been shifted, one cycle of refinement is complete; the refinement consists of several such cycles. Selected atoms may be kept flexibly tethered to target positions determined by fitting the model to the density manually. This prevents well-fit atoms from wandering too far, and also provides points of stability which constrain the entire idealized structure to lie within the electron density. It is also possible to encourage atoms to move in a particular direction by proper choice of target positions.

7. For reviews of the protein chemistry and pharmacology of snake venom neurotoxins see A. T. Tu [*Annu. Rev. Biochem.* **42**, 235 (1973)] and C. Y. Lee [*Annu. Rev. Pharmacol.* **12**, 265 (1972)]. A discussion of possible structure-function features in neurotoxins has been given by Ryden *et al.* (*8*).
8. L. Ryden, D. Gabel, D. Eaker, *Int. J. Pept. Protein Res.* **5**, 261 (1973).
9. For example, see J. P. Changeux, M. Kasai, C. Y. Lee, *Proc. Natl. Acad. Sci. U.S.A.* **67**, 1241 (1970).
10. D. Tsernoglou and G. A. Petsko, *FEBS Lett.* **68**, 1 (1976).
11. The Philippine sea snake toxin has not been sequenced. However, a sequence was available for neurotoxin b from Japanese sea snake venom [S. Sato and N. Tamiya, *Biochem. J.* **122**, 453 (1971)] and this was used. Although one might expect the two proteins to have very similar or identical sequences, chemical work had indicated considerable differences [A. T. Tu, B. Hong, T. N. Solie, *Biochemistry* **10**, 1295 (1971)]. Our fitting and subsequent refinement of the Philippine sea snake neurotoxin indicates that the two toxins are either identical or only slightly different. The sequence question is discussed in detail elsewhere (*12*). A complete description of the structure will be published separately (D. Tsernoglou and G. A. Petsko, in preparation).
12. D. Tsernoglou, G. A. Petsko, A. T. Tu, *Biochim. Biophys. Acta* **491**, 605 (1977).
13. Rotating the model to obtain depth perception during the fitting comes closest to the natural process of making small head movements, a technique for depth perception that is used to some extent by everyone. Two-image depth illusion techniques are available on the system, but we did not use them in fitting because one of us does not have stereoscopic vision and therefore cannot benefit from these techniques.
14. Another feature of GRIP that we found to be useful is its ability to produce dihedral angles on command. One can immediately inspect them, and if they fall in high-energy regions in Ramachandran-type diagrams other conformations can be considered. Such a process would be very difficult and time-consuming with conventional model-building.
15. It is possible that this is a sequence difference between our toxin and the Japanese sea snake toxin, but we regard this as unlikely (*12*).
16. A report has appeared concerning the backbone structure of another, almost identical, neurotoxin from a sea snake from the Sea of Japan [B. W. Low, H. S. Preston, A. Sato, L. S. Rosen, J. E. Searl, A. D. Rudko, J. S. Richardson, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 2991 (1976)]. The backbone structure appears identical to that of our toxin. No information on the structure of this homologous toxin was available to us during the work described in this report.
17. Constrained refinement is being carried out by the method of J. H. Konnert [*Acta Crystallogr. Sect. A* **32**, 614 (1976)]. The current R factor is 0.27 based on data at 5.0- to 2.0-Å resolution.
18. We thank F. P. Brooks, Jr., and W. V. Wright for help and advice at various stages of this work and M. E. Pique and J. S. Lipscomb for assistance. Supported by research grants from the National Institutes of Health (RR-00898 and HL-15958) and from the National Science Foundation (BMS74-21633). The GRIP system was built by the Department of Computer Science, University of North Carolina, following specifications laid out and regularly revised in conjunction with the system's early users: biochemists at UNC and crystallographers at Duke University (the latter included D. Richardson, J. Richardson, S. Kim, and J. Sussman). Major contributions were made by E. G. Britton, M. E. Pique, and J. S. Lipscomb under the direction of W. V. Wright and by J. E. McQueen, Jr., under the direction of J. Hermans. F. P. Brooks, Jr., is the principal investigator. Development of the GRIP system has been supported by AEC contract AT(40-1)-3817, NSF grant GJ-34697, NIH Biotechnology Research Resource grant RR-00898, and the IBM Corporation.

