated during multiple electrode stimulation of V1, however, is still not understood. Experiments to explore these characteristics appear to be the next logical step towards the development of a cortically-based visual prosthesis.

5. Conclusion

We have demonstrated several features associated with the chronic functionality of an array of penetrating microelectrodes implanted in V1 for use in a vision prosthesis. We have shown that this device is capable of evoking reliable visual percepts two years after implantation, and that photic thresholds, electrical thresholds, and impedances remained substantially stable over the course of the study. We have also shown that the subject can spatially discriminate the location of these visual percepts when separate regions of the array are stimulated. In order to reliably evoke visual percepts at safe current levels, it was necessary to expand the volume of cortex that was stimulated. This will likely reduce electrically-evoked visual acuity. However, it was still possible to evoke multiple spatially distinct phosphenes with a resolution comparable to the current epi-retinal prostheses. The spatial variance of saccades to electrically-evoked visual percepts suggests that these percepts may be spatially extended and amorphous rather than spatially restricted and punctate. To gain an in-depth understanding of the correlation between the spatio-temporal characteristics of cortical stimulation via multiple microelectrodes and the evoked visual percepts, it may be necessary to move into human experiments where a verbal description of the visual percepts is possible.

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References

1. Frick KD, Foster A. The magnitude and cost of global blindness: an increasing problem that can be alleviated. *Am. J. Ophthalmol.* 2003; 135:471–476. [PubMed: 12654362]
2. Brindley GS, Lewin WS. The visual sensations produced by electrical stimulation of the medial occipital cortex. *J. Physiol.* 1968; 196:479–493. [PubMed: 4871047]
3. Dobelle WH, Mladejovsky MG. Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. *J. Physiol.* 1974; 243:553–576. [PubMed: 4449074]
4. Pollen DA. Some perceptual effects of electrical stimulation of the visual cortex in man. *The Nervous System.* 1975; 2:519–528.
5. Bradley DC, et al. Visuotopic mapping through a multichannel stimulating implant in primate V1. *J. Neurophysiol.* 2005; 93:1659–1670. [PubMed: 15342724]
6. Schmidt EM, Bak MJ, Hambrecht FT, Kufta CV, O'Rourke DK, Vallabhanath P. Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. *Brain.* 1996; 119(Pt 2):507–522. [PubMed: 8800945]
7. Torab K, Davis TS, Warren DJ, House PA, Normann RA, Greger B. Multiple factors may influence the performance of a visual prosthesis based on intracortical microstimulation: nonhuman primate behavioural experimentation. *J. Neural. Eng.* 2011; 8 035001.
8. Bartlett JR, DeYoe EA, Doty RW, Lee BB, Lewine JD, Negrao N, Overman WH Jr. Psychophysics of electrical stimulation of striate cortex in macaques. *J. Neurophysiol.* 2005; 94:3430–3442. [PubMed: 16079195]
9. DeYoe EA, Lewine JD, Doty RW. Laminar variation in threshold for detection of electrical excitation of striate cortex by macaques. *J. Neurophysiol.* 2005; 94:3443–3450. [PubMed: 16079194]
10. Tehovnik EJ, Slocum MW. Depth-dependent detection of microampere currents delivered to monkey V1. *Eur. J. Neurosci.* 2009; 29:1477–1489. [PubMed: 19519630]
11. Rousche PJ, Normann RA. Chronic intracortical microstimulation (ICMS) of cat sensory cortex using the Utah Intracortical Electrode Array. *IEEE Trans. Biomed. Eng.* 1999; 7:56–68.
12. Rousche PJ, Normann RA. A method for pneumatically inserting an array of penetrating electrodes into cortical tissue. *Ann. Biomed. Eng.* 1992; 20:413–422. [PubMed: 1510293]
13. Kaas, J.; Collins, C. *The Primate Visual System.* Boca Raton, FL: CRC Press; 2004. p. 265–269.
14. Campbell PK, Jones KE, Huber RJ, Horch KW, Normann RA. A silicon-based, three-dimensional neural interface: manufacturing processes for an intracortical electrode array. *IEEE Trans. Biomed. Eng.* 1991; 38:758–768. [PubMed: 1937509]
15. Normann RA, Maynard EM, Rousche PJ, Warren DJ. A neural interface for a cortical vision prosthesis. *Vision Res.* 1999; 39:2577–2587. [PubMed: 10396626]
16. Baker, J.; Bishop, W.; Kellis, S.; Levy, T.; House, P.; Greger, B. Multi-scale recordings for neuroprosthetic control of finger movements; *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009. p. 4573–4577.
17. Hatsopoulos N, Mukand J, Polykoff G, Friehs G, Donoghue J. Cortically controlled brain-machine interface. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2005; 7:7660–7663. [PubMed: 17282055]
18. Linderman MD, Gilja V, Santhanam G, Afshar A, Ryu S, Meng TH, Shenoy KV. Neural recording stability of chronic electrode arrays in freely behaving primates. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2006; 1:4387–4391. [PubMed: 17946626]
19. Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB. Cortical control of a prosthetic arm for self-feeding. *Nature.* 2008; 453:1098–1101. [PubMed: 18509337]
20. Kim SJ, Manyam SC, Warren DJ, Normann RA. Electrophysiological mapping of cat primary auditory cortex with multielectrode arrays. *Ann. Biomed. Eng.* 2006; 34:300–309. [PubMed: 16496084]
21. Rousche PJ, Normann RA. Chronic recording capability of the Utah Intracortical Electrode Array in cat sensory cortex. *J. Neurosci. Methods.* 1998; 82:1–15. [PubMed: 10223510]
22. Hillman T, Badi AN, Normann RA, Kertesz T, Shelton C. Cochlear nerve stimulation with a 3-dimensional penetrating electrode array. *Otol. Neurotol.* 2003; 24:764–768. [PubMed: 14501454]

