Published in final edited form as:

Brain Res Rev. 2007 February ; 53(2): 337–343.

Phosphene Induction by Microstimulation of Macaque V1

Edward J. Tehovnik and Warren M. Slocum

*Department of Brain and Cognitive Sciences Massachusetts Institute of Technology, Bldg. 46-6041
Cambridge, MA 02139*

Abstract

Non-human primates are being used to develop a cortical visual prosthesis for the blind. We use the properties of electrical microstimulation of striate cortex (area V1) of macaque monkeys to make inferences about phosphene induction. Our analysis is based on well-established properties of V1: retino-cortical magnification factor, receptive-field size, and the characteristics of hypercolumns. We argue that phosphene size is dependent on the amount of current delivered to V1 and on the retino-cortical magnification factor. We suggest that to improve the correspondence between the site of stimulation within V1 and the visual field location of an elicited phosphene both eyes must be put under experimental control given that phosphene location is retinocentric and given that the vergence angle between the eyes might affect the position of a phosphene in depth. Knowing how electrical microstimulation interacts with cortical tissue to evoke percepts in behaving macaque monkeys is fundamental to the establishment of an effective cortical visual prosthesis for the blind.

Keywords

striate cortex; magnification factor; receptive field; electrical microstimulation; phosphenes; monkeys; cortical visual prosthesis

1. Introduction

Electrical stimulation of primary visual cortex (area V1) in humans has been shown to produce a visual percept, called a phosphene (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Schmidt et al., 1996). This finding has led to the suggestion that microstimulation of V1 in behaving monkeys could serve as a model for the implantation of a functional cortical visual prosthesis in clinically blind individuals (Troyk et al., 2003; Bartlett et al. 2005; Bradley et al., 2005; DeYoe et al., 2005; Tehovnik et al., 2005a). For over ten years since Schmidt and colleagues (1996) first implanted a microelectrode array in one blind patient for the study of phosphenes, the creation of a functional cortical visual prosthesis for the blind has not been realized. We believe that the major impediment hampering this effort is the absence of an animal model to guide the development of such a device. The development of an effective device could ultimately benefit over one million blind individuals in the United States (Leonard, 1999).

Electrical stimulation of neocortex activates a sphere of tissue about the electrode tip such that increases in current cause an increase in the sphere of activation (Tehovnik, 1996). When

Correspondence to: Edward J Tehovnik Dept. Brain and Cognitive Sciences Massachusetts Institute of Technology, Bldg. 46-6041
Cambridge, MA 02139 617-324-3726 (tel) 617-324-3725 (fax) tehovnik@mit.edu.

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evoked using currents above 10 μA and well into the milliampere range, phosphenes are commonly described as being featureless and circular in shape (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Schmidt et al., 1996). Furthermore, as the stimulating electrode is positioned more distant from the foveal representation of V1 the size of a phosphene increases from a fraction of a degree when evoked at the fovea to three degrees when evoked at the most extreme eccentricities of the visual field (Brindley and Lewin, 1968; Schmidt et al., 1996). At current levels below 10 μA , phosphenes can exhibit distinct colours of red, yellow, or blue (Schmidt et al., 1996).

Since electrical current affects the spatial spread of activation, understanding how it interacts with V1 tissue is central to determining whether stimulation evokes featureless versus feature-rich phosphenes. V1 is composed of neurons that respond to a range of visual attributes such as stimulus size, contrast, colour, depth, orientation, motion, and so on (Schiller, 1997). V1 cells respond maximally when a visual stimulus exhibiting the preferred features is positioned within the receptive field. One might speculate that activation of such a neuron should evoke a phosphene whose features are coded by the activated neuron. For example, if a neuron is maximally responsive to a two degree, red bar of light orientated at 45 degrees, then activation of this neuron should elicit a phosphene of two degrees in length, red in colour and oriented at 45 degrees. One of the problems with this example is that even at the lowest currents used for the induction of phosphenes (i.e. 1.9 μA , see Schmidt et al., 1996) several dozens of neurons (i.e. some 75 cells according to our estimate below) can be activated thereby producing a phosphene that contains the attributes of the group of neurons stimulated rather than those of an individual neuron. The following is a detailed calculation supporting this claim:

[The current spread and the number of elements stimulated with 1.9 μA is based on experiments conducted in macaque monkeys (Peters, 1994; Tehovnik et al., 2006). Using the current-distance equation, $I = Kr^2$, where I is current in μA , K is the current-distance constant in $\mu\text{A}/\text{mm}^2$, and r is the radial spread of current in mm, 1.9 μA is estimated to activate V1 tissue directly within 0.053 mm from the electrode tip. For this estimate a K value of 675 $\mu\text{A}/\text{mm}^2$ was used (Tehovnik et al., 2006). V1 contains about 120,000 neurons/ mm^3 of tissue (Peters, 1994). Activating 0.053 mm of tissue from the electrode tip is estimated to directly excite about 75 neurons (using $4/3\pi r^3$, for volume of a sphere).]

The discovery of hypercolumns imbedded within the retinotopic map of V1 by Hubel and Wiesel (1977) suggests that V1 consists of modules containing a similar cross-section of neurons that code for the same range of visual attributes. Therefore, activation of these modules might be expected to produce a similar phosphene except for its size and visual field location, which is related to the site of stimulation within the topographic order of V1. Stimulation confined to a subsection of a module might be expected to produce a phosphene exhibiting features.

2. Magnification factor and receptive-field size

In monkeys, the retino-cortical 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 retino-cortical magnification is the extent of V1 tissue measured in millimeters devoted to representing a particular portion of the visual field measured in degrees of visual angle (Talbot and Marshall 1941; Daniel and Whitteridge, 1961). This parameter is commonly expressed as the inverse magnification factor, whose units are degrees of visual field represented by 1 mm of cortical tissue. Figure 1A plots the inverse magnification factor as a function of visual field eccentricity coded by macaque V1 (Talbot and Marshall, 1941, Daniel and Whitteridge, 1961; Hubel and Wiesel, 1974; Dow et al., 1981; Tootell et al., 1982; Dagnelie et al., 1989). Notice that the inverse magnification factor increases with

eccentricity and that it is 0.055 degrees/mm at an eccentricity of zero degrees, which represents the center of the fovea.

The receptive-field size of V1 cells increases with visual field eccentricity such that at zero degrees eccentricity the average receptive-field size is approximately 0.2 degrees of visual angle (Fig. 1B; Hubel and Wiesel, 1974; Schiller et al., 1976; Dow et al., 1981; van Essen et al., 1984; Dagnelie et al., 1989). 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. 1AB). The receptive fields are therefore highly overlapped at the fovea as originally observed by Dow et al. (1981). It follows that the cortical-point image should increase at the lowest eccentricities, again, as observed by Dow et al. (Fig. 1C). The cortical-point image is the product of magnification factor (1/inverse magnification factor of Fig. 1A) and receptive-field size (Fig. 1B). At the foveal representation of V1 (e.g. at an eccentricity of 0 to 1 degree) an electrode must be repositioned by 2 to 3 mm horizontally within cortex in order to arrive at a new non-overlapped receptive-field location, whereas at a more peripheral field representation of V1 (e.g. at an eccentricity of 10 to 14 degrees) the electrode needs to be repositioned by less than 1 mm (Fig. 1C).

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 retino-cortical 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 Figure 1A. We estimate using the current-distance relationship that to activate 1 mm of V1 tissue requires 169 μ A (see caption of Fig. 2A for details). To activate less than 1 mm of V1 tissue requires some fraction of this 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 μ A (Fig. 2A). 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 figure 2Ba (based on data of Fig. 1B). 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 degrees and stimulation at a site coding for an eccentricity of 10 degrees, for example, should produce a phosphene no smaller than 0.7 degrees. Once suprathreshold currents are delivered to the neurons, phosphene size should increase further due to the recruitment of a larger volume of neurons.

