Phosphenes can exhibit chromatic properties. For the most part, the above results concur with the receptive field properties of V1 cells of nonhuman primates (Dagnelie et al. 1989; Daniel and Whitteridge 1961; Dow et al. 1981; Gawne and Martin 2002; Hubel and Wiesel 1968, 1974b, 1977; Livingston and Hubel 1984; Michael 1981; Schiller 1976a; van Essen et al. 1984): that is, that the receptive field of V1 neurons is roughly circular and stationary (when the eyes are immobile), that the size of a field increases for more peripheral representations of the visual field, and that the maximal receptive field size is within 3° of visual angle. Also, in accordance with the topographic layout of V1, cells above the calcarine fissure respond to visual stimuli presented in the lower visual field and cells below the calcarine fissure respond to visual stimuli presented in the upper visual field (Daniel and Whitteridge 1961; Hubel and Wiesel 1968). Finally, many V1 cells respond to colored stimuli (Dow 1974; Gouras 1974; Hubel and Wiesel 1968; Michael 1981; Ts’o and Gilbert 1988), which concurs with the observation that phosphenes can exhibit chromatic properties.

By studying etherized monkeys, Schäfer (1888) was the first to suggest a topographic organization for V1 in primates. He found that electrical stimulation of V1 evokes contraversive eye movements and that stimulation above the calcarine fissure produces downward eye movements, whereas stimulation below the calcarine fissure generates upward movements. Over the years others have replicated this basic result in a variety of primates from apes to monkeys (Doty 1965; Grünbaum and Sherrington 1901, 1903; Keating and Gooley 1988; Keating et al. 1983; Schiller 1972, 1977; Wagman 1964, Wagman et al. 1958; Walker and Weaver 1940). In fact, electrical stimulation of V1 evokes saccadic eye movements that terminate in the center of the visual receptive field of the stimulated cells, and long trains of stimulation produce a sequence of multiple saccades until the eyes reach the oculomotor limit (Keating and Gooley 1988; Keating et al. 1983; Schiller 1972, 1977; Tehovnik et al. 2003a). Each saccade within this sequence exhibits a similar size and direction. Thus the retinotopic coding scheme of V1 as described with electrical stimulation is in register with the scheme deduced using single cell recording.

A variety of investigations, from single-cell recording (e.g., Schiller et al. 1976a,b,c) to functional imaging experiments (e.g., Tootell et al. 1988a,b,c), have been used to study the visual functions of primate V1. These techniques have basically corroborated the original observations of Hubel and Wiesel (Hubel and Freeman 1977; Hubel and Wiesel 1968, 1972, 1974a,b, 1977; LeVay et al. 1975): that is, that V1 is...
organized according to ocular dominance and orientation columns. By the start of the twentieth century and well into the 1960s, electrical stimulation techniques played a central role in investigating the relationship of V1 function to the execution of ocular behavior (Doty 1965, 1969; Grünbaum and Sherrington 1901, 1903; Schäfer 1888; Wagman 1964; Wagman et al. 1958; Walker and Weaver 1940; Ward and Weiskrantz 1969). This line of work, however, was largely eclipsed by the seminal single-unit recording experiments of Hubel and Wiesel.

Nevertheless, a number of investigators have continued to use electrical stimulation techniques to ascertain V1 function as it pertains to ocular and visual responses in primates (Bartlett and Doty 1980; DeYoe 1983; Doty 1970; Keating and Gooley 1988; Keating et al. 1983; Schiller 1972, 1977). Anatomical studies have shown that the deepest layers of V1 (i.e., lamina V) innervate the superior colliculus (Fries 1984; Graham 1982; Lund et al. 1975; Spatz et al. 1970; Vogt-Weisenhorn et al. 1995). The superior colliculus mediates oculomotor responses (Schiller 1984; Wurtz et al. 2001). Schiller (1977) showed that lesions of the superior colliculus abolished all saccadic eye movements evoked electrically from V1 even when currents as high as 3,000 μA were used. Before any lesion, currents as low as 200 μA had been effective. These results have since been replicated (Keating and Gooley 1988; Keating et al. 1983). Accordingly, it appears that V1 can gain access to the brain stem saccade generator by the superior colliculus.

Using the method of Doty (1965), it has been found that monkeys can be conditioned to respond to electrical stimulation delivered to various layers within V1 (Bartlett and Doty 1980; DeYoe 1983). Monkeys were trained to release a lever for reward after the delivery of electrical stimulation. Doty assumed in these types of experiments that monkeys experience a punctate and unitary visual percept when electricity is delivered to any region within V1 because the conditioning effect attributed to stimulation of V1 is immediately generalized to any ipsilateral or contralateral location within the V1 map (Doty 1965, 1970) and because the conditioning response can be obtained using currents as low as 2 μA (Bartlett and Doty 1980; DeYoe 1983). Such low currents can activate V1 neurons confined to the extent of an ocular dominance column (Tehovnik et al. 2002), which is roughly 0.5 mm wide (Blasdel and Salama 1986; LeVay et al. 1975, 1985; Wiesel et al. 1974). The excitability properties of V1 elements mediating the conditioning response are restrictive (chronaxies ranging from 0.1 to 0.5 ms; a chronaxie, a measure of neuronal excitability, is the shortest duration of an effective electrical stimulation pulse having a strength equal to twice the minimum strength required for neuronal excitation), suggesting that a limited population of neurons mediates this response (DeYoe 1983). Furthermore, the excitabilities of these neuronal elements are similar to those that mediate stimulation-evoked phosphenes in human V1 (Brindley and Lewin 1968a; Dobelle and Mladjevoviy 1974; Rushton and Brindley 1978). Thus every time electrical stimulation is delivered to monkey V1 to elicit a conditioning response a visual phosphene is likely produced as well.

Over the past 10 yr many new advances have been made in the study of phosphenes and saccadic eye movements evoked by electrical microstimulation of primate V1. This review summarizes these advances with the purpose of providing a foundation for the development of a cortical visual prosthesis for the blind. Issues discussed are as follows: 1) properties of electrical stimulation with an emphasis on effective current spread in V1 ascertained by single-unit recording and behavioral methods; 2) properties of phosphene induction in relation to stimulation parameters, macrostimulation versus microstimulation, and phosphenes elicited in sighted and blind subjects; 3) monkey psychophysics and the study of phosphenes; 4) the generation of saccadic eye movements elicited by microstimulation of V1; and 5) the development of an effective cortical visual prosthesis for the blind.

PROPERTIES OF ELECTRICAL STIMULATION

Effective current spread in V1 based on single-cell data

The effective range of current spread from an electrode tip is proportional to the square root of the current divided by the square root of a constant (Tehovnik 1996). The constant, called the current–distance constant, can range from 300 to 3,000 μA/mm² for large pyramidal tract cells with an average of about 1,000 μA/mm² (Stoney et al. 1968). These values were computed with a single cathodal-current pulse having a duration of 0.2 ms. The constant reflects the excitability of a neural element 1 mm away from the electrode tip such that an element having a constant of 1,000 μA/mm² would require a 1,000-μA current to be activated 1 mm away 50% of the time. The greater the current–distance constant, the less the conduction velocity of an axonal element (Hentall et al. 1984; Jankowska and Roberts 1972; Roberts and Smith 1973). Therefore the size of a neuron’s axon and whether it is myelinated affects the current–distance constant.

To estimate the spread of a current pulse in V1, we use a current–distance constant of 1,000 μA/mm². This is a very conservative estimate for V1, given that the neuronal elements in V1 of primates tend to be smaller than those in other parts of the cerebral cortex (Cragg 1967; Fries 1984; O’Kusky and Colonnier 1982; Peters 1987; Rockel et al. 1980) and that the conduction velocity distributions of pyramidal tract neurons exiting V1 tend to be significantly lower than those of large pyramidal neurons (Finlay et al. 1976; Macpherson et al. 1982). Using the equation, r = (I/K)¹/², where r is the distance of effective current spread from the electrode tip in mm, I is the current used in μA, and K is the current–distance constant in μA/mm², a 1-, 10-, and 100-μA current pulse delivered to V1 is estimated to activate elements within 0.03, 0.10, and 0.32 mm, respectively, from the electrode tip. Thus a current pulse at or below 100 μA delivered to V1 can directly activate elements confined to a hypercolumn, which is about 1.0 mm wide (Hubel and Wiesel 1977; LeVay et al. 1985).

