What Delay Fields Tell Us About Striate Cortex

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Tehovnik EJ, Slocum WM. What delay fields tell us about striate cortex. J Neurophysiol 98: 559–576, 2007. First published June 13, 2007; doi:10.1152/jn.00285.2007. It is well known that electrical activation of striate cortex (area V1) can disrupt visual behavior. Based on this knowledge, we discovered that electrical microstimulation of V1 in macaque monkeys delays saccadic eye movements when made to visual targets located in the receptive field of the stimulated neurons. This review discusses the following issues. First, the parameters that affect the delay of saccades by microstimulation of V1 are reviewed. Second, the excitability properties of the V1 elements mediating the delay are discussed. Third, the properties that determine the size and shape of the region of visual space affected by stimulation of V1 are described. This region is called a delay field. Fourth, whether the delay effect is mainly due to a disruption of the visual signal transmitted through V1 or whether it is a disturbance of the motor signal transmitted between V1 and the brain stem saccade generator is investigated. Fifth, the properties of delay fields are used to estimate the number of elements activated directly by electrical microstimulation of macaque V1. Sixth, these properties are used to make inferences about the characteristics of visual percepts induced by such stimulation. Seventh, the disruptive effects of V1 stimulation in monkeys and humans are compared. Eighth, a cortical mechanism to account for the disruptive effects of V1 stimulation is proposed. Finally, these effects are related to normal vision.

INTRODUCTION

Electrical stimulation has been used to interrupt neuronal processes in the cerebral cortex to study both language and motor functions (Churchland and Shenoy 2007; Ojemann 1991; Penfield 1975; Penfield and Welch 1951). It has also been used to disrupt striate cortex to study visual behavior (Morell and Naitoh 1962; Schiller and Tehovnik 2001; Ward and Weiskrantz 1969).

In primates, the striate cortex (or area V1) is the first station of the visual pathway that receives an integrated visual signal from the two eyes before relaying this signal to higher cortical areas (Hubel and Wiesel 1977; Miezin et al. 1981; Trotter et al. 2004). Also this portion of neocortex contains the highest density of cortical neurons (O’Kusky and Colonnier 1982; Rockel et al. 1980), presumably to ensure that the visual scene can be analyzed at high resolution. V1 consists of neurons whose visual receptive fields are anchored to the fovea of the eyes and that respond maximally when a suitable visual target is positioned in the center of the visual receptive field (Hubel and Wiesel 1977). Electrical stimulation of V1 can evoke saccadic eye movements that terminate in the center of the visual receptive field of the stimulated neurons (Tehovnik et al. 2003a). This occurs most readily and at the lowest electrical currents (as low as 2 μA) when the stimulation is delivered while a monkey is not actively fixating a visual target (Tehovnik et al. 2003b). On the other hand, if the stimulation is delivered during active fixation the subsequent generation of a saccadic eye movement to a visual target situated in the receptive field of the stimulated neurons is delayed (Tehovnik and Slocum 2005, 2007a; Tehovnik et al. 2004, 2005b). We call the region of visual space affected by the microstimulation a delay field.

This review has the following aims: 1) to describe procedures and parameters to optimally delay saccadic eye movements by electrical microstimulation of macaque V1; 2) to assess the excitability properties of the elements mediating the delay; 3) to determine what properties within V1 determine the size and shape of a delay field; 4) to assess whether the delay effect is exclusive to the oculomotor system; 5) to use the properties of delay fields to estimate the number of elements activated directly by electrical microstimulation of V1; 6) to use these properties to study phosphenes evoked from V1; 7) to compare the disruptive effects of V1 stimulation in monkeys and humans; 8) to propose a cortical mechanism to account for the disruptive effects of V1 stimulation; and 9) to relate these effects of V1 stimulation to normal vision.

PROCEDURES NECESSARY TO DELAY SACCADES BY V1 MICROSTIMULATION

To delay visually guided saccades by microstimulating macaque V1 the following procedure is necessary (Tehovnik et al. 2004). First, a microelectrode is inserted into the gray matter of V1 (Fig. 1A, left) and the visual receptive field of the V1 cells at the electrode tip must be mapped (Fig. 1A, right). To demonstrate the delay effect, a monkey is required to generate saccadic eye movements to a visual target placed in the center of the receptive field of the cells to be stimulated at the electrode tip (Fig. 1B). The typical visual target used is 0.2° of visual angle, which corresponds to the minimal receptive-field size of cells within the operculum of macaque V1 (Dagnelie et al. 1989; Dow et al. 1981). Also the target is at 33% positive contrast (Michaelson), which makes it clearly visible to the monkey. While the monkey performs the task, electrical stimulation is delivered on 50% of trials at the end of the fixation period, immediately before the monkey generates a saccade to the visual target (Fig. 1B). The latency difference between stimulation and control trials for the visually guided saccades constitutes the primary psychophysical data for this experiment.

The following is a description of the electrical parameters that affect the delay of visually guided saccades (Tehovnik et al. 2004). Anode-first pulses (using a biphasic configuration) are more effective than cathode-first pulses for inducing a delay (Fig. 2A), and pulse frequencies between 100 and 400 Hz produce a maximal effect (Fig. 2B). These frequencies are well...
A and B). For visual targets >0.3° of visual angle the saccadic delay is negligible. Second, the current threshold to evoke a saccadic delay of fixed amount (i.e., 20 ms) is least between 1.0 and 2.25 mm below the cortical surface (Fig. 4C).

**Excitability Properties of Elements Mediating the Saccadic Delay**

Strength-duration functions can be used to assess the neuronal excitability of the directly stimulated elements mediating the saccadic delay by V1 stimulation (Tehovnik et al. 2006). In Fig. 5A, the electrical current necessary to induce a 20-ms saccadic delay (see footnote 1, cited earlier) is plotted as a function of pulse duration for ten different V1 sites to yield strength-duration functions. For all sites, the current threshold dropped with an increase in pulse duration reaching asymptote at a pulse duration of 0.6 ms. For the shortest pulse duration tested (i.e., 0.05 ms), the current threshold ranged from 34 to 174 μA and for the longest duration tested (i.e., 0.7 ms) the current threshold ranged from 4 to 50 μA.

To determine the excitability—or chronaxie—of the directly stimulated elements inducing the saccadic delay, the strength-duration functions (Fig. 5A) were normalized such that the current threshold to evoke a 20-ms delay was set to one for a pulse duration of 0.7 ms and all other thresholds were expressed as a multiple of this threshold (Fig. 5B). Power functions were fitted for every data set pertaining to a site. The chronaxie value for a site can be determined as the pulse duration at which the power function crosses two units of threshold (Fig. 5B, dotted horizontal line). The chronaxie values of the directly stimulated elements mediating the saccadic delay in V1 ranged from 0.13 to 0.24 ms. This range of values overlaps with that reported for cortical pyramidal neurons, which range from 0.1 to 0.4 ms (Asanuma et al. 1976; Stoney et al. 1968). Also the range of values overlaps with that reported for elements mediating stimulation-evoked saccades induced from V1 (0.08–0.41 ms; Tehovnik et al. 2003a). This suggests that the directly stimulated elements mediating the saccadic delay are pyramidal and similar to those that mediate saccades evoked electrically from V1. It is commonly presumed that chronaxies derived using behavioral measures reflect the current integration characteristics of the directly stimulated elements and not those of the follower cells or innervated muscles (for a review of arguments see Gallistal et al. 1981; also see Tehovnik 1987).

