Laminar Variation in Threshold for Detection of Electrical Excitation of Striate Cortex by Macaques

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Submitted 20 April 2005; accepted in final form 23 July 2005

DeYoe, Edgar A., Jeffrey D. Lewine, and Robert W. Doty. Laminar variation in threshold for detection of electrical excitation of striate cortex by macaques. J Neurophysiol 94: 3443–3450, 2005. First published August 3, 2005; doi:10.1152/jn.00407.2005. Macaques were trained to signal their detection of electrical stimulation applied by a movable microelectrode to perifoveal striate cortex. Trains of ≤100 cathodal, 0.2-ms, constant current pulses were delivered at 50 or 100 Hz. The minimum current that could be reliably detected was measured at successive depths along radial electrode penetrations through the cortex. The lowest detection thresholds were routinely encountered when the stimulation was applied to layer 3, particularly just at the juncture between layers 3 and 4A. On the average, there was a twofold variation in threshold along the penetrations, with the highest intracortical thresholds being in layers 4C and 6. Variations as high as 20-fold were obtained in some individual penetrations, whereas relatively little change was observed in others. The minimum detectable current was 1 μA at a site in layer 3, i.e., 10–100 times lower than that for surface stimulation. Because macaques, as do human subjects, find electrical stimulation of striate cortex to be highly similar at all loci (a phosphene in the human case), it is puzzling as to how such uniformity of effect evolves from the exceedingly intricate circuitry available to the effective stimuli. It is hypothesized that the stimulus captures the most excitable elements, which then suppress other functional moieties, producing only the luminance of the phosphene. Lowest thresholds presumably are encountered when the electrode lies among these excitable elements that can, with higher currents, be stimulated directly from some distance or indirectly by the horizontal bands of myelinated axons, the stria of Baillarger.

INTRODUCTION

Electrical stimulation of human striate cortex evokes the sensation of a unitary point of light—a phosphene—that usually is qualitatively invariant despite wide adjustments in the parameters and locus of stimulation (Bak et al. 1990; Brindley 1971; Brindley and Lewin 1968; Dobelle and Mladejovsky 1974; Henderson et al. 1979; Pollen 1975; Rushton and Brindley 1978; Schmidt et al. 1996). This encourages the idea of applying such stimulation prophetically to the striate cortex of the blind, excitation of multiple loci, thus allowing the evocation of visual patterns. Such usage would demand limitation of the size of each phosphene and thus presumably, the size of the excited neuronal field, to obtain a large number of nonoverlapping loci.

In most of these initial studies stimuli were applied to the pial surface and required rather high levels of excitatory current. This resulted in somewhat diffuse phosphenes, and restricted the allowable density of stimulated loci. It was then found, however, that macaques could respond to stimulation of as little as 2 μA with microelectrodes tracking through striate cortex (Bartlett and Doty 1980). After a successful exploration with microelectrodes in three sighted patients by Bak et al. (1990), Schmidt et al. (1996) proceeded to implant an array of microelectrodes in a blind volunteer. “Two-point discrimination” was some fivefold better than what had previously been achieved with surface stimulation, and thresholds for phosphene elicitation were comparable to stimulus levels detectable by macaques. Bradley et al. (2005) and Tehovnik et al. (2005) have continued to explore this approach, using an implanted array or movable microelectrodes in sighted macaques, and testing the animal’s ability to direct its gaze to the point in the visual field corresponding to the stimulated locus.

Our approach herein has been to explore the circuitry responsible for the putative phosphene in macaques. Because the animals find stimulation at all striate loci to be qualitatively equivalent (Bartlett et al. 2005), as is the human case, the profile of excitability by microelectrodes traversing the distinct cortical laminae may begin to define the elements involved. At the least, these observations, combined with findings in the companion paper (Bartlett et al. 2005), yield a prescription for generating detectable sensations with minimal currents and provide key insights into the neural mechanisms responsible for the putative phosphene sensation.

METHODS

Animals and behavioral task

Eight Macaca nemestrina were used, under veterinary care. The Guiding Principles in the Care and Use of Animals of the American Physiological Society were rigorously followed in all instances.

