Psychophysics of Electrical Stimulation of Striate Cortex in Macaques

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Psychophysics of electrical stimulation of striate cortex in macaques. J Neurophysiol 94: 3430–3442, 2005. First published August 3, 2005; doi:10.1152/jn.00406.2005. Macaques indicated their detection of onset or alteration of 0.2-ms pulses applied in various configurations through electrodes implanted in striate cortex. When microelectrodes were introduced and left in place, the threshold for detection of 100-Hz pulses nearly doubled within 24 h. However, for chronically implanted platinum-alloy microelectrodes detection thresholds usually remained stable for many months, independently of location within striate cortex or its immediately subjacent white matter. Thresholds were unaffected by the visual conditions, such as light versus darkness, or movement of the eyes; but in one animal blind after acute glaucoma thresholds for loci in striate cortex were permanently decreased by about 50%. Learning to respond to electrical stimulation of the optic tract produced no tendency to respond to such stimulation of striate cortex. Onset of stimulation at a given locus could be detected even in the face of continuous supraliminal stimulation at four surrounding loci on a 3-mm radius. The surround stimulation did alter the threshold of the central locus, but such stimuli could not summate if they were subliminal by some 10%. Cessation of stimulation that had been continuing for 1 min to 1 h could be detected if it were being applied at a level 20–75% above that needed for detection of stimulus onset. Continuous stimulation had a pronounced “priming” effect, in that modulation of frequency or intensity of such stimulation by as little as 5% could be detected (e.g., 20 μA in a background of 500 μA, or <2-ms interpulse interval with pulses at 50 Hz). Using pulses inserted in various phase relations to ongoing pulses at 2–5 Hz, it could be determined that stimulus pulses were surrounded by a strong facilitatory period for about 30 ms, which was then replaced by refractoriness. Given the congruence of macaque and human visual anatomy and psychophysics, these results further encourage efforts to develop a cortical prosthesis for the blind.

INTRODUCTION

Theoretically, it would seem possible to provide the blind with a certain degree of useful visual sensation by direct excitation of loci within the spatial representation across striate cortex. Perhaps encouraged by the evidence that macaques could distinguish between loci of cathodal excitation at loci <1 mm apart in striate cortex (Doty 1965), Brindley and Lewin (1968) implanted an array of electrodes over the striate cortex of a blind volunteer and unequivocally demonstrated the soundness, in principle, of such a prosthetic device. The ensuing 35 yr of similar work on human subjects has been reviewed by Tehovnik et al. (2005), and an example of progress in the technical requirements for the realization of a serviceable visual prosthesis has recently been reported (Bradley et al. 2005).

Among the first practical considerations in developing such a device is whether electrical charge transfer can be achieved innocuously between electrodes and brain (e.g., Bartlett et al. 1977; Brummer and Turner 1975; Doty and Bartlett 1981). This problem seems resolved with the development of the activated iridium electrode (Bradley et al. 2005; Robblee et al. 1983). The present experiments now explore the effectiveness of various parameters of electrical stimulation within striate cortex of macaques for producing a signal that they can detect. Such examination included temporal modulation of pulse trains, spatial discrimination between loci within striate cortex, and ability to detect onset of stimulation at one site during ongoing stimulation at adjacent sites. Studies with human subjects have also raised questions as to the effect of blindness, eye movements, or, in subjects having light perception, the effect of interaction between normal illumination and the detectability of the striate stimulation. These issues, and whether enduring stimulation may produce an enduring perception, were also studied in these experiments on macaques.

Given the anatomical and behavioral evidence indicating near perfect congruence between macaque and human visual systems, these data have direct relevance to expectations of detectability of such stimuli if and when applied to striate cortex of blind human patients. In certain instances they also provide significant insight into the characteristics of the neuronal circuitry that provides macaque as well as humans with elementary visual sensation.

Preliminary communications of these data have been presented (Bartlett et al. 1977; Lee et al. 1973).

METHODS

Animals and behavioral task

For this and the companion paper (DeYoe et al. 2005) data have been taken from observations on 56 adolescent male Macaca nemestrina. In all instances the animals have been under veterinary care, and the American Physiological Society’s Guiding Principles in the Care and Use of Animals has been followed. Some of the phenomena reported are based on data from only a few animals or in a few instances are unique to a given animal.

Using the procedure of Glassman et al. (1969) the animals were first trained to enter a restraining chair and were placed in a sound attenuating booth provided with white noise and a one-way observation window. They were then trained to press a lever to obtain a few milliliters of fruit juice when a given signal was presented. The futility of pressing the lever in the absence of the appropriate signal was
indicated by a tone, and the animals learned that such behavior merely delayed the opportunity to obtain a reward. Failure to respond to the stimulus, of course, also postponed the availability of reward.