23. Kim SJ, Badi AN, Normann RA. Selective activation of cat primary auditory cortex by way of direct intraneural auditory nerve stimulation. *Laryngoscope*. 2007; 117:1053–1062. [PubMed: 17545868]
24. McDonnall D, Clark GA, Normann RA. Selective motor unit recruitment via intrafascicular multielectrode stimulation. *Can. J. Physiol. Pharmacol.* 2004; 82:599–609. [PubMed: 15523517]
25. Maynard EM, Fernandez E, Normann RA. A technique to prevent dural adhesions to chronically implanted microelectrode arrays. *J. Neurosci. Methods*. 2000; 97:93–101. [PubMed: 10788663]
26. Warren DJ, Fernandez E, Normann RA. High-resolution two-dimensional spatial mapping of cat striate cortex using a 100-microelectrode array. *Neuroscience*. 2001; 105:19–31. [PubMed: 11483297]
27. House PA, MacDonald JD, Tresco PA, Normann RA. Acute microelectrode array implantation into human neocortex: preliminary technique and histological considerations. *Neurosurg. Focus*. 2006; 20:1–4.
28. Keller CJ, et al. Heterogeneous neuronal firing patterns during interictal epileptiform discharges in the human cortex. *Brain*. 2010; 133:1668–1681. [PubMed: 20511283]
29. Schevon CA, Goodman RR, McKhann G Jr, Emerson RG. Propagation of epileptiform activity on a submillimeter scale. *J. Clin. Neurophysiol.* 2010; 27:406–411. [PubMed: 21076338]
30. Schevon CA, Ng SK, Cappell J, Goodman RR, McKhann G Jr, Waziri A, Branner A, Sosunov A, Schroeder CE, Emerson RG. Microphysiology of epileptiform activity in human neocortex. *J. Clin. Neurophysiol.* 2008; 25:321–330. [PubMed: 18997628]
31. Schevon CA, Trevelyan AJ, Schroeder CE, Goodman RR, McKhann G, Jr. and Emerson RG. Spatial characterization of interictal high frequency oscillations in epileptic neocortex. *Brain*. 2009; 132:3047–3059. [PubMed: 19745024]
32. Waziri A, Schevon CA, Cappell J, Emerson RG, McKhann GM 2nd, Goodman RR. Initial surgical experience with a dense cortical microarray in epileptic patients undergoing craniotomy for subdural electrode implantation. *Neurosurgery*. 2009; 64:540–545. [PubMed: 19240617]
33. Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn RD, Donoghue JP. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*. 2006; 442:164–171. [PubMed: 16838014]
34. Kim SP, Simeral JD, Hochberg LR, Donoghue JP, Black MJ. Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *J. Neural. Eng.* 2008; 5:455–476. [PubMed: 19015583]
35. Ojakangas CL, Shaikhouni A, Friehs GM, Caplan AH, Serruya MD, Saleh M, Morris DS, Donoghue JP. Decoding movement intent from human premotor cortex neurons for neural prosthetic applications. *J. Clin. Neurophysiol.* 2006; 23:577–584. [PubMed: 17143147]
36. Truccolo W, Friehs GM, Donoghue JP, Hochberg LR. Primary motor cortex tuning to intended movement kinematics in humans with tetraplegia. *J. Neurosci.* 2008; 28:1163–1178. [PubMed: 18234894]
37. Vargas-Irwin CE, Shakhnarovich G, Yadollahpour P, Mislow JM, Black MJ, Donoghue JP. Decoding complete reach and grasp actions from local primary motor cortex populations. *J. Neurosci.* 2010; 30:9659–9669. [PubMed: 20660249]
38. Shushruth S, Ichida JM, Levitt JB, Angelucci A. Comparison of spatial summation properties of neurons in macaque V1 and V2. *J. Neurophysiol.* 2009; 102:2069–2083. [PubMed: 19657084]
39. Cogan SF. Neural stimulation and recording electrodes. *Annu. Rev. Biomed. Eng.* 2008; 10:275–309. [PubMed: 18429704]
40. Davis TS, Torab K, House P, Greger B. A minimally invasive approach to long-term head fixation in behaving nonhuman primates. *J. Neurosci. Methods*. 2009; 181:106–110. [PubMed: 19394360]
41. Mogyoros I, Kiernan MC, Burke D. Strength-duration properties of human peripheral nerve. *Brain*. 1996; 119(Pt 2):439–447. [PubMed: 8800939]
42. Ronner SF, Lee BG. Excitation of visual cortex neurons by local intracortical microstimulation. *Exp. Neurol.* 1983; 81:376–395. [PubMed: 6603370]
43. Tehovnik EJ, Slocum WM, Schiller PH. Microstimulation of V1 delays the execution of visually guided saccades. *Eur. J. Neurosci.* 2004; 20:264–272. [PubMed: 15245498]