Another method of assessing neuronal excitability is to determine whether the polarity of the pulses differentially affects the chances of evoking a particular response. Because anode-first pulses are superior to cathode-first pulses for inducing a saccadic delay (Fig. 2A), this implies that the directly stimulated elements are composed mainly of cell bodies and terminals over axons (Armstrong et al. 1973; Clendenin et al. 1974; McIntyre and Grill 2000; Porter 1963; Ranck 1975; Ratliff 1999; Stoney et al. 1968; Tehovnik and Slocum 2003; Tehovnik et al. 2003a). Action potentials are induced by stimulation when an outward electrical current is produced at the initial segment or nodes of Ranvier of a neuron. When an electrode is in a cell-body– or terminal-rich area, an anodal

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**Fig. 1.** Methods, A, left: all electrodes (e) were lowered into striate cortex (area V1) such that they penetrated V1 perpendicular to the cortical surface. Right: receptive fields (RFs) were mapped by moving a bar of light at different orientations across the visual field as the monkey remained fixated (fix). B: for all trials, an animal fixated a spot for 600 ms (fix); otherwise, the trial was aborted and no juice reward delivered. Two types of trials were interleaved to study stimulation-evoked delays of saccades: (I) After fixation, a target (targ) was presented in the receptive field of the stimulated neurons after the extinction of the fixation spot (also see illustration at bottom right). Animal was required to generate a saccade (sacc) to the target within 500 ms to obtain a juice reward (juice). A target was positioned between 1 and 5° from the fixation spot as indicated in the illustration at the bottom right. Target was typically set at 33% positive (Michaelson) contrast (a target luminance of 153 cd/m² on a background of 76.7 cd/m²) measuring 0.2° in size. (II) After fixation, a target (targ) was presented in the receptive field of the stimulated neurons after the extinction of the fixation spot. Before the end of the fixation period, a train of electrical stimulation (stim) was delivered to the neurons. Animal was required to generate a saccade (sacc) to the target within 500 ms to obtain a juice reward (juice). For a full description of methods see Tehovnik et al. (2004).

within the range of firing frequencies of V1 cells (Gawne and Martin 2002; Nowak et al. 1995). Also, pulse trains >40 ms are sufficient to evoke a delay (Fig. 2C) and trains presented at the end of the fixation period immediately before target onset produce the greatest delay (Fig. 2D). Finally, increasing electrical current from 50 to 200 μA yields a systematic increase in the saccadic delay (Fig. 3, A–C). This is a highly robust result in that the linear increase in the delay as illustrated in Fig. 3C is based on the stimulation of 35 V1 sites performed across two different monkeys. Based on these results, we selected the following standard parameters of stimulation, unless otherwise indicated, to conduct all of the following experiments in this review: 100-ms trains of biphasic anode-first pulses delivered at a frequency of 200 Hz commencing 100 ms before the end of the fixation period (see Table 1 for a complete list of standard parameters).

Two other factors affect the saccadic delay. First, the magnitude of the saccadic delay increases with a decrease in the size of the visual target from 0.3 to 0.1° of visual angle (Fig. 4, A and B). For visual targets >0.3° of visual angle the saccadic delay is negligible. Second, the current threshold to evoke a saccadic delay of fixed amount (i.e., 20 ms) is least between 1.0 and 2.25 mm below the cortical surface (Fig. 4C).
In an earlier section, we discuss some of the parameters that affect the magnitude of the delay effect induced by electrical microstimulation of V1. This section is devoted to describing the size and shape of the region of visual field affected by stimulating V1 as monkeys generate saccadic eye movements to a target positioned within or outside of the receptive field of the stimulated neurons (Tehovnik et al. 2004, 2005b). The region within which visually guided saccades are delayed—a delay field—is determined by presenting a punctate visual target (i.e., 0.2° in diameter, 33% positive contrast) at various locations with respect to the visual receptive field of the cells being stimulated and by having the animal generate saccades to targets placed at these locations (Fig. 6, A–C). In mapping a delay field 11 target positions are typically tested, one at the center of the receptive field, six along the axis of eccentricity, and four along the arc of meridian (Fig. 6C).

Figure 6, D–I illustrates data from one stimulation site containing multiple units whose aggregate receptive-field center was at 233° of meridian and at 4.3° of eccentricity from the fovea. The maximal increase in saccadic latency due to stimulation was observed when the target was positioned at the center of the receptive field of the stimulated neurons (Fig. 6, D and E). The magnitude of the latency increase dropped as the distance between the target and receptive-field center was increased. For target eccentricities >0.5° from the receptive-field center, the stimulation became ineffective (Fig. 6D). Also for target meridian values outside of the receptive field of the stimulated neurons, the stimulation became ineffective (i.e., at 10° of meridian from the receptive-field center, which corresponds to 0.8° of visual angle from the receptive-field center) (Fig. 6E). From these data (i.e., Fig. 6, D and E), the latency difference between stimulation trials and nonstimulation trials was computed. The greatest latency difference was observed when the target was situated at the receptive-field center of the stimulated neurons (Fig. 6, F and G). Accordingly, the neurons at the stimulation site responded maximally when the visual target—i.e., the same target as used in the stimulation experiment—was flashed in the center of the visual receptive field (Fig. 6, H and I). When the target was positioned further from the receptive-field center, the decline in the neuronal response was less rapid than the drop in the effect of stimulation. This indicates that the delay effect is confined to the receptive-field area of stimulated V1 cells.

This precision shows that the size of a delay field can be measured much like the size of a visual receptive field (e.g., Dow et al. 1981). Latency-difference data (Fig. 7A) can be normalized such that the maximum latency difference at the receptive-field center is set to one and all remaining values are made to span from zero to one (Fig. 7B). The size of a delay field can be measured by noting the difference between negative and positive target eccentricities values at 50% of the peak delay (Fig. 7C; size = [0.33 – (–0.16)] deg). In Fig. 7, the size of the delay field is 0.49° of visual angle.
The size of a delay field was found to vary with the receptive-field eccentricity of the stimulated V1 cells such that the size increased as the site of stimulation within the opercularum of V1 was more distant from the foveal representation within V1 (Fig. 8A). For these experiments, a fixed electrical current of 100 μA was used and the depth of stimulation ranged from 0.9 to 2.0 mm below the cortical surface, which corresponds to the most sensitive part of V1 for the induction of the delay effect (Fig. 4C). Sites coding for a receptive-field eccentricity of 2° exhibited delay fields of 0.14° of visual angle, on average, and sites coding for an eccentricity of 4° exhibited delay fields of 0.35 of visual angle, on average (Fig. 8A). For receptive-field centers over the range of 1.8 to 4.4°, the size of the delay fields varied from a minimum of 0.1° of visual angle to a maximum of 0.55° of visual angle.

