and in maternal plasma during the later half of pregnancy makes it unlikely that the increased brain histamine originates in the mother (18).

Our data suggest that histamine and spermidine are involved in processes related to rapid tissue growth in the central nervous system. It would appear that hormonal and other adaptive factors associated with birth and growth may be controlling influences. A further possible role for histamine in neurotransmission, however, cannot be excluded on the basis of present findings.

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References and Notes
6. Although both spermidine and histamine are present in the columns eluate, fluorescence due to histamine is not measurable with histamine concentration as low as that of brain at the dilutions used.
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**Visual Receptive Fields of Neurons in Inferotemporal Cortex of the Monkey**

Abstract. Neurons in inferotemporal cortex (area TE) of the monkey had visual receptive fields which were very large (greater than 10 by 10 degrees) and almost always included the fovea. Some extended well into both halves of the visual field, while others were confined to the ipsilateral or contralateral side. These neurons were differentially sensitive to several of the following dimensions of the stimulus: size and shape, color, orientation, and direction of movement.

Evidence from neuropsychological, electrophysiological, and anatomical experiments suggests that inferotemporal cortex in the monkey is involved in visual function. Removal of inferotemporal cortex produces a severe impairment in learning visual discriminations but does not affect visual acuity, the integrity of the visual fields, or discrimination learning in other modalities (1). Visual evoked responses may be recorded from macroneuroles on inferotemporal cortex (2), and single neurons in inferotemporal cortex are responsive to visual but not auditory stimulation (3). Inferotemporal cortex receives afferents from prestripate cortex and from the pulvinar (4), and both these structures are known to respond to visual stimuli (5, 6). In order to analyze further the role of inferotemporal cortex in vision, we studied the response of single neurons in inferotemporal cortex to presentation of a variety of visual stimuli.

The results presented here are based on seven Macaca mulatta weighing 3.4 to 8.2 kg. Two days before the start of recording they were implanted, under septic conditions and Nembutal anesthesia, with the base of an Evarts microdrive and with two bolts for subsequent fixation of the head (7), and then returned to their home cage. At the start of the recording session, the animals were anesthetized with intravenous Surital for the duration of a tracheotomy and then immobilized with a continuous intravenous infusion of gallamine triethiodide in a solution of 5 percent dextrose in lactated Ringer's (Abbott Laboratories), artificially respired, and anesthetized with a mixture of 30 percent oxygen and 70 percent

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**Fig. 1. (Top)** Side view of right hemisphere of Macaca mulatta. The dots on inferotemporal cortex show approximate site of entry of microelectrode passes. The passes in which the cells with receptive fields illustrated in Figs. 1 to 3 were recorded are designated with the letters A to E. (Middle) Coronal section through pass D, illustrating the approximate locations of cells whose receptive fields are shown below or in Fig. 2. A, Allocortex; ce, central sulcus; Cd, caudate nucleus; C1, claustrum; GLD, lateral geniculate body; H, hippocampus; ip, intraparietal sulcus; l, lunate sulcus; Io, lateral fissure; os, inferior occipital sulcus; Pu, putamen; ts, superior temporal sulcus; TA, TE, and TH designate cytoarchitectonic areas of von Bonin and Bailey (9). (Bottom) Size and position of receptive fields of three neurons recorded on pass D. Each rectangle is the largest rectangle oriented parallel or at 45 degrees to the meridians of the visual field, which could be fitted entirely within each receptive field. In each case, the stimuli used to define the field were the most adequate found. The cross in each figure represents the horizontal and vertical meridians of the visual field. The right visual field (which was always ipsilateral to the electrode) is shown on the right of each vertical meridian. All receptive fields shown are for the left eye. Unit D-1, receptive field plotted with 1- by 5-degree blue bar. Unit D-3, plotted with 1- by 5-degree dark rectangle. Unit D-4, plotted with 1- by 5-degree white bar. The receptive field for Unit D-2 is shown in Fig. 2. The scale is in degrees of visual angle.
nitrous oxide. Throughout the recording session the CO₂ content of the expired air was maintained between 3.5 and 4.2 percent, and rectal temperature was maintained at 37° to 39°C. The pupils were dilated with 0.3 percent scopolamine hydrochloride and covered with contact lenses selected with a slit retinoscope to bring the eyes in focus at a Polacoat tangent screen 57 cm away to an accuracy of ± 0.5 diopter. The fovea and center of the blind spot of each eye was projected onto this screen with a reversible ophthalmoscope to an accuracy of about 0.5 degree. The position of the eyes was repeatedly checked throughout the experiment and virtually never drifted more than 2 degrees between readings. Glass-coated platinum-iridium microelectrodes (8) were advanced with an Evarts microvitreous, and then displayed on an oscilloscope, put through an audio amplifier into a speaker, and recorded on magnetic tape. An electroencephalogram (EEG) was recorded from needle electrodes in the scalp, amplified with a Grass P511 preamplifier (time constants, 250 and 3 msec), displayed on an oscilloscope, and recorded on magnetic tape.