Cell counts have shown that V1 of macaque monkeys contains about 120,000 neurons per mm² of cortical tissue (Cragg 1967; O’Kusky and Colonnier 1982; Peters 1987; Rockel et al. 1980); therefore a 1-, 10-, and 100-μA current pulse should activate about 14, 500, and 16,400 neurons, respectively (calculated using 4/3π²). This calculation assumes a uniform cell density across all V1 layers.

Effective current spread in V1 based on behavioral data

We have found that if electrical stimulation is delivered to V1 before a monkey generates a saccadic eye movement to a...
visual target, the execution of the saccade is delayed progressively more the closer the visual target is to the receptive-field center of the stimulated neurons (Tehovnik et al. 2004). This method has been used to deduce the effective spread of trains of pulses delivered to V1. The visual target used in this experiment was a bright circular spot of light 0.2° in diameter, which is comparable to the smallest diameter of V1 receptive fields (Dagnelie et al. 1989). The maximum increase in saccadic latency arising from stimulation with a 100-ms train of 100-μA pulses (0.2-ms pulse duration) delivered at 200 Hz occurred when the target was positioned at the center of the receptive field of the stimulated neurons (Fig. 1A). The magnitude of the latency increase decreased systematically as the distance between the target and receptive-field center was increased. For target eccentricities beyond 0.5° from the receptive-field center, the stimulation became ineffective (Fig. 1A). This delay effect was studied at 3 levels of current. The latency difference for stimulation trials compared with nonstimulation trials was computed for 25-, 50-, and 100-μA currents while the target position was varied. The greatest latency difference was observed for all current conditions when the target was situated at the receptive-field center of the stimulated neurons (Fig. 1B). The magnitude of this effect varied positively with current intensity.

Based on these data, we now have the first behavioral estimates of how far 25-, 50-, and 100-μA currents spread in V1 by noting the extent of visual field affected by these currents at an eccentricity of 4° from the fovea. From each curve in Fig. 1B, we determined the extent of visual field affected by measuring the target eccentricity affected at 50% of the maximal latency difference. For the 25-, 50-, and 100-μA currents, the extent of visual field affected was found to be 0.31, 0.39, and 0.58°, respectively. At a 4° eccentricity, 0.5° of visual field spans 2 ocular dominance columns (LeVay et al. 1985), which represent 800 μm of V1 tissue (Blasdel and Salama 1986; LeVay et al. 1975, 1985; Wiesel et al. 1974). Therefore 25-, 50-, and 100-μA currents affect V1 tissue within 248, 312, and 464 μm from the electrode tip. These estimates are somewhat greater than those obtained by using the current–distance equation in the preceding section (25-, 50-, and 100-μA currents affect V1 tissue within 158, 224, and 316 μm from the electrode tip). This difference is likely related to the fact that the current–distance equation is based on the delivery of a single pulse, whereas the experiments described here are based on the delivery of a train of 20 pulses. This greater spread is probably related to transynaptic effects (Jankowska et al. 1975; McLlwain 1982).

In conclusion, when a train of stimulation using microamper currents is delivered to the cortex, a relatively punctate region of cortex is activated. This conclusion is consistent with other reports for cortical microstimulation (Nichols and Newcombe 2002; Salzman et al. 1990).

**Does electrode tip size matter?**

It is well known that the larger the surface area of an electrode tip, the greater the current that is required to activate neuronal tissue (Bagshaw and Evans 1976; DeYoe 1983; Keating and Gooley 1988; Milner and Laferriere 1986; West and Wolsencroft 1983; Yeomans et al. 1985). It is for this reason that milliamper currents are required to evoke neuronal responses when macroelectrodes are used (i.e., tips sizes of 0.5 mm² or more), whereas microamper currents are sufficient when delivered through microelectrodes (i.e., tips sizes of 0.01 mm² or less). The larger the electrode tip, the less the current density generated at the tip for a given amount of total current. It is current density that determines whether neuronal elements are activated, and it is the current density at the tip that determines whether the stimulation produces tissue damage (Tehovnik 1996). A cathodal pulse with a charge density as high as 438 nC/mm² per phase is required to activate relatively unexcitable neurons (as derived from Nowak and Bullier 1996: 27,500 μA/mm² × 0.2 ms pulses/4π per phase), whereas charge densities exceeding 16,000 nC/mm² per phase produce histological damage after delivering pulses through a microelectrode (tip size = 0.007 mm²) continuously for many hours (McCreery et al. 1990). Because most studies use different parameters of stimulation, no one criterion is suitable for...
setting a damage threshold. Usable stimulation parameters are those that yield stable responses over time (McCreery et al. 2002; Yeomans 1990). Pulse durations, however, should be routinely set to the chronaxies of the directly stimulated elements (Tehovnik 1996). Durations that surpass the chronaxies do not contribute significantly to the evoked response. Charge-balanced biphasic pulses should be used to reduce damage resulting from electrode polarization (Tehovnik 1996).

PHOSPHENE INDUCTION

Stimulation parameters

As mentioned earlier, electrical stimulation of V1 in humans tends to evoke a phosphen that conforms to the receptive-field properties of V1 cells: i.e., a circular spot that is stationary as long as the eyes are immobile. Parameters of stimulation such as current, pulse duration, train duration, pulse frequency, and pulse polarity affect the generation of phosphenes.

A broad range of currents has been used to evoke phosphenes. Currents in the milliampere range are required to elicit phosphenes when stimulation is delivered through a macro-electrode located on the surface of V1 (Brindley and Lewin 1968a; Dobelle and Mladenovsky 1974; Lee et al. 2000; Rushston and Brindley 1978), and currents as low as 2 μA are effective when using a microelectrode positioned in the deepest layers of V1 (Schmidt et al. 1996). When using surface macroelectrodes, increasing current initially increases the brightness of a phosphen, and further increases subsequently increase the size (Dobelle and Mladenovsky 1974; Rushston and Brindley 1978). The effect of increments in current is more complicated when using depth microelectrodes. Although increases in current produced brighter phosphenes, such increases do not have a uniform effect on phosphen size (Schmidt et al. 1996). For some sites an increment in current produces an increase in phosphen size, for other sites it produces a decrease, and still for others it produces an increase followed by a decrease (Schmidt et al. 1996).

Pulse durations used to evoke phosphenes have been as short as 0.01 ms and as long as 1 ms (Brindley and Lewin 1968a; Dobelle and Mladenovsky 1974; Schmidt et al. 1996). The chronaxie of phosphen induction is typically <0.4 ms (Brindley and Lewin 1968a; Dobelle and Mladenovsky 1974; Rushston and Brindley 1978); therefore increases in pulse duration beyond 1 ms do not contribute substantially to phosphen induction. Increasing the pulse duration increases the brightness of a phosphen (Brindley and Lewin 1968a; Dobelle and Mladenovsky 1974; Schmidt et al. 1996).

A train of between 5 and 15 pulses delivered at 50 Hz is needed to produce the sensation of a phosphen (Dobelle and Mladenovsky 1974). The onset and offset of a phosphen is locked to the onset and offset of the stimulation train (Dobelle and Mladenovsky 1974; Schmidt et al. 1996). When using surface macrostimulation, phosphenes extinguish before the termination of stimulation for train lengths >10 to 15 s (Dobelle and Mladenovsky 1974), whereas when using depth microstimulation, they extinguish at train lengths >1 s (Schmidt et al. 1996). The brightness and size of a phosphen are increased with an increase in train duration (Schmidt et al. 1996).

