Experimental Model and Subject Details

The participants for this study consisted of three sighted participants with medically intractable epilepsy (all male; anonymized subject codes YBN, YAY, YBH, ages 20-54) tested at Baylor College of Medicine (BCM); one blind participant (female, age 35; anonymized subject code BAA) tested at University of California, Los Angeles (UCLA); and one blind participant (male, age 58; anonymized subject code 03-281) tested at Baylor College of Medicine. In all participants, subdural electrodes were implanted on the surface of the occipital lobe. The electrodes were stimulated, and the resulting percepts examined. The Institutional Review Boards of BCM and UCLA approved all research protocols, and all participants gave written informed consent.

A preliminary version of this manuscript was deposited in the bioRxiv preprint server (https://www.biorxiv.org/content/10.1101/462697v1).

Epileptic participants

Clinical electrodes were implanted for monitoring of epileptogenic activity, with electrode placement guided solely by clinical criteria. Additional research electrodes (embedded in the same silastic strips used for clinical monitoring) were implanted and stimulated for the studies described here. Clinical monitoring continued uninterrupted during experimental sessions. Participants were hospitalized in the epilepsy-monitoring unit for 4 to 14 days after electrode implantation. During experiments, the participants remained seated comfortably in their hospital bed. A ground pad was adhered to the participant's thigh and except where noted, all electrical stimulation was monopolar. Electrical stimulation currents were generated using a 16-channel system (AlphaLab SnR, Alpha Omega, Alpharetta, GA) controlled by custom code written in MATLAB (Version 2013b, The MathWorks Inc., Natick, MA). For all participants, the epilepsy seizure focus was determined to be distant from visual cortex. For participant YBN, the research electrodes consisted of a six by

four grid of electrodes (total of 24 electrodes). Each electrode was 0.5 mm in diameter with a center-to-center spacing of 2 mm. For sighted participants YAY and YBH, the research electrodes consisted of 16 electrodes. Each electrode was 0.5 mm in diameter with a center-to-center spacing of 4 mm or 6 mm.

Blind participants

Blind participant BAA acquired blindness at age 27 and had minimal residual light perception. As a component of an early feasibility study for the development of a visual cortical prosthetic, BAA underwent surgical implantation of a responsive neurostimulator developed to treat epilepsy (RNS System, Neuropace, MountainView, CA) containing electrodes located on two separate silastic strips. Each strip contained 4 electrodes. Each electrode was 3.18 mm in diameter with a center-to-center spacing of 10 mm. Participant BAA was tested as an outpatient as described in (Niketeghad et al., 2019).

Blind participant 03-281 (male, age 58) acquired blindness at age 46 and had no light perception. The participant was implanted with the Orion Visual Cortical Prosthesis System (Second Sight Medical Products, Inc., Sylmar, CA) at age 57. The Orion contained 60 electrodes arranged in 10 rows, with interelectrode spacing of 4.2 mm within rows and 3.0 mm across rows.

Method Details

Electrode Localization and Visualization

Before surgery, T1-weighted structural magnetic resonance imaging scans were used to create cortical surface models with FreeSurfer (Dale et al., 1999; Fischl et al., 1999) and visualized using SUMA (Argall et al., 2006). Participants underwent a whole-head CT after the electrode implantation surgery. The post-surgical CT scan and pre-surgical MR scan were aligned using Analysis of Functional Neuroimaging (AFNI) software (Cox, 1996) and all electrode positions

were marked manually on the structural MR images. Electrode positions were then projected to the nearest node on the cortical surface model using the AFNI program *SurfaceMetrics*.

Screening to Determine Responsive Electrodes

First, all electrodes were screened to identify responsive electrodes *i.e.* those that produced a phosphene when electrical stimulation was delivered. In each trial, participants verbally reported whether they experienced a localized, brief, visual percept similar to a flash of light. During each trial, an auditory warning tone cued the participants to fixate visual crosshairs. This was followed by a second tone that indicated the beginning of the electrical stimulation period. Electrical stimulation consisted of a train of biphasic pulses (-/+), with 0.1 ms pulse duration per phase, delivered at a frequency of 200 Hz, with an overall stimulus train duration of 200 or 300 ms. Currents tested ranged from 0.3 - 4.0 mA in sighted participants and up to 7.5 mA in blind participants, with maximum charge delivered per screening trial of 4 μC for sighted and 9 μC for blind. For each electrode, trials were initiated with a low current (0.3-1.0 mA) that gradually increased on successive trials until the participant reported a phosphene. If no phosphene was obtained at the maximum current levels of 4 mA in sighted and 7.5 mA in blind then the site was considered unresponsive.