Receptive fields were usually plotted in two ways. In the first, the tangent screen was transilluminated with light slits, edges, circles, and checkerboards of various sizes and orientations. The color of the stimuli was varied with Wratten filters. Dark bars, circles, and rectangles were moved by hand on the back of the screen. Receptive fields were detected by listening to the discharges of the unit over a loudspeaker. In the second method, a stimulus was repeatedly moved, orthogonally to its long axis, across the screen at a constant rate. The movement of the stimulus was synchronized with the horizontal sweep of a Mnemotron computer of average transients (CAT) set in a digital histogram mode. The isolated unit triggered a pulse which was fed into the Y-axis of the CAT. Thus, the CAT provided a plot of the frequency of firing of the unit as a function of the location of the stimulus on the screen and its direction of movement. Only histograms produced by unambiguously isolated units were used as data.

With both methods, when transilluminated stimuli were used, an analog signal indicating their position on the screen was also recorded on magnetic tape. Usually, the background illumination of the screen was about 1 cd/m², and the intensity of the projected white stimuli was 1.3 log units higher. If a neuron appeared to be differentially sensitive to colored stimuli, it was also tested with the white stimuli attenuated up to 2 log units in intensity.

At the completion of each experiment, the monkey was perfused with saline followed by formalin, and the brain was blocked in the coronal stereotaxic plane, cast in dental impression compound, and then cut in 25-μm frozen sections, which were stained with cresyl violet. The site of entry of each electrode pass was marked on the cast, and its path was reconstructed from the serial sections. Estimates were then made of the approximate site of each cell studied. As shown in Fig. 1, all data reported were from passes in area TE as characterized by von Bonin and Bailey (9).

The main findings were that inferotemporal units have receptive fields, that virtually all these fields were extremely large and included the fovea, and that these units had highly specific response properties. Of 51 units studied in detail, we were able to detect the receptive fields of 41. (In successive preparations the use of a greater variety of stimuli and greater attention to the EEG resulted in increasing the proportion of cells with definable receptive fields.)

All the receptive fields were more than 10 by 10 degrees in size, many were over 30 by 30 degrees, and one neuron responded to the appropriate stimuli everywhere on the 70- by 70-degree screen (Figs. 1 to 3). Surprisingly, all receptive fields, with the exception of two, included the fovea (10). About one-third of the fields not only included the fovea but extended more than 7 degrees into both hemiretinae.

Fig. 2. Receptive fields (left) and histograms of number of spikes plotted against retinal locus of stimulus (right) for three units. The letters designating each unit correspond to the passes shown in Fig. 1, and the numbers refer to units isolated on that pass. The scale for degrees of visual angle for all receptive fields and all histograms is shown under the first histogram. The vertical scale (number of unit discharges) is the same for all histograms. Above the histograms for each unit are shown 32 superimposed action potentials of that unit. Unit C-2, left eye, receptive field plotted with 1- by 5-degree red bar. The histograms were generated by ten sweeps, in the indicated directions, of a 1- by 70-degree red bar moving at 6.7 deg/sec. Unit D-2, right eye, plotted with 1- by 5-degree green bar. The histograms were generated by ten sweeps, in the indicated directions, of a 1- by 70-degree red bar moving at 6.7 deg/sec. Unit E-1, right eye, plotted with 1- by 70-degree red bar. The histograms were generated by five sweeps of a 1- by 70-degree red bar moving at 4.5 deg/sec (see also legend for Fig. 1).

