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New methods devised specify the size and color of the spots monkeys see when striate cortex (area V1) is electrically stimulated

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Creating a prosthetic device for the blind is a central future task. Our research examines the feasibility of producing a prosthetic device based on electrical stimulation of primary visual cortex (area V1), an area that remains intact for many years after loss of vision attributable to damage to the eyes. As an initial step in this effort, we believe that the research should be carried out in animals, as it has been in the creation of the highly successful cochlear implant. We chose the rhesus monkey, whose visual system is similar to that of man. We trained monkeys on two tasks to assess the size, contrast, and color of the percepts created when single sites in area V1 are stimulated through microelectrodes. Here, we report that electrical stimulation within the central 5° of the visual field representation creates a small spot that is between 9 and 26 min of arc in diameter and has a contrast ranging between 2.6% and 10%. The dot generated by the stimulation in the majority of cases was darker than the background viewed by the animal and was composed of a variety of low-contrast colors. These findings can be used as inputs to models of electrical stimulation in area V1. On the basis of these findings, we derive what kinds of images would be expected when implanted arrays of electrodes are stimulated through a camera attached to the head whose images are converted into electrical stimulation using appropriate algorithms.

electrical brain stimulation | prosthetics | perception

A major task in ameliorating the plight of the blind is to create a prosthetic device to reinstate vision. Several different approaches are now underway to accomplish this aim (1). One promising procedure is to convert visual signals through a camera and a computer system for the electrical stimulation of primary visual cortex (area V1), which remains intact even many years after vision is lost, most commonly, as a result of damage to the eyes (2–6). To succeed in this endeavor, we advocate that the initial research be carried out in animals (7, 8). Area V1 in the rhesus monkey is a promising region for this effort. It occupies a large area in the brain. The visual field is laid out in an orderly fashion, and the neurons have well-defined small receptive fields (9). The organization of area V1 in monkeys is very similar to that in humans (10).

An early step in this research is to determine what monkeys see when area V1 is electrically stimulated at individual sites, a line of research that is built on the classic experiments done in both blind and sighted humans showing that electrical stimulation of area V1 evokes a star-like image that is typically punctate and circular, dim, whitish or colored, and stationary with respect to the eyes, and whose size increases as stimulations are delivered to more peripheral representations of the visual field in area V1 (2–4, 6, 11–14). These properties remain many years after blindness has occurred (2, 3, 6), although there is some suggestion that colored phosphenes are more readily evoked in sighted subjects (4).

The initial experiments carried out by Robert Doty and his colleagues (15–18) on monkeys established beyond a doubt that monkeys can detect electricity delivered to area V1 (19–27). These experiments also established that similar groups of neurons in area V1 are activated in both monkeys and humans for the generation of phosphenes (16, 19, 23). What remains unanswered

is what the visual characteristics are of phosphenes evoked from monkey area V1. We have developed two previously undescribed behavioral paradigms to address this question: one to assess the size and brightness of evoked phosphenes and another to determine the internal characteristics of the phosphenes, such as contrast polarity and color.

Results

The conventions we used for specifying the visual field and its cortical representation in the monkey are shown in Fig. 1. The nasal retina of the left eye and the temporal retina of the right eye, which receive input from the left visual field (shown in blue; Fig. 1, *Upper*) send projections to the right lateral geniculate nucleus (LGN), whose neurons, in turn, project to area V1 of the right cortical hemisphere. Conversely, the temporal retina of the left eye and the nasal retina of the right eye, which receive input from the right visual field (shown in black; Fig. 1, *Upper*) send projections to the left LGN, whose neurons, in turn, project to area V1 of the left cortical hemisphere. The topographical layout of the visual field for the central 7° to 8° is shown in the posterior view of the monkey brain in the lower portion of Fig. 1. The layout of the central 5° of the visual field is shown in the overlay with red lines. This region in the monkey brain is largely lissencephalic and is located right below the skull, thereby allowing for easy and accurate access for electrode placement.

Table S1 provides a distribution of the receptive field locations of the stimulated neurons in two monkeys in which a total of 130 sites were stimulated successfully. Table S2 provides the distribution of depths in the cortex at which electrical stimulation was administered.