One of the challenges in evoking phosphenes from macaque monkeys is to devise behavioural methods to infer what monkeys perceive when stimulation is delivered to V1. We have previously shown that microstimulating V1 while a monkey is fixating a spot of light delays the execution of a subsequent visually guided saccadic eye movement as long as the saccade is directed toward the receptive field of the stimulated cells (Tehovnik et al., 2004). In addition, we have observed that such microstimulation also delays forelimb movements made in response to a visual target placed in the receptive field of the stimulated cells. We therefore believe the delay effect is due to a disruption of the visual signal as it is transmitted along the geniculostriate pathway (for arguments see Tehovnik and Slocum, 2006) and we would suggest that a temporary scotoma is produced by the stimulation after the evocation of a phosphene,

as seems to occur with migraine phosphenes generated by activation of human V1 (Grüsser, 1995). The scotoma induced during migraines is of similar size and shape to that of the evoked phosphene. The neurons that mediate the delay effect exhibit excitability properties that are similar to those of neurons in V1 of humans that mediate electrically evoked phosphenes (i.e. chronaxies ranging from 0.1 to 0.4 ms; Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Rushton and Brindley, 1978; Tehovnik et al., 2004). Therefore, every time stimulation evokes a delay in visually guided saccades, a phosphene is likely being experienced by the monkey at the time of stimulation, which is then followed by a temporary scotoma of comparable size and shape to that of the phosphene.

We found that the size of the visual field affected by the stimulation to induce a delay in visually-guided saccades, called a delay field, increases as a function of the visual field eccentricity coding by the stimulated neurons (Tehovnik et al., 2005b). Also the size of the delay field increases with current (Tehovnik et al., 2004, 2005b; Tehovnik and Slocum, 2006). A summary of these data is illustrated in figure 2Aab. The size of the delay fields using 50 and 100 μ A (a and b, respectively of Fig. 2A) overlaps with the size predictions made for the 50 and 100 μ A conditions using the inverse retino-cortical magnification factor. Notice that the size of the delay fields was less than the lower limit predicted from size estimates based on the receptive fields of V1 cells (Fig. 2Ba). If phosphene induction during stimulation is responsible for the delay of visually guided saccades in macaque monkeys, then the size of the delay field (or putative phosphene) is more dependent on properties related to the magnification factor than to the size of receptive fields. To further substantiate this claim a broader range of currents and more sites along the retinotopic expanse of V1 will need to be tested. Also other behavioural methods will need to be devised and employed to study phosphene-induction in monkeys, especially methods that divorce the effect of stimulating V1 from the elicitation and/or disruption of saccadic eye movements (Tehovnik et al., 2005a). Finally, phosphene size needs to be studied in humans using a range of currents delivered through microelectrodes implanted in various retinotopic locations of V1 as had been started by Schmidt and colleagues (1996). So far, the most complete estimates of phosphene size have come from experiments in which milliamperage currents were delivered to the surface of V1 (e.g. Brindley and Lewin, 1968; Rushton and Brindley, 1977).

We believe that the functional unit for phosphene induction in V1 is most likely the hypercolumn, which is about 1 mm by 0.7 mm of tissue composed of layers spanning some 2 mm of tissue (Fig. 2C-E). The 1-mm axis of a hypercolumn consists of a pair of ocular dominance columns and the 0.7 mm axis contains orientation columns coding for zero to 180 degrees of line orientation (Hubel and Wiesel, 1977). The ocular dominance columns run perpendicular to the V1/V2 border, which represents the vertical meridian (LeVay et al., 1975). Also the retino-cortical magnification factor for the vertical meridian is about 1.4 times greater than the retino-cortical magnification factor for the horizontal meridian (Tootell et al., 1982; van Essen et al., 1984; Tootell et al., 1988b). This ratio corresponds to the ratio between the length (1 mm) and width (0.7 mm) of a hypercolumn (Blasdel and Campbell, 2001). Since electrical stimulation activates a sphere of tissue of a given radius, one might expect that an evoked phosphene should be somewhat elongated parallel with the axis of the horizontal meridian. Phosphenes evoked from human V1 tend to be circular, although elongated phosphenes have been reported (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Schmidt et al., 1996). Thus far, we have studied the shape of delay fields and found them to be roughly circular (Tehovnik et al., 2005b).