44. Cogan SF, Guzelian AA, Agnew WF, Yuen TG, McCreery DB. Over-pulsing degrades activated iridium oxide films used for intracortical neural stimulation. *J. Neurosci. Methods.* 2004; 137:141–150. [PubMed: 15262054]
45. Parker RA, Davis TS, House PA, Normann RA, Greger B. The functional consequences of chronic, physiologically effective intracortical microstimulation. *Prog. Brain Res.* 2011; 194:145–165. [PubMed: 21867801]
46. Bak M, Girvin JP, Hambrecht FT, Kufta CV, Loeb GE, Schmidt EM. Visual sensations produced by intracortical microstimulation of the human occipital cortex. *Med. Biol. Eng. Comput.* 1990; 28:257–259. [PubMed: 2377008]
47. Murphey DK, Maunsell JH. Behavioral detection of electrical microstimulation in different cortical visual areas. *Curr. Biol.* 2007; 17:862–867. [PubMed: 17462895]
48. Frampton JP, Hynd MR, Shuler ML, Shain W. Effects of glial cells on electrode impedance recorded from neural prosthetic devices in vitro. *Ann. Biomed. Eng.* 2010; 38:1031–1047. [PubMed: 20336824]
49. Griffith RW, Humphrey DR. Long-term gliosis around chronically implanted platinum electrodes in the Rhesus macaque motor cortex. *Neurosci. Lett.* 2006; 406:81–86. [PubMed: 16905255]
50. McCreery D, Pikov V, Troyk PR. Neuronal loss due to prolonged controlled-current stimulation with chronically implanted microelectrodes in the cat cerebral cortex. *J. Neural. Eng.* 2010; 7:036005.
51. Kane SR, Cogan SF, Ehrlich J, Plante TD, McCreery DB. Electrical performance of penetrating microelectrodes chronically implanted in cat cortex. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2011; 2011:5416–5419. [PubMed: 22255562]
52. Negi S, Bhandari R, Rieth L, Solzbacher F. In vitro comparison of sputtered iridium oxide and platinum-coated neural implantable microelectrode arrays. *Biomedical materials.* 2010; 5:15007. [PubMed: 20124668]
53. Weiland JD, Anderson DJ, Humayun MS. In vitro electrical properties for iridium oxide versus titanium nitride stimulating electrodes. *IEEE Trans. Biomed. Eng.* 2002; 49:1574–1579. [PubMed: 12549739]
54. Tehovnik EJ, Slocum WM, Carvey CE, Schiller PH. Phosphene induction and the generation of saccadic eye movements by striate cortex. *J. Neurophysiol.* 2005; 93:1–19. [PubMed: 15371496]