A wide range of pulse frequencies from as low as 25 Hz to as high as 4,000 Hz have been used to generate phosphenes (Bak et al. 1990; Brindley and Lewin 1968a; Dobelle and Mladenovsky 1974; Schmidt et al. 1996). Frequencies above 30 Hz are the best for producing steady phosphenes with minimal or no flicker (Bak et al. 1990; Brindley and Lewin 1968a; Dobelle and Mladenovsky 1974; Schmidt et al. 1996). The most effective frequencies range between 100 and 200 Hz (Dobelle and Mladenovsky 1974; Schmidt et al. 1996), which is within the range of firing frequencies of V1 cells activated by a visual stimulus (Gawne and Martin 2002; Nowak et al. 1995). Higher frequencies have been reported to produce brighter phosphenes (Dobelle and Mladenovsky 1974; Schmidt et al. 1996).

Mixed reports have arisen regarding the effects of pulse polarity on phosphen induction. Using surface macrostimulation, no threshold differences were reported between cathodal and anodal pulses for the induction of phosphenes (Dobelle and Mladenovsky 1974). For surface stimulation, it is commonly believed that anodal pulses are superior to cathodal pulses for evoking a response (Ranck 1975). Using depth microstimulation, cathodal pulses were always more effective than anodal pulses for producing phosphenes (Schmidt et al. 1996). This result concurs with what would be expected for depth stimulation (Ranck 1975).

Two visual features that are affected systematically by manipulating the parameters of stimulation are the brightness and size of phosphenes. Increases in current or pulse duration increase the brightness and size of a phosphen, particularly when using surface macrostimulation (Brindley and Lewin 1968a; Dobelle and Mladenovsky 1974; Rushston and Brindley 1978; Schmidt et al. 1996). Increasing current can increase the firing rate of the stimulated elements (Ronner 1982). This agrees with the unit properties of cells in V1. That is, as the brightness (or contrast) of a visual stimulus is increased, the firing rate of cells increases to some asymptotic level (Albrecht and Hamilton 1982; Sclar et al. 1990; Tolhurst 1989; Tolhurst et al. 1981). Also, increments in current or pulse duration increase the number of elements activated because of the higher current densities generated at the electrode tip and because of the greater overall volume of tissue activated (Tehovnik 1996). The higher current densities at the tip would maximally activate more neurons, thereby generating a high-contrast phosphen (Albrecht and Hamilton 1982; Sclar et al. 1990) and the increase in the volume of neurons activated should produce an increase in the size of the phosphen as additional hypercolumns are activated.

Increases in pulse frequency and train duration also increase the brightness and size of phosphenes (Dobelle and Mladenovsky 1974; Schmidt et al. 1996). These parametric increases would drive the directly stimulated cells at a higher rate (Finlay et al. 1976), which would translate into a brighter phosphen (Albrecht and Hamilton 1982; Sclar et al. 1990; Tolhurst 1989; Tolhurst et al. 1981) and produce greater intracortical synaptic spread of the signal (Jankowska et al. 1975; McIlwain 1982), thereby increasing phosphen size.

Accommodation to repeated bouts of stimulation

The brightness of an evoked phosphen accommodates after repeated bouts of stimulation. When a 125-ms train of 0.1-ms pulses (with pulse frequency of 200 Hz) was presented every 4 s and repeated 50 times, the relative brightness between the first and last bout of stimulation decreased by 80% (Schmidt et
al. 1996). Increasing the train and pulse duration of stimulation to 250 ms and 0.4 ms, respectively, reduced accommodation. Furthermore after repeated bouts of stimulation over a period of many months, V1 tissue became more resistant to accommodation. Accommodation occurs for both surface and depth stimulation and it is observed in both sighted and blind subjects (Dobelle and Mladejovsky 1974; Rushton and Brindley 1978; Schmidt et al. 1996). Brightness accommodation must be understood and controlled to develop an effective V1 prosthesis.

**Macro- versus microelectrodes**

Most studies that have evoked phosphenes from V1 in humans have used surface macroelectrodes (Brindley and Lewin 1968a; Dobelle and Mladejovsky 1974; Lee et al. 2000). Fewer studies have used intracortical microelectrodes (Bak et al. 1990; Schmidt et al. 1996). With surface macroelectrodes, the electrode spacing must be >2 to 3 mm for subjects to report 2 distinct phosphenes (Brindley and Lewin 1968a; Dobelle and Mladejovsky 1974), whereas with intracortical microelectrodes 2 distinct phosphenes can be resolved with an electrode spacing as little as 0.5 mm (Bak et al. 1990; Schmidt et al. 1996). This minimal spacing agrees with that reported for monkeys trained to discriminate between the activation of 2 closely spaced intracortical electrodes (Doty 1965). Also, with the use of intracortical microelectrodes, currents in the microampere range can be used (Schmidt et al. 1996), the current spread of which may be confined to within one hypercolumn (Tehovnik et al. 2002, 2004). Confining current to one hypercolumn is not possible with surface macroelectrodes because currents above 1 mA and as high as 15 mA are routinely needed to evoke phosphenes (Brindley and Lewin 1968a; Dobelle and Mladejovsky 1974; Lee et al. 2000). Typically, phosphenes generated by surface macroelectrodes fail to exhibit chromatic features (Brindley and Lewin 1968a; Dobelle and Mladejovsky 1974; Lee et al. 2000). This is less true when using intracortical microelectrodes, provided a current of <10 μA is used (Schmidt et al. 1996). Colored phosphenes are more readily evoked with low currents, perhaps because fewer V1 neurons are activated. Activating regions of V1 that are known to contain neurons mediating chromatic vision might increase the chances of evoking colored phosphenes (Livingston and Hubel 1984; Michael 1981). Whether other visual features coded by single cells can be studied at the lowest current levels remains to be seen.

**Stimulating through multiple electrodes**

Electrical stimulation has been delivered through multiple electrodes in V1 of humans to induce the perception of patterns such as horizontal and vertical lines as well as letters (Dobelle et al. 1974, 1976; Schmidt et al. 1996). With the use of microelectrodes, Schmidt et al. (1996) found that a train duration of over 200 ms is sufficient to evoke a pattern of phosphenes, and as mentioned earlier a pair of electrodes need to be separated by 0.5 mm or more to evoke 2 separate phosphenes. A major concern in evoking patterns is that each phosphenes constituting a pattern must be of comparable brightness; otherwise a human subject judges the collection of phosphenes as separate objects (Schmidt et al. 1996). For one object to be perceived, currents delivered through each electrode have to be adjusted until all phosphenes of a pattern are of comparable brightness.

**Phosphenes induction in sighted versus blind subjects**

When electrical stimulation is delivered to V1 of humans, the evoked phosphenes is most often described as a bright spot of light, and only rarely is it described as a dark spot (Brindley and Lewin 1968a,b; Dobelle and Mladejovsky 1974; Schmidt et al. 1996). Based on what we know about the visual system, there is no reason to think that light-on responses should be more common than light-off responses (Schiller 1992). Cells in V1 respond to light and dark edges and spots, as well as to the onset and termination of flashed light and dark stimuli (Hubel and Livingstone 1990; Hubel and Wiesel 1968; Schiller et al. 1976a). So why are bright phosphenes overreported by human subjects? Two factors might account for this, one related to blindness and the other to the way subjects are tested. Regarding blindness, most studies of electrically evoked phosphenes have been performed using blind subjects. In the one study that has successfully evoked both bright and dark phosphenes from V1, all of the subjects were sighted (Lee et al. 2000). It is therefore possible that in blind subjects the default phosphenes is always bright because the OFF channels have been rendered inoperative by the blindness, which has fixed the background illumination level of the visual system to pitch black, as happens when one closes one’s eyes.

The way sighted subjects are tested for phosphenes induction should determine whether white or black phosphenes are reported. If the background illumination during testing is set to pitch black then once again the default phosphenes should be white. On the other hand, if the background illumination is of intermediate brightness then both white and black phosphenes should be evoked, as found by Lee et al. (2000).