The general procedures have been detailed in the companion paper (Bartlett et al. 2005). In brief, the animal placed its hand on a 13 × 20-cm capacitatively tuned plate, proper contact being signaled by a low, continuous tone. Stimulation was presented at some random interval between 2 and 30 s after contact, and if the animal broke contact within 300–1,300 ms thereafter, it was rewarded with a small quantity of fruit juice. The time window for correct detection was set according to the animal’s previously determined reaction times and, for a 1-s stimulus, was typically between 300 and 1,300 ms. Failure to respond to the stimulus within this time frame, or if contact was broken at inappropriate times, activated a loud horn.

Because obtaining a “psychophysical function” (see Bartlett et al. 2005) at each point in the traverse of the microelectrode was impractical, threshold at a tested locus was defined as the lowest current
detected in three of five presentations. Although this method does not yield an unbiased measure of the detection threshold (McNicoll 1972), it could be deduced within 25–30 presentations and was reliably repeatable. Of course, changes in the animal’s criterion, attention, or motivation could introduce error. To guard against such unrecognized fluctuations, permanently implanted macroelectrodes were used throughout each session to determine the threshold for a standard, invariant stimulation. So long as this threshold remained constant, it was assumed that changes in threshold from one to another microelectrode site reflected true differences in detectability, and were not attributable to changes in the animal’s behavioral inclination.

Electrodes, aseptic precautions, and surgery

Macroelectrodes, fashioned from 127-μm Teflon-coated platinum alloy wire (92% Pt, 8% W), cuffed, and cut to a 45° chisel point (Doty and Bartlett 1981), were implanted in striate cortex using full aseptic precautions while the animal was at a surgical level of anesthesia, maintained with halothane or intravenous pentobarbital. At the same time, to provide comfortable stabilization of the animal’s head during recording sessions with microelectrodes, a half-circle of aluminum was secured to keyholes in the skull, as described by Evarts (1968). Subsequently, during an experiment and after the animal had assumed a posture to its liking, the aluminum piece could be clamped, thus painlessly and temporarily preventing the animal from making sudden movements of its head.

Using surgical-grade methacrylate, a 1-cm diameter Nylon recording chamber (FHC, Bowdoinham, ME) was also cemented to the skull surrounding a trephine hole over opercular striate cortex, leaving the dura mater intact. This chamber was filled through a pressure relief port with sterile mineral oil or petroleum jelly. When used in an experimental session, the cover of the chamber was removed after first cleansing its surface with 70% isopropyl alcohol (being meticulously careful, of course, not to permit contact of the alcohol with skin around the implant) followed by H2O2. Strict asepsis was maintained for the interior of the chamber and no infection occurred.

The microelectrodes were held in a miniature hydraulic microdrive (FHC) accommodated to the Nylon chamber, which was refilled with sterile mineral oil to provide a gas-free seal over the dura mater. The platinum–iridium, glass-insulated microelectrodes (FHC) had exposed, conically etched tips roughly 10 μm long and 5 μm at the base and, after penetrating the dura mater, had an impedance of 0.5–1.5 MΩ. They readily recorded single or multiunit activity as the electrode was advanced.

Microelectrode recording and stimulation included both foveal and perifoveal striate cortex, whereas macroelectrode sites were restricted to foveal cortex, as judged by published retinotopic maps (Daniel and Whitteridge 1961; Tootell et al. 1982; Van Essen et al. 1984).

Electrical stimulation and recording

As indicated by Ranck (1975), the change in membrane potential at a cell stimulated by an extracellular electrode is proportional to the stimulus current rather than to the stimulus voltage. Consequently, the typical stimulus consisted of cathodal current pulses delivered in a 1-s burst of 100 pulses of 0.2 ms. The stimuli were generated by a digitally controlled pulse generator (Pulsar 6B, FHC) optically coupled to a constant-current amplifier (FHC CCIU-8). This unit was modified to obtain more precise stimulus waveforms at low amplitudes. An additional low-current range was added (1 μA/V) and the operational amplifier-integrated circuits in the output stage were replaced with circuits having a faster slew rate so that very short stimulus pulses (10 μs) could be produced. Calibration of the digitally controlled stimulus amplitude was monitored by observing the voltage produced across a precision 1.00-kΩ resistor in series with the current return path. To avoid potentially harmful polarization of the stimulating electrodes, an exhaust circuit (Doty and Bartlett 1981; available from FHC) was added, which shunted the stimulating and return electrodes between each stimulus pulse, thereby dissipating the charge accumulated by the electrode capacitance. As an additional precaution, a high-input impedance oscilloscope (10 MΩ) could be placed momentarily across the electrode leads to determine whether the electrode potential during stimulation exhibited signs of excessive polarization during each pulse (Brummer and Turner 1975). Because connecting the oscilloscope in this way compromised the electrical isolation of the stimulator, it was used only momentarily and only when stimulus currents were sufficiently high to suspect that hazardous polarization might occur within the duration of a single pulse.