In an occasional experiment it was necessary to restrict the animal’s head movement, such as when using a Ganzfeld. In such cases this was accomplished by restraining lateral movement of the head with a padded plastic hoop placed over the snout. However, for the great majority of the experiments the animal was free to direct its gaze about the lighted interior of the chamber in any manner that it chose.

At the end of each session of some 25–50 trials the animals were given unrestricted access to water and then deprived until the following daily session. In addition, they had full access to water on weekends, with deprivation beginning some 12–18 h before the Monday session.

A signal for availability of reward was presented at pseudorandom intervals between 10 and 40 s, and lasted 1–4 s, customarily 1 s once the animal was trained. For initial training a series of clicks and/or illumination of a 3-mm light bulb or light-emitting diode was used as the signal. After implantation of electrodes the animal was trained to respond to the stimulation of striate cortex by presenting it concurrently with, say, the light, and then gradually decreasing the intensity of the latter until response was made to the striate stimulation alone. Great care was always taken to be certain that no inadvertent extraneous cue accompanied the central stimulation. This was routinely checked by disconnecting the stimulator from the animal or by changing the reference electrode for the current return path.

The timing of the signal, the reward and punishment contingencies, and the duration (and thus amount) of the reward were controlled by solid-state devices and/or computer.

Because thresholds were repeatedly determined for a variety of stimuli, it was essential to adopt a simple, reliable, and rapid means of assessing the animal’s ability to detect the signal. The criterion used was three or more correct responses in five presentations. [See DeYoe et al. (2005) for further validation of this procedure.] It was not uncommon for the animals to begin offering random presses in the absence of the signal when working with stimuli near threshold, and it was thus necessary to reject “responses” that occurred with less than an animal’s usual latency and to suspend testing before again delivering the stimuli at pseudorandom times. The repeatability of threshold determinations for a given condition over a number of days fully confirmed the validity of this three out of five criterion when used with suitable care.

In certain instances (e.g., Fig. 5) the threshold was tracked by a computer program in which the applied current was diminished by a set amount after each trial in which the animal responded correctly and increased by the same amount after each trial in which it failed to detect the signal.

Electrodes and stimuli

Two types of electrodes were used: pairs of side-by-side, conically tipped, 200-, 130-, or 80-μm-diameter wires of 70% platinum–30% iridium with 1-mm-tip separation; and single or pairs of side-by-side, chisel-pointed, 130-μm-diameter wires of 92% platinum–8% tungsten, with 1-mm-tip separation in the case of the pairs. The electrodes were made from varnish-insulated (e.g., Ionel-31), commercially available wire (see Doty and Bartlett 1981). Although the geometrical surface area of the Electrode tips can be calculated, their effective electrical area in tissue is dependent on a number of factors (Brummer and Turner 1975). In the actual case, no difference was found for thresholds among the different diameters and types of penetrating electrodes, whereas stimulation at the pial surface required an average of fivefold greater current for detection (Bartlett et al. 1977). The platinum–tungsten electrodes were provided with a Teflon cuff that served as a depth gauge and stop when the electrodes penetrated the intact dura mater and passed into the cortex at the time of implantation (Doty and Bartlett 1981). When single wires were used as electrodes, a 3 × 40-mm piece of platinum foil was secured subcutaneously just ventral to the lambdoidal suture, and served as the return electrode, whereas the electrode pairs were used in the “bipolar” configuration, the deeper electrode serving as cathode.

Constant current, rectangular stimuli, 0.2 ms in duration unless noted otherwise, were derived from a variety of pulse generators and, in the majority of the animals, were delivered with optical isolation (Bartlett in Doty and Bartlett 1981). The animal was isolated from ground. To prevent accumulation of charge on the electrodes by successive pulses an “exhauster” circuit was included in the head stage, which effectively shorted the electrodes between pulses. In most of those instances where protracted, “background” stimulation was required the Anapol stimulation circuit (Bartlett et al. 1977) was used. This still further forestalls the occurrence of detrimental electrolysis by gaining much of the stimulating cathodal current from discharge of the anodal polarization gradually supplied to the electrodes in the interpulse interval.

Surgery and testing

The electrodes were sterilized for 24 h in benzalkonium chloride and, using full aseptic precautions, were inserted into the striate cortex of the occipital operculum while the animal was anesthetized with a surgical level of intravenous secobarbital. For the larger Pt–Ir electrodes sufficient bone was removed to allow incision of the dura mater and placement of the electrodes under direct vision in relation to blood vessels. In many instances a channel was cut in the bone that allowed the insertion of several pairs of electrodes several millimeters apart in a row or pattern. With the Pt–W electrodes only a 1-mm hole was drilled, and the electrode or pair thrust through the dura until stopped by the Teflon cuff. Experience proved the latter procedure to be significantly less traumatic to the cortex than the former, although in either case later histological data indicated that the injury was usually minor. The electrodes were held in position by surgical-grade methylmethacrylate, and brought to a coded 34-pin connector similarly bonded to the skull (Doty and Bartlett 1981).

