

# Probing visual cortical function with discrete chemical lesions

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*Recent anatomical and physiological experiments suggest that a neural pathway in primate visual cortex selectively analyses visual motion information. By creating small chemical lesions in identified visual areas of this pathway, a new link has been established between the physiological properties of cortical neurons and the behavioral capabilities of rhesus monkeys. Such lesions elevate psychophysical thresholds in motion-related tasks while leaving non-motion thresholds unaffected. Small chemical lesions also impair a monkey's ability to employ motion information to guide eye movements, but have no effect on eye movements to static targets. This technique creates the opportunity for a detailed functional analysis of the motion pathway and may be employed in other visual pathways as well.*

One of the most intriguing developments in the study of the mammalian visual system has been the discovery of multiple cortical areas that perform an extensive analysis of the visual image beyond that carried out by the primary visual area (striate cortex, or V1). In the macaque monkey, investigators from a number of laboratories have identified more than 20 'extrastriate' visual areas in the occipital, temporal and parietal lobes. Many of these areas are illustrated in Fig. 1, and together they comprise roughly half of the neocortex of the macaque<sup>1,2</sup>. A major task now confronting investigators in this field is to understand how these extrastriate visual areas contribute, individually and collectively, to visual perception and visually guided behavior.

Initial glimpses into the functional roles played by several of these visual areas emerged from single-unit recordings in anesthetized monkeys. Zeki and co-workers reported that a striate-recipient zone of the superior temporal sulcus contained a preponderance of direction-selective neurons<sup>3</sup>, whereas other extrastriate areas appeared relatively enriched in color-selective neurons<sup>4,5</sup>. Zeki suggested that the extrastriate visual areas function in parallel, with each area being specialized for the analysis of a particular aspect of the visual image such as motion, color, disparity, or orientation<sup>6</sup>. More recently, the complex serial as well as parallel nature of extrastriate organization has been emphasized by the notion of functionally specialized 'pathways' or 'streams of processing' in visual cortex<sup>7,8</sup>. In this view, parallel extrastriate pathways indeed process distinct types of visual information, but serial principles are incorporated within each pathway as indicated by extensive feedforward and feedback connections within a pathway and by progressively more complex response properties at higher levels of a pathway (reviewed in Ref. 2).

The most intensively studied pathway in primate extrastriate cortex appears to be devoted to the analysis of visual motion. This pathway is characterized at each stage by neurons that respond selectively to the direction of motion of a visual stimulus while being relatively unselective for other aspects of the stimulus. The motion pathway originates in layer B of striate cortex, or V1, and may include the 'trick'

cytochrome oxidase stripes of area V2. These anatomical subdivisions of V1 and V2 project to area MT which appears to be the first stage of the pathway where an entire cortical area is devoted to the analysis of motion information. MT in turn transmits this information to visual areas of the parietal lobe including MST and VIP (see Fig. 1). Identification of this pathway as a 'motion analysing' system is strengthened by several observations that neurons at successive levels of the pathway encode progressively more complex information concerning motion in the visual environment (see Ref. 2 for a review of the anatomy and physiology of this pathway). Interestingly, recent neurological observations suggest that a selective pathway for analysing visual motion exists in the human visual system as well<sup>9</sup>.

Though the physiological and anatomical evidence for an extrastriate motion pathway is impressive, such data cannot demonstrate a firm link between neural activity in the pathway and the animal's perceptual or behavioral responses to motion. Lesion experiments hold promise for demonstrating such a linkage, but lesions of this pathway are complicated by the relatively inaccessible location (buried in deep sulci) of several of the relevant visual areas. However, in recent years, investigators in several laboratories have successfully carried out such experiments by injecting small volumes of a neurotoxin, ibotenic acid, into area MT. In these experiments, the representation of the visual field in MT is first mapped with microelectrodes, and the neurotoxin (usually 1–4  $\mu$ l) is then injected into a selected region of MT. Since the toxin selectively kills cell bodies, lesions can be made without damage to the underlying white matter<sup>10</sup>. Using this technique, small cortical lesions can be placed at known topographic locations within an identified visual area. Figure 2 shows an MT lesion created in this manner.

### Motion perception

In one class of experiments conducted using this technique, investigators have measured the effects of MT lesions on perception of visual motion<sup>11–13</sup>. The basic strategy of these experiments is to determine the effects of MT lesions on psychophysical thresholds for motion-related perceptual tasks and for non-motion-related tasks. If MT lesions elevate motion thresholds relative to non-motion thresholds, one may infer that a link exists between neural activity in MT and motion perception.