1304

SCIENCE, VOL. 166
Of the remaining fields, chiefly ipsilateral ones were about as common as those largely confined to the contralateral field. We do not yet have sufficient data to relate the anatomical locus of the neuron with the quadrants in which its receptive field fell.

All units encountered were spontaneously active. In most of them, the receptive fields could be detected by listening to the loudspeaker, and averaging techniques were not necessary. However, the ease of plotting them was usually much less than for units we have studied in prestriate and striate cortex (11). Many of the units showed waning of response with repeated stimulation, and it was often necessary to use interstimulus intervals of several seconds or more in order to recover the full response. Particularly after 24 hours of recording, the EEG often showed periods of relatively synchronous and high-voltage activity. In many units, the responsivity to visual stimulation would partially or totally disappear during these slow-wave periods. Strong acoustic or somatic stimulation would return the EEG to its desynchronized state and restore the responsivity of these units to visual stimulation (12).

The large size of the receptive fields could not have been due to some optical artifact, because, with the same apparatus and procedures and often in the same animal, neurons with small extrafoveal receptive fields were recorded from the adjacent area OA of von Bonin and Bailey (9). Similarly, stray light could not account for the size of the fields, since equally large fields were found when dark stimuli were used.

Of the neurons tested, with light and dark stimuli, about half responded to both light and dark stimuli, about one-fourth to light only, and about one-fourth to dark stimuli only. Some of the neurons responsive to light stimuli, almost all responded strongly to moving bars of white or colored light. About half the neurons with receptive fields responded preferentially to a particular orientation, or orientations, of the stimulus. A similar proportion showed differential sensitivity to direction of movement of the stimulus. In a few units, levels of illumination of the stimulus or the background other than the standard ones were optimum. More than half of the responsive units increased rather than decreased their rate of firing to the best stimulus. In some cases, whether the unit's firing was increased or decreased depended on the particular stimulus, its location, orientation, and direction of movement. Although none of the units sampled responded to the uniform diffuse light stimulation, in about half of them post-stimulus histograms did reveal some activity time-locked to a diffuse light. The mean latency of the peak of these responses was 198 msec (13).

Receptive fields for seven units were plotted in both eyes. For each unit, the size and location of the receptive fields in the two eyes were similar. In two of these units, the preferred direction of movement in the receptive field of each eye was mirror symmetric along the vertical meridian. For example, if the receptive field in the left eye preferred a temporal to nasal direction of movement, so did the receptive field in the right eye. One of these units had another extraordinary property. It had a large receptive field that extended into both half fields, and the preferred direction of movement was opposite in the half fields (Unit C-1, Fig. 3). (Perhaps in the unparalyzed animal, this type of unit may be related to convergence.)

Some of the characteristics of the units we sampled are shared by the complex and hypercomplex units described in striate and prestriate cortex of the cat and monkey (5, 14). Other properties, such as the large fields, long response latency, and rapid waning of response to repeated stimulation, seem to be similar to those of units in the “posterior-pulvinar system” of the cat (6). These findings, and the facts that inferotemporal cortex receives afferents from both prestripate cortex and the pulvinar (4), strongly suggest that this tissue receives and processes visual information from both the ipsilateral and the contralateral occipital lobes (15) and, perhaps, from the pulvinar as well. Thus, inferotemporal cortex may be an integrating mechanism for information about “what the stimulus is,” received from the geniculostriate system and “where it is in behavioral space” from a superior colliculus-pulvinar system (16).