In many of the animals electrodes were also implanted in bone at the nasion and lateral edge of the orbit to record the electrooculogram. Three of the animals under deep, surgical levels of secobarbital anesthesia were blinded, two of them within a few days of birth, by acute glaucoma. A 27-gauge hypodermic needle was inserted into the posterior chamber of each eye and for 2 h connected to a reservoir of isotonic saline at a pressure of 220 mmHg (Sakakura and Doty 1976). In four other animals the right optic tract was cut just posterior to the chiasm, using a neurosurgical procedure that involved contraction of the brain by intravenuous administration of a sterile, 40% solution of urea, 2.5 ml/kg, and careful, gradual retraction of the frontal lobe.

A week or so after their implantation each electrode or electrode pair was checked for the response they recorded when the animal viewed stroboscopic flashes, 0.3 Hz, provided by a Grass photic stimulator at maximum intensity; and for the overt behavior elicited by application of 0.2-mu. puls, 50 Hz, ≈500 μA. Both these measures provided some assurance that the electrode was in viable tissue. Although directly elicited behavior was often undetectable, especially with electrodes in the foveal representation in striate cortex, in the majority of cases a series of rapid, extremely fine saccades could be elicited whose direction was appropriate to the location of the electrodes in striate cortex.

Postmortem appraisal

At termination of the experiments the animal was deeply anesthetized and perfused through the ascending aorta, first with isotonic saline, and then with 4% formaldehyde. The entire brain was removed and photographed. After it had hardened for a few days, a cast was made of the brain on which to record the location of electrode penetrations. Most of the sites within the brain were then recovered on
histological sections, cut frozen at 50 µm, and stained by the Nissl and Weil techniques.

RESULTS

General features of threshold for detection

The mean current to detect onset of stimulation in striate cortex, or immediately subjacent white matter, using 50- or 100-Hz, 0.2- or 0.5-ms monophasic rectangular cathodal pulses applied through permanently implanted electrodes 80–200 µm diameter, was 92 ± 57 µA SD (Fig. 1). There was no statistical difference in threshold for 58 loci confined to gray matter (98 ± 47 µA) versus 31 loci entirely within white matter (95 ± 50 µA). Neither was any difference apparent in relation to location of the electrodes within the representation of the visual field, which ranged from the fovea to far periphery within the deep calcarine cortex: 109 ± 57 µA for 10 loci in foveal gray, 93 ± 48 µA for 27 loci in gray matter of the operculum within 15 mm of the midline, and 105 ± 38 µA for 15 loci within gray matter of the calcarine fissure.

For 8% of the implanted electrodes no response could be obtained with currents of 1,000 µA, in most instances reflecting failure of electrical connection, but also including gross investiture of the electrodes with connective tissue growth and/or hemorrhagic injury. Anodal stimuli were consistently less effective, their detection often requiring a severalfold increase above the threshold for cathodal pulses. An exception was application of pulses to the pial surface, where anodal pulses were consistently more effective than cathodal, but again requiring much higher current than that for cathodal pulses irrespective of depth within the cortex.

The animal’s ability to detect stimulation increased from chance levels to near perfect performance over a narrow range of stimulus amplitudes. The shape of these “psychometric functions” was remarkably similar among the various loci and types of electrode tested, including microelectrodes (Figs. 2 and 3; and DeYoe et al. 2005). As can be seen in Fig. 2C, a change of 16.5% in stimulus current was all that was required to pass from 10 to 90% detection of the stimulation.

When tested repeatedly over a number of hours, days, or months, in the great majority of cases fluctuations in threshold remained well below 30%, unless some deleterious form of stimulation were delivered to the electrodes (Bartlett et al. 1977). Commonly, however, over a period of several months there was a gradual elevation of threshold, probably associated with a thickening of the fibrous barrier that inserts itself between the electrodes and the brain. That this process may begin immediately on implantation of an electrode is illustrated in Fig. 4, where a microelectrode was gradually advanced into striate cortex over a period of days. The threshold remained relatively stable and low for the first hour or so after an advance, but during the ensuing 20+ h, while the animal was in its home cage (and possibly shaking its head as part of its grooming pattern), a significant elevation ensued.

Somewhat surprisingly, once an animal was accustomed to the working conditions, the thresholds for striate stimulation and/or psychometric functions were unaffected, whether it was working in total darkness, in bright light (e.g., Fig. 5), in the presence of stroboscopic flashes, surrounded by a random visual environment of illuminated, crinkled aluminum foil, or closely facing a television screen speckled with random noise.