Because the average receptive-field size of single units in V1 increases with increased distance from the foveal representation (Fig. 8B, I: Hubel and Wiesel 1974; Fig. 8B, II: Dow et al. 1981), the size of a delay field might be thought to vary with the size of the visual receptive fields. However, the slope of the function for the size of delay fields across eccentricity differs from that of the function for the size of visual receptive fields (Fig. 8B, I and II). Also at the lowest eccentricities (e.g., 2°), the size of the delay fields is less than the size of the receptive fields. An alternative interpretation, which we prefer, is that the size of delay fields varies with the retinocortical magnification factor of V1 (Dow et al. 1981; Hubel and Wiesel 1974; Tootell et al. 1988b). Note that the concept of the receptive field provides a point-to-point mapping between cortical and visual space (i.e., between a neuron’s location in cortex and the center of the neuron’s receptive field). By extension, one can map a contiguous region of cortical space to a contiguous region of visual space. One therefore can map the region of current spread (in cortex) to a corresponding region in visual space (the delay field). If one assumes that the distance that current spreads effectively in V1 is invariant for a given current, regardless of the location of the stimulation in V1, this model predicts that delay-field size should increase with eccentricity due simply to the retinocortical magnification factor. If one wishes to use this model to precisely predict delay-field size, one must supply a specific mapping function between cortex and visual space. One such mapping is the complex logarithmic function offered by Schwartz (1994). Using this model, with a realistic model parameter for macaque (a = 0.3; Schwartz 1994), it is possible to calculate the size of the delay field as a function of eccentricity for a given size of current spread. For current equal to 100 μA (which corresponds to activation of V1 tissue in a region with diameter 0.75 mm; see caption of Fig. 8B), anticipated delay-field size as calculated using the Schwartz model is shown (Fig. 8B, III). Note the substantial agreement between the model and the experimental result for delay-field size (Fig. 8B, delay field at 100 μA). That is, the size of a region of current spread in V1, when mapped to visual space under reasonable assumptions, closely agrees with the size of the corresponding delay field. Certainly, the agreement is better than that between either the Schwartz model or the delay-field data, on the one hand, and receptive-field size on the other hand. Thus the change in delay-field size with the visual-field eccentricity coded by the V1 site stimulated covaries best with the retinocortical magnification factor.

What about the shape of a delay field? The shape was found to be roughly circular. Data are shown for two sites (Fig. 9) in which the size of the delay field was determined by measuring the delay effect for different target locations with respect to the center of the receptive field; i.e., along the axis of eccentricity and along the arc of meridian, which pass through the receptive-field center (see Fig. 6C). All values in the abscissa of Fig. 9 are calculated covaries best with the retinocortical magnification factor.

| Electrode type | Glass-coated platinum–iridium @ 0.3–0.6 MΩ (1 kHz) |
| Electrode depth | 1.0–2.25 mm below cortical surface |
| Stimulation type | Monopolar |
| Pulse type | Anodal-first biphasic pulses |
| Range of currents | 15–100 μA @ 0.2-ms-pulse duration per phase |
| Train duration | 100 ms |
| Pulse frequency | 200 Hz |
| Time of stimulation | 100 ms before the end of the fixation period |
| Target size | 0.2 degree of visual angle |
| Target contrast | 33% positive contrast (Michaelson) |
| Target shape | Circular |
| Target location | At the visual receptive field |

For details see Tehovnik et al. (2004) and Tehovnik and Slocum (2005).
Perhaps the delay effect is largely due to a disruption of the cascades elicited electrically from V1 (Tehovnik et al. 2003a), similar to those of elements mediating the evocation of sac-
dand largest pyramidal cells (Peters 1994). These properties are delay occur in the deepest layers of V1, which contain the
hovnik et al. 2004). Also the best sites for evoking a saccadic
site (Fig. 9) and 0.21 and 0.20°, respectively, for the second
field measured along the axis of eccentricity and along the arc
of meridian was 0.21 and 0.21 mm, respectively, for the first site (Fig. 9A) and 0.21 and 0.20°, respectively, for the second site (Fig. 9B). Similar results were found for the shape of the receptive field of the neurons at the site of stimulation (Fig. 9A: 1.2 × 0.9° multiple-unit field; Fig. 9B: 0.9 × 0.8° multiple-unit field). Because only two axes were tested for measuring the size of a delay field, off-axes distortions of the field not conforming to a circle cannot be precluded.

In conclusion, delay fields tend to be circular and exhibit sizes that increase with the eccentricity of the visual receptive field coded by the stimulated V1 cells. This size relationship can be accounted for by the retinocortical magnification factor of macaque V1.

Is the delay effect an exclusive property of the oculomotor system?

Based on chronaxie measures and the effectiveness of anode-first versus cathode-first pulses, the directly stimulated elements mediating the delay effect are composed mainly of pyramidal cell bodies and terminals rather than axons (Tehovnik et al. 2004). Also the best sites for evoking a saccadic delay occur in the deepest layers of V1, which contain the largest pyramidal cells (Peters 1994). These properties are similar to those of elements mediating the evocation of sac-
cades elicited electrically from V1 (Tehovnik et al. 2003a).

Perhaps the delay effect is largely due to a disruption of the saccadic system as the signal is transmitted between V1 and the brain stem saccade generator (Tehovnik and Slocum 2007a).

The results of the following experiments make this interpretation unlikely.

A train of electrical stimulation was delivered before or after the termination of the fixation spot as a monkey generated a saccadic eye movement to a visual target presented at the receptive-field location of the stimulated cells. When the stim-
ulation was delivered before the termination of the fixation spot, a characteristic delay field was observed: the maximal delay occurred when the target was positioned within the receptive field of the stimulated neurons and the delay diminished as the target was positioned further away from the center of the receptive field (Fig. 10, A–D, top). However, when the stimulation was delivered after the termination of the fixation spot and at the time of target onset there was no longer a delay and instead the saccadic latency was shortened appreciably (Fig. 10, A–D, bottom). Importantly, the decrease in saccadic latency did not vary systematically with the location of the visual target. Indeed, the shape of the latency curves for stimulation during the fixation period (Fig. 10, A–D, top) was different from the shape of the latency curves for stimulation at target onset (Fig. 10, A–D, bottom). If a similar mechanism were mediating both latency effects, one might have expected the curves to have a similar shape with the greatest latency difference occurring when the target was centered in the visual receptive field.

A more direct way to address the question of whether the delay effect is a property of the oculomotor system (and not the
FIG. 5. Excitability of neurons mediating the delay in visually guided saccades to a target located in the RF of the stimulated neurons. A: current threshold for inducing a 20-ms increase in latency for saccades generated to a target located at the RF of the stimulated neurons is plotted as a function of pulse duration. Each curve represents data from a different stimulation site. For all stimulation trials, anode-first pulses were used and the train duration and pulse frequency were fixed at 100 ms and 200 Hz, respectively. Target used was brighter than background at 33% contrast (Michaelson) and was 0.2° in diameter. For other details see Fig. 1. B: normalized threshold current based on the data in A is plotted as a function of pulse duration using power functions. For a pulse duration of 0.7 ms, the current required to induce a 20-ms latency shift is set to one and all other values are expressed as a multiple of the current used at the 0.7-ms pulse duration. For normalized data making up a power function, the R² values were always >0.8. Pulse duration at which a curve intersects 2 units of threshold (designated by the dotted horizontal line) indicates the chronaxie of the stimulated elements at a site of study. [Data from Tehovnik et al. (2004).]

In conclusion, microstimulation of V1 delays not only saccades generated to targets located in the receptive field of stimulated cells, but it also delays the execution of manual responses made to such targets. This suggests that the delay of saccades induced by microstimulation of V1 is mainly due to a disruption of the visual signal at the level of V1.

Behavioral methods have been used to deduce how far electric current spreads in neural tissue, and these methods have yielded estimates that correspond to those derived from single-cell recordings (Fouriezos and Wise 1984; Milner and Lafarriere 1986; Olds 1958; Tehovnik et al. 2006; Yeomans et al. 1986). The advantage of using behavioral methods to study current spread is that the spread properties are based on the neurons that participate in the evocation of the behavior under study and not on neurons that just happen to be activated by the stimulation. As alluded to earlier (Fig. 8B), the study of delay fields can be used to provide an estimate of how far particular currents spread in V1 tissue.