In order to activate subregions of a hypercolumn using a microelectrode, currents of less than 100 μ A would be necessary (Fig. 2C-E). To confine current to a single ocular dominance column spanning 0.5 mm, a current of less than 40 μ A is required. This estimate is consistent with the finding that currents under 40 μ A 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). To confine current to a column coding for a colour or line orientation [*which spans about 0.17 mm of tissue; Hubel et al. (1978); Michael (1981)*] currents of 5 μA or less are needed. In the case of colour, this estimate concurs with the observation in humans that currents under 10 μA were required to evoke coloured phosphenes (Schmidt et al., 1996).

3. Minimal currents for the activation of phosphenes from foveal V1

Recently it has been shown that activation of a single pyramidal neuron in cortex can elicit a motor response when activated with trains of nano-ampere currents (Brecht et al., 2004). Based on the excitability properties of the directly stimulated elements in V1 it is presumed that the elements that mediate phosphenes are comprised mainly of the largest pyramidal fibres (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Rushton and Brindley, 1978; Tehovnik et al., 2005a; Tehovnik et al., 2006). It is at the deepest layers of human V1 from which phosphenes can be evoked using the lowest currents (Bak et al., 1990; Schmidt et al., 1996). We know that the deepest layers of macaque V1 contain large pyramidal neurons and that these neurons arranged in modules are aligned perpendicular to the cortical surface and are spaced by roughly 30 μm (Peters, 1994). In order to activate one of these pyramidal modules with the electrode in the deepest layers of V1, the current would have to spread by 15 μm . To establish such an effective spread some 152 nA would be required [$I = 675 \mu\text{A} / \text{mm}^2 \times (0.015 \text{ mm})^2$]. Using such nano-ampere currents for the activation of the foveal representation of V1 is estimated to evoke a phosphene whose size is within the range of a single cone, which corresponds to the minimal angle of resolution of a fraction of a minute of visual angle [*i.e. phosphene size = inverse magnification factor at the fovea $\times$ field of activation: phosphene size using 152 nA = 0.055 degrees/mm $\times$ 0.03 mm = 0.002 degrees or 0.12 minutes of visual angle; see Dow et al. (1981) for details about the minimal angle of resolution at the fovea*]. This estimate assumes that phosphene size scales with the retino-cortical magnification factor and not with receptive-field size (Fig. 2A). However, if phosphene size is restricted by receptive-field size (Fig. 2B), then at the fovea this would represent some 20 or so cone widths, on average [*i.e. 12 minutes per receptive field / 0.6 minutes per cone width, Dow et al. (1981)*].

Remarkably, Dobelle and Mladejovsky (1974) have evoked phosphenes as small as 5 minutes of visual angle when delivering milliamperic currents to the surface of human V1. Whether phosphenes measuring a fraction of a minute can be elicited from V1 using nano-ampere currents needs to be investigated.

4. Coding for phosphene brightness

If the size of a phosphene is coded by the region of V1 activated as well as by the amount of tissue excited, then how is the brightness of a phosphene represented in V1. Rushton and Brindley (1978) have suggested that blind humans can discriminate between 12 levels of phosphene brightness induced by changes in current level. Increases in current, pulse duration, train duration, or pulse frequency of stimulation evoke a brighter phosphene (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Rushton and Brindley, 1978; Evans et al. 1979; Schmidt et al., 1996). We know that the brighter the visual target the greater the firing frequency of V1 cells until some upper limit of discharge is attained (Albrecht and Hamilton, 1982). Similarly, as the frequency of pulses is increased from 12 to 400 Hz the brightness of phosphenes tends to increase until the brightness saturates at frequencies greater than 200 Hz (Evans et al. 1979). What is not known is whether phosphene brightness can be manipulated independently of phosphene size by changing one parameter of stimulation, such as pulse frequency, for example, while holding the other parameters constant.