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Visual Input to the Visuomotor Mechanisms of the Monkey's Parietal Lobe

Abstract. *A newly identified class of neurons of the parietal cortex, studied in waking monkeys* (Macaca mulatta), *is activated by visual stimuli, perhaps via the retino-collicular visual pathway. This afferent input is thought to provide the visual cues activating the visuomotor mechanisms of the parietal lobe for the direction of visual attention.*

When a stimulus is presented in the peripheral visual field of a monkey, the monkey may, after a latency of 150 to 200 msec, make a saccadic eye movement to bring the image of the target onto its fovea. The neural mechanisms that mediate this eye movement are of great interest, and considerable progress has been made in elucidating the neural circuitry of the brainstem that controls eye movements (*1*). Less is known about the cortical mechanisms thought to link the central neural representation of such targets of interest with those brainstem circuits. It was thought that neurons of area 8 of the frontal lobe, in the so-called frontal eye fields, form the cerebral efferent pathway for voluntary or "spontaneous" eye movements, and that visually evoked eye movements are mediated via the visual cortical areas of the occipital lobe. However, electrophysiological studies of the frontal eye fields and of the geniculo-striate visual system in waking animals have not revealed neurons that discharge before eye movements occur (*2*). In recent studies of the cerebral cortex of alert, behaving monkeys we found several classes of neurons of the inferior parietal lobule that have visuomotor functions. They appear to provide a neural mechanism for the direction of visual attention; that is, for the fixation of gaze upon objects of interest, for maintaining fixation of the object when it moves slowly, and for loosening fixation and initiating saccadic eye movements toward new objects that appear in the visual field (*3*).

Here we describe the results of another series of experiments in which we sought to define the visual input to this area. A class of cells previously called visual space neurons (*3*) has been found to be sensitive to light and to subtend large, peripherally placed receptive fields. We suggest that these cells and the pathways that project upon them provide one afferent input to the visuomotor mechanisms of area 7 that are active before visually evoked eye movements.

The electrical signs of the activity of single cells of area 7 were recorded by way of platinum-iridium microelectrodes inserted transdurally into the cortex of waking rhesus monkeys trained on the visual fixation task described by Wurtz (*4*). The behavioral training procedures and electrophysiological methods were described perviously (*3*). Four male monkeys (*Macaca mulatta*) were used. Each was trained to fixate a small gallium-arsenide (λ = 660 nm) light-emitting diode (LED) positioned on a tangent screen in the animal's primary line of gaze, 34 to 57 cm in front of him. The screen contained an array of 16 other LED's; several different spatial arrays of the target lights were available. The animal was required to depress the key after the central light came on, and to hold it down until he detected a dimming cue in order to receive a drop of liquid reward. He also learned, if the center LED disappeared and another appeared simultaneously, to saccade to the second light and fixate it until it dimmed (after a preset delay). If the center light remained on, the monkey maintained fixation of it until it dimmed, and made no eye movements toward any other light that came on during the fixation period. The head was held stationary and eye movements were monitored by recording the horizontal and vertical electroculograms (EOG's) with silver–silver chloride electrodes implanted in the orbital bone. A PDP 11/20 computer was used to control light intensity, deliver rewards, and monitor EOG signals, behavioral events, and cell discharges. Small electrolytic lesions were made at the end of each penetration by passing current through the tip of the microelectrode (4 μa for 4 seconds); they were used to identify the location of neurons after histological preparation of the brains. A total of 350 neurons was studied in this series of experiments, in six hemispheres. All cells were located in area 7.

The light-sensitive cells of area 7 (98 cells out of 350) are activated when visual stimuli are presented at or near the far peripheral edges of the visual fields, whether or not a saccade is made in that direction. Figure 1 illustrates the results of the study of one such cell, located in the right hemisphere of a monkey. When the animal was fixating the central point, *FP*, and a test light positioned 30° to the left came on midway through the fixation

period, the rate of discharge of the neuron increased abruptly and was maintained, as shown in Fig. 1A. Tests at other points showed that the cell was activated by stimuli located in a receptive field that nearly filled the left upper quadrant of the visual field (Fig. 1B); the most intense activity was evoked by stimuli placed most distant from the central line of gaze (Fig. 1C).