The size of a delay field varies as a function of the site of stimulation in V1 as well as with the magnitude of electrical current (Fig. 13A). For stimulations of cells having receptive-field centers at 2, 3, and 4° from the fovea, the diameter of the delay field was 0.14, 0.24, and 0.35° of visual angle when using 100 μA, and was 0.09, 0.19, and 0.29° of visual angle when using 50 μA. The diameter of the visual field affected by stimulation can yield an estimate of how far the current spreads in V1 by using the retinocortical magnification factor for V1 to convert size of visual field to area of tissue responsive to that field (see caption of Fig. 13 for detailed calculation). The amount of V1 tissue activated with 50- and 100-μA current was estimated to be 0.57 and 0.74 mm², respectively. This yields a radial effective current spread of 0.29 and 0.37 mm from the electrode tip. Knowing the current and the radius of tissue activated from the electrode tip, one can use the squared relationship $I = KR^2$, where $I$ is current in μA, $K$ is the current distance constant in μA/mm², and $r$ is the radial spread of current from the electrode in mm] to calculate the current–distance constant from which current spread can be estimated for a range of currents (for complete details see Tehovnik et al. 2006; also see Tehovnik 1996). The average current–distance constant of the activated elements in V1 is estimated to be 675 μA/mm² [$K = \{50 \mu A/(0.286 mm)^2 + 100 \mu A/(0.368 mm)^2\}/2$]. Using this value, the distance of the effective radial spread of stimulation in V1 is plotted as a function of current ranging from 2 to 150 μA (Fig. 13B). This estimate is comparable to that reported for the activation of pyramidal fibers within neocortex, but is a fraction of that observed for the activation...
of neurons in V1 using functional magnetic resonance imaging (Tehovnik et al. 2006; Tolias et al. 2005).

Cell counts have shown that V1 of macaque monkeys contains about 120,000 neurons per mm³ of cortical tissue (Peters 1994). Because electrical currents from 2 to 150 μA are estimated to activate V1 tissue from 0.05 to 0.5 mm from the electrode tip (Fig. 13B), such currents should activate roughly from 60 to 62,000 neurons on average (calculated using the volume equation, $4/3\pi r^3$). This calculation assumes a uniform cell density through V1 and it also assumes that all the elements within the affected volume are activated by the stimulation. The number of elements activated directly might

![Diagram](http://jn.physiology.org/)

**FIG. 6.** Mapping delay fields. A: receptive fields (RFs) were mapped by moving a bar of light at different orientations across the visual field, as the monkey remained fixated (fix). B: monkey was required to generate saccadic eye movements to a target presented within or outside the RF of the cells under study. C: to map a delay field, a target was presented at various locations with respect to the center of the RF of the stimulated neurons. Target could occur from positive to negative 10° of meridian with respect to the center of the RF of the stimulated neurons and from positive to negative 2° of eccentricity with respect to the center of the RF. Target used was brighter than background at 33% contrast (Michelson) and was 0.2° in diameter. Fixation location (fix) of a monkey's center of gaze and the RF location of the stimulated neurons are indicated. For a full description of methods see Tehovnik et al. (2005b). Also see Fig. 1. Effect of stimulation on saccadic latency for different target positions at and outside of the RF of the stimulated neurons. D: latency of visually guided saccades to the target is plotted as a function of target eccentricity with respect to the RF of the stimulated neurons. A zero eccentricity along the x-axis indicates that the target and the RF center of the stimulated neurons were in register (see C). Negative values along the x-axis indicate target positions situated between the fixation position and RF center of the stimulated neurons. Positive values indicate target positions eccentric to the RF center of the stimulated neurons. Solid curve represents data from stimulation trials and the dashed curve represents data from nonstimulation trials. Stimulation was composed of 100-μA anode-first pulses (at 0.2-ms duration) delivered at 200 Hz using a 100-ms train. For other details see A–C and Fig. 1. E: latency of visually guided saccades to the target is plotted as a function of target meridian with respect to the RF of the stimulated neurons. A zero meridian value along the x-axis indicates that the target and the RF center of the stimulated neurons were in register (see C). Negative values along the x-axis indicate that the target positions had low meridian values and positive values indicate that the target positions had high meridian values. Meridian values in parentheses are in degrees of visual angle. Solid curve represents data from stimulation trials and the dashed curve represents data from nonstimulation trials. For other details see D, F: latency difference between stimulation and nonstimulation trials for the generation of visually guided saccades to the target is plotted as a function of target eccentricity with respect to the RF center of the stimulated neurons for a 100-μA current (data derived from D). See D for other details. G: latency difference between stimulation and nonstimulation trials for the generation of visually guided saccades to the target is plotted as a function of target eccentricity with respect to the RF center of the stimulated neurons for a 100-μA current (data derived from D). Meridian values in parentheses are in degrees of visual angle. See E for other details. H: net spike count of the multiple neurons activated by the target within the RF is plotted as a function of the target eccentricity at which the target used in the stimulation experiments (D and F) was flashed for 100 ms about the RF of neurons at the site of stimulation in D and F. Net spike count was determined by subtracting the spike rate of the blank trials from the spike rate of the target trials. Target used was brighter than background at 33% contrast (Michelson) and was 0.2° in diameter. For other details see D and F and A–C of figure and Fig. 1. I: net spike count of the multiple neurons activated by the target in the RF is plotted as a function of the target meridian at which the target used in the stimulation experiments (E and G) was flashed for 100 ms about the RF of neurons at the site of stimulation in D and F. Meridian values in parentheses are in degrees of visual angle. Net spike count was determined by subtracting the spike rate of the blank trials from the spike rate of the target trials. Target used was brighter than background at 33% contrast (Michelson) and was 0.2° in diameter. For other details see E and G and A–C of figure and Fig. 1. [Data from Tehovnik et al. (2005b).]
Invited Review

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Electrical stimulation of neocortex activates a sphere of tissue about the electrode tip; increasing the current increases the radius of activation (Tehovnik 1996; also see Fig. 13). Phosphenes generated using electrical currents >10 μA (and well into the milliampere range) are often described by human subjects as being featureless and circular in shape (Brindley and Lewin 1968; Dobelle and Mladejovsky 1974; Schmidt et al. 1996). Furthermore, as the electrode position is located more distant from the foveal representation of V1, the size of the phosphenes increases from a fraction of a degree when evoked at the fovea to a maximum of 3° when evoked at the most extreme eccentricities of the visual field (Brindley and

Using Delay Fields to Study Phosphenes Evoked from Macaque V1

Electrical stimulation of area V1 in humans has been found to produce a visual percepts, called a phosphene (Brindley and Lewin 1968; Dobelle and Mladejovsky 1974; Schmidt et al. 1996). There is growing evidence that similar percepts are generated by stimulation of V1 in monkeys and that microstimulation experiments on monkey V1 could accelerate the development of a cortical visual prosthesis for clinically blind humans (Bartlett et al. 2005; Bradley et al. 2005; DeYoe et al. 2005; Murphey and Maunsell 2007; Tehovnik and Slocum 2007b; Tehovnik et al. 2005a; Troyk et al. 2003).