One major difference between the properties of striate and prestripate neurons and those of inferotemporal neurons was that the responses of the latter tended to be less clear and thus their receptive fields more laborious to determine (11). There are two possibilities that may account for this difference. The first is that by largely confining the stimuli to bars, edges, rectangles, and circles we may never have found the “best” stimulus for each unit. There were several units that responded most strongly to more complicated figures. For example, one unit that responded to dark rectangles responded much more strongly to a cut-out of a monkey hand, and the more the stimulus looked like a hand, the more strongly the unit responded to it. The second possibility is that the activity of units in inferotemporal cortex may be a function of variables besides the physical nature of the stimulus. This is supported by our finding that, in many units, a low-voltage, fast (“aroused”) EEG was necessary to demonstrate receptive fields. This observation, coupled with the fact that inferotemporal cortex is the only part of the monkey brain whose removal produces visual learning deficits, suggests that “stimulus adequacy” for inferotemporal units might be a function of the significance of a stimulus for the animal as well as of its physical characteristics.

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Fig. 3. Receptive fields for three units, one showing mirror symmetry in its directional preference. Unit A-2, right eye, plotted with 1-degree white bars of various lengths. Unit B-1, right eye, plotted with dark stimuli of various sizes. Unit C-1, the side flanks of the field were most responsive to a 5- by 5-degree dark square. For each side flank of the field the arrows show the only direction of horizontal movement of this stimulus which would elicit a response. Vertical movement had no effect. Within each eye, stimulation of the area labeled with a solid arrow gave a stronger response than that labeled with the dotted arrows; L, directional preference of left eye; R, directional preference of right eye. The central part of the field was most responsive to a 1- by 5-degree red bar (see also legends for Figs. 1 and 2).
Operant responding in three monkeys was maintained by intravenous presentations of morphine. Nalorphine produced reliable increases in morphine-reinforced responding. With successive daily nalorphine injections there was a decreased latency of self-administration responding for morphine, and substituted saline injections produced conditioned increases in morphine-reinforced responding.

Nalorphine counteracts many pharmacological and behavioral effects of morphine. In organisms dependent upon morphine, nalorphine induces a severe withdrawal syndrome, which includes restlessness, piloerection, vomiting, salivation, body tremors, and general irritability. Certain of these changes induced by nalorphine can be elicited by stimuli associated with withdrawal, for example, a mock injection (1), which suggests that components of the morphine-withdrawal syndrome are susceptible to classical conditioning. Wikler proposed that relapse of narcotic addicts to drug taking after treatment may be due in part to the failure of treatment programs to extinguish previously conditioned environmental stimuli associated with withdrawal distress and its relief by administration of a narcotic (2). In rats, both a classically conditioned morphine-abstinence phenomenon (increased "wet dog" shake frequencies) and increased oral consumption of an opioid (Etonitazene) can persist for many months after withdrawal of morphine (3). However, such behavior is independent of whether the environmental-conditioned stimuli had been temporally contiguous with relief from morphine-withdrawal distress (3). We now report that presentation of previously neutral environment utilized in morphine-dependent rhesus monkeys following repeated nalorphine-induced withdrawal episodes results in large conditioned increase in self-administration of morphine.

Morphine: Conditioned Increases in Self-Administration in Rhesus Monkeys

Abstract. Operant responding in three monkeys was maintained by intravenous presentations of morphine. Nalorphine produced reliable increases in morphine-reinforced responding. With successive daily nalorphine injections there was a decreased latency of self-administration responding for morphine, and substituted saline injections produced conditioned increases in morphine-reinforced responding.

Three rhesus monkeys Macaca mulatta were placed in cubicles and adapted to stainless steel restraining arms and a metal catheter-protection harness. After this adaptation period chronic jugular catheters were surgically implanted. Each cubicle contained a lever, which when depressed delivered 1.0 mg of morphine sulfate per kilogram of body weight (4). Once the monkeys began to respond, the morphine dosage was reduced gradually to 0.1 mg/kg per injection. Responding increased and stabilized within 1 to 2 months. After stability was reached, the monkeys administered 110 to 180 injections per day (11 to 18 mg/kg per day). At this point the monkeys were assumed to be strongly dependent on morphine (5). On this base line of self-administration, nalorphine (0.1 mg/kg) was administered intravenously once on