During experimental sessions in which we performed electrical stimulation, a microelectrode was inserted into area V1. Recordings were made to map out the location of the receptive field at the tip of the electrode while the monkey maintained fixation on a small spot in the center of the computer monitor that the animal was facing (19, 25, 28, 29). We then performed electrical stimulation to establish effective thresholds for eliciting saccadic eye movements that shifted the center of gaze from the fixation spot into the receptive field location of the stimulated neurons. Electrical stimulation was applied at 200 Hz for 80–130 ms using biphasic pulses with a duration of 0.2 ms at a current of 15–160 μ A. We then proceeded to determine what percept the electrical stimulation creates by testing the monkeys with two tasks on which they had been extensively trained.

In the first task, two visual targets were presented (the two-target task), one of which was varied either in contrast or in size. The monkeys had been trained to make a saccadic eye movement

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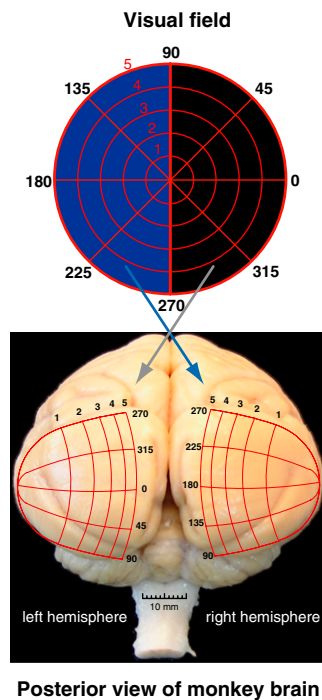


Fig. 1. Topographic layout of the visual field representation for the central 5° of the visual field in the monkey striate cortex (area V1). (Upper) Central 5° of the visual field. (Lower) Posterior view of the rhesus monkey brain. The overlay in red depicts the central 5° of visual field representation. Images from the left half of the visual field, shown in blue, impinge on the nasal retina of the left eye and the temporal retina of the right eye. The retinal ganglion cells from these regions project to the right LGN, whose neurons project to area V1 of the right cortical hemisphere. Conversely, the images from the right half of the visual field, shown in black, impinge on the temporal retina of the left eye and the nasal retina of the right eye. The retinal ganglion cells from these regions project to the left LGN, whose neurons project to area V1 of the left cortical hemisphere.

to the target that had either a higher contrast or was larger in size than the other target. Fig. 2A and B shows data obtained using these procedures. As shown in Fig. 2A, *Inset*, the lower target contrast or size was kept constant; the contrast or size of the upper target was varied from trial to trial. The data show that when the two targets are identical, the monkey's performance is at chance. To assess the contrast and size of the percept created by electrical stimulation, we then paired the electrical stimulation with a single visual target whose contrast or size was systematically varied. Fig. 2C shows data obtained at three current levels using various contrasts, and Fig. 2D shows data obtained by varying size. The 50% crossover point represents equivalence in the percept created by the electrical stimulation and the simultaneously presented visual target. The black arrows projected to the abscissae specify the points of equivalence. Varying current levels produced relatively small changes in the contrast and size of the percept. Fig. 2E and F plots the equivalence points for contrast and for size at 42 and 30 sites, respectively. The overall variability was quite small, with contrast ranging between 2.6% and 10% and size ranging between 9 and 26 min of visual angle for the data we had gathered at eccentricities between 1.8° and 4.2°.

The purpose of the second task was to assess the sign of contrast and the color composition of the visual percept created by the electrical stimulation (the shifted background task). To accomplish this, following fixation, the entire background of the display was changed just before the appearance of a visual target or the electrical stimulation. The background shift was varied in magnitude, in sign of contrast, and in color. When the background shift had the same color and contrast value as the visual target, the

target was not visible and the monkey did not generate a saccadic eye movement. The color and the contrast of the shifted background were varied systematically until a saccadic eye movement was no longer evoked. Fig. 3A shows the percent correct data from two monkeys when visual stimuli were used. Performance dropped to near 0% when the background shift value was the same as the composition of the target. We then proceeded to use the same method when electrical stimulation was applied on some of the trials instead of a visual stimulus. The sign of contrast and the color of the background were systematically varied until the electrical stimulation failed to elicit a saccadic eye movement to the receptive field site of the stimulated neurons. We considered performance at or below 20% correct to be attributable to a block of the percept created by the electrical stimulation; we obtained such blocks at 77 sites. Surprisingly, the best blocks at 65 of these sites were obtained with background shifts that were dimmer than the initial background; at 12 sites, the best blocks were obtained with background shifts that were brighter than the initial background. Thus, we infer that the electrical stimulation produced a small spot that was dimmer than the background 84% of the time and brighter than the background 16% of the time.