**Visual adaptation and afterimages**

Experiments in which images are stabilized on the retina have shown that after a relatively short time, measured in seconds, the images fade and disappear. Numerous studies have explored this dramatic effect (e.g., Pritchard et al. 1960). In large part this phenomenon is the result of adaptation processes that occur in the retina (Schiller 1996). Thus when a stimulus is presented and maintained, the responses of the retinal ganglion cells gradually decline to their spontaneous activity. Subsequent removal of the image elicits a new set of responses. A persistent bright spot of light elicits an initial vigorous response in ON-center ganglion cells followed by a gradual decline in their activity. When the stimulus is then turned off, a vigorous response is produced in the OFF-center ganglion cells whose receptive fields fall within the region of the spot. This activity elicits the perception of a negative afterimage. The magnitude and duration of the initial responses as well as those of the afterimage is a function of the contrast of the stimulus: the higher the contrast the greater the initial response and the more pronounced and longer lasting the afterimage. The effect works equally with light-incremental and light-decremental stimuli. By contrast, images do not fade with prolonged electrical stimulation of V1. Phosphenes can be generated for over 1 min using a continuous train of stimul-
Stimulation-induced interference

It has been known for some time that electrical stimulation of V1 disrupts a monkey’s performance of visual tasks (Ward and Weiskrantz 1969). When electrical stimulation is delivered concurrently with the presentation of a visual target placed in the receptive field of the stimulated neurons, saccades generated toward the receptive-field target can be either suppressed or facilitated, depending on the cortical layers activated (Schiller and Tehovnik 2001). In the upper layers of V1 interference is most commonly obtained: the stimulation decreases the probability of saccades and increases the latency of saccades made to the receptive-field target. By contrast, in the lower layers stimulation generally produces facilitation: the probability of saccades being generated to the receptive-field target increases and the latency of saccade initiation decreases.

To illustrate these effects, monkeys were presented with paired targets such that one target of a pair was positioned in the receptive field of the stimulated neurons and the other target of a pair was located in the mirror-position of the opposite hemifield (Fig. 2, A and B). On a fraction of trials a train of electrical stimulation was delivered that began 30 ms after the presentation of the first target (Fig. 2C). Thirty milliseconds is about the minimal time it takes for cells in V1 to discharge after the presentation of a visual stimulus (Miller and Glickstein 1967; Nowak et al. 1995; Vogels and Orban 1994). In the absence of electrical stimulation, monkeys will generate saccades to each target of a pair roughly 50% of the time when the targets are presented simultaneously (Schiller and Tehovnik 2001), although there can be subtle position habits (Tehovnik et al. 2002). If one target of a pair leads the other target, however, monkeys tend to produce saccades to the first target. By varying the temporal offset between the targets, a psychophysical function can be generated showing the probability of saccades being made to the receptive-field target (Fig. 2D, Control). When electrical stimulation of a site produces interference, this function is shifted rightward (Fig. 2D, Interference), whereas when electrical stimulation of a site produces facilitation this function is shifted leftward (Fig. 2D, Facilitation).

The interference and facilitatory effects observed for V1 have been explained as follows: stimulation of the superficial layers of V1 disrupts the flow of visual information between...
the retina and higher cortical areas, thereby producing interference, whereas stimulation of the deep layers of V1 activates the corticotectal pathway that has access to the saccade generator in the brain stem, thereby causing facilitation (Tehovnik et al. 2002). Several experiments have been conducted to investigate these ideas (Slocum and Tehovnik 2004; Tehovnik and Slocum 2003a,b; Tehovnik et al. 2002).

After testing for interference and/or facilitation at fine depth increments with respect to the cortical surface, it was found that the most pronounced interference occurred at 0.8 mm below the cortical surface and the most pronounced facilitation occurred at 1.7 mm below the cortical surface (Fig. 3). Additionally, it was discovered that anodal pulses were superior to cathodal pulses for inducing interference (Fig. 4). This suggests that cell bodies and axon terminals are being activated disproportionately more than axons to produce the interference effect (Ranck 1975). According to Ranck, effective stimulation of neural tissue induces an outward current at the initial segment and nodes of Ranvier, thereby triggering an action potential. When cathodal current is delivered adjacent to a neural element, an outward current is induced, causing the membrane to depolarize, whereas when an anodal current is delivered the resulting inward current causes the membrane to be hyperpolarized. For this reason cathodal pulses are more effective than anodal pulses at activating axons (Armstrong et al. 1973; McIntyre and Grill 2000; Porter 1963; Rattay 1999; Stoney et al. 1968). When an anodal current is delivered to a cell body or axon terminal an inward current is produced at the cell body or terminal, whereas an outward current occurs at the axon. This outward current activates the neuron. This property makes anodal pulses superior to cathodal pulses for inducing an interference effect and the fact that the electrode must be situated within the visual input layers of V1 (located between 0.6 and 1.2 mm below the cortical surface) to induce interference suggests that interference is a consequence of activation of the visual input fibers of V1 (Tehovnik and Slocum 2003a). If interference were a result of activation of the visual inputs originating from the lateral geniculate nucleus, interference should vary according to which eye is presented with the visual stimuli, given that these inputs are organized according to eye dominance (Hubel and Wiesel 1972; LeVay et al. 1975, 1985). After targeting the visual input layers with our stimulating electrode (Tehovnik and Slocum 2003b), we found that stimulation here produced maximal interference when visual stimuli were presented to the eye with the primary (i.e., ocular dominant) input to the stimulated column, and produced less interference when presented to the eye with the lesser (i.e., ocular inferior) input to the stimulated column (Fig. 5). This result was also obtained when an animal generated saccades to

FIG. 3. Distribution of interference and facilitation effects as a function of cortical depth. Depth at which a significant \((P < 0.001)\) interference or facilitation effect was observed is illustrated for 13 penetrations made into V1. Significance is based on a stimulation-evoked curve shift of 29 ms or more. Significance value of 29 ms is 3 SDs greater than the variance exhibited by 128 pairs of control curves whose SD was 9.6 ms. All data were collected while the monkeys performed the paired-target task. Approximate location of the cortical layers is indicated to the \textit{left} and \textit{right} of the figure (Peters and Sethares 1991). Data from Tehovnik et al. (2002).

FIG. 4. Cathode-first vs. anode-first induced interference. Probability of evoking saccades toward the receptive-field target is plotted as a function of the temporal offset between targets. Each plot, from \textit{left} to \textit{right}, shows interference effects induced at one site using cathode-first pulses (Cathode-first) and anode-first pulses (Anode-first) followed by a nonstimulation control (Control). Within a panel, the solid black curve is the control and the dashed curve represents the effect of stimulation or the effect of dummy stimulation. Each point on a curve is based on 6 trials. A positive shift indicates that the animal selected the nonreceptive-field target more often than the receptive-field target during stimulation. Curve shifts are significant \((P < 0.001)\) when they are greater than or equal to 28 ms in the positive direction. Significance value of 28 ms is 3 SDs greater than the variance exhibited by 52 pairs of control curves whose SD was 9.5 ms. Data from Tehovnik and Slocum (2003a).
a single target located in the receptive field of the stimulated neurons.

Interference might be induced by activation of geniculostraiate fibers as well as by recruitment of γ-aminobutyric acid (GABA)ergic interneurons that are concentrated near the input layers of V1 (Fitzpatrick et al. 1987; Hubel and Wiesel 1972; Lund et al. 1975). There is evidence supporting both possibilities. Stimulating V1 with a single pulse renders neurons in the lateral geniculate nucleus, as well as neurons within V1, unresponsive to visual stimuli for tens of milliseconds (Chung and Ferster 1998; Schiller and Malpeli 1977), and injection of GABAergic agents into V1 disrupts both the selection and detection of visual targets (Newsome et al. 1985; Schiller and Tehovnik 2003).

Accordingly, interference that is produced while delivering stimulation concurrently with the presentation of visual targets seems to occur by activation of the visual input fibers of V1, whereas facilitation under such conditions is produced by activation of the output fibers. In subsequent sections, we will return to the issue of activating the output fibers of V1.