FIG. 7. Measuring the size of a delay field. A: latency difference between stimulation and nonstimulation trials for the generation of visually guided saccades to the target is plotted as the distance of the peak delay (along the axis of eccentricity) with respect to the RF center of the stimulated neurons for a V1 site. Stimulation was composed of 100-μA anode-first pulses (at 0.2-ms duration) delivered at 200 Hz using a 100-ms train. Target used was brighter than background at 33% contrast (Michaelson) and was 0.2° in diameter. For other details see Fig. 6. B: latency data from above were normalized such that the values spanned the range from zero to one. C: size of a delay field was measured by noting the negative and positive target-eccentricity values at 50% of latency difference from peak delay (size = [0.33 – (−0.16)] deg). Size of the delay field (s) derived from the data in A is 0.49° of visual angle, which is indicated in B. [Data from Tehovnik et al. (2005b).]

FIG. 8. Size of the delay field varies with the site of stimulation within the operculum of V1. A: size of the delay field is plotted as a function of the eccentricity of the RF center of the V1 cells stimulated. Size of a field was determined using the method of Fig. 7C. A total of 41 V1 sites (located from 0.9 to 2.0 mm below the cortical surface) were studied. At each site, stimulation was composed of 100-μA anode-first pulses (at 0.2-ms duration) delivered at 200 Hz using a 100-ms train. Target used was brighter than background at 33% contrast (Michaelson) and was 0.2° in diameter. Solid curve is a regression line representing the data (r = 0.81, n = 41, P < 0.01). For other details see Fig. 6. A–C: B: relationship between average RF size (in visual-field coordinates) for macaque V1 and RF eccentricity [(I) Hubel and Wiesel 1974; (II) Dow et al. 1881] and the relationship between amount of visual field represented by activation of a 0.75-mm-diameter region of macaque V1 and RF eccentricity using the complex logarithmic function of Schwartz (1994) (III) are compared with the relationship between the size of the delay field and RF eccentricity using a 100-μA current (from A). Using the delay-field data of A, a calculation can be made of how far the 100-μA current was spreading in V1. At an eccentricity of 3°, the size of the visual field affected by the 100-μA current was 0.24° (on average). At a 3° eccentricity, 1,000 μm of V1 tissue represents about 0.32° of visual field, which is based on the retinocortical magnification factor of macaque V1 (Dow et al. 1981; Hubel and Wiesel 1974; Tootell et al. 1988b). Therefore 100 μA affects V1 tissue within 375 μm from the electrode tip (i.e., 0.24 deg/0.32 deg × 1,000 μm/2). A simplified version of the Schwartz (1994) algorithm was used to compute the function (III) in B representing the amount of visual field affected by activating a sphere of tissue with radius of 0.375 mm: visual-field size = K × E × R, where K is a constant of 0.23 deg·deg⁻¹·mm⁻¹, E (in deg) is the visual-field eccentricity coded by the stimulated cells, and R (in mm) is the radial spread of the current, i.e., 0.375 mm. [Data from Tehovnik et al. (2005b).]
At current levels \(<10\ \mu A\), phosphenes can exhibit distinct colors of red, yellow, or blue (Schmidt et al. 1996). It is possible that these colored phosphenes result at low currents from stimulation of small numbers of similarly tuned neurons.

It has been suggested by Troyk et al. (2003) that electrical stimulation of V1 may generate phosphenes that exhibit features (e.g., colors, oriented line segments, texture, depth). This is plausible because of the well-known tuning properties of V1 neurons (Hubel and Wiesel 1977). Presumably, elucidation of featured phosphenes would require using a current low enough to primarily excite neurons coding for that feature. For example, if a neuron is maximally responsive to a 2° red bar of light at 45° orientation, then activation of this neuron might be expected to elicit a phosphene of 2° in length, red in color, and oriented at 45°. One of the problems with this example is that even at the lowest currents used for the induction of phosphenes (e.g., 2 \(\mu A\); see Schmidt et al. 1996) several dozens of neurons can be activated (based on calculations in the previous section using delay fields) thereby producing a phosphene that contains the attributes of the entire group of neurons stimulated rather than those of an individual neuron. Nevertheless, V1 contains columns of cells spanning some 0.17 mm of tissue that code for common visual attributes such as a line orientation or a color (Hubel et al. 1978; Michael 1981). To confine current to one of these columns our current-spread estimates indicate that currents of \(\leq 5\ \mu A\) are needed. This concurs with the observations of Schmidt et al. (1996) who evoked colored phosphenes using such minute currents.

The retinocortical magnification factor of V1 and the receptive-field size of V1 cells provide clues as to how electrical microstimulation might interact with cortical tissue to elicit phosphenes. The magnification factor is commonly expressed as an inverse magnification factor, which specifies the size of the visual angle (in degrees) represented by 1 mm of cortical tissue. Figure 14A plots the inverse magnification factor as a function of visual-field eccentricity coded by macaque V1 (Dagnelie et al. 1989; Daniel and Whitteridge 1961; Dow et al. 1981; Hubel and Wiesel 1974; Talbot and Marshall 1941; Tootell et al. 1982). The inverse magnification factor increases with eccentricity, and it is 0.055/\(mm\) at an eccentricity of 0°, which represents the center of the fovea.

In a manner similar to the inverse magnification factor, the receptive-field size of V1 cells increases with visual-field eccentricity and at 0° eccentricity the average receptive-field size is approximately 0.2° of visual angle (Fig. 14B; Dagnelie et al. 1989; Dow et al. 1981; Hubel and Wiesel 1974; Schiller et al. 1976b; Van Essen et al. 1984). Given that the inverse
magnification factor and receptive-field size of cells of V1 do not change in parallel at the lowest eccentricities (i.e., the y-intercept of the function for inverse magnification factor is less than that for receptive-field size and the function for inverse magnification factor is of greater slope; Fig. 14, A and B), the receptive fields are therefore highly overlapped at the fovea as originally observed by Dow et al. (1981). As mentioned, the size of phosphenes increases as a function of visual-field eccentricity coded by the stimulated V1 neurons in humans (Brindley and Lewin 1968). The retinocortical magnification factor of V1 and receptive-field size properties of V1 neurons yield somewhat different predictions about how the size of a phosphene might change by activating different regions of V1. According to the inverse magnification factor for macaque monkeys, activation of 1 mm of cortical tissue should produce a phosphene whose size in degrees of visual angle varies with eccentricity in such a way that it conforms to the relationship shown in Fig. 14A. We estimate using delay-field data that to activate 1 mm of V1 tissue requires 169 μA (see caption of Fig. 15A for details). To activate <1 mm of V1 tissue requires some fraction of this electrical current. The field size (or putative phosphene size) produced by activating V1 at sites coding for different eccentricities of the visual field is shown for currents ranging from 3 to 169 μA (Fig. 15A). Notice that field size increases with both eccentricity and current according to estimates based on the inverse magnification factor.

If phosphenes are largely dependent on the receptive-field properties of V1 neurons, then activation of these neurons should elicit phosphenes whose size concurs with the size of the receptive field of the stimulated neurons, as illustrated in Fig. 15B, curve I (based on data of Fig. 14B). The receptive-field size puts a lower bound on the size of phosphenes evoked from V1 so that stimulation at the foveal representation should produce a phosphene no smaller than 0.2°; stimulation at a site coding for an eccentricity of 10°, for example, should produce a phosphene no smaller than 0.7°. Once suprathreshold currents are delivered to the neurons, phosphene size should increase further due to the recruitment of a larger volume of neurons.