We then systematically varied the color of the background shift as defined on the International Commission on Illumination (CIE) 1931 chromaticity diagram (Fig. 4). Fig. 3B shows data obtained with six different background shifts at one site; the background shift having a value of 0.304/0.206 on the CIE chromaticity diagram produced a full block. Fig. 3C provides eight examples of the composition of percepts created by the electrical stimulation. Detailed data of the color values of the blocks we obtained are shown in Table S3 and Fig. 4. Table S3 shows the distribution of the color values that blocked the percept of the phosphene generated by electrical stimulation. There were 77 stimulation sites at which full blocks were obtained. Fig. 4 provides a summary view of these blocks on the CIE chromaticity diagram for 26 of the 77 blocks we obtained, which are marked with black circles. For the sake of clarity, only nonoverlapping circles are shown from our sample. Within the area of the blue oval, there were 65 blocked points (84% of the total), of which 13 nonoverlapping circled points are shown. The dotted white oval shows the area within which 97.4% of the blocked values fell. Thus, at most sites stimulated in area V1, the visual stimulus created by the electrical stimulation appears to produce relatively unsaturated colors.

The effectiveness with which electrical stimulation of neurons in area V1 elicited a saccadic eye movement into their receptive fields was also examined using three steady background levels. The results obtained lend further support to the finding that in most cases, the electrical stimulation in our monkeys created the percept of a small spot that was darker than the background. Three background levels were used: 0.1, 10.5, and 43.9 cd/m². In the two monkeys, 73 sites were studied using these procedures. For monkey H, the percent correct performance under the 0.1-, 10.5-, and 43.9-cd/m² background level conditions for the electrical stimulation was 25% (SEM = 1.6%), 90% (SEM = 1.1%), and 95% (SEM = 0.79%), respectively; the mean latencies were 330 ms (SEM = 2.1), 243 ms (SEM = 1.1), and 210 ms (SEM = 1.0), respectively. For monkey C, the percent correct performance under the 0.1-, 10.5-, and 43.9-cd/m² background level conditions for the electrical stimulation was 7.5% (SEM = 1.7%), 71% (SEM = 2.7%), and 76% (SEM = 2.5%), respectively; the mean latencies were 365 ms (SEM = 4.7), 302 ms (SEM = 5.0), and 289 ms (SEM = 4.3), respectively. For monkey H, the overall performance on trials when a visual target was presented was over 94%; the latencies ranged between 158 and 182 ms. The differences in percent correct and latencies for the electrical stimulation at the three background levels were statistically significant beyond the $P = 0.001$ level.

Discussion

We draw the following inferences from our study. Electrical stimulation of area V1 in the monkey using currents between 15 and 160 μ A within a range of 1.8° and 4.7° of eccentricity creates