Figure 1.
Surgical image of the implanted UEAs. Data for this study were collected using the posterior array indicated with the asterisk.

Figure 2.

Increasing the volume of activated tissue during microstimulation by simultaneously stimulating groups of 4 and 9 contiguous electrodes resulted in an increased percentage of responsive regions across the UEA and lower response thresholds. Data were collected from 566 to 687 days after implantation for plots a–c and 505 days after implantation for plot d. (a) Average psychometric response thresholds to microstimulation of overlapping groups of 4 contiguous electrodes across the UEA. Values for the individual electrodes of this plot, represented by the colored boxes, were calculated by taking the average threshold of all groups common to that particular electrode. 26 of 32 groups produced response thresholds at or below 300 μA . 6 groups did not elicit responses at levels up to 300 μA . 7 electrodes were common to one or more of the 6 unresponsive groups and are represented by black boxes and labeled as no response (NR) electrodes. White boxes represent electrodes that were not stimulated (NS). (b) Average response thresholds to microstimulation of non-overlapping groups of 9 contiguous electrodes. 8 of 8 groups produced response thresholds at or below 300 μA . (c) Nonlinear fits of the Weibull function to the psychometric data from stimulation of groups of 4 and 9 contiguous electrodes across the UEA. Thresholds were taken at the 50% response probability. The mean threshold for all groups of 4 was significantly higher

than all groups of 9 electrodes ($p < 0.05$) with values of 204 ± 49 and $91 \pm 25 \mu\text{A}$ (mean $\pm$ std), respectively. (d) Myometric curves for microstimulation of groups of 1, 4 and 9 contiguous electrodes in chronically implanted feline motor cortex. The average rectified EMG value recorded during muscle twitch evoked by stimulation was used as a response metric. Each point on the myometric curves represents the mean of 10 trials at the specified stimulus intensity. The error bars represent the standard error of the mean. At stimulation levels of 200 and 250 μA , a significant ($p < 0.05$) increase in EMG amplitude occurred as the number of electrodes per group increased.

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Figure 3.

Strength-duration curves for a group of 4 contiguous electrodes. Electrodes were stimulated using 40 symmetric biphasic cathodic-first pulses with increasing pulse durations at a frequency of 200 Hz. Response thresholds for current and charge density were measured. (a) The relationship between pulse duration and threshold current was estimated using the following hyperbolic function: $I * t = I_{th} * (t + \tau_{SD})$, where I = threshold current, t = pulse duration, I_{th} = rheobase current, and τ_{SD} = chronaxie. Chronaxie and rheobase were calculated to be $0.16 \pm 0.06 \text{ ms}$ and $102 \pm 13 \mu\text{A}$, respectively. (b) A linear relationship existed between pulse duration and threshold charge density. Pulse durations of 0.2 ms or less were determined to be safe to tissue and electrode according to a study by Cogan et al. (2004).

