ACTA NEUROBIOL. EXP. 1980, 40: 713-728

Lecture prepared for the Warsaw Colloquium on Instrumental Conditioning and Brain Research
May 1979

AN EXPLORATION OF THE ABILITY OF MACAQUES TO DETECT MICROSTIMULATION OF STRIATE CORTEX

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Abstract. With its head steadied within a form-fitting mask, a macaque was first taught to signal when it detected the application of 0.2-ms electrical pulses at 50 Hz through electrodes chronically implanted within its striate cortex. Stimuli were then applied via a movable microelectrode and the threshold for the animal's detection determined at intervals of 50–250 μm. With permanently implanted 130– 200-μ diameter electrodes such thresholds range between 50 and 250 μA (and are highly stable), whereas with the microelectrodes sites were encountered, estimated to be primarily within cortical layers V–VI, where the monkey could reliably detect as little as 2–4 μA. The threshold at most sites within striate cortex with the microelectrode, however, was 15–25 μA. Background unit activity recorded with the microelectrode varied greatly in different laminae and survived the microstimulation, but has so far provided no clear basis for predicting threshold. It is tentatively hypothesized that the relatively rare points where the threshold is as much

[1] John R. Bartlett died unexpectedly 5 November 1978, full of plans and enthusiasm for the experiments whose beginnings are described herein. We had made the observations jointly for the 13 penetrations in the right striate cortex and produced Figs. 2 and 3. I am thus confident, in making him first author of this paper, that I can represent his views with considerable accuracy; although I suspect we would have had some warm and lengthy arguments over the suitability of exposing our speculations on the cells of Meynert — R. W. Doty.

as 10 times less than that in the surround arise because the giant, solitary cells of Meynert provide the exclusively effective output for the behavioral response. This hypothesis would also explain the singular uniformity of sensation (a "phosphene") evoked in human subjects by such stimuli, and the equivalence of all such stimuli in striate cortex found for the macaque.

INTRODUCTION

The consequences of applying electric currents to the striate cortex in man are particularly fascinating in two respects. First, is the fact that this crude interjection of massive synchrony into the activity of thousands of otherwise independently active neurons produces a subjective sensation of light, appropriately localized according to the position of the intrusion into the retino-cortical "map" of visual space (7, 15–17). However, given the exquisite organization of the anatomical fabric (e.g., 27, 41) and the intricacy of its physiology (e.g., 4, 25, 26, 34), it is perhaps even more surprising that only a simple, singularly uniform sensation is produced, i.e., a "phosphene" of white, slightly flickering light, wherever the electrode is placed. In other words, in the sensation aroused there is no indication of the color, movement, orientation, binocular disparities and ocular motility which the physiologist finds so clearly represented in activity of the striate cortex nor, seemingly, of the rich interconnectivity of the central visual system.

It must be admitted that most of the relevant anatomical and physiological knowledge of the striate cortex is derived from work on macaques whose subjective experiences can only be inferred. However, the remarkable congruence of anatomy, physiology and psychophysics of the visual system in Old World primates (6, 8, 9, 11–14, 30, 31, 33, 36, 38, 39) gives considerable assurance that the monkey's experience when its striate cortex is stimulated electrically is comparable to that of man. Certainly the monkey finds such stimulation uniform for any locus in striate cortex; for having once learned to signal its detection of such stimulation at one point, it unhesitantly responds to stimulation at any other point so long as that is in area 17: and the monkey remains generally indifferent to stimulation in other cytoarchitectonic areas (18–20, 22) or even the lateral geniculate nucleus or optic tract (37, and Doty, unpublished) unless it is specifically trained to respond to stimulation there. This holds true whether stimuli are applied to the pial surface, as in man, or within the gray or white matter of the striate area, the only difference being that it takes several fold less current to elicit a response with electrodes which penetrate the cortex (5).