Measurement of electrode impedance was accomplished using a 1-kHz impedance meter (Bak IMP-1) that could be connected to the electrode in place of the pulse generator. According to the manufacturer, sinusoidal current passed during a measurement was about 0.2 μA root mean square (rms).

A standard AC coupled recording amplifier and high-impedance headstage (Bak MDA-4) could also be connected to the electrode to record the amplitude of the multiunit activity or flash-evoked potentials. To record background multiunit activity, the signal was band-pass filtered with half-amplitude at 200 Hz and 5 kHz. An index of the amplitude of background activity was computed by digitally sampling the signal at 16 kHz for 100 ms and then computing the SD of the sample. (This measure is effectively proportional to the rms amplitude of the signal.) Field potentials were recorded in response to brief flashes generated by a xenon strobe light shining on the back of an opalescent viewing screen. In this case the band-pass filter limits were set at 2 Hz and 2 kHz and the evoked response was averaged for as many as 50 flashes.

Verification of microelectrode locations

Establishing an accurate association between the stimulation/recording sites and the cortical laminarization was difficult, especially given the variable compression of the superficial cortical layers as the electrode was advanced through the intact dura mater. As one aid to this alignment process, electrolytic lesions, 10–15 μA DC for 10–15 s, were made at the terminus of an electrode’s advancement or at identified positions along the track during retraction. Such currents produce lesions of a few hundred microns in diameter, which proved to be a satisfactory compromise between accurate localization versus preservation of the lesion site for ≤6 wk.

To recover these lesions and reconstruct the electrode tracks, euthanasia was induced with a lethal dose of barbiturate. After cardiac perfusion with 4% formalin, the brain was removed and blocked in the plane of the microelectrode tracks. Frozen brain sections were cut at a thickness of 60 μm, mounted, and then stained with cresyl violet. Finished slides were placed in a photographic enlarger and projected onto paper for sketching cortical laminar boundaries and lesion sites. In addition, quantitative measurements of track length and lesion depths were made directly from the slides using a microscope equipped with a calibrated eyepiece reticle.

Marking lesions were only partially useful in establishing the laminar registration. They invariably elevated detection thresholds within ±500 μm of a lesion site and, consequently, could not be used to mark multiple points during the electrode’s advancement. To provide additional data for aligning tracks and laminae, background multiunit activity and flash-evoked potentials were recorded, both of which show unique changes when advancing from layer 4 into layer 5. At this border, the amplitude of the background activity drops substantially, and the evoked potential shows an inversion of the early N1 and P3 waves (Snyder et al. 1979). Thus the depth at which these changes occur provides a laminar reference point within the cortex. This is especially useful when, as in the present experiments, it is not feasible to use single-unit receptive field properties to characterize different laminae.
RESULTS

Physiological identification of laminar position

As noted by Vaughan (1982), the level of background activity and the polarity of photically evoked potentials provide "on-line" clues as to the laminar location of a microelectrode within striate cortex. Such assessment was particularly useful, and proved to be reasonably accurate. To assess the reliability of changes in background activity in relation to laminar location it was measured in 15 penetrations in which identifying lesions were made (Fig. 1). As the microelectrode penetrates deeper into layer 4 there is a large, but gradual, buildup in activity, and then within a few micrometers a very abrupt drop. This drop corresponded closely to the border of layers 4 and 5, as determined by the location of the identifying lesions and the readings from the microdrive. The greatest discrepancies (Fig. 1, lesions L and O) were associated with two of the deeper lesions that, consequently, are likely to be the least accurate.

To obtain a complete laminar profile of background activity, data were pooled from 15 penetrations through all or most of cortex (Fig. 1). Measured distances along each track were adjusted for differences in individual laminar thickness and overall cortical depth, and adjusted for histological shrinkage (about 15%). Because corresponding sites were rarely in exactly the same laminar position, sites within 50 μm of a given position were pooled. The laminar boundaries marked along the x-axis demarcate the average width for each lamina as computed from the pooled sample. A statistical 95% confidence interval for this curve was computed from the SE of each point on the solid curve and is shown by the stippled region. As can be seen (Fig. 1), background activity begins to increase as the electrode approaches and enters layer 4, reaching a maximum within layer 4C, then falls abruptly as the electrode passes out of layer 4 and into layers 5 and 6.