The visual receptive fields of light-sensitive parietal neurons are unusually large compared with those of neurons of the geniculo-striate component of the visual system. Moreover, the fovea was not included in the field of any parietal neuron, although those of some neurons extended to within 2° of the fovea. Most neurons in one hemisphere are related to fields in the contralateral half-field of vision, a few to bilateral fields. When all the fields of neurons of this type from both hemispheres are superimposed the summed field resembles a doughnut extending to the very edges of the visual field, in all directions, with a hole in its center. In all except 3 out of 21 cells, the fields extended to the edge of our 60° by 60° tangent screen. The position of the stimulus which evoked maximum activity was at or close to the edge for 16 of the 21 cells studied in this way. We have not observed any systematic differences between neurons of the right and the left hemispheres.

There appear to be two subclasses of light-sensitive neurons which differ in functional properties. Those of the largest subclass discharge with average latencies of 79 ± 6 msec (standard deviation) after light onset, subtend peripheral receptive fields such as that illustrated in Fig. 1C, and continue to discharge during maintained stimulation; that late discharge is suppressed if the animal makes a saccadic movement toward the stimulus light (Fig. 2A). Light-sensitive cells of the smaller subclass are less uniform in response characteristics, have longer and more variable latencies (116 ± 26 msec), subtend smaller receptive fields with points of maximum sensitivity near their centers, and adapt more rapidly to a sustained light stimulus. The onset discharge of cells of this subclass is enhanced if the onset of the light stimulus is followed by a saccadic movement to it (Fig. 2B), much in the manner of some neurons of the superior colliculus (*5*). Both of these groups of light-sensitive cells differ from true saccade cells, which discharge in a conditional manner linked to saccadic eye movements (*3*), and are not activated by light stimuli per se; this essential control, which defines a saccade neuron, is illustrated by the his-