Blindness

The effects of blinding by acute glaucoma were studied in one juvenile animal in which “bipolar” electrodes had been implanted for 14 mo and thresholds had been stable for ≥5.5 mo. The blinding produced a roughly 50% reduction in threshold for detection of pulses applied to striate cortex (Fig. 6). Thresholds at all 10 of the tested loci were little changed on the day after the blinding, but those that were to fall began to do so on days 3–5. Points in the middle of the lateral geniculate nucleus and in the radiation just posterior to the posterior pole of the lateral geniculate body, in ipsi- and contralateral prelunate gyri, and in white matter deep to the prelunate gyrus, showed no change, and there was a decline for the parahippocampal gyrus, from 100–150 to 60–80 µA. Electrophysiological failure of synaptic transmission from the tract to the lateral geniculate nucleus seemed to be complete by day 9 (see

FIG. 1. Distribution of thresholds for detecting onset of stimulation, 50- to 100-Hz, 0.2- to 0.5-ms pulses, at 221 loci within striate cortex or its immediately subjacent white matter.
also Fentress and Doty 1971; Sakakura and Doty 1976), although the electrodes were not well aligned. Stimulation at the optic tract locus, which had been detected at 200 μA before blinding, ultimately required 1 mA to produce a detectable effect, presumably by current spread to adjacent tissue.

**Eye movements**

In one animal thresholds for striate stimulation were unaffected by triggering onset of stimulation at various times from 0 to 500 ms after onset of a saccadic eye movement, even though such saccades can alter the electrical responses elicited at these electrodes by pulses applied to the optic radiation (Bartlett et al. 1976). All animals were consistently observed, with or without electrooculography, to determine whether eye movements were associated with the detection of stimulation. For loci some distance from the representation of the point of fixation a series of rapid microsaccades, to casual observation appearing deceptively like smooth pursuit, was commonly evoked the first few times stimulation was applied. The level of stimulation required for this overt response was usually several times greater than that required for the animal’s detection of stimulation at that locus after training. As also observed by Tehovnik et al. (2003), even with a high intensity of stimulation these eye movements almost never persisted beyond a few trials, presumably because the animal either suppressed them or chose to ignore whatever sensory effect the stimulation might have engendered. In rare instances, loci were encountered from which these microsaccades were consistently elicited on every stimulation, even at intensities equal or close to the threshold for stimulus detection. With this exception, no relation could be discerned between movement of the eyes and the animal’s detection of the stimulation.

**Absence of seizure discharge**

In none of the animals was there any evidence of “kindling”; and in the few cases examined no afterdischarge in the EEG was observed in close temporal or spatial proximity to the stimulation until intensities 5–10 times detection threshold were used. Even when such afterdischarge was deliberately evoked, there were no overt manifestations; and an epileptic fit

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**FIG. 2.** Representative “psychometric functions,” i.e., detectability vs. applied current. A and B: single loci with macro- and microelectrodes, respectively. C: 17 measurements from 10 macroelectrodes and 4 measurements from 4 microelectrodes in 3 different animals. For C “threshold” is defined as the point where 50% of the stimuli would have been detected; SE, as indicated, is sufficient in only a few instances to exceed the points marking the mean.

**FIG. 3.** Linear relation (correlation coefficient \( r = +0.93 \)) for micro- and macroelectrodes between threshold and psychometric function (Fig. 2C); slope = 0.33.
was never evoked from stimulation of striate or circumstriate cortex. This is in striking contrast to our studies on rabbits (unpublished observations), where in each of five Dutch Belted and five New Zealand white rabbits afterdischarge and/or overt seizures resulted from stimulation of area 17 with 50–300 μA at 50 Hz with 0.2-ms, rectangular, monophasic cathodal pulses using the exhauster circuit. Conditioned responses from the nictitating membrane in such instances had a threshold approaching 500 μA. Proximity to white matter or hippocampus did not seem to be a factor in this seizure susceptibility.

**Reaction times**

No effort was made to encourage response with minimal reaction time, but essentially all animals displayed consistent latencies within the range of 400–800 ms when 50–100 Hz stimuli were applied. With stimulation at lower frequencies, 1–10 Hz, there was a tendency toward longer reaction times.