As a further aid in establishing cortical depths, the N1 and P3 components of the flash-evoked potential (Snyder et al. 1979) reversed sign at or near the 4/5 border. Figure 2 shows examples of evoked potentials recorded at regular intervals along five penetrations through perifoveal striate cortex. In all cases but E, the N1 inversion occurs just at or below the point of abrupt diminution of background activity (Fig. 1). Although this measure was not as consistently accurate as the transition in spontaneous activity, it also provided useful corroboration during the experimental sessions.

Laminar profiles of detection threshold

Figure 3 summarizes a typical traverse in which the detection threshold and background activity were recorded at 100-μm intervals. The primary reference point for aligning tracks with the laminar pattern is shown as a solid triangle in Fig. 3C, where the sudden drop in background activity marks the layer 4/5 boundary (at L in Fig. 3A). Note that this activity profile (Fig. 3C) is very similar to the average curve shown in Fig. 1. The corresponding detection threshold profile (Fig. 3B) displays characteristics typical of many penetrations (Fig. 4). Below layer 1 there is a broad region of quite uniform low threshold, followed by a sizable increase in layer 4C (Fig. 3B, lesions K and L). Thresholds are again low in layer 5 but then rise as the track enters layer 6. The star (Fig. 3B) indicates a threshold that was >25 μA, the maximum tested.
Abscissa indicates depth, estimated from microdrive readings; identical scale sites L and M, as a marker for the 4/5 border. Major laminar divisions transition in background activity, according to Figs. 1 and 2, occurring between are shown in normalized form in Fig. 4 indicated by a dashed line (Fig. 4). The thresholds of Fig. 3 triangles). The mean threshold current for each profile is relative to the depth of the 4/5 border (marked by filled triangle.

Threshold profiles from most penetrations shared the general features illustrated in Fig. 3, although there were significant variations. Detailed profiles spanning most of the cortical layers were obtained for 16 penetrations. The associated background activity records, evoked potentials, and lesions were used to align these penetrations with each other and with the laminar architecture. Figure 4 shows six such threshold profiles, chosen to illustrate the maximum degree of variation observed among the individual penetrations. Because each penetration had a somewhat different average threshold, the stimulus currents are expressed as a percentage deviation from the mean for each penetration. Cortical depths are expressed relative to the depth of the 4/5 border (marked by filled triangles). The mean threshold current for each profile is indicated by a dashed line (Fig. 4). The thresholds of Fig. 3B are shown in normalized form in Fig. 4A. Profiles of background activity and electrode impedance were similar for each penetration and have thus been omitted.

The first three variations, A, B, and C in Fig. 4, depict common threshold profiles, characterized by an extended course of low thresholds in the supragranular layers. Occasionally, as in Fig. 4B, this was preceded by a zone of sharply elevated thresholds as the electrode passed through the meninges to enter the brain, possibly reflecting the consequences of pressure. Usually, however, the electrode was advanced rapidly to penetrate the dura mater, and this high initial threshold was not observed.

In almost all penetrations, the supragranular region of low thresholds contained the point of greatest sensitivity (lowest threshold) within the penetration. In contrast, a region of high threshold was routinely encountered just superficial to the layer 4/5 boundary (Fig. 4, filled triangles on abscissa). Within layers 2–6, the highest thresholds were usually encountered within layer 4C or at the end of the penetration (Fig. 4, C–F).

Another consistent feature was the low-threshold “notch” just below the 4/5 boundary. Although most penetrations shared these general features, four of 16 profiles displayed more complex forms having secondary peaks (Fig. 4, D and E). Also in four of 16 penetrations low thresholds persisted throughout layers 3, 4, and 5 (e.g., Fig. 4F), but in all cases the lowest thresholds occurred in the superficial layers whereas the highest thresholds were in deeper laminae.

The average threshold for each penetration tended to be more similar within individual animals than between animals. For one monkey, thresholds near 10 μA were the rule, whereas our best animal had thresholds routinely <5 μA. The lowest individual threshold recorded was approximately 1 μA (Fig. 6, lesion J), Equipment limited testing with still lower currents. The ratio of highest to lowest threshold within each penetration ranged from >20 (22 vs. 1 μA, penetration D in Fig. 6) to <2 (7.5 vs. 3.8 μA in penetration C; Fig. 6). Even higher ratios may have existed but could not be measured because the maximum test current was usually limited to 25 μA to avoid hydrolytic damage.