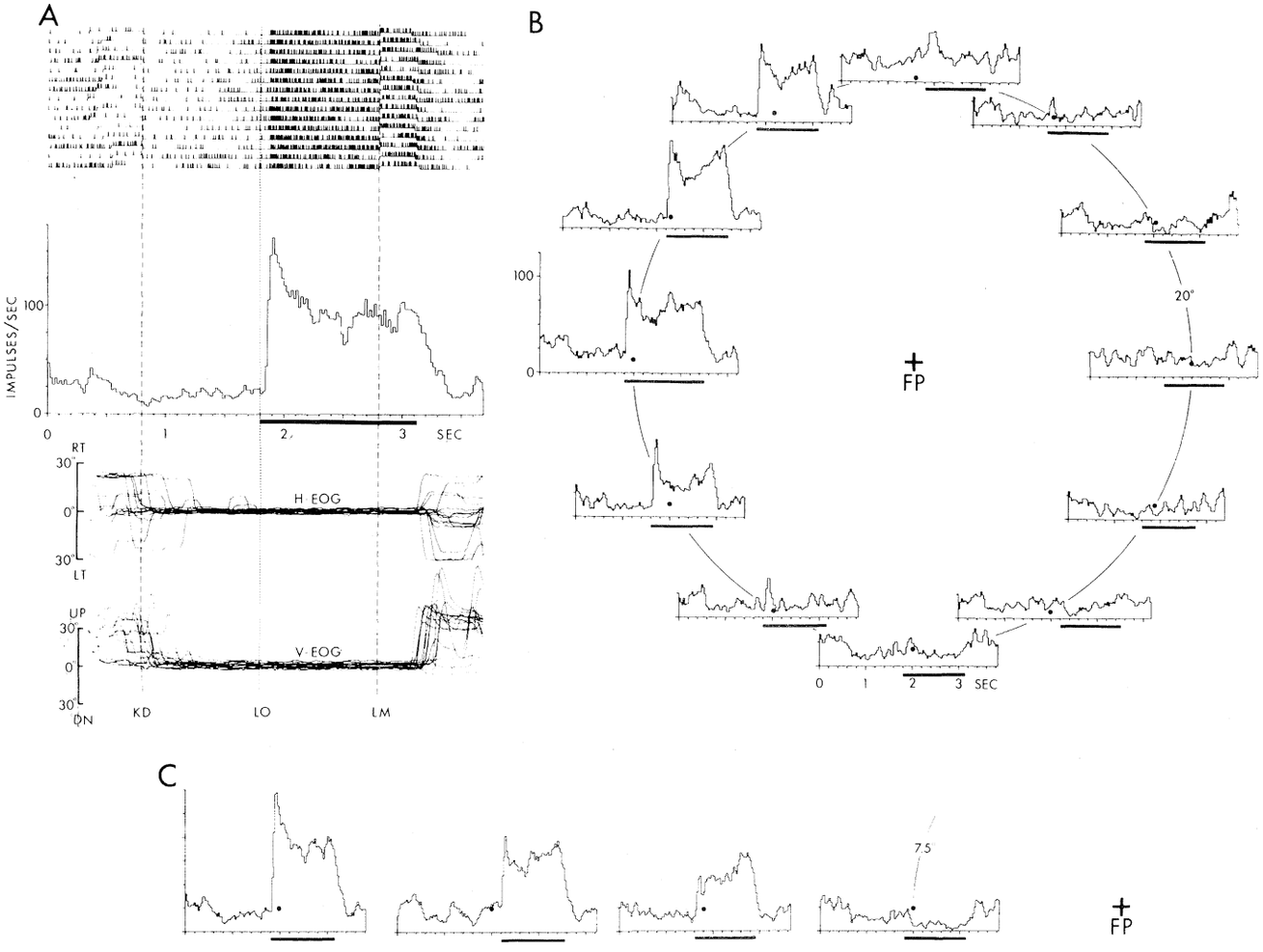

Fig. 1. Results of a study of a light-sensitive neuron of area 7. In all cases the monkey was fixating the point *FP* at the center of the screen placed 34 cm in front of him. (A) Sets of records from above downward are: 1, replicas of the impulse discharges for a sample of 15 trials, each upstroke marking the instant at which a nerve impulse was discharged; the successive small upward and downward movements of the line mark, from the left, light on (*LO*), closure of the signal key (*KD*), dimming of the light (*LM*), and its detection; 2, a histogram of the average discharge rate during these trials, the solid line below the histogram marking the time during which the LED light placed 30° to the left was on; and 3, the horizontal (*H*) and vertical (*V*) electroculograms. (B) The histograms obtained from tests at 12 different spots on the screen placed at equal intervals around a circle (20° radius). The locations of the test spots are shown by the small solid spot on each histogram; the LED was on during the time marked by the solid line below each. The histograms were obtained from the average of 9 to 13 trials. (C) Histograms obtained from four test spots placed on a line at successive 7.5° intervals in distance to the left of *FP*.