**Parametric features**

The relation between the duration of stimulus pulses and their threshold intensity was similar for microelectrodes and the various types of macroelectrodes. When measured with 100 pulses at 100 Hz (Fig. 7), the chronaxie for the former averaged 247 versus 229 μs for the latter, even though there was a fivefold difference in the average rheobase for the two types of electrodes. Similar values were obtained even when still higher anodal currents were used for electrodes resting on the pia mater. As can be seen in Fig. 7, there is a reasonable fit between the data and Hill’s equation (1936), \( Y = \frac{A}{1 - e^{-X/B}} \), where \( Y \) is the threshold current; \( X \) is the pulse duration; \( A \) is the rheobase; and \( B \), the time constant, is 1.443 × chronaxie.

A similar relation held between threshold and pulse frequency (Fig. 8). The slope of this relation between threshold and stimulus frequency, however, varied considerably from one locus to another, particularly at frequencies at or below 10–20 Hz. No correlates could be found for this variation and
it seemed to be equally present in blind as in sighted hemispheres.

There was also a log–log relation between threshold and number of pulses at 100 Hz, plateauing at about 100 pulses, i.e., a 1-s burst (Fig. 9). However, when the number of pulses was limited to <100 delivered within 1 s, their effectiveness, of course, also varied as a function of rate of delivery. Thus for example, two pulses at 100 Hz had the same 300 μA threshold as five pulses at 10 Hz, whereas the threshold was 330 μA for five pulses at 5 Hz versus 90 μA for the same number at 100 Hz, and so forth.

Detection of modulation of continuing stimulation

Several macaques were trained to ignore continuing stimulation of striate cortex and to respond only when some parameter of the stimulation was abruptly changed for a second or two. It could thus be demonstrated that the animal was exquisitely more sensitive to modulation of existing stimulation than to the onset of stimulation per se. In other words, a small perturbation in the number, timing, or intensity of otherwise continuous, monotonic stimulation of striate cortex readily elicited a response from the animal. Figure 10 provides a striking example of such an effect, as little as a 5% increase in intensity of continuously applied stimuli at 10 or 50 Hz being detected, rather independently of the original level of the ongoing stimulation. This is particularly impressive in comparison to the basic threshold for detection of de novo stimulation, which in this case was 250 μA; and with stimulation being constantly supplied at 500 μA, a 20-μA transition to 520 μA evoked an immediate response. This fraction, of about a 5% change, was almost constant in the range tested extensively in two animals, once currents about 1.5 times threshold were used for the background stimulation.

Similar sensitivity prevails in the temporal domain (Fig. 11). With a background at 50 Hz, the most sensitive animal could detect a change to 52.5 Hz (5% modulation) occurring about 2.5 times/s for a few seconds; i.e., an alteration of <2 ms in the interpulse timing. The reaction time in such cases was usually <1 s. Again, however, such performance at the eight electrode sites tested required stimuli at an intensity 50–300% greater than the threshold for detection of onset of the 50-Hz stimuli. If the background intensity was held near threshold, the degree

FIG. 6. Changes in threshold after blindness from acute bilateral glaucoma. Preoperative thresholds had remained stable for 5.5 mo or longer. Note roughly 50% fall in threshold for detection of stimulation at striate cortex. See text.

FIG. 7. Average strength–duration relation for 14 macro- and 3 microelectrodes, using 100 pulses at 100 Hz. SE indicated. Solid lines are the solutions for the Hill equation in the 2 instances, after determination of the rheobase and chronaxie. See text.
of frequency modulation (FM) had to be 60–80%. This is probably the reason for the greater modulation required at the lower frequencies in Fig. 11 because there the detection threshold was significantly higher than that at the 50 Hz used to set the intensity of the background stimulation in that series of observations.

Some of the basis for this remarkable sensitivity to interpulse intervals could be discerned in a series of experiments in which the thresholds were measured for “extra” pulses added with varying phase relation to the occurrence of the ongoing, background pulses (Figs. 12 and 13). The animal was trained to ignore continuous stimulation at relatively low frequencies, 2–5 Hz (the “A” pulses), and to respond to the insertion of “B” pulses for 1–4 s in a defined temporal relation to the “A” pulses. The threshold for the detection of the “B” pulses was measured as a function of their time of occurrence relative to the “A” pulses (Figs. 12 and 13), often only a single added “B” pulse being required. When delivered within some 30–50 ms after an “A” pulse, the “B” pulses could be detected at intensities significantly less than needed were they to be applied alone at the same or doubled frequency; and the same held true even for “B” pulses occurring before “A” pulses (Figs. 12 and 13). There was, indeed, strikingly little asymmetry in detectability relative to this phase relation between “A” and “B” pulses (Fig. 13). At a time of ≥100 ms before or after the “A” pulses, a higher intensity of “B” pulses was required than would have been the case for their de novo application (Fig. 13). The functions were essentially identical at “bipolar” versus “monopolar” electrodes. The variation of the threshold for detection of the “B” pulses in their phase relation to the “A” pulses was similar when the “A” pulses were themselves subthreshold, except that in such a case their effect on detection of the “B” pulses was purely facilitatory. On the other hand, if the “A” pulses were delivered at double or more the threshold for their detection, their depressive effect on detection of the “B” pulses at the phase angle of 180° was greatly enhanced, with little influence on the facilitatory effect at 10–20 ms before or after the “A” pulses.