Figure 4.

Thresholds for 4 groups of 4 and 7 groups of 9 contiguous electrodes were monitored over time. Two curves from each group are shown. Groups of 4 electrodes showed a significant increase in threshold of $0.7 \pm 0.3 \mu\text{A day}^{-1}$ (weighted average $\pm$ 95% confidence interval). Groups of 9 electrodes showed a significant increase of $0.2 \pm 0.1 \mu\text{A day}^{-1}$. The average root-mean-squared-error about the linear trend was 33 and 21 μA for groups of 4 and 9, respectively. The group of 4 electrodes shown with a solid line was stimulated 7.5 times more frequently and at higher levels than other groups. An average charge density of 2.9 mC cm^{-2} with a maximum of 7 mC cm^{-2} was delivered to this group throughout the course of experimentation. An average charge density of 1.9 mC cm^{-2} with a maximum of 2.9 mC cm^{-2} was delivered to the 3 remaining groups of 4. The groups of 9 were stimulated using an average charge density of 0.9 mC cm^{-2} and a maximum of 1.5 mC cm^{-2} . The increase in threshold for the high stimulation group of 4 was not found to be significantly different from the other groups of 4 ($p = 0.6$, ANOVA).

Figure 5.

Electrode impedances measured before stimulation sessions and voltage traces acquired during stimulation sessions confirm the functionality of the implant and do not indicate significant device damage. (a) Mean impedances of all array electrodes demonstrate an initial increase followed by a gradual decrease over time. The start of the current study, approximately 18 months post-implantation, is indicated with an arrow. No significant changes in impedance occurred after this point in time ($p = 0.4$, ANOVA) as a result of stimulation. (b) Voltage traces during 100 and 200 μ A constant current stimulation for 2 electrodes. These electrodes show a maximum cathodic voltage excursion that is under the generally regarded safe limit of -0.6 V for a stimulus current of 100 μ A and exceeds this limit for 200 μ A. Both electrodes provided consistent behavioral responses to stimulation throughout the study.

Figure 6.

Saccades to electrical stimulation of 3 groups of 9 contiguous electrodes demonstrate discrimination of 3 spatially distinct percepts. The mean saccade centres to photic targets are depicted as black dots bounded by black ellipses that represent the Mahalanobis distance of the scatter. An example of the photic saccade scatter is shown in the upper-right corner. Each photic centre is near the corresponding photic target shown as a black plus. The mean saccade endpoints to microstimulation (electric targets) are represented with colored dots and are bounded by colored ellipses. Colors match the estimated target locations depicted with the inset plot of the UEA. A non-linear, least-mean-square method was used to position the inset UEA by minimizing the distances between the actual receptive field centres and the

coordinate transforms of each electrode into visual space. The mean electric saccade centres showed a significant separation ($p < 0.05$, MANOVA).

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Table 1

Summary of chronaxie/rheobase data from select neural stimulation studies

Citation	Model System	Electrode Location	Electrode Type	Chronaxie (ms)	Rheobase (μA)
Davis et al. (2012) ^a	Macaque	V1	Intracortical	0.16	102
Bartlett et al. (2005)	Macaque	V1	Intracortical	0.23	75 ^b
Tehovnik et al. (2004)	Macaque	V1	Intracortical	0.13–0.24	NR ^c
Schmidt et al. (1996)	Human	V1	Intracortical	0.22 ^b	9.1 ^b
Ronner et al. (1983)	Feline	V1	Intracortical	0.22	160
Dobelle et al. (1974)	Human	V1	Surface	0.35 ^b	1800 ^b
Mogyoros et al. (1996)	Human	Median nerve	Surface	0.67	1270

^aCurrent study

^bEstimation based on data provided in figure/table

^cNot reported