The study of delay fields can be used to ascertain the size and shape of phosphenes evoked from macaque V1. As argued previously, the delay effect is due to a disruption of the visual signal as it is transmitted through V1—we believe this effect is a consequence of phosphene induction. Two pieces of evidence support the latter assertion. First, V1 neurons that mediate the delay effect exhibit excitability properties (see Fig. 5) that are similar to those of V1 cells in humans that mediate electrically evoked phosphenes (i.e., chronaxies ranging between 0.1 and 0.4 ms; Brindley and Lewin 1968; Dobelle and Mladejovsky 1974; Rushton and Brindley 1978). Second, during migraines associated with the activation of human V1, Grüsser (1995) as well as others (e.g., Airy 1870; Dahlem et al. 2000; Hadjikhani et al. 2001; Lashley 1941; Richards 1971) observed that a temporary scotoma is produced immediately after the evocation of a phosphene (for a review see Grüsser 1991). The size and shape of the scotoma are identical to those of the phosphene and both are anchored to the fovea, given that their positions shift with changes in gaze or with the tilting of the head. Delay fields, like the visual receptive fields of V1 neurons, are also anchored to the fovea (Tehovnik et al. 2005b). Therefore every time stimulation is delivered to macaque V1, a phosphene followed by a temporary scotoma of comparable size and shape may be experienced by the animal.
A visual target falling within such a scotoma could explain the delay effect. Indeed, we observed that decrements in target contrast <20% (Michaelson) over background produced response delays comparable to those observed after microstimulation of V1 (cf. Fig. 12, A and C). Finally, delay fields exhibit a characteristic frequently observed in scotomas (e.g., those caused by retinal damage): when the size of the visual target used to map a scotoma (or delay field) is increased, the size of the scotoma (or delay field) decreases (Tehovnik and Slocum 2007a; Timberlake et al. 1986).

We now use delay fields to make predictions about phosphenes evoked from macaque V1. The size of delay fields produced using 50 and 100 μA (I and II, respectively, of Fig. 15) overlaps with the size predictions made for the 50- and 100-μA conditions using the inverse magnification factor. Notice that the size of the delay fields is less than the lower limit predicted from size estimates based on the receptive fields of V1 cells (cf. Fig. 15A, I and II and B, I). If phosphenic induction during stimulation is responsible for the delay of visually guided saccades in macaque monkeys, then the size of the delay field (or putative phosphenic) is more closely related to properties related to the magnification factor than to the size of receptive fields. To establish further that phosphenic size covaries best with the retinocortical magnification factor (and less well with receptive-field size) other behavioral paradigms will need to be developed to study this problem in both monkeys and humans. Additionally, phosphenic size will need to be studied for stimu-
FIG. 12. Microstimulation of V1 delays visually triggered lever presses and visually guided saccade eye movements made to targets situated in the visual receptive field of the stimulated neurons. **A**: magnitude of the lever delay is plotted as a function of site of stimulation in V1 (sites 1–9). All delays are statistically significant (P < 0.01). During nonstimulation trials, the average latencies of the lever presses ranged from 312 to 357 ms (n = 9) after target onset. **B**: magnitude of the saccade delay is plotted as a function of site of stimulation in V1 (sites 1–9). These sites correspond to those represented above in **A**. All delays are statistically significant (P < 0.01). During nonstimulation trials, the average latencies of the saccadic eye movements ranged from 132 to 141 ms (n = 9) after target onset. Data from site 4 are illustrated in Fig. 11. Other details regarding data in **A** and **B** can be found in Tehovnik and Slocum (2007c). **C**: lever delay is plotted as a function of percentage contrast (Michaelson) of the left target, as indicated by the solid curve. A target was 0.2° in diameter and brighter than background (at 76.7 cd/m²). A target could occur on one of 2 locations with respect to central fixation (fix, see top panels). **Left**: 215° of meridian at an eccentricity of 3.5°. **Right**: 325° of meridian at an eccentricity of 3.5°. Lever delay was computed by taking the difference between control trials for the left target whose contrast was fixed at 33% and contrast trials for this target whose contrast was the same or <33%. Contrasts <20% (i.e., 15 to 7.5%) yielded a significant lever delay (P < 0.01). For lower contrasts the monkey typically failed to depress the lever, as indicated by ×. Each value is based on 50 control trials and 50 contrast trials. Dotted curve indicates the overall average delay for lever presses made to the right target whose control and contrast conditions were the same at 33% contrast. Because the targets were identical here, no significant delay was expected. Top 2 insets summarize the control and contrast conditions for the left and right targets. Each of 4 conditions (control/left; control/right; contrast/left; contrast/right) was randomized across trials and repeated 50 times. Animal’s performance was always >95% correct, except when the target contrast was set to 5% (here the animal depressed the lever on 4 of 50 occasions). Same monkey was used to generate the data in **A**, **B**, and **C**.

Lattions of V1 sites coding for the peripheral visual field (i.e., >20° of eccentricity). It is noteworthy that at visual-field eccentricities of 40°, for example, phosphenes tend to be <2° of visual angle (Schmidt et al. 1996), even though at these eccentricities receptive fields can be between 2 and 10° of visual angle (Van Essen et al. 1984).

The slope of the functions (I, II) of Fig. 15A is somewhat greater than that predicted from the retinocortical magnification factor for 50 and 100 µA. After doing additional experiments and analyzing delay-field data for only the deepest stimulations of V1 (i.e., from 1.5 to 2.0 mm below the cortical surface) we found that the slope of the functions conformed even better to the retinocortical magnification factor. This, along with the finding that the deepest layers of V1 are the most sensitive for producing saccadic delays (Fig. 4C), is consistent with the observation that the deepest layers of V1 are critically involved in the generation of phosphenes (Bak et al. 1990; Schmidt et al. 1996).

The functional unit for phosphen induction in V1 is most likely the hypercolumn, which is about 1 × 0.7 mm of tissue composed of layers spanning 2 mm of tissue from the surface of cortex (Fig. 15, C–E). The 1-mm axis of a hypercolumn consists of a pair of ocular-dominance columns and the 0.7-mm axis represents orientation columns coding from 0 to 180° (Hubel and Wiesel 1977). The ocular-dominance columns run perpendicular to the V1/V2 boarder, which represents the vertical meridian (LeVay et al. 1975). The retinocortical magnification factor for the vertical meridian is about 1.4-fold greater than the retinocortical magnification factor for the horizontal meridian (Tootell et al. 1982, 1988b; Van Essen et al. 1984). This ratio corresponds to the ratio between length (1 mm) and width (0.7 mm) of a hypercolumn (Blasdel and Campbell 2001). Because electrical stimulation activates a sphere of tissue of a given radius, one might expect that an evoked phosphen should be somewhat elongated parallel with the axis of the horizontal meridian. So far, delay fields—and thus the putative phosphene evoked from macaque V1—have been found to be roughly circular (Fig. 9). Phosphenes evoked from human V1 also tend to be circular, although elongated phosphene have been reported (Brindley and Lewin 1968; Dobelle and Mladjeovsky 1974; Schmidt et al. 1996).