The converse of these experiments with detection of added pulses is the situation in which pulses are elided from an otherwise continuous, monotonic series. Dropping two pulses from within a 50-Hz train was readily detected. Of course, it is not clear in such an instance whether it is the gap in excitation that is detected or whether it is the resumption of stimulation...
that provides the cue. To determine whether the simple cessation of stimulation could serve as a signal, stimuli were applied at 50 Hz, using intensities well above those required for detection of the onset of such stimulation, and the animal was required to respond to 4-s lapses in this stimulation at intervals of several minutes to 1 h. This was a difficult task for the animals to learn, and required the Anapol stimulation system to prevent an undue rise in threshold consequent to the protracted stimulation. However, once the task was learned, performance was entirely equivalent to that for detection of onset of stimulation and reaction times were comparable. Most of the observations were made on a 5-yr-old *M. fascicularis* that had only rudimentary light perception consequent to bilateral, acute perinatal glaucoma. The data were acquired when the animal was 5 yr old, some 8 mo after implantation of the electrodes. Detection of cessation of ongoing stimulation required the level of that stimulation always to be considerably greater (20–75%) than that for the detection of its onset. As can be seen in Fig. 14, complete cessation of the background stimulation was not required. A decrease of 20–25% in the intensity of the ongoing stimulation was readily detected when higher levels of background current were used, although the effect varied considerably for different electrode sites (Fig. 14).

**“Generalization”**

Previous work (Doty 1965, 1969; Doty and Negrão 1973; Doty et al. 1973) had shown that once a macaque had learned to respond to the electrical excitation of striate cortex at one location it unhesitantly responded to such excitation applied at other loci if such loci were within the striate cortex of either hemisphere. Responses at the test loci were neither rewarded nor punished. The test trials were randomly interspersed among trials where stimuli were applied to the originally trained locus, and no test was considered negative unless the animal was subsequently able to respond reliably, after training, to stimulation at intensities equal to or less than those used for the test. Continuing such tests at over 200 striate loci on some 50 macaques in the present experiments provided extensive and uniform confirmation of this “generalization” of detection of increase in stimulus intensity at 2 sites within striate cortex, for different intensities and frequencies of continuous, “background” pulses. Modulation consisted of 3 periods of 500 ms of the higher-amplitude pulses punctuated by 500 ms at the background level. This is loosely diagrammed in the inset (not accurately scaled), where the top trace is the stimulus applied to the cortex and the bottom trace indicates the period of modulation. Note that when the intensity of continuing stimulation was 2 or more times the de novo 50-Hz threshold, an increase of <5 to 10% could be detected at 50 Hz. B-7 was a single, intracortical electrode, whereas C-7 was a pair of side-by-side electrodes.

**FIG. 10.** Detection of increase in stimulus intensity at 2 sites within striate cortex, for different intensities and frequencies of continuous, “background” pulses. Modulation consisted of 3 periods of 500 ms of the higher-amplitude pulses punctuated by 500 ms at the background level. This is loosely diagrammed in the inset (not accurately scaled), where the top trace is the stimulus applied to the cortex and the bottom trace indicates the period of modulation. Note that when the intensity of continuing stimulation was 2 or more times the de novo 50-Hz threshold, an increase of <5 to 10% could be detected at 50 Hz. B-7 was a single, intracortical electrode, whereas C-7 was a pair of side-by-side electrodes.

**FIG. 11.** Detection of change in frequency of applied pulses at the same 2 loci in striate cortex depicted in Fig. 10. Background stimulation was continually applied at an intensity 3 times the threshold for detection of de novo stimulation at 50 Hz. Inset: diagrams a 25% change in frequency, which in the actual tests occurred, without phase-locking with background stimulation, at different frequencies depending on the background frequency: 0.5 Hz for <10 Hz, 1 Hz for 10 and 20 Hz, and 2.5 Hz for >20 Hz. Note that even a 10% modulation at 100 Hz corresponds to detection of only a 1-ms change in timing of the stimulus pulses.
responding to points in striate cortex for which the animal had never been trained. In contrast, in such tests at some 86 loci in circumstriate cortex, after training to stimulation of a striate point, only 13% were clearly positive, with another 15% displaying partial or questionable generalization. In addition, the observations of Schuckman et al. (1970) were also confirmed, on one animal, in that after training to stimulation of the optic tract, generalization to stimulation of the lateral geniculate nucleus was complete, although no responses whatever were given initially for stimulation of striate cortex at several loci. Similarly, effective training to stimulation of striate cortex conferred no effectiveness in that regard for stimulation of the optic radiation.