Threshold data from 16 penetrations that sampled the full depth of the cortex were combined to generate an average threshold profile (Fig. 5). To accomplish this, all penetrations were converted to the form used in Fig. 4, where depth measurements were converted to normalized form and thresholds were expressed as percentage deviation from the mean for each penetration. The data at corresponding laminar positions (within 50-μm bins) were then averaged. The 95% confidence
In three more penetrations (Fig. 6, K–M), lesions were placed at sites where the threshold fell below 10 μA during retraction of an electrode initially advanced into the lower cortical layers. These lesions indicated that the superficial zone of low thresholds has a lower limit that is no deeper than layer 4B. (Control experiments in which threshold profiles were compared during both insertion and retraction of the electrode indicated virtually no alteration of thresholds in superficial layers by passage of the electrode.) Taken together, all the lesions in Fig. 6 indicate that a particularly sensitive region of cortex having the lowest thresholds includes layers 3, 4A, and at least part of 4B.

Thresholds were not routinely measured in white matter because it was usually encountered late in an experimental session if at all. On three occasions, however, the experiment continued long enough to traverse the white matter. Generally, thresholds were found to be significantly higher (two- to fourfold) than in gray matter but the variability was large and occasional low thresholds (e.g., 2.2 μA) were also observed. In one penetration, the electrode passed from opercular cortex, through white matter, and into calcarine cortex. On entering calcarine gray matter the thresholds became lower and more consistent. This suggested that the threshold variability in white matter was not an artifact but rather reflected a true heterogeneity. Altogether, calcarine V1 was encountered on three occasions and in each case thresholds were found to be comparable in magnitude to those obtained in opercular cortex. Thus there were no obvious differences between stimulation of peripheral versus central visual field representations.

DISCUSSION

The tantalizing question is not what do the macaques see, but how the intrusion of electrical stimulation into the exquisite neuronal complexity of the striate cortex consistently yields a perceptual effect that is uniformly recognizable despite variation in (micro) locus or stimulus parameters. The evidence for this putative uniformity is that, once trained to respond to stimulation at one striate location, a macaque responds almost unfailingly to stimulation of another locus, so long as it is in striate cortex (Bartlett et al. 2005; Doty 1965, 1969; Doty and Negrão 1973; Doty et al. 1973), as consistently found herein. Furthermore, Tehovnik et al. (2005) and Bradley et al. (2005) find that macaques, trained to saccade to 0.1–0.2° lights flashed at random loci, also make saccades to positions corresponding to the visual field location of stimulated points in striate cortex, the presumption being that the animal experiences the stimulation as a localized phosphen. All this, of course, is consonant with the human experience of the phos-
phene. It, too, has a consistent uniformity across a sizable scale of stimulus parameters and is similar from one striate locus to another. As noted previously (Bartlett et al. 2005), the congruence between macaque and human visual systems, from anatomy to psychophysics, strongly suggests that the macaque experience is highly similar to that of humans, and that the “phosphene circuit,” for want of a better term, has a peculiar prevalence. In other words, it must be that essentially the same type of elements and processes are engaged regardless of where in striate cortex the stimulus is applied, and that the differences in threshold noted herein simply represent the distance at which the electrode lies relative to the critical elements. Location is paramount only insofar as the phosphene acquires a subjective spatial projection relevant to the site of stimulation. Angular form is absent in human reports despite its prevalence in another nonvisual intrusion into the striatal network, the flickering geometrical patterns of the scintillating scotoma (Grüsser 1995). Transcranial magnetic stimulation, on the other hand, elicits the familiar phosphene (Fernandez et al. 2002).

It must be appreciated that the precisely ordered tangle of fibers and neurons among which the microelectrode passes would seem to offer numerous possibilities for exciting a wide variety of effects (see, e.g., Douglas and Martin 2004); yet either they do not, or the animal ignores them and awaits the consistency of the putative phosphene. This is probably unknowable; but, given the fastidiousness with which macaques persist in adhering to a successful modus operandi, one should hesitate to predict that they confidently respond to pink lines on one trial and blue stars on another as the electrode passes from one to another assortment of stimulated elements. If, indeed, the microstimulation does evoke a wide variety of visual effects, this will seriously complicate prosthetic application of the procedure, the assumption hitherto being that a uniformity of effect allows ready presentation of patterns formed by stimulation at multiple loci.