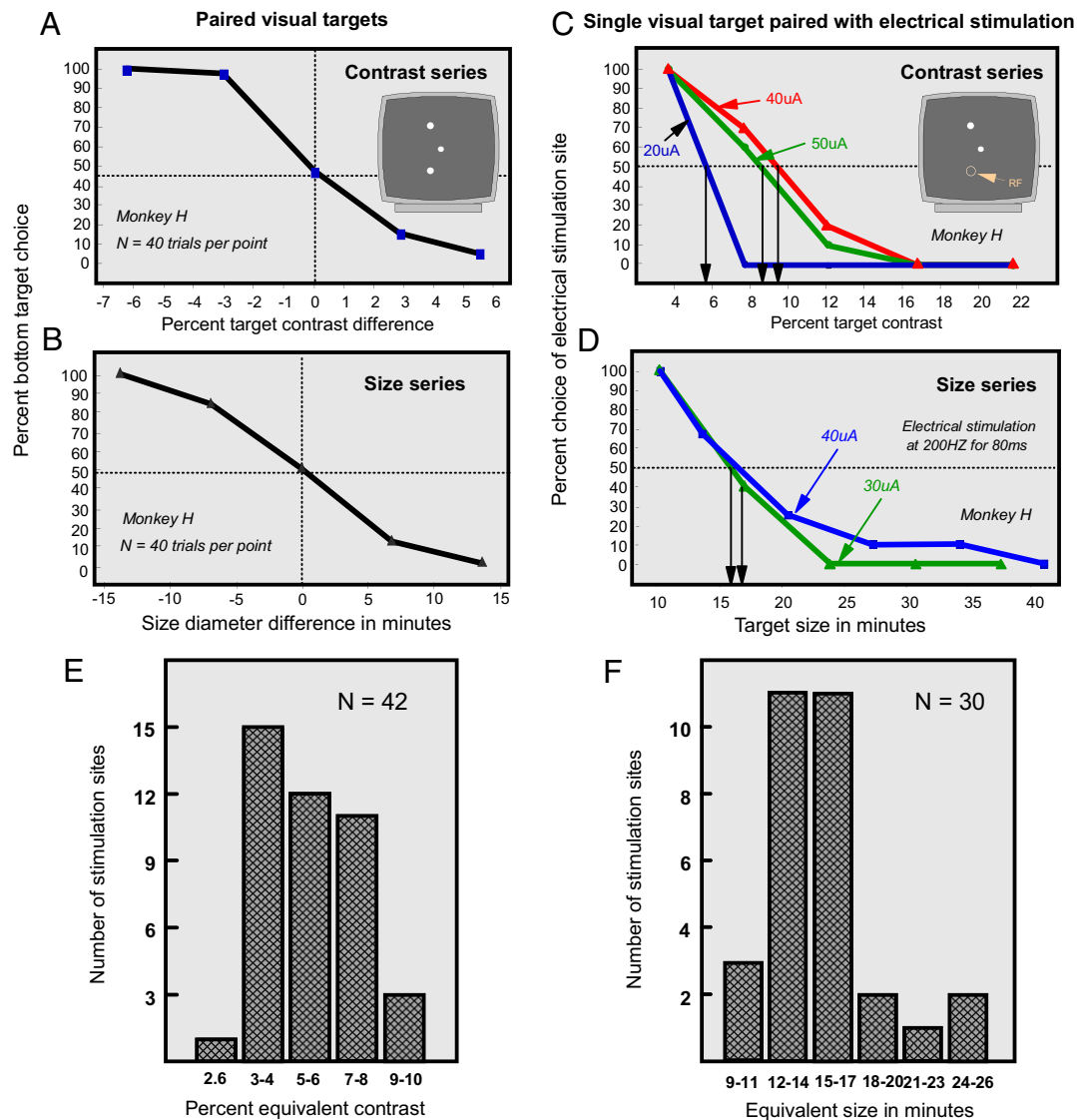


Fig. 2. Contrast and size of percepts created by electrical stimulation of area V1 using the paired target task. (A and B) Percent choice of lower target when two visual targets are presented and the contrast or size of the upper target is varied. (C and D) Percent choice of the receptive field location of the neurons electrically stimulated as a function of the contrast and size of the visual stimulus in the upper field and the current levels used. Vertical arrows mark the 50% crossover point representing stimulus equivalence. (E) Distributions for equivalent contrasts obtained at 42 sites. (F) Distributions for equivalent sizes in minutes of arc from 30 sites.

a small spot ranging between 2.6% and 10% in contrast and 9–26 min of arc in spot diameter. For 84% of the sites examined, the percept created by the electrical stimulation was dimmer than the background, and for 16% of the sites, it was brighter. The internal composition of the percept created by the electrical stimulation consisted of relatively washed-out color images. These results concur with those reported for humans in that electrically evoked phosphenes from area V1 are punctate and dull and often exhibit colors (2–4, 6, 13, 30). Contrary to our findings, the evoked phosphenes in humans are typically brighter than background (30).