An important exception to this rule of “generalization” from one striate locus to another was its failure when testing in a blind hemisphere after training in the sighted hemisphere. This was true in two animals in which the optic tract had been sectioned unilaterally, but was not the case in another where section of the tract was incomplete, as evidenced by survival of photically evoked responses.

Interpretation is complicated, however, by two other cases. In one, the corpus callosum had been cut in addition to the optic tract, leaving the anterior commissure intact. After the animal learned to respond to stimulation of striate cortex in the “sighted” hemisphere, generalization occurred to “parafoveal” but not to more peripheral striate loci in the blind hemisphere (and, of course, to all striate loci in the sighted hemisphere). The anterior commissure and its distribution into the temporal lobe (Demeter et al. 1990; Zeki 1973) is likely to play some role in this effect (see Doty and Negrao 1973). In the other instance the optic tract had been cut 1 yr before implanting the electrodes. Even though the EEG was abnormal in striate cortex ipsilateral to this transection (Sakakura and Doty 1976), there was complete generalization to initial stimulation at four striate loci in this hemisphere after training to striate stimulation in the other. The only peculiarity, other than the prolonged postsurgical period, which might offer a clue to this “exception,” was the fact that this animal, unlike the others, consistently used the hand contralateral to the blind hemisphere to make its responses.
studies that the monkey is able to make its discriminations (see DeYoe et al. 2005). These facts need be kept in mind in efforts to discern the basis of the neuronal activity on which the sensorial counterpart in the monkey. The latter assumption is unnecessary to the data reported here, but it is helpful in providing a certain intuitive grasp of what the stimulated neural circuitry is doing. For instance, from most reports by human observers (Brindley 1971, 1973; Brindley and Lewin 1968; Brindley and Rushton 1974; Dobelle and Mladejovsky 1974; Dobelle et al. 1974, 1976; Pollen 1975), changing the parameters of stimulation alters only brightness, size, or degree of flicker of the elicited phosphenes, other qualities generally being absent for stimulation within striate cortex. From this it would seem that the electrical stimulation accesses only certain components of the cortical matrix and that these in turn must suppress the activity or effectiveness of other circuitry that would subserve sensations of color, various shapes, and shading, for example. It remains surprising, however, that by means of eye movements macaques can assign a spatial location to the site of stimulation in striate cortex (Bradley et al. 2005; Tehovnik et al. 2005). These facts need be kept in mind in efforts to discern the basis of the neuronal activity on which the monkey is able to make its discriminations (see DeYoe et al. 2005).

**Blindness**

If electrolysis is avoided (Bartlett et al. 1977), and disruptive connective tissue growth remains in abeyance, the thresholds for detecting the stimulation are stable indefinitely. The possible change in character of the effects with blindness, as evidenced by the difficulties in generalizing from a “sighted” to a blind hemisphere, may reflect the hyperexcitability of the system after such profound deafferentation (Fig. 6).

Although the geniculate in macaques constitutes but 6–8% of the input to striate cortex (Kara and Reid 2003; Latawiec et
al. 2000; Peters et al. 1994; but see Doty 1983), there is an immediate elevation in striate excitability for evoking cortical responses (Fentress and Doty 1971; Sakakura and Doty 1976) after bilateral retinal loss. Effects suggestive of hyperexcitability have, indeed, been reported for stimulation of striate cortex in the human blind (Brindley and Rushton 1974; Dobelle et al. 1974), particularly in that phosphenes may be larger and/or produced by electrical excitation of circumstriate cortex. Within the uncertainties of electrode placement in human subjects, the latter effect is probably not obtained in normally sighted individuals (Dobelle et al. 1974). It is noteworthy that increased electrical excitability has been observed in the auditory system after destruction of the cochlea (Gerken 1979; Kotak et al. 2005).

Bradley et al. (2005) provide no data on thresholds for detection of electrical stimulation of striate cortex in their semiblind macaque. However, the animal was able to respond to such stimulation after recovery from an infection that destroyed visual responsivity at the electrode sites. Their animal, as did ours with blindness by retinal destruction, displayed the common nystagmus of the blind (Ohm 1950). Such constant movement of the eyes in blind subjects discourages ideas of delivering prosthetic pulses to the retina, as does the high impedance of the sclera (Doty and Grimm 1962).