To activate subregions of a hypercolumn, electrical currents of <100 µA are necessary (Fig. 15, C–E). To confine current to a single ocular-dominance column spanning 0.5 mm, a current of <40 µA is required. This estimate is consistent with the finding that currents of 30 µA— and as low as 3 µA— interfere with the selection and detection of visual targets presented to the eye preferentially innervated by the ocular-dominance column stimulated electrically (Slocum and Tehovnik 2004).
neural circuits (Cowey 2005). TMS over the occipital cortex of humans interferes with visual perception or induces phosphenes (Afra et al. 1998; Amassian et al. 1989; Aurora et al. 1998; Barker et al. 1985; Kammer et al. 2001; Kastner et al. 1998). The field strength necessary to interfere with the detection of a flashed punctate visual target is higher than the field strength necessary for eliciting phosphenes (Kammer 1999; Kammer et al. 2005; Kastner et al. 1998). The phosphenes are described as whitish flashes but sometimes they are colored (Afra et al. 1998; Aurora et al. 1998; Gothe et al. 2002; Kammer 1999; Kammer et al. 2001; Kastner et al. 1998). Both the interference and the phosphenes are confined to the same part of the visual field, and the part of the visual field affected by TMS roughly corresponds to the site of stimulation over V1 (Kammer 1999; Kastner et al. 1998). It is believed that the locus of activation during TMS over the occipital cortex is mainly area V1 because phosphenes could not be evoked in a patient with lesions of V1 (Cowey and Walsh 2000).

TMS delivered to the neocortex of humans is known to delay the execution of visually guided saccadic eye movements as reported by Priori et al. (1993). In their study, regions within the frontal lobes (and perhaps the parietal cortex) were activated. Interestingly, it was found that only regular saccades were affected by the stimulation, and not the short-latency saccades (called express saccades) induced by imposing a gap between the termination of the fixation spot and target onset (Fischer 1986). For regular saccades, the greatest delays occurred when TMS was delivered after the onset of the visual target, some 50 to 80 ms before the normal execution of

This section arrives at several conclusions: 1) To evoke phosphenes exhibiting features electrical currents of \( \approx 5 \) \( \mu \)A are necessary and to activate subregions of a hypercolumbar currents of \( <100 \) \( \mu \)A are required; 2) the study of delay fields can be used to infer the size and shape of phosphenes evoked from macaque V1; and 3) these studies suggest that the size of phosphenes covaries with the retinocortical magnification factor of V1.

**INTERFERENCE INDUCED BY STIMULATING HUMAN V1**

Much like electrical stimulation, transcranial magnetic stimulation (TMS) affects the brain by electrical excitation of

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**FIG. 13.** Estimating effective current spread from the size of delay fields. A: size of a delay field is plotted as a function of the eccentricity of the RF center of the V1 cells stimulated for 2 levels of current: 50 and 100 \( \mu \)A. Delay-field data points were fitted to linear functions. Parameters of stimulation were 100-ms trains of 0.2-ms anode-first pulses delivered at 200 Hz. Monkeys were required to generate saccadic eye movements to a 0.2° target at 33° positive contrast (Michaelsen) while stimulation was delivered at the end of the fixation period immediately before the presentation of the target, which could occur within or outside of the RF of the stimulated neurons (see Fig. 6C for other details). [Data from Tehovnik et al. (2006).] B: distance of effective current spread is plotted as a function of current. Function is derived from the data in A as follows: the amount of visual field affected by 50 and 100 \( \mu \)A was used to infer the amount of tissue activated at V1 sites coding for 2, 3, or 4° of visual-field eccentricity. Based on this, the amount of tissue activated in V1 was determined by noting the magnification factor for V1 sites coding for 2, 3, and 4° of visual-field eccentricity. Amount of tissue activated per current level was then used to estimate the average \( K \) (i.e., 675 \( \mu \)A/mm\(^2\)) using the current–distance equation, \( K = I/(R^2) \), where \( I \) is the current (\( \mu \)A) and \( R \) (mm) is the radial spread of current from the electrode tip. Following is a detailed calculation for the derivation of a single \( K \) value from the data in A: at an eccentricity of 3°, the size of the delay field was 0.24° using 100 \( \mu \)A. Magnification factor at this eccentricity is 0.32°/mm, on average (Dow et al. 1981; Hubel and Wiesel 1974; Tootell et al. 1988b). Therefore the estimated current spread at this V1 site is 0.375 mm [(0.24 deg · 0.32 deg \( \cdot \) mm\(^{-1}\)) × \( 1/2 \)]. Current–distance equation yields a \( K \) value of 711 \( \mu \)A/mm\(^2\) [100 \( \mu \)A/(0.375 mm)\(^2\)]. See Tehovnik et al. (2006) for complete details.

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**FIG. 14.** A: inverse magnification factor is plotted as a function of visual-field eccentricity for V1 of macaque monkeys. Data were obtained from Dagenele et al. (1989), Daniel and Whitteridge (1961), Dow et al. (1981), Hubel and Wiesel (1974), Taub and Marshall (1941), and Tootell et al. (1982). A regression line (i.e., inverse magnification factor = 0.085 × eccentricity + 0.055) was fitted to the data (\( R^2 = 0.92, n = 39 \)). B: RF size is plotted as a function of visual-field eccentricity for V1 of macaque monkeys. Data were obtained from Dagnelie et al. (1989), Dow et al. (1981), Hubel and Wiesel (1974), Schiller et al. (1976b), and Van Essen et al. (1984). A regression line (i.e., receptive-field size = 0.051 × eccentricity + 0.214) was fitted to the data (\( R^2 = 0.77, n = 24 \)). [Data from Tehovnik and Slocum (2007b).]
saccades. Recent studies have shown that TMS delivered unilaterally to area V1 of humans disrupts both visually guided saccades directed to a target positioned in the affected hemifield and visually triggered saccades directed away from a visual target positioned in the affected field (Lalli et al. 2006). These results support the notion that magnetic stimulation of V1 in humans affects visual perception rather than motor programming, which is consistent with our findings in the monkey using electrical stimulation (Figs. 11 and 12). Whether the delivery of TMS over V1 would also delay the execution of visually guided saccades and visually triggered manual responses is not known.

Finally, TMS over V1 has been used to both suppress and enhance the effects of visual masking (for review see Kammer 2006). Some believe that visual masking occurs beyond V1 (Lalli et al. 2006). It is unclear at this time just how the delay effect observed by V1 stimulation in macaques is related to visual masking.

Inhibitory Circuits Mediating the Disruptive Effects of V1 Stimulation

The delivery of a single stimulation pulse to V1 renders neurons in V1 and in the lateral geniculate nucleus unresponsive to a visual stimulus for many tens of milliseconds after eliciting an initial burst (Chung and Ferster 1998; Schiller and Malpeli 1977). The hyperpolarizing effect of electrical stimulation is believed to be mediated by GABAergic interneurons (Butovas and Schwarz 2003; Douglas and Martin 1991; Knytevič and Schwartz 1967). V1 stimulation might be delaying visually guided saccades by indirect activation of inhibitory interneurons after the direct excitation of pyramidal neurons. This idea is supported by three observations: 1) injection of the GABAergic agonist muscimol into V1 disrupts visually guided saccadic eye movements (Newsome et al. 1985; Schiller and Tehovnik 2003); 2) the excitability of the directly stimulated elements mediating the delay of saccades is similar to that of pyramidal fibers (as discussed previously); and 3) single-pulse stimulation of V1 evokes a burst of activity followed by a 100- to 200-ms period of hyperpolarization within V1 pyramidal fibers (Douglas and Martin 1991). V1 pyramidal fibers are known to innervate GABAergic interneurons (Jones et al. 1994), which are believed to hyperpolarize pyramidal fibers locally by a feedback connection (Douglas and Martin 1991).