In our goal to create a prosthetic device using implanted arrays of electrodes to stimulate area V1, we have previously argued that the most effective way to accomplish this is to use a proportional array that minimizes the number of electrodes needed to achieve reasonable acuity (1). Fig. S1A shows schematically how 256 dots presented in the visual field activate the neurons in monkey area V1 within an eccentricity of 4°, where the cortical surface is lissencephalic. Fig. S1B shows the size and location of the visual percepts created when these 256 sites, with 128 in each hemi-

sphere, are stimulated simultaneously. Because of the proportional array, the spatial arrangement is preserved, but the size of the spots created increases with increasing eccentricity because of the increase in receptive field size (1). Fig. S1C schematizes a camera that views a square. The image from the camera is subdivided into 256 square sections, each of which, through a computer system, is connected with one electrode in monkey area V1. Each square section is connected with the appropriate corresponding electrode. Each electrode is selectively activated only when there is a luminance change within the appropriate little square section. The electrodes activated through the camera by the square are shown in red. Fig. S1D and E demonstrates a detailed approximation of the percepts created when a square or a circle with a diameter of 1° is presented to the camera centered on the display. By increasing the number of electrodes in the array to 448, with 192 added within the central 2° visual angle representation, acuity can be doubled. Were one to use an evenly spaced array, equivalent acuity would necessitate 1,220 electrodes.

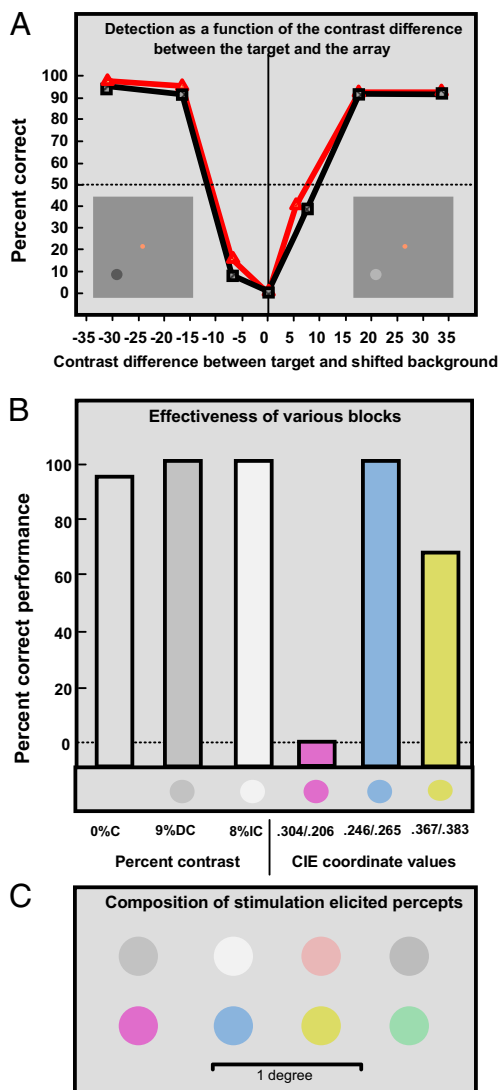


Fig. 3. Blocking the perception of visual stimuli and electrical stimulation with background shifts. (A) Percent correct choices of single targets in two monkeys as a function of the composition of the shifted background. When the background and the target compositions were identical, the monkeys failed to perceive the target. (B) Sample of percent of saccadic eye movements made into the receptive field of the stimulated neurons using six different background shifts. Perception was blocked with a background shift of CIE 0.304/0.206. The shift values used are shown by the disks along the x axes. DC, decreased contrast; IC, increased contrast. (C) Sample of eight color and contrast values yielding blocks obtained at eight different sites.

Numerous brain areas other than area V1 have been advocated as possible targets for a prosthetic device. These include the LGN, the superior colliculus (SC), and several extrastriate areas (21, 31, 32). The LGN, although a beautiful and topographically laid out area, is quite small and resides in the thalamus, deep in the brain (32).