Quantitative Phosphene Mapping Using Electrical Stimulation

To quantify phosphene locations, additional experiments were performed on each of the electrodes identified in the screening stage. The participant fixated visual crosshairs and electrical stimulation was delivered to a single electrode using the parameters that elicited a phosphene for that electrode in the screening stage. The participant drew the outline of the phosphene on a touchscreen; a cloth tape measure was used to measure the distance between the participant's face and the touchscreen in order to accurately assess visual angle. The distance was adjusted so that

the participant could draw on the touchscreen comfortably. Three to five trials per electrode were typically conducted. On the first trial, the participant was instructed to draw the shape as accurately as possible. On subsequent trials, the participant adjusted the size and location of the phosphene using a custom designed graphical user interface so that it matched the phosphene as precisely as possible. For participant YBH, phosphenes were drawn with a pen and paper instead of a touchscreen. The participant inspected the drawing following the trial. If it did not match the percept, an additional trial was performed, and a new drawing created. The paper drawings were digitized using a flatbed scanner. Phosphene drawings for each electrode (touchscreen or pen and paper) were fit with an ellipse for quantification and display. Blind participants were instructed to touch (and attend to) a small Velcro square placed on a touchscreen and trace the location or outline of the phosphene percept on the touchscreen.

Quantification and Statistical Analysis

Receptive Field Mapping Using Visual Stimuli

For sighted participants YBH and YBN the visual responses of each electrode were measured (Bosking et al., 2017b; Ozker et al., 2018; Yoshor et al., 2007); Supplementary Figure 1 illustrates receptive field mapping for two sample electrodes from participant YBN. The participant viewed an LCD screen at a distance of 57 cm. Square checkerboards were presented at screen locations that varied randomly from interval to interval (checkerboard duration 167 ms, blank interval of 167 ms between locations). Each checkerboard subtended 2° and contained a five-by-five grid of black and white checks, resulting in a spatial frequency of 2.5 cycles per degree. To ensure fixation, participants performed a letter detection task at the fixation point. A Cerebus amplifier (Blackrock Microsystems, Salt Lake City, UT) record electrode signals referenced to an inactive intracranial electrode implanted facing the skull. Signals were amplified,

filtered (low-pass: 500 Hz, Butterworth filter with order 4; high-pass: 0.3 Hz, Butterworth filter with order 1) and digitized at 2 kHz. For each electrode, the average visual response evoked by the checkerboards presented at each location was measured. Outliers were discarded and the visual response was smoothed with a Savitzky-Golay polynomial filter (order 5). The evoked potential at each location was converted to a single value by calculating the root mean square deviation from baseline during the time window from 50 ms to 250 ms after stimulus onset. To estimate the spatial receptive field of the ensemble of neurons underlying the electrode, the amplitudes of the evoked responses were fit with a two-dimensional Gaussian function. To allow visualization of the receptive field as a single discrete shape, the half-maximum value of the fitted Gaussian was plotted.

Electrical stimulation details

All stimulation consisted of cathodic-first biphasic (charge-balanced) pulses with a frequency of 200 Hz and a pulse width per phase of 100 microseconds, unless noted otherwise. For monopolar stimulation, the stimulation ground was a conductive pad, typically attached to the participant's leg. Bipolar stimulation (for current steering) occurred between adjacent stimulating electrodes.

The current amplitude for each electrode was held constant and was the same amplitude as that used for phosphene mapping of individual electrodes (equal to the minimum current that reliably produced a phosphene during the screening stage).

Dynamic current steering (monopolar)

Monopolar dynamic current steering was used to create virtual electrodes in between the physical electrodes on the array by using current steering. Current steering consisted of simultaneous stimulation of two adjacent electrodes in the sequence at a particular current ratio.

The ratio is adjusted to change the location of the virtual electrode. The ratio can be held constant for an entire pulse train (as illustrated in Figure 2) or varied for each individual pulse within the pulse train (as illustrated in Figure 3). The rate of change of the current ratio determines how rapidly the pattern is "drawn" on the cortex and how dynamic the pattern is perceived to be.

A sample dynamic current steering sequence, using three virtual electrodes in between each real pair of electrodes, would consist of electrode 1 stimulation at 100% current, followed by electrode 1 stimulation at 80% current and electrode 2 stimulation at 50% current (creating a virtual electrode near electrode 1), then electrode 1 stimulation at 70% current and electrode 2 stimulation at 70% current (creating a virtual electrode midway between electrodes 1 and 2), then electrode 1 stimulation at 50% and electrode 2 stimulation at 80% (creating a virtual electrode near electrode 2), and then electrode 2 stimulation at 100% current, and so forth throughout the remainder of the sequence.

Dynamic current steering (bipolar)

In bipolar dynamic current steering sequences, virtual electrodes were generated by using bipolar stimulation between two electrodes in the sequence. A typical bipolar dynamic current steering sequence would begin with monopolar stimulation of electrode 1 alone, followed by bipolar stimulation between electrode 1 and 2, and then monopolar stimulation of electrode 2 alone, etc., throughout the remainder of the sequence.

Dynamic stimulation sequences used

Sighted participant YBN: Dynamic stimulation sequences were used with a current range of 1.2-1.5 mA per electrode. Each electrode was stimulated for a duration of 50 ms with a gap interval between successive electrodes of 50 ms.