In one study, Newsome and Paré<sup>12</sup> trained monkeys to discriminate the net direction of motion in a dynamic random dot display. The visual stimulus used in this study is illustrated in Fig. 3A. In the display shown in the left-hand panel, dots are flashed briefly and in rapid succession at random positions on a CRT screen. In this display, referred to as the 'uncorrelated' or '0% correlation' state, there are many local-motion events due to random associations of the briefly flashed dots, but there is no net motion in any single direction. In the display depicted in the right-hand panel, an initial sequence of random dots is flashed on the CRT, but as each dot disappears, it is replaced by a partner dot with a uniform offset in space ( $\delta x$ ) and time ( $\delta t$ ). Thus one perceives a random dot pattern in which the motion of each dot is identical to the net motion of the entire pattern. This

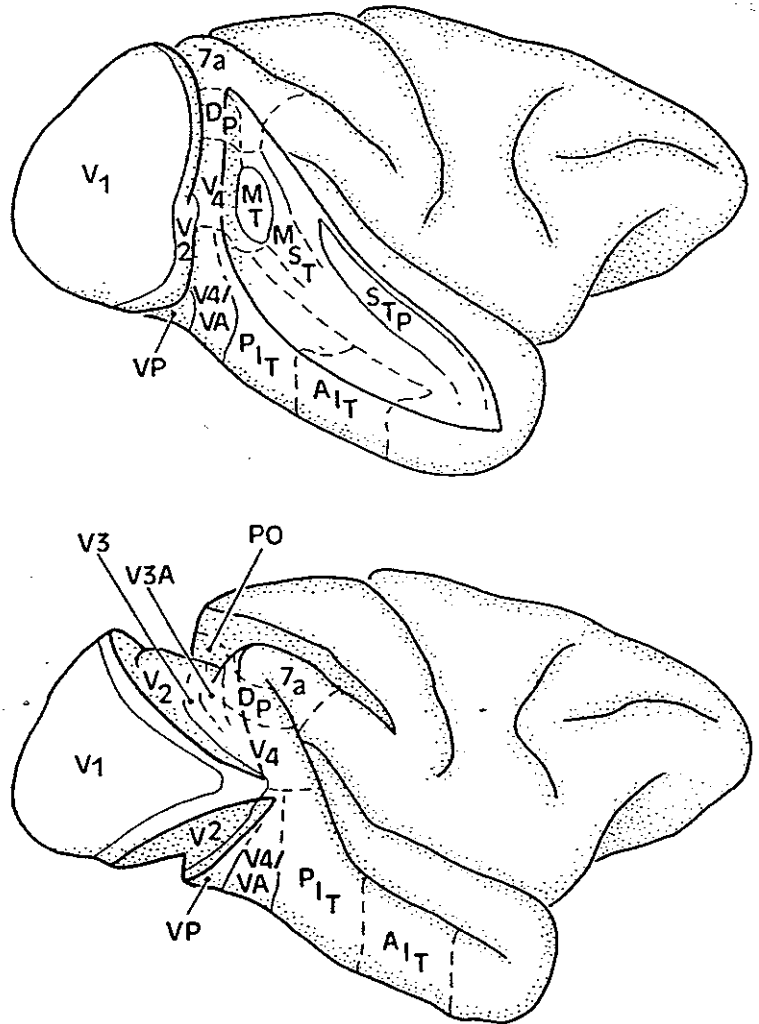


Fig. 1. The location of visual areas in macaque cerebral cortex. Upper diagram. The superior temporal sulcus has been unfolded so that visual areas normally hidden from view can be seen. Lower diagram. The lunate, inferior occipital and parieto-occipital sulci have been partially unfolded. The thin lines indicate the boundaries of visual areas that are well-established; the dashed lines mark borders that are less well defined. The primary visual area, V1 or striate cortex, can be seen at the occipital pole of the hemisphere, and many extrastriate areas are also visible. The extrastriate areas are identified on the basis of several criteria including visual topography, anatomical connections, architectonics and neuronal response properties. MT and MST, important extrastriate components of the motion pathway, are located within the superior temporal sulcus as seen in the upper diagram. Abbreviations: AIT, anterior inferotemporal; DP, dorsal prelunate; MT, middle temporal; MST, medial superior temporal; PIT, posterior inferotemporal; PO, parieto-occipital; STP, superior temporal polysensory; VA, ventral anterior; VP, ventral posterior. (Reproduced, with permission, from Ref. 2.)

display is referred to as 100% correlated motion. In practice, the monkey generally viewed an intermediate form of the display such as that shown in the center panel. In this display, 50% of the dots move in a correlated fashion, but this net motion signal is embedded in random motion noise provided by the 50% of the dots in uncorrelated motion. For each trial, the experimenter could specify the percentage of dots in correlated motion as well as the spatiotemporal composition of the correlated motion events ( $\delta x$  and  $\delta t$ ).

Fig. 2. A Nissl stained section showing an ibotenic acid lesion of extrastriate area MT. The section shows a parasagittal cut through the superior temporal sulcus. MT is located deep in the sulcus on the posterior bank. The lesion (arrows) appears as a region of dramatic cell loss with consequent disruption of the normal cortical pattern of lamination. Posterior is to the left in the micrograph, and dorsal is upward.



In a typical threshold measurement, the monkey indicates on each trial whether the net motion in the random dot display is upward or downward. The monkey is rewarded with a drop of water for identifying the direction of motion correctly. The minimum correlation value for which the monkey could successfully execute the discrimination was designated as threshold<sup>12</sup>. During threshold measurements, the monkey viewed the dot pattern peripherally while maintaining fixation on a separate point of light. In this manner, thresholds could be measured independently for dot patterns placed in either visual hemifield. Since MT is a bilateral structure that contains a topographic representation of the contralateral half of visual space, the hemifield ipsilateral to the MT lesion could be used to measure control thresholds while performance in the contralateral hemifield revealed the effects of a unilateral MT lesion.