In species lower on the mammalian phylogenetic scale, the SC is the prime center for visual processing. In higher mammals, as a result of encephalization, visual analysis has become relegated predominantly to the cortex; the SC is under the control of the cortex. The cortex receives its visual input from the retina predominantly through the LGN. Ablation of the LGN renders monkeys virtually blind, indicating that the SC in higher mammals plays a minimal role in direct visual processing (33, 34).

The direct input to the SC from the retina is predominantly from a special class of retinal ganglion cells often termed W cells (35). The cells projecting from the layer 5 cells of the striate cortex

to the SC are driven selectively by the parasol cells that originate in the retina (36). Consequently, in higher mammals, there is limited input to the SC from the retinal midget cells that process fine detail and color (37). In line with this is the finding by Tasker et al. (38) that phosphenes evoked from the SC are colorless white spots.

The generation of saccadic eye movements involves extensive processing in the brain accomplished by interactions between excitatory and inhibitory circuits (33). Eye movements made under normal conditions occur in a visual environment with many objects. Thus, numerous stimuli impinge on the retina after each saccadic eye movement, one of which then has to be chosen as the next target to which the center of gaze is shifted. Such areas as the SC and the frontal eye fields (FEFs) are closely linked to the execution of saccadic eye movements (39, 40). Stimulation in these areas elicits saccades with very short latencies (20–30 ms) and can do so at very low current levels (1–20 μ A) (33, 34, 41). That the FEFs and the SC are closely linked to motor execution is exemplified by the fact that when two sites are stimulated simultaneously, with each generating a different magnitude and direction saccade when singly stimulated, the paired stimulation elicits a vector-averaged saccadic eye movement (33, 34, 41). Thus, these areas send signals to the brainstem oculomotor centers after a choice has been made as to which visual stimulus in the visual scene the center of gaze should be shifted. By contrast, in area V1, electrical stimulation elicits saccades with longer latencies, somewhat higher currents are needed, and, significantly, paired electrical stimulation does not generate vector-averaged saccades, indicating that the decision processes involved in target selection occur in other brain areas before the signals that are sent to the SC and/or the FEFs, which, in turn, then activate the brainstem oculomotor centers (33, 34). The decision processes involved, of which we are mostly unaware, are complex and require the identification of objects in the visual scene as well as the calculation of their spatial location. It should be acknowledged, however, that dissociating sensory and motor influences unequivocally in areas involved in vision and eye movement control is difficult to accomplish and requires careful assessment.

Studies have also examined the effects of stimulating extrastriate areas in both humans and monkeys (15, 21, 30, 42–45). Although the characteristics of the phosphenes evoked from these areas have been described for humans (e.g., from white, black, or colored spots to moving patterns), such characteristics have yet to be investigated in monkeys. Our behavioral paradigms could be used in such an endeavor to accelerate further the development of a cortical visual prosthesis for the blind.

Regarding the stability of the evoked phosphene, Dobelle et al. (4) found that the phosphene map for area V1 appeared stable for 2 decades in the blind patient under study when the same parameters of stimulation were used. When there is instability, it is likely related to the movement of the implant or attributable to changes in the degree of blindness of the patient (i.e., degree of neural degeneration). The movement of an implant or change in the degree of blindness is not an issue in our experiments, given that only one penetration site (perpendicular to the cortical surface) was studied per experimental session and our monkeys had intact vision.

Studies have revealed that electrical stimulation of area V1 in blind humans evokes fewer colored phosphenes than in intact individuals (4). Although the size and internal composition of phosphenes have not been previously studied in monkeys, a modest lowering in detection thresholds in blind monkeys has been reported (16). To assess changes that may arise in the size and composition of phosphenes created by electrical stimulation of area V1 in blind monkeys, the most reliable approach will be to make restricted retinal lesions that allow concurrent comparisons of the effects of electrical stimulation at intact and deafferented area V1 sites in the same animal (29).