Sighted participant YAY: Bipolar dynamic current steering sequences were used with a current range of 0.7-1.5 mA per electrode. The stimulation duration for each real or virtual electrode was 200 ms and the gap interval between electrodes was 125 ms.

Sighted participant YBH: Dynamic sequences were used with a current range of 2.0-3.0 mA. The stimulation duration for each electrode was 50 ms and the gap interval between electrodes was 10 ms.

Blind participant BAA: Dynamic stimulation sequences were used with all electrodes stimulated at 2.0 mA. The stimulation duration for each electrode was 200 ms and the gap interval between electrodes was 2000 ms. The long gap interval on this participant was due to limitations of the control system for the implanted device.

Blind participant 03-281: At each testing session, current values were determined for the electrodes under investigation. For the first electrode (F10), a stimulation pulse of 120 Hz pulse frequency with 100 ms pulse train duration (biphasic, symmetric, cathodal first) was delivered at low current. The current was gradually increased until the participant reported a clearly visible and distinct phosphene. This current value was used as the baseline current for all testing for electrode F10. This procedure was repeated for all electrodes used in the pattern sequence. For each electrode being calibrated, the participant was asked if the phosphene was of approximately equivalent brightness as the previous electrode; if it was dimmer, the current was increased until the brightness was equated. At higher currents, the participant reported that the brightness saturated and the phosphene increased in size. If this phenomenon was observed, the current was reduced to a value that produced a phosphene of equivalent brightness without an increase in size. Currents ranged between 3.5 and 7.5 mA per electrode.

Behavioral Tests in Participants with Implanted Electrodes

To assess the participants' ability to make perceptual discriminations between different electrical stimulation sequences we used a forced choice discrimination task. Before discrimination testing, the participants drew the perceived pattern on the touchscreen several times and they were instructed to associate a particular letter with each stimulation sequence. During each trial of the discrimination task, a single sequence was presented while the participant fixated, or attended to, a defined place on the touchscreen, and then the participants gave a verbal report to indicate which of the sequences they had perceived. Sequences were presented in pseudo-random order. The statistical significance of the accuracy values was obtained using the binom.test() function in "R".

In the blind participants, we used multidimensional scaling (MDS) to assess the reliability of differences between the percepts elicited by different electrical stimulation sequences. For participant BAA, one of seven stimulation sequences was presented on each trial corresponding to one of 7 forms (G, N, R, U, V, W, Z; electrodes shown in Figure 5D). Each shape was repeated 4 times for a total of 28 trials. For each trial, the drawing made by the participant on the touchscreen was converted into an ordered set of hundreds of evenly spaced circles using Adobe Illustrator. The x and y location of the center of each circle, and hence each point in the original drawing, was then obtained using the regionprops() function in Matlab. The list of coordinates corresponding to each trial was resampled to obtain exactly 100 points and a correlation matrix 28 x 28 in size was created by obtaining the correlation between the ordered list of x, y points from each trial, and the ordered list of points from every other trial, using the corr2() function in Matlab. The correlation matrix was used as input to Matlab code that performed the MDS analysis. For

participant 03-281, a similar analysis was performed, except that only four different stimulation sequences were tested (W, N, M, U; electrodes shown in Figure 6D).

In participant 03-281, two experiments examined the rate at which forms could be delivered using dynamic stimulation. In the first experiment, two stimulation sequences were tested in which four electrodes were successively stimulated for 50 ms each (no gap between successive electrodes), producing a total sequence time of 200 ms. In the first sequence, the electrodes were stimulated in an order from the highest to the lowest in the visual field, producing the percept of a line drawn in a downward direction (electrode order F10, E07, C06, B10; see Figure 6C for individual phosphene locations). In the second sequence, the electrodes were stimulated in the reverse order, producing the percept of a line drawn in an upward direction. All stimulation was delivered at 120 Hz and the current for each electrode was F10, 6.0 mA; E07, 6.5 mA; C06, 6.5 mA; B10, 6.5 mA. Following each 200 ms sequence, there was a 500 ms response window during which the participant verbally reported his percept ("down" or "up").

In the second experiment, three sequences were tested in which four electrodes were successively stimulated for 100 ms with a 100 ms gap between successive electrodes for a total sequence time of 700 ms. In the first sequence, the electrodes were stimulated to produce the percept of a "C" shape (electrode order F01, F10, B10, C04; see Figure 6C for individual phosphene locations). In the second sequence, the electrodes were stimulated to produce the percept of a "U" shape (F10, B10, C04, F01). For the third sequence, the percept was a backwards "C" (B10, C04, F01, F10). All stimulation was delivered at 120 Hz and the current for each electrode was B10, 7.0 mA; C04, 7.0 mA; F01, 6.5 mA; F10, 6.5 mA. Following each 700 ms sequence, there was a 1300 ms response window during which the participant verbally reported the percept.

Additional Resources

Blind participant 03-281 was tested under the auspices of a clinical trial entitled "Early Feasibility Study of the Orion Visual Cortical Prosthesis System" (NCT03344848).