Persistence

For human subjects reports are variable as to whether an evoked phosphene continues as long as the stimulus endures. The data from macaques are thus of some import here, showing as they do that suprathreshold stimulation yields a continuing effect (Fig. 14). One can speak only of an “effect” in the monkey, but because cessation or diminution of the stimulus is detectable, it would seem that this effect of the stimulation is constantly present throughout its application. It is thus logical to infer that elements supporting this effect enjoy a remarkable resistance to fatigue or adaptation, not unlike many of the so-called luxotonic units of striate cortex in primates (Bartlett and Doty 1974; Kayama et al. 1979) or the persistence of perception in the binocular Ganzfeld (Bolanowski and Doty 1987).

Circuitry

It is futile to guess what sensation may ensue from stimuli that are far subliminal when applied alone but are fully effective in combination with ongoing stimulation. There are several instances of this puzzle, such as the “B” pulses, either preceding or following stronger stimuli (the “A” pulses) in Figs. 12 and 13. It is apparent that the processes underlying such detectability have a time course of several tens of milliseconds. A period of peripulse facilitation, peaking around 5–10 ms, is followed (or preceded!; Fig. 12) by a refractory or inhibitory period some 50 ms before or after a background pulse. An interval of facilitation can, to some degree, also be inferred from Fig. 11, where the sensitivity to modulation of pulse timing is maximal at pulse intervals between about 12 and 50 ms (80–20 Hz). Brindley (1971) reported a great enhancement of brightness of the phosphene perceived by his patient when a second electrical pulse was applied 25 ms after the first.

The processes, and their location, underlying the biphasic peripulse fluctuation in excitability revealed in Figs. 12 and 13 are not immediately obvious. Although earlier work on cats (Rutledge and Doty 1962) suggests a corticofugal path for primary effectiveness, and there is a strong projection from striate cortex back onto the lateral geniculate and thalamic reticular nuclei (Kayama et al. 1984; also see Fig. 1 in Steriade and Llinás 1988) that can produce highly rhythmic effects, the timing in the present case is not indicative of circuitry involving such a subcortical loop. Furthermore, the independence of detectability from visual input does not encourage the idea that activity in the lateral geniculate nucleus is involved. However, neither does the timing of this biphasic effect seem to fit any of the electrically or photically evoked, or spontaneous, rhythms previously described for macaque striate cortex (Doty and Kimura 1963; Doty et al. 1964), nor, for that matter, any of the many examples of membrane or network properties offered by Steriade and Llinás (1988).

Critical duration

The chronaxies for micro- and macroelectrodes seem more compatible with excitation of neurons than of their fibers (see, e.g., Asamuma et al. 1976; Ranck 1981), although participation of smaller-diameter fibers certainly cannot be excluded (West and Wolsencroft 1983). The values appear to be close to those derived from the more limited data on human subjects (e.g., Pollen 1975) and essentially identical to those obtained by Ronner and Lee (1983) with microstimulation of single neurons in the visual cortex of the cat. The commonality of chronaxies for the two widely different types of electrodes used in the present study, and their independence of cortical locus, raises the possibility that it is excitation only of a specific, low-threshold system in striate cortex that forms the basis for detection of the stimulation. This idea is strongly supported by the reports from the great majority of human trials, as noted above, that only a single, simple percept is produced: a small, starlike, stationary but flickering phosphene. Still, there are many reports of colored phosphenes by some human subjects (Bak et al. 1990; Dobelle and Mladejovsky 1974; Shakhnovich et al. 1982; Talalla et al. 1974), as well as double or noncircular phosphenes. Such inconsistencies, however, probably arise from electrode placements in circumstriate cortex or straddling of sulcal boundaries, for example. It is noteworthy that the typical phosphene displays none of the fluctuating geometrical patterns (“fortifications”) that characterize another form of nonvisual excitation of the striate cortex, the scintillating scotoma, common in migraine.

Thus although much of the evidence favors the idea that a single, unique system is engaged by electrical stimulation of striate cortex, the issue as to the elements engaged (see DeYoe et al. 2005) cannot presently be resolved. The data herein, however, are consistent with the thesis that it involves the most electrically excitable elements, which in turn activate neuronal circuitry to “capture” a system capable of generating phosphenelike percepts and locally suppresses neuronal activity that might subserve other sensorial effects. The uniformity of sensation produced in most human subjects, the consistent generalization found between all striate cortical loci in macaques, the similarity in chronaxies and general characteristics for macro- and microstimulation, and the absence of influence...
from retinal input all suggest that electrical excitation perturbs the cortical network in such a way as to produce a discrete sensorial experience, distinct from those of ordinary vision. Electrical stimuli offer precisely timed intrusions into ongoing cortical activity, and thus should be traceable in the time-tagged effects propagated throughout the brain. By manipulating the intensive parameters of these stimuli and obtaining the corresponding assessment by the monkey of their effectiveness, it should ultimately be possible to discern the nature and distribution of the neuronal activity that produces the experience of a phosphene.

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