For a sample of 200 electrode sites in striate cortex in 14 macaques the threshold for detection of stimulation with 0.2- or 0.5-ms pulses at 50 Hz through chronically implanted 200-μm Pt–Ir electrodes lay between 50 and 250 μA. Assuming that this 5-fold variation in threshold among various locations reflects a true physiological difference rather than a technical flaw (e.g., trauma) or pathology (e.g., variation in tissue encapsulation of the chronically implanted electrodes), it would be of great interest to understand the nature of the differences in the detectability of such interjected excitation, i.e., phosphenes, within the neuronal circuitry of striate cortex. We thus sought to determine whether changes in threshold might be systematically related to position of an electrode within one or another cytoarchitectonic lamina, the white matter, or some other, possibly physiologically definable, location within area 17. As shown by Asanuma and his colleagues (1, 2, 29, 43) stimulation through microelectrodes can provide critical information concerning the capabilities and interconnections of neocortical systems. In the present instance there is the added advantage that a relatively constant psychophysical criterion (detection) can be related not only to anatomical location but to the type of single unit activity in the immediate vicinity of the stimulating microelectrode. By securing the microelectrode in place it should also be possible to follow over the course of several days or weeks any consistent alteration in threshold, thereby gaining some assessment of the possible role played by the connective tissue investiture of the electrode in the threshold obtained.

METHOD

Only a single, 4.0–kg, male macaque, *Macacca nemestrina,* has been used in these preliminary experiments. It was first trained to make manual contact with a rod. The change in electrical capacitance of the rod activated circuitry to deliver fruit juice if and only if a signal was present such as acoustic clicks or electrical stimulation of striate cortex. Random touching of the rod was discouraged by prolonging the intertrial interval and/or delivering a puff of air to the face. When suprathreshold stimuli were being used consistently, there was essentially no random activity; but when the threshold was being repeatedly probed, as it was with microstimulation, tentative contacting of the rod became somewhat troublesome. In the interest of determining the absolute minimum of current which the animal could detect, one did not wish to punish it too severely for errors, otherwise the monkey would change its criterion to one of a higher level of certainty. On the other hand, great care, obviously, hand to be taken to be certain that the responses

arose from genuine detection of the signal by the animal rather than its merely guessing that the stimulus was occurring. In practice, this distinction was rather easily made on the basis of latency and consistency of the response to actual detection. The stimulus lasted for 2 s and the intertrial interval ranged randomly between 5 and 40 s. A criterion of three unequivocal responses, i.e., unhesitant and at appropriate latency, in five presentations was taken as the threshold.

An array of 12 electrodes 3–8 mm apart was implanted within the representation of central vision in striate cortex of the left hemisphere. These were constructed of 92% Pt–8% W enamel-insulated, 127-μm diameter wire cut at a 60° angle with a scalpel to make a sharp point. Depth of insertion beyond the intact dura mater was controlled by gluing a 0.5-mm cuff of Teflon 2.5–3.0 mm above the tip of the wire with cyanoacrylate. A 1-mm hole was drilled through the skull in the anesthetized monkey and the wire inserted until the cuff contacted the dura. It was then cemented in place with methyl methacrylate and brought to a coded receptacle affixed to the skull (4, 5, 18). A piece of platinum foil anchored at the occiput, and a stainless steel screw in midline bone served as reference electrodes for stimulation and recording.

The monkey was trained to respond to stimulation at one cortical locus, using 0.2-ms cathodal pulses at 50 Hz, and subsequently responded to stimulation at the other loci without further training. This gave the animal experience in detecting electrical excitation of striate cortex, and in the following experiments with microstimulation provided an important control on the state of motivation of the animal to make responses to barely supraliminal stimuli.

The animal was then anesthetized with secobarbital, tracheal intubation performed using an "infant" size laryngoscope, and the head was immersed in artist's moulage to make a mold. The mold was then filled with plaster of Paris, making a model of the animal's head, and this model in turn was used to construct a form-fitting mask of fiberglass and resin to restrain the monkey's head during the sessions using microelectrodes. The animal was habituated for a few days to working in this mask. It was then anesthetized again. Under microscopic control a 1-mm diameter hole was carefully drilled through the skull overlying striate cortex. A truncated, plastic hypodermic needle hub was affixed to the skull concentric with this hole. The hub accommodated the microelectrode drive, which was constructed from a glass tuberculin syringe (Fig. 1). This light weight assembly has the advantage, besides its moderate cost, of readily following the slight movements which the monkey makes within the mask; and single units can be held

as well with this as with more elaborate arrangements (e.g., 26), i.e., frequently for 10–60 min if desired. The hub opening was sealed with sterile bone wax when not in use, and precautions to maintain sterility were taken whenever it was open. No sign of infection developed.