It bears note that although macaques readily respond to the projected spatial position associated with electrical stimulation of the corresponding anatomical loci in striate cortex or lateral geniculate nucleus (Bradley et al. 2005; Pezaris and Reid 2004; Tehovnik et al. 2005), they fail to find equivalence between geniculate and striate stimulation (Bartlett et al. 2005; Schuckman et al. 1970). Were the animals simply responding to any form of visual perturbation, at various loci in the visual field, then the geniculate and striate effects, each having a projection into the visual field, should be equated. Because they are not, it implies that the animals are not responding merely to detection of some visual effect at whatever locus it may appear, but rather respond to some quality, putatively uniform throughout striate cortex, that differs significantly from that produced by electrical stimulation of the lateral geniculate nucleus.

Thus the most useful clue, and assumption, presently available as to the nature of the underlying neuronal processes is the variation in threshold with laminar position. If the phosphene phenomenon is, as it seems, prepotent, the expectation is that the most excitable elements must produce it. These would likely be the small myelinated fibers revealed by electron microscopy in horizontal bands, the inner and outer stripes of Baillarger (the outer being the stria of Gennari), and the vertical bundles of axons extending throughout the gray matter (Peters and Sethares 1996). These vertical bundles incorporate, on average, about 34 myelinated fibers, mostly <1.0 μm, as well as dendrites and unmyelinated fibers, roughly 2,000 such bundles/mm². They are clearly associated with the columnar organization of cortical circuitry.

The choice is thus most likely to be between, or attributable to both, the bands of Baillarger and the vertical bundles of myelinated fibers, mostly emanating from the pyramidal cells of layer 2/3. The latter fibers might be good candidates, until it is recalled that the densest gathering of these vertical bundles occurs in layer 6 (see Fig. 19 in Peters and Sethares 1996), where thresholds are distinctly high. On the other hand, although the lowest thresholds do seem to impinge on the stria of Gennari in layers 4B and upper 4Cα (Figs. 3; 4, A, B, and C; and 6, lesions A, B, D, E, H, I, K, L, and M), there are exceptions, and there is an impressive stretch of low thresholds throughout layer 2/3. Some encouragement to the participation of the horizontal bands is seen in the abrupt fall in threshold as the electrode enters the less-dense inner band of Baillarger (layer 5); and, commensurate with the lower fiber density, the threshold there is higher than that in supragranular layers (Figs. 3 and 5).

Another logical candidate for higher excitability is the magnocellular system, the afferent input of which lies primarily within layer 4Cα, just below the stria of Gennari and the groups of small Meynert cells (Peters and Sethares 1991). The recipient cells of the magnocellular input project into layers 4A and 3, where they intermingle with afferents of the blue/yellow, parvocellular system (Chatterjee and Callaway 2003; Yabuta and Callaway 1998). Both are thus in ready range of the lowest threshold loci. The magnocellular afferent terminals cover sixfold as great an area as the parvocellular afferents (Fitzpatrick et al. 1985), thus presenting a more diffuse target. Furthermore the axons to the magnocellular system have a relatively large diameter, thus greater excitability, and convey a noncolor, luminance signal appropriate to phosphene production. However, the magnocellular system is essentially absent at the fovea, and at 15° eccentricity is sevenfold more prevalent than parafoveally (Assopardi et al. 1999), yet there is no corresponding difference in threshold for striate loci representing parafoveal versus peripheral fields. In other words, were the magnocellular system to play a major role in phosphene initiation, low-threshold points should be found more frequently in calcarine rather than parafoveal areas, and this is not the case; there appears to be no difference in threshold in relation to location in the visual field.

Schmidt et al. (1996) in humans, Bartlett and Doty (1980), Tehovnik et al. (2005), and the present study all found thresholds of 2 μA or lower with microelectrodes in striate cortex; yet most thresholds are considerably above this (Figs. 3, 4, and 6). It must thus be concluded that certain points of exquisite sensitivity exist. Because they are not reliably encountered by sampling in the vertical dimension, there must be some special columnar system linked to detectability that is infrequently traversed; but can be excited from some distance at slightly higher thresholds, particularly by the horizontal bands. Tangentially directed tracks might reveal such an organization. Nevertheless, even if such relatively sparse columns exist, a puzzle remains as to why the high background activity of the parvocellular recipient layer, 4CB, is consistently associated with a higher threshold. This is all the more perplexing in that layer 4CB sends five times as many synapses to layers 2/3 as
does layer 4Cα (Yabuta and Callaway 1998). Because there is no interaction between threshold and level or type of illumination (Bartlett et al. 2005), the higher threshold seems unlikely to arise from some form of surround inhibition. Refractoriness from the background activity, and the lower excitability of the smaller, “parvocellular” system might be called on for explanation.