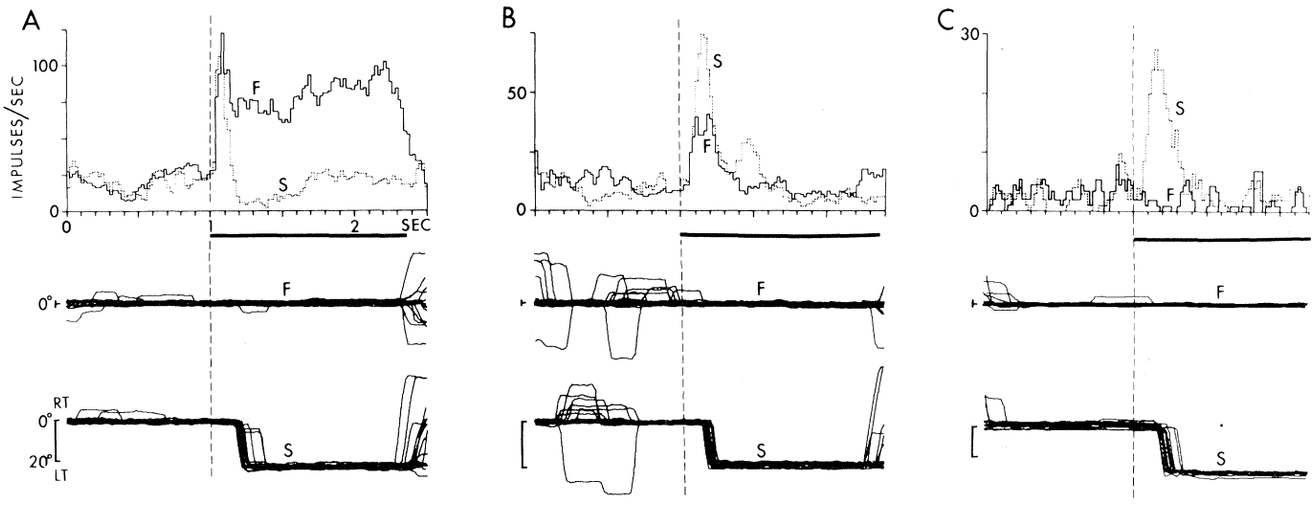

Fig. 2. Superimposed histograms for three different parietal neurons, together with horizontal EOG's obtained during steady fixation (*F*) of the center light, and during trials in which saccades were elicited (*S*). The bar beneath the histograms shows the time during which the test light was on during the fixation cases, and the center light was off in the saccade cases. The horizontal EOG's for each trial are shown below; the calibration represents 20° in all records. (A) A light-sensitive neuron with no saccadic enhancement of the onset transient, and with saccadic suppression of the sustained component of the response to light. (B) A light-sensitive neuron with enhancement of the onset discharge. (C) A visuomotor saccade neuron, insensitive to light per se.

tograms of Fig. 2C. We have confirmed in this study the existence of a large class of saccade neurons in the inferior parietal lobule (62 cells out of 350). Their average latency of discharge after light on is 126 ± 39 msec (N = 33), on average 47 msec after the onset of activity in light-sensitive neurons.

We have found no differential distribution of light-sensitive parietal neurons in regard to cortical layer, or by location within the inferior parietal lobule, but a much larger population must be studied to establish this point with certainty.

A large number of neurons of area 7 are visual fixation cells; that is, they become active when the animal fixates objects of interest in the surrounding environment, not during casual fixations (*3*). Of these, a small proportion (7 percent) is active when the animal fixates such objects or the target light, regardless of stimulus position; they are related to "full" gaze fields. Thus some ambiguity might arise in differentiating between this group of fixation cells and light-sensitive cells with foveal receptive fields, should the latter exist in area 7. No one of the parietal light-sensitive cells we observed was activated by light stimuli positioned at or near the fovea. We believe it is the behavioral act of fixation which correlates best with the incremented activity of fixation cells with full-gaze fields, and that these are not mistakenly identified light-sensitive cells with foveal receptive fields, for without motivation for the target there is no associated activity of full-field fixation cells. For fixation cells that subtend limited gaze fields no confusion arises, for they are not active during even the most interested fixation of targets outside those limited gaze fields (*3*).

We have not yet tested light-sensitive parietal cells with precisely controlled stimuli of different forms moving across their peripheral receptive fields. However, by using a laser beam deflected by a system of mirrors mounted on galvanometers we did observe that many of them are activated more intensely by movement of the laser beam spot than by a stationary stimulus, independently of any evoked saccadic eye movement. They are particularly sensitive to rapid movement of the stimulus into or out of their peripheral receptive fields at their far lateral edges, within the monocular field of view.

The functional properties of the light-sensitive cells of area 7 suggest that afferent visual signals driving them are transmitted from the retina via the retino-collicular component of the central visual system. This fits with the well-known projections from the colliculus and the pretectal region of the brainstem to the nucleus lateralis posterior and part of the pulvinar of the dorsal thalamus, and from thence upon areas of the cerebral cortex, including the inferior parietal lobule (*6*). The representation of the visual world composed by this system is consonant with the concept of peripheral or ambient vision proposed by Trevarthen (*7*), or the panoramic vision suggested by Denny-Brown and Fischer (*8*). It could provide an afferent inflow leading to directed visual attention by activation of the visuomotor mechanisms of the parietal lobe, and the differential latencies of sight-sensitive and saccade neurons fit this idea. Some uncertainty remains, however, whether this system can specify the spatial locations of eccentric visual targets with an accuracy matching that of saccadic movements evoked by those stimuli. Only further experiments can disclose whether, and if so to what degree, that accuracy depends on convergent projections from the geniculo-striate system.

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