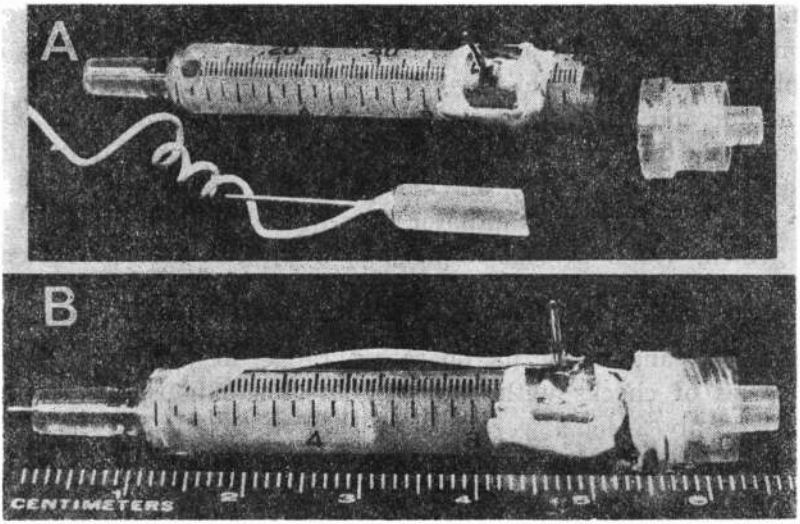

Fig. 1. Microdrive made from glass tuberculin syringe. *A*: components prior to assembly: above, syringe barrel with hole cut for passage of electrical connection, and mounted gold pin connector; right, Luer-lok tip cut from plastic syringe; below, piston with attached hypodermic needle tubing and highly flexible lead wire. *B*: assembled microdrive, piston in fully advanced position with hypodermic needle tubing protruding and ready to receive microelectrode which will be inserted into it. Electrical connection passes from the tubing via coiled, flexible wire to mounted connector pin. In use, the microelectrode is withdrawn into the syringe tip and the syringe inserted snugly into plastic needle hub mounted on skull (see text). Microelectrode is advanced by hydraulic pressure on piston, controlled by a micrometer driving a distant, matching syringe via Teflon tubing and a needle fitting the Luer-lok tip. While the short piston length in the Figure allows a travel of about 15 mm, it has some danger of very slow leakage of the hydraulic fluid, 200-centistoke silicone. This can be rectified by using a longer piston (with less travel in this length barrel), or higher viscosity fluid.

With the animal fixed in the mask and performing to stimulation through permanently implanted electrodes, the microelecrode was advanced until electrical contact was signalled by the change in impedance (measured with 1 KHz sinusoidal current, 0.1 μA). The glass-insulated Pt–Ir electrodes (Frederick Haer Co., Brunswick, Maine, 04011) had an initial impedance of roughly 5 MΩ, but this was reduced to about 200

kΩ by stimulation in most instances. The electrode was slowly advanced, particularly at the point where it was estimated it was passing through the dura mater. The threshold at which the monkey could detect stimulation was tested each 50–250 μm, and the spontaneous, background activity was noted or tape recorded at each location. Switching between the recording and stimulation modes with the microelectrode was done remotely via a miniature reed relay in the head stage of the preamplifier. Single unit activity could be selected with a bilevel window discriminator and, via an analog delay line, the entire waveform of the spike could be displayed to provide additional assurance that the same unit was being sampled from one moment to the next.

The constant current stimulator was provided with an "exhauster" circuit which, via a 2N6450 transistor, kept the electrodes connected through 15 kΩ in the interpulse intervals, thereby discharging ("exhausting") the charge which would otherwise quickly accumulate on the microelectrode and carry its operating range to the hydrolytic level (5). A series of checks with and without this exhauster circuit when currents of only 2–4 μA were needed showed that it had no influence on threshold even at these low levels.