The relationship of phosphene generation to interference and facilitation is not known. Whether stimulating individual layers within V1 differentially induces phosphenes and whether phosphene induction is related to interference and facilitation needs to be determined in both monkeys and humans.

**Stimulation-induced saccadic delays**

Saccadic eye movements to a visual target positioned in the receptive field of stimulated V1 neurons are systematically delayed when stimulation is delivered to those neurons while monkeys are actively fixating (Tehovnik et al. 2004). This effect is confined to the receptive-field location of the stimulated neurons (Fig. 1). The greatest delay occurs when a train of stimulation is delivered during the fixation period immediately before the onset of the visual target. The optimal parameters of stimulation for the delay are as follows: 1) anodal pulses (as opposed to cathodal pulses); 2) train durations of >40 ms with frequencies >100 Hz; and 3) pulse durations of <0.4 ms. Delays are evoked with currents as low as 4 μA.

The chronaxies of V1 elements mediating the saccadic delay were determined and compared with those of V1 elements mediating phosphenes in human V1 (Tehovnik et al. 2004). A chronaxie is a measure of neuronal excitability such that axons have shorter chronaxies than cell bodies (axons: 0.03–7 ms; cell bodies: 7–31 ms; Nowak and Bullier 1998; Ranck 1975), and large, myelinated axons have shorter chronaxies than small, nonmyelinated axons (large: 0.03–0.7 ms; small: >1.0 ms; Li and Bak 1976; Ranck 1975; West and Wolstencroft 1983). Chronaxies have been determined for elements mediating a functional MRI signal, neurotransmitter release, classical conditioning, self-stimulation, phosphene induction, and saccadic eye movements (Brindley and Lewin 1968a; DeYoe 1983; Dobelle and Mladjevsky 1974; Farber et al. 1997; Matthews 1977; Tehovnik and Lee 1993; Tehovnik and Sommer 1997; Tehovnik et al. 2003a; Tolias et al. 2003).

To determine the excitability of the directly stimulated elements inducing the saccadic delay, current–duration functions (Fig. 6A) were normalized such that the current threshold to evoke a 20-ms delay was set to unity for a pulse duration of 0.7 ms and all other thresholds were expressed as a multiple of this threshold (Fig. 6B). The average latency difference of 20 ms is greater than 3 SDs of the mean difference observed when comparing nonstimulation and dummy stimulation trials (SD = 4.3, n = 35; Tehovnik et al. 2004). 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 2 units of threshold (Fig. 6B, dashed horizontal line). The chronaxie values ranged from 0.13 to 0.24 ms. This range of chronaxies overlaps with those reported for elements that mediate phosphene induction in human V1 (Brindley and Lewin 1968a; Dobelle and Mladjevsky 1974; Rushton and Brindley 1978). Therefore every
time electrical stimulation produces a saccadic delay, monkeys probably experience a visual phosphenes, as is presumed to occur when conditioning responses are evoked by stimulation of macaque V1 (Bartlett and Doty 1980; DeYoe 1983; Doty 1965).

Given that interference and facilitation occur at different depths within V1 when stimulation is presented concurrently with the execution of visual tasks (Schiller and Tehovnik 2001; Slocum and Tehovnik 2004; Tehovnik and Slocum 2003a; Tehovnik et al. 2002) we wanted to see whether the current threshold for producing a saccadic delay also varied as a function of cortical depth (Tehovnik et al. 2004). The current threshold to induce a 20-ms saccadic delay was determined as a function of cortical depth (Fig. 7). It was found that the lowest current thresholds for the induction of a saccadic delay occurred in the deepest layers of V1 (from 1.5 to 2.25 mm below the top of V1).

This result differs from that obtained when stimulation is delivered concurrently with the execution of visual tasks; in which case the best interference occurred for stimulations of the intermediate but not the deep layers of V1 (Schiller and Tehovnik 2001; Slocum and Tehovnik 2004; Tehovnik and Slocum 2003a; Tehovnik et al. 2002). By delivering electrical stimulation during active fixation instead of during saccade execution (i.e., concurrently with the execution of the visual task), the excitability of the cells between the deepest layers of V1 and the saccade generator in the brain stem that mediates saccades is suppressed (Fig. 8); currents as high as 1.500 μA fail to evoke saccades from V1 during active fixation (Tehovnik et al. 2003b). We believe that this suppression of saccades enables the neurons within the deepest layers of V1 to participate in the saccadic delay.
What might account for this delay? The delivery of a single stimulation pulse to the optic tract or area V1 renders neurons in the lateral geniculate nucleus unresponsive to a visual stimulus for several tens of milliseconds (Schiller and Malpeli 1977). The duration of this effect tends to be longer when the pulse is delivered to V1 as compared with the optic tract. Also, the delivery of a single pulse to superficial V1 mainly dampens the responsivity of cells within V1, whereas stimulation of deeper regions of V1 affects cells in V1 plus those in the lateral geniculate nucleus (Chung and Ferster 1998). Chung and Ferster (1998) suggested that the deeper stimulation might be activating the lateral geniculate nucleus antidromically from lamina IV as well as orthodromically by a corticothalamic projection originating from lamina VI (Fig. 8).

The excitability properties of the elements that mediate the saccadic delay are similar to those of pyramidal neurons whose chronaxies vary from 0.1 to 0.4 ms (Asanuma et al. 1976; Stoney et al. 1968). Stimulation of these elements may delay saccades by activating pyramidal fibers intrinsic to V1 and by exciting such fibers that feedback to the lateral geniculate nucleus. The pyramidal elements can then activate GABAergic elements intrinsic to these structures (Fitzpatrick et al. 1987; Montero 1986), thereby interrupting the transmission of visual information. This idea is consistent with the observations of Schiller and Malpeli (1977) and Chung and Ferster (1998) and with known projections between the striate cortex and the lateral geniculate nucleus. The pyramidal elements can activate the lateral geniculate nucleus antidromically from lamina IV as well as orthodromically by a corticothalamic projection originating from lamina VI (Fig. 8).

Using saccadic eye movements to study phosphenes

To assess phosphen induction using saccadic eye movements, we trained a monkey to generate saccadic eye movements to the receptive field of the stimulated V1 neurons using 6 conditions, all randomized (Fig. 9, right). For all conditions, the monkey had to acquire the fixation spot and remain fixated for 300 ms. After termination of the fixation spot one of the 6 conditions could occur.

CONDITION A. A visual target was presented in the visual field of the cells under study 100 ms after the termination of the fixation spot and the monkey was required to generate a saccade to the target location within 300 ms to get a juice reward.

CONDITION B. A visual target was presented in the visual field of the cells under study similar to that of condition a; electrical stimulation was delivered to those cells 30 ms after the onset of the visual target; and the monkey was required to generate a saccade to a target location to get a juice reward.

CONDITION C. No visual target was presented and electrical stimulation was delivered to the cells under study 130 ms after the termination of the fixation spot; a juice reward was provided to the monkey if a saccade was generated to the receptive-field location after the onset of stimulation. We interpret an increase in the probability of evoking saccades under this condition as a monkey responding to a putative phosphen produced by stimulation.

CONDITION D. No visual target was presented and electrical stimulation was delivered to the cells under study 130 ms after the termination of the fixation spot; a juice reward was provided to the monkey if it generated a saccade to the receptive-field location. This condition matched condition c except for the absence of electrical stimulation.

CONDITION E. The monkey was provided with juice immediately after termination of the fixation spot. Electrical stimulation was delivered 130 ms after the offset of the fixation spot. The time of stimulation with respect to fixation-spot offset was the same as in conditions b and c. Condition e determined whether electrical stimulation could drive the eyes into the receptive-field location after reward delivery.

CONDITION F. A juice reward was delivered immediately after termination of the fixation spot, but no stimulation was delivered. This condition tested whether the monkey spontaneously generated saccades into the receptive-field location after reward delivery.