Electrical stimulation studies in somatosensory cortex, which have revealed several similarities to those obtained by stimulating the visual cortex, may prove to be useful in the quest for creating a prosthetic device for the blind (48–50). Numerous

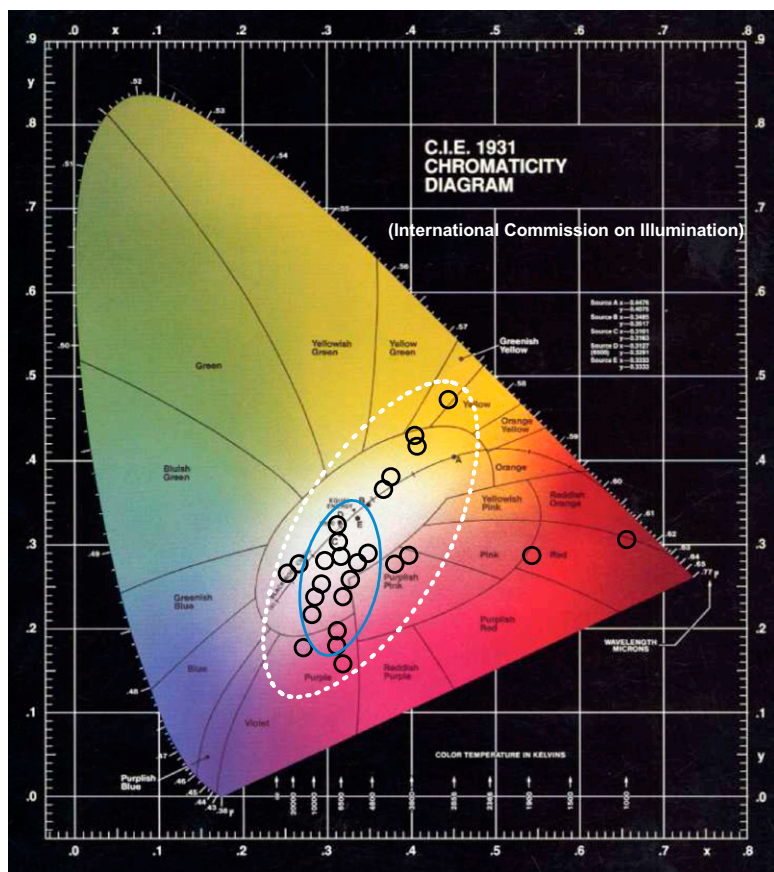


Fig. 4. Distribution of the percepts created by electrical stimulation on the CIE chromaticity diagram. The small circles show the blocked values, of which 26 nonoverlapping points are shown in the diagram. Within the blue oval, a total of 65 blocks were obtained, of which 13 are shown that do not overlap. Overall, we obtained blocks at 77 sites, of which 97.4% fall within the dotted white oval.

neural network models have been proposed to explain inherent features of area V1. Electrical stimulation studies like ours may prove useful in testing and calibrating these models (1, 51).

Materials and Methods

The two monkeys (H and C) we used in the experiments were trained on the behavioral tasks for many months. After this training, we began the experiments in which electrical stimulation was applied, typically once a week. During other days of the week, we continued training, using only visual stimuli. The data were collected over a period of more than 2 y. Monkeys ran between 1,000 and 3,000 trials during each experimental session.

Surgical Procedures. While under anesthesia, a head post and an eye coil were implanted. After extensive behavioral training, a well was implanted in the right hemisphere through which we were able to insert platinum iridium microelectrodes for recording neuronal activity and for electrical stimulation (46, 47). During the experimental sessions, each animal was seated in a monkey chair and faced a color monitor placed at a distance of 57 cm from the eye, whereby an extent of 1 cm on the screen equals 1° of visual angle.

All surgical procedures were carried out in accordance with the National Institutes of Health (NIH)-approved guidelines of the Department of Comparative Medicine at Massachusetts Institute of Technology as specified in the NIH *Guide for the Care and Use of Laboratory Animals* (52).

Receptive Field Mapping. After inserting a microelectrode into area V1, the receptive field location of the neurons at the tip of the electrode was mapped out by moving a bar of light of various sizes and orientations across the visual field while the animal maintained fixation on a central fixation spot (47). On each trial, the bar was swept across the visual field in one direction, after which a red dot appeared in one of four locations. A saccadic eye movement made to this dot was rewarded with a drop of apple juice. The evoked potentials were amplified through an audio system; listening to the sounds created by the action potentials when the bar of light moved in the visual field enabled us to map out receptive field locations accurately.

Behavioral Procedures. To establish the visual percept created by the electrical stimulation, monkeys were trained on two basic behavioral tasks.