5. Effects of blindness

V1 of a blind human may not be comparable to that of a sighted human. Both light and dark phosphenes have been evoked in sighted humans but rarely in blind humans (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Schmidt et al., 1996; Lee et al., 2000). Also there is some suggestion that the evocation of coloured phosphenes occurs less frequently (and often not at all) in blind humans (Dobelle, 2000). Bartlett, Doty and colleagues (2005) report that the threshold to detect currents delivered to V1 drops in monkeys that are blinded by retinal ablations. A related observation is that the threshold to evoke a phosphene from V1 using transmagnetic cranial stimulation is appreciably lower after human subjects are dark adapted for 45 minutes (Boroojerdi et al., 2000). Interestingly, the responsivity of V1 cells is greatly increased in monkeys that have been dark adapted (Talbot and Marshall, 1941). Just how these various observations pertaining to blindness are related is unclear at this time.

6. Eye movements and phosphene induction

An often overlooked issue regarding the generation of phosphenes is that the topographic map of V1 is anchored to the eyes and not to the head or the body (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974; Schmidt et al., 1996). One consequence is that the perceived position of a cortically induced phosphene changes with eye movements. Also the depth of a phosphene with respect to the subject might be affected by the vergence angle between the eyes. This was best appreciated by Rushton and Brindley (1977) who found that when mapping the position of an evoked phosphene the stimulation would often compel a blind patient to direct his gaze in the direction of the phosphene thereby causing an under-estimation of the true position of the phosphene with respect to the fovea. Moreover, the position of a phosphene could change in depth, which further interfered with their measures of position. The relationship between the location of an evoked phosphene and the topographic order of striate cortex is often very poor in blind patients (Dobelle et al., 1976). Whether this is related to spurious eye movements or other factors is uncertain. This issue could be resolved by performing phosphene experiments on blind monkeys whose eye movements (conjugate as well as vergence) are monitored continuously.

7. Stimulations delivered through many electrodes

The discussion thus far has centered on the delivery of currents through a single cortical electrode. Delivering currents through multiple electrodes in V1 can produce patterned percepts (i.e. lines and letters) in humans, but interactions between electrodes can interfere with the perception (Dobelle et al., 1976; Schmidt et al., 1996). Using microelectrodes, it was found that interactions between adjacent electrodes were minimized if spaced by more than 0.5 mm when currents up to 30 μ A were delivered to V1 (Schmidt et al., 1996). Our current-distance estimates agree with this observation in that currents under 40 μ A are restricted to a 0.5 mm ocular dominance column in macaque V1 (Fig. 2C). Restricting the field of activation for a given inter-electrode distance is central to diminishing unwanted interactions between electrodes. Auditory physiologists have found that the field of activation about an electrode is more focused going from monopolar to bipolar to tripolar stimulation even though the lowest current threshold for neuronal excitation is with monopolar stimulation (e.g. Kral et al., 1998; Bierer and Middlebrooks, 2002; Middlebrooks and Bierer, 2002; Bierer and Middlebrooks, 2004; Snyder et al., 2004). Previously, we used delay fields to assess the extent of neuronal excitation and this was based entirely on monopolar stimulation (Tehovnik et al., 2006). The interactive effects of different fields of activation during multipolar stimulation could be investigated by studying the size and shape of delay fields.