A geniculate “loop” is not indicated, either from antidromic stimulation or orthodromically by excitation of the corticothalamic system of layer 6, to produce an inhibitory effect, to account for the high thresholds of that lamina. Similarly, it is hard to imagine that antidromic effects into circumstriate areas are significantly involved, although orthodromic transmission out of striate cortex is obviously required to produce any evidence of detection.

Finally, there is the puzzle that electrical, or mechanical, stimulation of the retina in human subjects also produces a “phosphene” (e.g., Humayun et al. 2003). Indeed, the very word phosphene originated with the Greeks, in the clever idea that the eye itself produced the light required for seeing (Grüsser and Hagner 1990). The question then is whether the retinally produced phosphene is basically the same as that produced by electrical or transcranial magnetic stimulation of striate cortex. Preliminary data (Weiland et al. 1999), from local electrical stimulation of the retina, are not typical of cortically elicited phosphenes. Were there a high degree of similarity between retinally and cortically elicited phosphenes, there should be an “inherent” cortical circuit to decode the retinal phosphene-producing input. In such a case the cortically elicited phosphene might result from activation of this inherent pathway, rather than as a mere perceptual accompaniment of the bizarre simultaneous activation of a hodgepodge of cortical elements otherwise subserving normal visual processing. Without a careful comparison in man of the qualitative characteristics of the two (?) types of phosphene, retinally versus cortically produced, the question is moot.

However, the basis for a possibly productive speculation has just emerged. Dacey et al. (2005) recently described in macaques giant retinal ganglion cells (RGCs), containing melanopsin, that are inherently photically responsive and, unlike their congeners in rodents, project to the lateral geniculate nucleus. In addition to their inherent responsiveness, these cells also convey a broad range of rod and cone inputs. Overall, their characteristics suggest a luminance channel, described as the luxotonic units by Kayama et al. (1979) in macaque striate cortex. In the unanesthetized macaque some 20% of the units in striate cortex respond for several minutes to steady, diffuse, featureless illumination, the “photogenic” variety of luxotonic activity (as opposed to 8%, the “scotogenic” units, that respond correspondingly to darkness). Such photogenic units are clearly relevant to phosphenes, but most also respond to other types of visual input, i.e., they are “simple” and “complex” cells as well (Riso et al. 1979). From the observations of Dacey et al. (2005) the mixed receptor input plus their melanopsin signal suggest that the giant RGCs provide a reasonable basis for the characteristics of the photogenic units of striate cortex. Furthermore, the giant size of these cells is concordant with their being the most electrically excitable elements of the retina and, by extrapolation, possibly maintaining that size and excitability advantage into the cortex as well. The major constraint in this argument is the rarity of the giant RGCs, only about 0.2% of the retinal population. Yet they have an exceedingly wide distribution of dendrites and, given that the geniculate input to striate cortex is a mere 6–8% (Kara and Reid 2003; Latawiec et al. 2000; Peters et al. 1994), to provide the full gamut of visual experience, the giant RGCs might well feed a cortical photogenic circuit sufficient to yield the simplicity of a phosphene, and likewise to support such an effect from electrical stimulation of the retina. Prima facie, this is contradictory to the observation that threshold for detection of electrical stimulation in striate cortex is independent of illumination (Bartlett et al. 2005). The electrical stimulation, however, may well be prepotent over the less-vigorous discharge elicited by normal visual input.

Such speculation, however, fails to provide insight into the laminar profiles of detectability. Explaining the isolated points of high excitability, together with the wide variation from one penetration or locus to another, will probably remain a perplexing question for some time. The microstimulation is, perforce, being applied at random within an intricate and highly organized network, with multiple functional nodes, and the simplicity of the “phosphene output,” if such it be, need bear no direct relation to the pathways by which it is accessed.

ACKNOWLEDGMENTS

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REFERENCES


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J Neurophysiol • VOL 94 • NOVEMBER 2005 • www.jn.org