Several penetrations which had yielded significant data were marked by passing 35 μA DC, positive current through the microelectrode for 10 s at intervals as it was withdrawn. At the termination of the experiments using the right striate cortex, the monkey was anesthetized and a right occipital lobectomy was performed to obtain the tissue for histological analysis. The experiments then proceeded 5 mos later with the left hemisphere, and finally the monkey was again anesthetized and perfused with 0.9% NaCl followed with 10% formalin. Serial frozen sections were cut horizontally at 50 μm and stained with thionin.

RESULTS

A total of 18 traverses to various depths through striate cortex with microelectrodes, usually in steps of 250 μm, was made at four loci. The multiple penetrations at each locus over a period of days in these initial explorations has, unfortunately, resulted in considerable uncertainty in most instances as to the exact laminar location at which the observations were made. The most reliable reconstruction of a microelectrode penetration is that in Fig. 2, and here the electrode failed to penetrate deeper than layer III. One of the locations of a series of penetrations was found to be centered on a very well developed external calcarine sulcus in this monkey. This explained some of the otherwise inconsistent results from repeated penetrations at this location. Apparently on

some occasions the electrode passed within the sulcus and on others briefly nicked the curvature of the gyrus, but reconstruction of these traverses proved to be impossible.

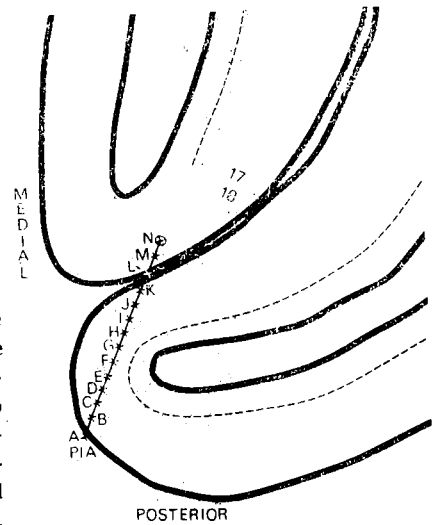

Fig. 2. Reconstruction of microelectrode track passing in 250-μm steps from striate cortex on the medial surface of the occipital pole across the calcarine fissure into area 18. Area 17 designated by heavy dashed line. Letters *A, B, C,* etc. indicate positions at which recordings were made and thresholds determined, as given in Fig. 3.

On several occasions stimuli were applied through the microelectrode as it approached and passed through the dura mater. As judged for location primarily by the level at which single unit activity appears (Fig. 3), but also on those initial occasions at each locus when the surface of the dura had not been obscured by exudate and fibroblasts, the monkey could not detect stimuli of 1.0 mA until the electrode had advanced enough to penetrate the dura. For instance, the penetration illustrated in Figs. 2 and 3 was made 24 h after exposure, and the fresh dura mater was clearly visible. Electrical contact was made, presumably with a thin layer of plasma on the dura mater, at a point 1.7 mm above that labelled "A-pia" in Fig. 2. Stimuli were applied at 1.0 mA there and after each advance of 0.25 mm, but no response was obtained until point "A" (Fig. 2) was reached, 6 min after contact. The threshold there was 250 μA.

Naturally, this high current disrupted the insulation of the microelectrode, and its impedance (Fig. 3) fell to only 0.2 MΩ. Nevertheless, excellent unit activity could still be recorded (Fig. 3).