**FIG. 9.** Left: percentage of saccades made into the receptive field (RF) window is plotted as a function of different conditions to test for the induction of phosphenes by electrical stimulation of V1. Each bar graph is based on 20 trials. Z-statistic was used to compare the results of the different conditions. Right: 6 different conditions (a–f) were used. Receptive field of the stimulated neurons was located at 265° of meridian and at 2.6° of eccentricity [as depicted on the right: saccade (arrow), receptive field (RF), and fixation spot (fix)]. During stimulation trials, a 100-ms train of stimulation was delivered 130 ms after the termination of the fixation spot. Train was composed of 30–μA, 0.2-ms duration anode-first pulses delivered at 200 Hz. Depth of stimulation was 1.25 mm below the cortical surface. Juice delivery occurred after the monkey entered the target window (a, b, c, d) or immediately after the termination of the fixation spot (e, f). Other details regarding the conditions can be found in the text.
Electrical stimulation occurred with respect to the onset of the visual target whether real (as for condition b) or virtual (as for conditions c and e). The stimulation commenced 30 ms after target onset. This is roughly the minimum time for a visual signal to be transmitted from the retina to V1 (Miller and Glickstein 1967; Nowak et al. 1995; Vogels and Orban 1994).

The percentage of saccades made to the receptive target across the 6 conditions varied (Fig. 9, left). For conditions a and b the monkey generated saccades to the receptive-field location over 95% of the time as defined by the location of the visual target. For condition c, the monkey generated saccades to the receptive-field location over 60% of the time as defined by the stimulation. This condition was considered the test for phosphene induction. On the various control trials (conditions d, e, and f) the monkey generated saccades to the receptive-field location <20% of the time. Because saccades were rarely evoked into the receptive-field location of the stimulated neurons in condition e, it is highly unlikely that the effect attributed to phosphene induction in condition c is the result of a simple motor response. Also the latencies of saccades generated to the visual target were comparable to those generated during stimulation in condition c. If the phosphene induced were identical to that of the visual target (i.e., monochromatic, bright circular, 0.2° in diameter at 100% contrast) one might expect the performance of the monkey to be closer to 95% than to 65%. On initial inspection, however, these results suggest that the monkey was generating saccades to a stimulation-induced phosphene in condition c.

Better evidence that monkeys can detect phosphenes during electrical stimulation of V1 would be to have them generate memory-guided saccades to the location of the phosphene long after the stimulation has been terminated. This type of experiment dissociates the sensory aspects of phosphene induction from the possibility that the stimulation is just driving the eyes into the receptive-field location. This type of experiment was recently done by Bradley and colleagues (2004). They trained a monkey to generate saccadic eye movements to remembered locations as defined by stimulations delivered to the V1 map using a microelectrode array implanted in one hemisphere. A relationship was found between the endpoint of a memory-guided saccade and the receptive-field location of the stimulated neurons.

Application of the Schwartz model to phosphenes

The logarithmic conformal mapping model of Schwartz (1994) can be extended to predict the size and shape of the visual field represented by the activation of a particular region of cortical tissue in the V1 map of the rhesus monkey. The use of a conformal mapping accounts for the magnification factor of V1, while preserving the angular relationship between nearby points in the visual field. Electrical stimulation activates a tissue with a radial spread confined to within 0.5 mm for currents of 100 μA or less (Tehovnik et al. 2004). The size and shape of the visual field coded by an area of V1 tissue depends on the site of stimulation in the V1 map. Figure 10 shows how stimulation within different regions of the operculum would be expected to activate the central 7° of a hemifield.

As discussed previously (Tehovnik et al. 2004), stimulation of V1 in rhesus monkeys induces a saccadic delay that occurs only when the visual target is positioned within the receptive-field location of the stimulated neurons, and the excitabilities of neurons that mediate this delay are similar to those described for elements mediating phosphene induction in human V1. Stimulation-induced saccadic delay could be used to infer the size and shape of a visual phosphene by noting the size and shape of the delay field. Once deduced, the size and shape of the delay field could be compared with the size and shape of the phosphene as predicted by the conformal mapping scheme of Schwartz (1994).

Retinal convergence onto V1 elements

An issue of some concern is how much visual field resolution is lost by stimulating elements in V1 rather than stimulating earlier portions of the retinostriate pathway. The smallest receptive-field size of V1 neurons is 0.2° (or 12 min) (Dagnelie et al. 1989; Dow et al. 1981; van Essen et al. 1984). The diameter of such a receptive-field size is spanned by roughly 12 cones. The minimal acuity in monkeys is about 1 min of arc, which is the separation between 2 adjacent cones. Therefore stimulating a single element in V1 that codes for a minimal receptive-field size might be expected to produce a phosphene whose size is an order of magnitude greater than that coded by retinal receptor elements.

Saccadic Eye Movements

Excitability properties across V1 laminae

As mentioned, it has been known for over 100 yr that eye movements can be evoked electrically from V1 (Doty 1965; Grünbaum and Sherrington 1901, 1903; Schäfer 1888; Wageman 1964; Wagman et al. 1958; Walker and Weaver 1940). These eye movements are saccadic and the saccadic vectors generated are the same at any gaze angle, thus always terminating in the receptive field of the stimulated neurons (Keating and Gooley 1988; Keating et al. 1983; McCullwain 1988; Schiller 1972, 1977; Schiller and Tehovnik 2001; Tehovnik et al. 2002, 2003a). Recently, we found that if electrical stimulation is delivered after the termination of the fixation spot and if stimulation trials are interleaved with trials that induce an animal to prepare to generate a saccade to the receptive field of the stimulated cells, saccades can be evoked from V1 using currents as low as 2 μA. This behavioral manipulation has enabled us to describe the excitability properties of V1 elements mediating saccadic eye movements using the lowest microampere currents (Tehovnik et al. 2003a).

Four measures of neuronal excitability related to saccadic production were made as a function of cortical depth within macaque V1 (Tehovnik et al. 2003a): current threshold, saccadic latency, anode–cathode ratios, and chronaxies. The current threshold to evoke saccades into the receptive-field location of the stimulated neurons on 50% of stimulation trials was determined. At the surface of V1, saccadic eye movements could not be evoked with currents as high as 30 μA (Fig. 11). As the electrode was advanced into the brain the current threshold dropped, reaching a minimum of 3 μA at 1.75 mm below the top of V1. This depth is situated near lamina V, the major output layer of V1 that innervates the superior colliculus (Fig. 8) (Fries 1984; Graham 1982; Lund et al. 1975; Spatz et al. 1970; Vogt-Weisenhorn et al. 1995).
The saccadic latency of stimulation-evoked saccades elicited from V1 was determined as a function of cortical depth. For a fixed level of current (i.e., 10, 20, and 30 μA), the shortest saccadic latency occurred when the electrode was positioned in the deepest layers of V1 at 2 mm below the cortical surface (Fig. 12). The shortest latency for the evocation of saccades at 10 times threshold current was on average 49 ms. This minimal latency is twice as great as that reported for saccades evoked from the frontal and medial eye fields (Robinson and Fuchs 1969; Tehovnik and Lee 1993; Tehovnik et al. 1994). We believe that this longer latency is attributable to the tonic inhibition that is exerted on the superior colliculus (Hikosaka and Wurtz 1985). The superior colliculus is a major conduit of neuronal transmission between V1 and the brainstem saccade generator and this transmission likely depends on both excitatory and inhibitory inputs (Hikosaka and Wurtz 1985; Keating and Gooley 1988; Keating et al. 1983; Schiller 1977).

Anode–cathode ratios indicate the effectiveness of anodal pulses relative to cathodal pulses for the elicitation of some response. A ratio of <1 indicates that anodal pulses are more effective than cathodal pulses; a ratio of >1 indicates that cathodal pulses are more effective. Anodal pulses activate cell bodies and terminals effectively, whereas cathodal pulses activate axons more readily (Armstrong et al. 1973; McIntyre and Grill 2000; Porter 1963; Rattay 1999; Stoney et al. 1968). Between 0 and 1.75 mm below the cortical surface anodal pulses were superior to cathodal pulses for evoking saccades from V1, whereas beyond 1.75 mm cathodal pulses were superior (Fig. 13). This suggests that between 0 and 1.75 mm below the cortical surface the stimulated elements for the evocation of saccades are composed primarily of cell bodies and terminals and beyond 1.75 mm the stimulated elements are primarily axonal. The latter reinforces the notion that the output layers of V1, whose axons project to the superior colliculus, carry the saccade signal to the brainstem saccade generator (Fig. 8).