Two-target task. In the initial training, two visual targets were presented. One of the targets, typically the one in the lower field, was kept constant in contrast and size; the contrast or size of the other target was systematically varied. The animals were trained to select the higher contrast or larger target by making a saccadic eye movement to it. To accomplish this, a reward was provided only when the monkey made a saccadic eye movement to the higher contrast or the larger of the two targets. By systematically varying the contrast or size of one of the targets, we could generate psychometric functions as depicted in Fig. 2 *A* and *B*, which shows that when the two visual targets were identical, they were chosen with equal probability. Subsequently, electrical stimulation was paired with the appearance of a single visual target whose contrast or size was systematically varied. The monkey was rewarded for making a saccadic eye movement to either the visual target or the location of the phosphene induced by the electrical stimulation. The contrast or size at which the monkeys selected the visual target and the electrically induced percept with equal probability (50% choice of each target) was presumed to represent the contrast and size of the evoked phosphene. During repeated testing for the contrast series, the size of the visual stimulus was set to be equivalent to the size of the percept created by the electrical stimulation; for the size series, the contrast was set to equal that created by the electrical stimulation. Contrast was calculated using the formula $\text{Contrast} = (\text{luminance 1} - \text{luminance 2}) / (\text{luminance 1} + \text{luminance 2}) \times 100$, thereby yielding a percent contrast value. The background illumination level was constant at 10.5 cd/m^2 .

Shifted background task. The purpose of this task was to determine what the composition is of the visual percept elicited by electrical stimulation. To accomplish this, the luminance and/or color of the entire background was shifted either before the presentation of a visual stimulus or before electrical stimulation. The contrast and color composition of the shifted background was systematically varied until the monkey failed to perceive the visual stimulus or the percept created by the electrical stimulation. The initial background level, as before, was 10.5 cd/m^2 . The temporal delay between the background and the target onset was chosen through a series of earlier tests; for visual targets, the background shift was initiated 130 ms before the

target onset, and for electrical stimulation, it was initiated 100 ms before stimulation onset. The 30-ms difference is attributable to the fact that it takes ~30 ms for the neural activity generated by the photoreceptors to reach area V1 through the cascade of neurons in the retina and the LGN. When visual stimuli were used, their perception was blocked, as expected, when the composition of the shift and the target were identical. This is shown in Fig. 2 A and B, establishing that the performance on this task was excellent. For the electrical stimulation, the shift in the background was varied systematically using contrast levels near those established with the two-target task but, in addition, by varying the color composition of the shifted background. This was done repeatedly by systematically varying the contrast and color parameters until a saccade was no longer generated to the target location or the receptive field site of the stimulated neurons, thereby indicating that perception was successfully blocked. We can infer, therefore, that the shifted background value at which the block was obtained is the same as the composition of the percept created by the electrical stimulation.

Electrical Stimulation Procedures. Subsequent to mapping the receptive fields of the neurons at the tip of the microelectrode, electrical stimulation was applied. Current levels were varied initially to establish the point at which saccadic eye movements could be reliably generated. The total range of current levels was between 15 and 160 μ A. One to three current levels were

used at each site for the various testing conditions. Overall, we used currents between 15 and 55 μ A in 64% of the stimulation trials and between 60 and 160 μ A 36% of the time in the entire set of experiments. The above-threshold stimulation levels we used elicited saccades that shifted the center of gaze from the fixation spot into the receptive fields of the stimulated neurons. Stimulation duration was between 80 and 130 ms using biphasic pulses at 200 Hz, with each pulse duration at 0.2 ms. The depth in area V1 gray matter where we stimulated was assessed when, at the end of each experimental session, we withdrew the electrode slowly, recording again while stimulating the receptive field area with visual stimuli to determine when neuronal activity ceased. The distribution of the depths at which electrical stimulation was applied is shown in Table S2.

The consequence of above-threshold electrical stimulation, as expected, was to generate a saccadic eye movement that shifted the center of gaze from the fixation spot into the receptive fields of the stimulated neurons. We stimulated 140 sites in the two monkeys, from which data were obtained successfully from 130 sites. The distribution of the receptive field locations is shown in Table S1.

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