As also can be seen in Fig. 3, there were very large differences in background activity at different loci along this penetration (Fig. 2). It is clear that the threshold bears no close relation to the magnitude of the background activity. However, at all locations where the threshold was $\leqq$ 10 μA, as occurred somewhere along the course of eight

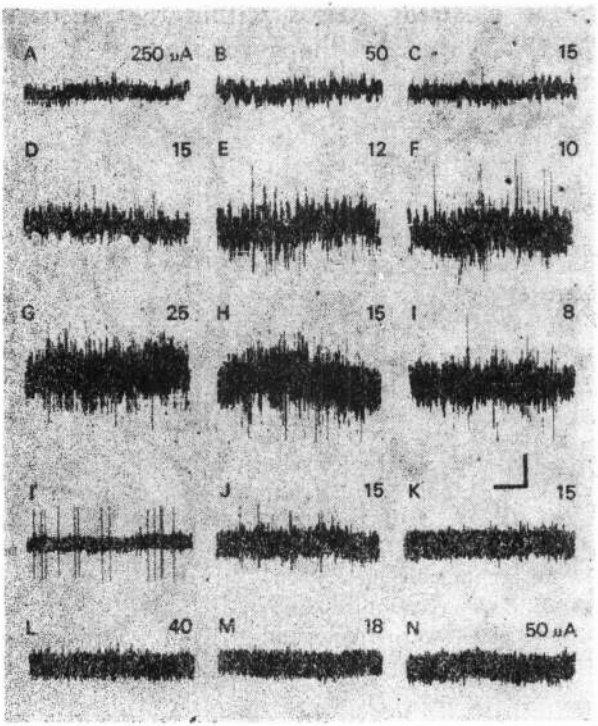

Fig. 3. Electrical activity recorded from microelectrode each 250 μm as it passed along track reconstructed in Fig. 2. Letters *A, B, C,* etc. correspond between the two Figures. The threshold in μA for the monkey to detect stimulation with 0.2-ms pulses at 50 Hz shown at upper right of each record. Electrode impedance was unchanged at only 0.2 MΩ throughout this run. Clearly, there is little correspondence between the threshold and the background activity at a given point, although the lower thresholds do occur where background is relatively high. Single unit activity was first encountered at "C". Record "I′" from same point as "I", but at lower gain to show single unit whose activity was still unchanged after applying the stimulation about 25 times at 6–15 μA. Note elevation of threshold at point "L", probably near pial surface. The higher threshold at "N" 25 min later, however, may reflect a waning motivation of the animal. Calibration: 20 ms, and 200 μV, except 500 μV for "I′".

of the 18 penetrations made, there was a rich background of single unit discharge. It thus seems likely that the presence of vigorous unit discharge is an indication of the conditions necessary for detection of the weakest stimuli, but that it is not wholly sufficient.

At restricted points along four penetrations the monkey was able with unequivocal reliability to detect stimuli of 2–4 μA. The dimensions of these highly effective points remain uncertain and, of course, probably depend upon the orientation of the penetration with respect to the laminar organization of the cortex. In one instance, however, advancing the electrode 100 μm changed the threshold for detection from 4 to 15 μA. On the other hand, in two instances the threshold remained at 3–4 μA despite an advance of the electrode by 250 μm. Two of these low threshold points were encountered about 1.5 mm below the pia mater, whose position was estimated from the point at which the threshold became $\leqq$ 250 μA. In six other instances the position of the low threshold points was compatible with the microelectrode having passed across white matter and into the lower layers of striate cortex subjacent to that on the surface. Four of these eight low threshold points were actually found at intervals $\leqq$ 250 μm along a single penetration, which histology showed to have passed through three folds of striate cortex, starting near the foveal representation. All of the data for these eight points are consistent with the location of these low threshold points lying within layers V and/or VI of area 17; and this receives added support from the absence of such points on the three penetrations made at the position illustrated in Fig. 2, which never attained these layers. Two other facts are perhaps relevant: (1) None of these low threshold points were encountered on the first day after anesthetizing the monkey to prepare the site, but were found 3–9 days thereafter; and (2) additional penetrations at the same locus usually did not encounter such a low threshold point even at roughly the same depth within the cortex.

The electrode impedance ranged from 0.2 to 2.1 MΩ on the various occasions when low threshold points were found. Single unit activity was always present at these points, but the level of background activity was consistently lower than that at, e.g., Fig. 3*F–H*, nor was there a very prominent, well isolated unit in the field of microelectrode recording on any of these occasions. Probable luxotonic units (4, 26, 34) were frequently observed, as could be readily done, of course, simply by turning the room lights on or off (the monkey's mask not being light proof); but the presence or absence of such activity did not appear to be associated with any particular level of threshold.