Chronaxies have been determined for the directly stimulated elements mediating saccades in V1. The overall range of chronaxies for both superficial and deep layers of V1 spanned from 0.08 to 0.41 ms. These values overlap with those reported for cortical pyramidal fibers (Asanuma et al. 1976; Stoney et al. 1968). The chronaxies for elements mediating saccades in superficial V1 were longer than the chronaxies for elements mediating saccades in deep V1 (Fig. 14). Indeed, pyramidal fibers in superficial V1 are smaller and therefore less excitable than those of deep V1 (Peters and Sethares 1991).
The pyramidal fibers of superficial V1 innervate those of deep V1 (Lund and Boothe 1975; Peters and Sethares 1991; Spatz et al. 1970). The neuronal activation of superficial V1 might gain access to the saccade generator by this connection. If true, blockade of the deep layers should abolish all saccades evoked from the superficial layers.

In conclusion, the deepest layers of V1, which are known to innervate the superior colliculus, are the most excitable for the generation of saccadic eye movements.

Effect of behavioral state

The behavioral state of an animal can affect the chances of evoking saccadic eye movements electrically from neocortex (Tehovnik and Slocum 2004). During active fixation, currents as high as 1,500 μA are ineffective at evoking saccades from macaque V1, whereas saccades can be evoked from dorsomedial frontal cortex and frontal eye fields using currents below 1,500 and 100 μA, respectively (Fig. 15). When stimulation is delivered when an animal is not actively fixating, currents below 100 μA are uniformly effective at evoking saccades from all these cortical regions. We have suggested that during active fixation V1’s access to the brain stem saccade generator is cancelled by tonic inhibition of the superior colliculus (Tehovnik et al. 2003b). If true, reducing this tonic inhibition by infusing bicuculline (a GABAergic antagonist) into the superior colliculus, for example, should reduce the current threshold for evoking saccades from V1.

The tonic inhibition of the superior colliculus might arise from neurons that discharge during active fixation. Such neurons are found in the frontal and medial eye fields and the lateral intraparietal area (Bizzi 1968; Lee and Tehovnik 1995; Lynch et al. 1977). Electrical stimulation of the medial and frontal eye fields and the lateral intraparietal area can inhibit the execution of saccades (Burman and Bruce 1997; Schiller and Tehovnik 2001; Tehovnik and Lee 1993).

Manipulating the behavioral state of monkeys affects the expression of V1 neurons such that the execution of saccadic eye movements is either facilitated or suppressed. We are able to facilitate stimulation-evoked saccades by delivering electrical stimulation to V1 after the termination of the visual fixation spot and by randomly interleaving stimulation trials with trials that induce an animal to prepare to generate a saccade to the receptive field of the stimulated neurons (Tehovnik et al. 2002, 2003a,b). On the other hand, by delivering electrical stimulation to V1 during active fixation we can suppress all stimulation-evoked saccades and delay the execution of saccades made to visual targets placed into the receptive field of the stimulated neurons (Tehovnik et al. 2004). By manipulating the behavioral state, different behavioral responses (i.e., saccade production and saccade delay) can be studied at the same site of stimulation in V1. Previously, we had argued that different
FIG. 14. Excitability properties of neurons mediating saccades in superficial and deep V1. A: current–duration functions are plotted for superficial and deep layers of V1. Superficial sites were from 0 to 1.0 mm below the top of superficial V1 and deep sites were from 1.1 to 2.35 mm below the top of superficial V1. Top: current to evoke saccades into the receptive field on 50% of stimulation trials is plotted as a function of pulse duration. Each curve in a panel represents data from one stimulation site; 18 sites were studied: 9 superficial sites and 9 deep sites. Bottom: normalized threshold current based on the data from above is plotted as a function of pulse duration. For a pulse duration of 0.7 ms, the current required to evoke saccades on 50% of stimulation trials is set to unity and all other values are expressed as a multiple of the current used at the 0.7-ms pulse duration. 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 the site of study. B: from the above curves, a distribution of chronaxies for superficial and deep V1 sites is shown. Data from Tehovnik et al. (2003a).

FIG. 15. Current threshold for evoking saccades from V1, the dorsomedial frontal cortex (DMFC), and the frontal eye fields (FEF). The current threshold for eliciting saccades on 70% of stimulation trials is plotted as a function of stimulation onset time for V1, the DMFC, and the FEF. Dashed part of the curves for V1 indicates that saccades could not be evoked with currents as high as 1,500 μA. For all experiments (see inset), the fixation duration (fix) was 600 ms after which time a juice reward (juice) was delivered to a monkey for maintaining fixation. Stimulation onset time (stim) is with respect to the end of the fixation period. Pulse duration, frequency, and train duration were fixed at 0.2 ms, 200 Hz, and 200 ms, respectively. Data from Tehovnik et al. (2003b).
populations of neurons mediate saccade production and saccade delay: saccade production by the corticocollicular pathway and saccade delay by the corticogeniculate pathway (Fig. 8).

Because the behavioral state of an animal can so greatly affect the current threshold for evoking saccades from V1, V1 cannot be as intimately connected to the saccade generator in the brain stem as are the frontal eye fields, for instance. Thus just because saccades can be evoked electrically from V1 using microampere currents does not mean that V1 is a motor area.

Finally, how much of the electrically evoked response pertaining to saccade production from V1 in monkeys is the result of a stimulation-triggered visual phosphene? Because saccadic eye movements can be evoked from regions of neocortex not normally associated with the production of visual phosphenes [e.g., the lateral intraparietal area, the frontal and medial eye fields, prefrontal cortex, and so on (Tehovnik and Slocum 2004)], the electrical evocation of saccades alone cannot be used to argue for the generation of phosphenes. Nevertheless, the recent results of Bradley et al. (2004) suggest that monkeys are able to generate memory-guided saccades to the receptive-field locations of V1 neurons that have been stimulated electrically. We now need to determine whether the effects of Bradley et al. are unique to V1 and to assess psychophysically what a monkey experiences perceptually while electrically stimulating V1.

How V1 gains access to the saccade generator

Unlike the eye fields in the frontal lobes, V1 can gain effective access to the saccade generator in the brain stem by the superior colliculus (Fig. 16). Much evidence supports this contention. First, the deepest layers of V1 innervate the superior colliculus (Finlay et al. 1976; Fries 1984; Graham 1982; Lund et al. 1975; Spatz et al. 1970; Vogt-Weisenhorn et al. 1995). Second, the lowest current threshold and shortest latencies for evoking saccades electrically occur with stimulation of the deepest layers of V1 (Tehovnik et al. 2003a). Finally, lesions of the superior colliculus abolish all saccades normally evoked from V1, even using current in the milliampere range (Keating and Gooley 1988; Keating et al. 1983; Schiller 1977).

If the superior colliculus is the primary relay between V1 and the brain stem saccade generator, lesions that do not include the superior colliculus should have negligible effects on the electrical evocation of saccades from V1. After lesions of the intraparietal cortex or the frontal eye fields or both, the evocation of saccades from V1 was unaffected (Keating and Gooley 1988; Keating et al. 1983). This further supports the notion that V1 gains access to the brain stem saccade generator primarily by the superior colliculus (Fig. 16).

Does V1 send a signal to trigger saccades?