The excitability of neurons mediating the delay of saccades coincides with that of neurons mediating phosphenes in human V1 (Brindley and Lewin 1968; Dobelle and Mladejovsky 1974; Rushton and Brindley 1978; Tehovnik et al. 2004). Therefore the delay of saccades might be a by-product of phosphene induction such that the pyramidal fibers are activated by the stimulation first (thereby producing a phosphene), followed by activation of GABAergic interneurons that inhibit the pyramidal elements thereby causing a saccadic delay. This concurs with the previously mentioned observations of Grüsser (1991, 1995) that activation of human V1 causes the evocation of a phosphene that is followed by a scotoma of comparable size and shape.

Even though we prefer the preceding explanation for the delay effect, impairment of the sodium–potassium pump of V1 neurons after their activation cannot be ruled out (Grüsser 1991; Hadjikhani et al. 2001). Such a mechanism is often associated with spreading cortical depression and epileptiform discharges. The latter, however, were never observed in our monkeys while the delay effect was being induced electrically from V1.

Are the Inhibitory Effects of V1 Stimulation Related to Vision?

It has been argued that the inhibitory inputs to simple and complex cells are engaged only once these cells have been activated and that the inhibition prevents their unabated excitation (Douglas and Martin 1991). This unabated excitation seems to occur when the GABAergic antagonist bicuculline is applied to them (Sillito 1975). This supposition concurs with
the finding that the excitatory and inhibitory inputs to simple and complex cells exhibit the same orientation tuning (Douglas et al. 1991; Ferster 1986) and that these inputs to simple cells have the same direction tuning despite differences in relative timing (Preibe and Ferster 2005). Also it has been shown that an increase in visual contrast first depolarizes a V1 cell and subsequently hyperpolarizes the cell (Tucker and Fitzpatrick 2006). The magnitude and duration of hyperpolarization is related to the magnitude of the change in contrast. This suggests that once V1 cells are activated by a particular feature of visual stimulation, inhibitory neurons can hyperpolarize the cells to prevent their reexitation. Thus the indirect activation of these inhibitory cells by pyramidal microstimulation might delay movements generated in response to the visual stimuli coded by the stimulated pyramidal cells. For such effects to be realized, however, electrical currents <10 μA would be necessary so that select groups of V1 cells coding for specific visual attributes are activated (see previous section for arguments).

On this point, we found that electrical currents between 15 and 100 μA failed to differentially delay saccades made to a punctate target varying in contrast polarity (i.e., whether the target was lighter or darker than the background; Tehovnik and Slocum 2005). According to our estimates such currents activate a radial swath of tissue from 150 to 400 μm from the electrode tip. This spatial resolution is likely too poor to selectively activate clusters of “on” or “off” cells in V1 (Habel and Livingston 1990; Schiller 1976a; Tehovnik and Slocum 2005).

OUTSTANDING ISSUES

Some questions still remain regarding the delay effect. 1) Is the delay effect a property of V1 only or can it be induced by electrically stimulating other structures? Microstimulation of V2, the lateral intraparietal area, and the prefrontal cortex has been found to disrupt visually guided saccades made to targets situated in the receptive field of the stimulated cells (Opris et al. 2005; Schiller and Tehovnik 2001). 2) Is the delay effect mediated by GABAergic interneurons? Delivering minute quantities of GABAergic drugs to V1 should affect the timing of motor responses made to visual targets presented in the affected field. 3) It has been suggested that express saccades are mediated by a pathway that projects from the retina through V1 to gain access to the superior colliculus (Schiller and Tehovnik 2001; Tehovnik et al. 2003a). If this is true, then microstimulation of V1 should delay not only regular saccades (as shown) but it should also delay express saccades. 4) Given that phosphens evoked from V1 are perceived in depth (Dobelle and Mladjeovsky 1974; Rushton and Brindley 1977; Schmidt et al. 1996), it is plausible to assume that delay fields are also represented in depth. Whether these fields are anchored to the plane of fixation or some other frame of reference is not known. 5) Can the delay effect be used to study the current spread properties of V1 stimulation delivered through multiple-electrode arrays? Effective current spread is diminished as the number of electrodes passing current is increased (Beirer and Middlebrooks 2001). Also stimulating many sites simultaneously, a requirement for a visual prosthesis, is different from stimulating these sites serially (Lovell et al. 2005; but see Sekirnjak et al. 2006). Understanding the current spread properties using multipolar stimulation is central to the development of an effective cortical prosthesis for blind humans.

SUMMARY AND CONCLUSIONS

1) The delivery of a 100-ms train of microampere anode-first pulses to area V1 in the macaque monkey through a microelectrode systematically delays the execution of visually guided saccadic eye movements generated to a punctate target (e.g., 0.2° in size) located in the receptive field of the stimulated neurons. Optimal delays (i.e., >20 ms) are observed using electrical currents of 15 to 100 μA delivered as 0.2-ms pulses at a rate of 200 Hz. The lowest current thresholds for evoking a delay (<50 μA) occur from 1.0 to 2.25 mm below the cortical surface in V1. This suggests that the most excitable neurons for the generation of this effect are in the deep layers of V1.

2) The chronaxies of the neurons that mediate the delay effect range from 0.13 to 0.24 ms. Such values suggest that the directly stimulated neurons are composed mainly of pyramidal fibers. Anode-first pulses were more effective than cathode-first pulses at evoking a delay. This indicates that the stimulated substrate is primarily made up of cell bodies and terminals over axons.

3) The region of visual space within which visually guided saccades are delayed is called a delay field. This field is centered on the visual receptive field of the stimulated neurons. The size of a delay field increases from 0.1 to 0.55° of visual angle when the stimulating electrode is moved from a region of V1 coding for a receptive-field center at 1.8° of eccentricity to a region coding for a receptive-field center at 4.4° of eccentricity. The shape of a delay field is roughly circular. The size of a delay field scales with the retinocortical magnification factor of V1.

4) Stimulation of V1 not only delays the execution of visually guided saccades, but it also delays manual responses triggered by a visual target placed in the receptive field of the stimulated cells. Thus the delay effect is due to a disturbance of the visual signal at the level of V1 and not due to a disruption of the motor signal passing between V1 and the saccade generator in the brain stem.

5) By studying the size of delay fields we calculate how far microampere currents spread in V1. Electrical currents of 2 to 150 μA are estimated to activate a radial swath of tissue of 50 to 500 μm from the electrode tip. Such currents activate from 60 to 62,000 neurons in V1. We suggest that to activate a portion of a hypercolumn currents of <100 μA are sufficient, and to evoke phosphens exhibiting features currents of ≤5 μA would be required.

6) Using the properties of delay fields we propose that the size of electrically evoked phosphens scales with the retinocortical magnification factor (rather than with receptive-field size). Additional behavioral paradigms will need to be performed on monkeys as well as humans to further substantiate this idea.

7) Whether the interference effects observed using TMS of V1 in humans are comparable to the delay effects observed by V1 stimulation in monkeys is unclear. TMS experiments will need to be performed on monkeys to...
assess whether such magnetic stimulation can induce saccadic and manual delays.

8) We argue that GABAergic circuits in V1 might mediate the delay effect. We posit that the direct stimulation of the pyramidal fibers in V1 produces a phosphen, which is then followed by a GABAergic hyperpolarization of the pyramidal cells, thereby inducing a saccadic delay. Thus V1 microstimulation engages a cortical microcircuitry that normally functions to rapidly respond to visual stimuli; this is followed by a period of transient inhibition that prevents unabated cortical excitation.

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