Thresholds at the majority of points ranged between 15 and 25 μA, and were probably roughly the same for white matter immediately adjacent to striate cortex. On the other hand, a penetration which apparently passed deep into white matter associated with area 18 at a slightly different angle but at the same locus as in Fig. 2, held monotonously a threshold of 100–120 μA as measured each 250 μm over a distance of 5 mm. This high threshold, however, may result more from the monkey's unfamiliarity with stimulation of circumstriate areas (18–20) than with the fact that the penetration passed within white matter.

When the stimuli being applied were in the range of 30 μA or less, single unit activity, as observed within 1–2 s after stimulation, was seemingly unaltered in its background characteristics. This held true even for units with an amplitude on the order of 1 mV or more which, presumably, are rather near to the electrode tip.

On one occasion stimulation was applied for 10 min at 200 μA (with the usual 0.2-ms, 50-Hz pulses). As evidenced by the rapid, small fluctuations in the applied voltage (8 V peak), it could be inferred that hydrolysis (5) occurred throughout this period. The theshold rose from 20 μA to 70 μA, and when tested 30 and 45 min later, was still at 50 μA. Single unit activity was completely eliminated. Subsequently determining the threshold after each advancement of the electrode in 100 μm steps, the following figures were obtained: 50, 40, 40, 30, 20, 15 μA; i.e., within 250 μm the threshold was as low as at the tetanized site prior to the 10 min of tetanization. Unfortunately, return of single unit activity was not monitored.

At two positions along a single penetration the effects of altering stimulus frequency were studied. At the first point about 1 mm into the cortex the threshold at 50 Hz was 10 μA and 25, 30 and 60 μA for 10, 5 and 1 Hz, respectively. At the other point estimated to lie just above white matter (from the abrupt decrease in background and unit activity subsequently observed as the electrode advanced) the threshold was 5 μA at 50 Hz, and 10, 20 and 60 μA for 10, 5 and 1 Hz, respectively.

The effect of changing stimulus polarity was assayed at one point, being 4 μA with cathodal pulses applied via the microelectrode, and 25 μA when anodal pulses were used.

DISCUSSION

The quick success of these exploratory experiments considerably exceeded what had been anticipated, and while this contributed to certain obvious deficiencies in the data, two major facts nevertheless seem

firmly established: (1) the threshold for the monkey to detect microstimulation at one versus another site within striate cortex can vary by more than tenfold, and (2) single unit activity can be consistently recorded via the same electrode as used for stimulation, and it too is grossly variant from one location to another (Fig. 3).

The validity of the experiments depends, of course, on the reliability of the macaque as a psychophysical observer. It is to some degree difficult to convey to the reader the basis for one's confidence that well trained macaques report their detection threshold consistently with a high degree of accuracy. This, however, is readily verified, by repeatedly changing the intensity of the stimulation between threshold and subthreshold levels for a given position of the microelectrode, and by affirming the constancy of the threshold from day to day or moment to moment at any of the implanted electrodes.

The question thus arises as to why there should be such a great difference between thresholds at various points within striate cortex. It had earlier been inferred that it was probably the most excitable elements in the cortex which provided the basis for the macaque's ability to respond to electrical stimuli applied essentially any place in neocortex (18). It would now seem that these "most excitable elements" are rather sparsely distributed, at least in striate cortex. Were this true, it would account for the relative rarity of encountering points at which stimuli of as little as 2–4 μA could be detected.

There is, of course, the problem that the best estimates of the degree to which applied electrical stimuli are elaborated in the neocortical network would not predict such a result (1, 23, 29, 32, 43). The direct excitation of pyramidal (Betz) cells by currents in the range of 2 μA for 0.2 ms is of the order of 50 μm, but the indirect effect, from exciting fibers of passage, dendrites, etc., may range out to 1 mm. Phillips and Porter (32) estimate for the precentral cortex of the macaque that 5 μA will engage a field of roughly five Betz cells and 900 small pyramids. These figures probably give the correct order of magnitude for the population of neurons in the striate cortex of the macaque with a comparable stimulus of 2 μA; for while the effective radius of excitation would be substantially smaller for the 2-μA stimulus, the packing density of neurons in striate cortex is double that of precentral gyrus (35).