Supèr et al. (2004) found that V1 cells begin to discharge between 100 and 200 ms before the onset of saccadic eye movements generated across a textured background, with the best response occurring when the saccades were made to the receptive field of the neurons under study. Similarly, Boch (1986) found that cells in V1 fire immediately before the execution of a saccade made to a visual target positioned in the corresponding receptive field; however, most of the response was related to the offset of the fixation spot rather than to the onset of the visually guided saccade. Others have failed to find any discharge before the execution of visually guided saccades for a majority of cells tested (Wurtz and Mohler 1976). As mentioned previously, cells in the deepest layers of V1 send projections to the superior colliculus, and stimulation of these layers is believed to activate this pathway (Finlay et al. 1976; Tehovnik et al. 2003a). Whether corticocollicular cells of V1 (Fig. 8) are activated during the execution of visually guided saccades remains to be determined.

TOWARD THE DEVELOPMENT OF AN EFFECTIVE VISUAL PROSTHESIS

Some 1.1 million people in the United States are legally blind, with the vast majority of this group exhibiting blindness attributed to retinal damage (e.g., age-related macular degeneration, retinal damage resulting from diabetes, etc.; Maynard 2001). Therefore the development of an effective visual prosthesis that bypasses the retina is of major importance.

To a large extent, the development of an effective V1 prosthesis for the blind has been hampered by 3 factors. First, much of the reported work conducted on human subjects over the past 40 yr has been done by delivering milliampere currents to the surface of V1 (e.g., Brindley and Lewin 1968a,b; Button and Putnam 1962; Dobelle and Mladejovsky 1974; Dobelle et al. 1974, 1976; Lee et al. 2000; Penfield and Peret 1963; Pollen 1975). Such a procedure activates the neuronal elements within V1 en masse with no regard for its laminar or columnar microstructure and occasionally evokes sensations of pain resulting from meningeal or scalp stimulation. Second, engineers designing visual prosthetic implants for human V1 do not have an effective animal model by which to guide the placement of their microelectrodes. Nor do they have a way of determining systematically the range of visual percepts that are evoked when stimulation is delivered to various portions of V1.

Third, detailed assessment of the effects of electrical stimulation can be done only on a limited basis in human
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subjects; by contrast animals can be studied over extended time periods by collecting thousands of trials daily using a variety of psychophysical procedures and the circuits involved in the electrical generation of visual percepts can be manipulated using lesions and pharmacological agents.

We suggest that the use of macaque monkeys to study phosphene induction along with continued testing on humans with microelectrode implants in V1 should accelerate the development of an effective visual prosthesis for the blind, an idea advanced by Troyk, Bradley, and colleagues (Bradley et al. 2003; Troyk et al. 2003). Before this can be accomplished, however, some issues need to be addressed.

1) We believe that on delivery of stimulation to V1 in macaques phosphes are induced that are oculocentric, punctate, and confined to the receptive field of the stimulated neurons as long as microampere currents are used. We have yet to determine the featural characteristics of these phosphes such as their shape, brightness, color, and so on, and whether stimulating through many electrodes can produce patterns of phosphes. This will require the use of psychophysical tests whereby monkeys are made to match the features of phosphes with those of some real image.

2) As discussed, electrical stimulation of macaque V1 immediately before the animal generates a saccade to a visual target in the receptive field of the stimulated cells delays the execution of the eye movements (Tehovnik et al. 2004). The directly stimulated elements accounting for this effect exhibited a narrow range of excitabilities, indicating that a restricted population of V1 elements mediates this effect. We know that the delay effect is dependent on the location and size of the visual target such that the visual target needs to be situated in and confined to the receptive field of the stimulated neurons. If the contrast, brightness, color, and shape of the visual target also influence the delay effect, then this method will be useful in determining the visual features mediated by the directly stimulated neurons. For instance, if the delay effect were best for dark targets as compared with light targets, this would suggest that the directly stimulated elements produce a dark phosphene. We suspect that such effects would be best realized at the lowest currents that recruit the fewest number of V1 elements.

3) The receptive field size of cells increases as an electrode is advanced from superficial to deep layers of V1 (Hubel and Wiesel 1968). If receptive-field size in V1 can be used as an indicator of phosphene size (as we believe), advancing an electrode from superficial to deep sites in V1 should increase the size of a phosphene.

4) The elements in macaque V1 that mediate behaviors, such as classical conditioning and saccades, exhibit chronaxies similar to those that mediate phosphes in humans. This suggests that every time stimulation induces behavioral effects from macaque V1, a visual percept is also produced; however, the chronaxies determined for human subjects were all done using surface cortical stimulation (Brindley and Lewin 1968a; Dobelle and Mladjevsky 1974; Rushton and Brindley 1978). The chronaxies for phosphene induction in humans need to be determined using depth microelectrodes. Whether these chronaxies vary across depths within V1 would be instructive, given that they do so for saccade production in monkeys (Tehovnik et al. 2003a).

5) In monkeys cathodal pulses are best at evoking saccades from the deepest layers of V1, and anodal pulses are best at evoking saccades from the upper layers (Tehovnik et al. 2003a). When electrical stimulation is delivered to the deepest layers of human V1, cathodal pulses are superior to anodal pulses for the elicitation of phosphes (Schmidt et al. 1996). Whether cathodal and anodal pulses are differentially effective for the elicitation of phosphes from the upper layers of human V1 needs to be investigated.

6) As trains of stimulation are delivered repeatedly to V1, the effectiveness of the stimulation for evoking a phosphene of a given brightness drops until some asymptotic level is achieved (Schmidt et al. 1996). Issues pertaining to brightness accommodation for phosphes are important for the establishment of a stable percept when using implanted electrodes. Factors affecting response variability arising from repeated stimulation of V1 could very well be studied in monkeys as they relate to stimulation-evoked saccades and stimulation-evoked interference.

7) Saccades can be evoked for V1 using currents as low as 2 μA as long as electrical stimulation is delivered to V1 while a monkey is not actively fixating a fixation spot and as long as the stimulation trials are interleaved with nonstimulation trials in which the monkey is required to generate a saccade to the receptive-field location of the stimulated neurons for reward (Tehovnik et al. 2003a). It remains to be determined whether such saccades can be evoked electrically from V1 of humans once subjected to similar behavioral conditions. If effective, this method could be used to probe the effectiveness of electrical stimulation of human V1 in addition to traditional methods, that is, self-reports of phosphes induced by stimulation.

8) Does blindness prevent the elicitation of dark phosphes and can both light and dark phosphes be evoked in sighted humans? This issue needs to be investigated further in both humans and monkeys.

9) It is known that if monkeys are retinally blind from birth, the conditioning response attributed to stimulation of V1 is transferred immediately to any other region in extrastriate cortex without additional training (Doty et al. 1980). Training is always necessary when transferring such a conditioning response between striate and extrastriate regions in retinally intact monkeys (Doty 1965, 1970). This means that early visual input is necessary to make striate and extrastriate regions functionally distinct. Just how this fact impacts phosphene induction in the blind needs to be studied.

10) How should one best train humans as well as monkeys to make visual discriminations based on a limited set of illuminated pixels, which is what the first generation of V1 prosthetics will provide? Cha et al. (1992a,b,c) found that 625 pixels (25 × 25) projected onto 1.7 × 1.7° of retina monocularly gave sighted subjects enough visual information to permit them to read at over 50% of their normal reading rate. In these studies, the stimuli were text images, which were viewed through a grid of pinholes each measuring 1.62 min of arc. Designing and testing a range of pixelized stimuli that match the range of percepts evoked electrically from V1 will need to be accomplished in both humans and monkeys.

11) Further development of high-density electrode arrays that can be permanently and safely implanted into V1 is necessary (Norman et al. 1999). Although using fine-tipped metal microelectrodes has been the most common approach,
some investigators have considered going to a tetrode configuration, whereas others are working on silicon-based technologies (Jones et al. 1992; Norman et al. 1999; Tobias et al. 2001). Which of these approaches will prove to be superior for inducing phosphenes from V1 is not yet known.

In conclusion, the use of macaque monkeys to study phosphene induction from V1 should accelerate the development of a V1 prosthesis for the blind. The challenge now is to describe the range of percepts generated by electrically activating the fewest number of neurons within the various laminae and columns of V1 and to see how this corresponds to the range of percepts mediated by single cells in V1.

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