8. Conclusion

By combining properties of effective current spread and retino-cortical magnification factor, we may begin to study the characteristics of phosphenes evoked from V1 of monkeys (as well as humans) in some systematic way. Also, having meticulous control over eye movements should improve our estimates of how well V1 might code for the position of phosphenes in three-dimensional space. Finally, the size and shape of delay fields could be used to study the interactions of delivering currents through many electrodes situated in V1, which would assist in the design and development of a microelectrode cortical implant for human use.

Acknowledgments

This work was supported by NIH EY014884. We thank reviews for their helpful comments.

Abbreviations

V1, striate cortex.

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Figure 1.

(A) Inverse magnification factor is plotted as a function of visual field eccentricity for V1 of macaque monkeys. Data were obtained from Talbot and Marshall (1941), Daniel and Whitteridge (1961), Hubel and Wiesel (1974), Dow et al. (1981), Tootell et al. (1982), and Dagnelie et al. (1989). A regression line (i.e. inverse magnification factor = $0.085 \times \text{eccentricity} + 0.055$) was fitted to the data ($R^2 = 0.92$, $N = 39$). (B) Receptive-field size is plotted as a function of visual field eccentricity for V1 of macaque monkeys. Data were obtained from Hubel and Wiesel (1974), Schiller et al. (1976), Dow et al. (1981), van Essen et al. (1984), and Dagnelie et al. (1989). A regression line (i.e. receptive-field size = $0.051 \times \text{eccentricity} + 0.214$) was fitted to the data ($R^2 = 0.77$, $N = 24$). (C) Cortical-point image is plotted as a function of

visual field eccentricity for V1 of macaque monkeys. Cortical-point image is the produce of magnification factor and receptive-field size for a given visual field eccentricity. The function was derived from A and B by multiplying $1/(0.085 \times \text{eccentricity} + 0.055)$ by $(0.051 \times \text{eccentricity} + 0.214)$ for a particular visual field eccentricity.

Figure 2.

(A) Visual field size represented by activating V1 using a range of currents (3 to 169 μA) is plotted as a function of visual field eccentricity coded by the site of stimulation. We know that a 169 μA current directly activates 1 mm of V1 tissue [using the current-distance equation for effective radial, current spread (in mm) from an electrode tip: $r = (I/K)^{1/2}$, where I is current (in μA) and $K = 675 \mu\text{A}/\text{mm}^2$; see Tehovnik et al. (2006) for details]. The function in the figure for 169 μA was derived from Fig. 1A, which indicates the amount of visual field represented by a 1 mm region of tissue in V1. Functions for the remaining currents (3 to 100 μA) represent a fraction of the visual field activated by 169 μA . This fraction was determined for each current by noting the amount of tissue activated at these current levels using the current-distance equation from above. The fraction of visual field activated was 0.134, 0.188, 0.278, 0.386, 0.544, and 0.770 for 3, 6, 13, 25, 50, and 100 μA , respectively. To show that the estimates are reasonable, functions for the size of a delay field produced using 50 and 100 μA are shown (a and b, respectively). Notice that these functions overlap with the 50 and 100 μA lines. (B) Same plot as in A. The receptive-field size of V1 neurons is plotted as a function of visual field eccentricity coded by the site of stimulation (a). Data obtained from Fig. 1B. (C) Two ocular dominance columns are illustrated for macaque V1. Using the current-distance equation in A, effective current spread for 25 μA or less is shown by the gray circles to be confined to a 0.5 mm ocular dominance column, which represents the approximate width of such a column.

(Hubel and Wiesel, 1972; Hubel and Freeman, 1977; LeVay et al., 1985; Blasdel and Salama, 1986; Tootell et al., 1988a; Horton and Hocking, 1996). Layers I through VI are indicated in the figure. (D) Effective current spread is shown by the gray circles for 50 and 100 μ A in a hypercolumn. (E) Size of a hypercolumn looking at the surface of V1 is illustrated. The black circles represent cytochrome oxidase patches spaced by 0.5 mm when situated between two adjacent ocular dominance stripes and spaced by 0.7 mm when situated within a stripe (Blasdel and Salama, 1986).