There must be some reason for this great discrepancy between the expectation that even a 2-μA stimulus would be diffusely effective, and the fact that it is not. It is thus tempting to suppose that only highly specific and relatively rare neurons in striate cortex exclusively provide the output on which the monkey's response is based. The cells of

Meynert seem highly suitable for such a role. LeGros Clark (27) estimated their entire population in striate cortex as numbering only 1.300, although recent work of Chan-Palay et al. (10) suggests that the figure is nearer to 60,000. The hypothesis, that the cells of Meynert, or similar units are exclusively responsible for the monkey's learned response to stimulation of striate cortex, is attractive not only in explaining the otherwise puzzling rarity of the low threshold points and their seeming clustering in deeper cortical layers, but in providing as well for the surprising uniformity of sensation, the phosphene, produced in man (7, 15–17), and the immediate, inherent equivalence of stimulated striate loci in macaques (18–22).

There are, also, difficulties with this hypothesis; perhaps the major one being that, from the interweaving of the basilar dendrites of the Meynert cells (10), it should not be possible to pass a stimulating microelectrode vertically through the cortex without their coming within the effective radius of stimulation. One would also expect, upon tangential penetration of the cortex, similarly, to bring the apical dendrites within range. Perhaps this is all true, and the relatively gross movements of the microelectrode in 250 μm steps in the present experiments commonly brought it to rest somewhat remote to these critical structures. Since there are upwards of 36,000 synaptic spines on a Meynert cell (10), it would be reasonable to imagine that it might take considerable convergence to excite it indirectly via its afferent inputs, thus requiring a larger current to recruit this population when the electrode lies some distance from the cell, versus the case where the electrode is sufficiently near to excite it directly.

Other problems with the hypothesis, however, do not have even these tentative answers. For instance, Lund et al. (28) are loath to distinguish Meynert cells from the other pyramidal cells in layer V; i.e., perhaps there really is no population of relatively rare, morphologically unique neurons to fit the physiological-psychophysical hypothesis. And, of course, what would there be about the output characteristics and destination of the Meynert cells which would make them such exclusive purveyors of the signal that the ongoing activity of striate neurons had been disrupted by the interjected electrical stimuli? Together with the other pyramidal cells of layer V the cells of Meynert project to the superior temporal cortex, inferior pulvinar and superior colliculus and seem undistinguished in this regard (28, 40, 41).

Finally, the logical thrust of the "Meynert cell" hypothesis leads to the supposition that a single neuron could be responsible for the critical output when the microelectrode is at the point of lowest threshold. The triggering of a behavioral response by even a single quantal neural

or receptor event (e.g., 3, 24, 42) is, of course, a possibility, but in the present instance a train of roughly 20–100 pulses was being utilized in the measurements of threshold. The threshold increased greatly (6–12 times) on the two occasions when only a single pulse was used. This suggests that considerable numerical recruitment is required in such circumstance, but whether its effective output might then still all be channelled via one or several Meynert cells or via a different path is problematical, to say the least. However, while it seems rash to speculate that only a single, highly specialized type of cell conveys the information relevant to the behavior, the existence of isolated points with thresholds many times less than the surround forces the consideration of some such degree of specialization; if not of single cells, then of clumped colonies of cells somehow having a preferential, high impact output.

In any event, it is a challenge to understand how nerve impulses interjected by the electrical stimuli can be detected as differing in pattern from among the thousands already occurring each second within a cubic millimeter of striate cortex. With the ability to register the presence or absence of detection, and to manipulate site and parameters of the applied stimuli while recording their effect upon surrounding neural activity, it now seems possible to assay this problem with some chance of success.

Work performed under Contract NIH 70-2279 from the National Institutes of Health. We are grateful to Richard A. Sloane for help in training the monkey, to Scott M. Borden for construction of the mask, and to E. A. DeYoe for much helpful discussion.

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