The left-hand panel of Fig. 3B depicts pre-lesion and post-lesion motion thresholds measured in the hemifield contralateral to the MT lesion ('test' hemifield). Thresholds are shown for five different spatial intervals corresponding to a range of speeds. Before the MT lesion, thresholds were as low as 2% for the optimum spatial intervals - impressively low values that compare favorably with the best performance of human observers under similar conditions. However, on the day following the lesion, thresholds were elevated by 500-800%, demonstrating a gross impairment of the animal's ability to discriminate the direction of motion. In contrast, the center panel of Fig. 3B shows that motion thresholds measured simultaneously in the ipsilateral ('control') hemifield were entirely normal. This observation indicates that the impairment revealed in the test hemifield did not result from general fluctuations in the animal's attentional or motivational state.

Each monkey also performed an orientation discrimination as a non-motion control task. In this task the monkey reported the orientation of a stationary sine wave grating presented within the stimulus aperture. The contrast of the grating was varied randomly between trials until a threshold contrast value could be determined. The right-hand panel in Fig. 3B illustrates pre- and post-lesion contrast thresholds measured in the test hemifield on the same days as the motion thresholds in the left-hand and center panels. Clearly the lesion had little, if any, effect on contrast sensitivity.

In a related set of experiments, Siegel and Andersen<sup>13</sup> have reported similar results. They trained monkeys to detect the onset of shearing motion in a static random dot pattern and to detect the presence of 3-D structure in dynamic random dot patterns. They found that small chemical lesions of MT impaired performance on both of these tasks while leaving contrast sensitivity unaffected. Together, these results demonstrate that MT lesions can selectively impair motion perception. The experiments thus establish a link between the physiological properties of motion pathway neurons and the animal's perceptual performance.

### Smooth pursuit eye movements

Visual motion information can be used for the guidance of movement as well as for perception. For example, smooth pursuit eye movements are employed by primates to match movement of the eyes to the motion of a target in the visual environment. Clearly, performance of this task depends upon accurate visual information about the motion of potential targets, and the chemical lesion technique described above can be used to determine whether the cortical motion pathway contributes such information to the pursuit system.

With this goal in mind, Newsome *et al.*<sup>14,15</sup> trained monkeys to pursue horizontally moving targets in order to obtain a liquid reward. Each trial began with the monkey fixating a stationary visual target on a tangent screen. After a variable fixation period, the target disappeared and subsequently reappeared in motion at a randomly chosen location on the horizontal meridian. The monkey's task was to move its eyes to the target and then track it with smooth pursuit eye movements for the duration of the trial. Figure 4A depicts a monkey's eye movements in response to such a stimulus. The upper traces depict ten superimposed responses (solid lines) obtained in a normal monkey. Following the fixation period, the target (dashed line) 'stepped' 5 deg. to the monkey's right and then moved rightward at 16 deg./s toward the edge of the screen. Note that the monkey's response had two components: a rapid, or saccadic eye movement that brought the fovea near the target, and then a smooth pursuit eye movement that kept the fovea on the target for the duration of the trial.

The initial 80 ms interval of pursuit following the saccade is of particular interest. Since the pursuit response has a latency of at least 80 ms, this initial interval of pursuit must be programmed using visual motion information obtained before the saccade occurred, that is, while the eyes were still pointed toward the original fixation position. In Fig. 4A, for example, this initial interval of pursuit depended upon motion

information obtained on the horizontal meridian, 5–7 deg. eccentric in the right visual hemifield. By varying the size and direction of the initial target 'step', the critical interval of target motion could be placed at any desired location in the visual field. The efficacy of the target motion for pursuit initiation could then be assessed by measuring the speed of the pursuit movement during the initial 80 ms interval following the saccade (see also Ref. 16).

The lower traces in Fig. 4A show the responses of the same monkey to this stimulus on the day after an injection of ibotenic acid into MT of the contralateral (left) hemisphere. The most striking deficit is that the speed of the smooth pursuit eye movement was reduced during the initial interval of pursuit. This can be seen from the reduced slope of the post-lesion eye movement traces in Fig. 4A, and is even more evident in the averaged eye-speed traces in Fig. 4B. After approximately 200 ms of impaired pursuit, the monkey made a corrective saccade and tracked the moving target accurately for the duration of the trial.

The ability of the monkey to pursue accurately near the end of the trial suggests that the deficit in pursuit initiation was visual rather than motor in origin. The monkey was able to correct the initially faulty pursuit movement because the large saccadic eye movement placed the target image in a portion of the visual field that was undamaged by the small MT lesion. In fact, pursuit initiation was impaired only for target motion in a small region of the visual field that corresponded topographically to the location of the lesion in the contralateral MT. Pursuit initiation was normal at all other locations in the test as well as control hemifields.

In addition to this pursuit deficit, the monkeys were also impaired in their ability to adjust the amplitude of their saccades to compensate for target motion. In Fig. 4, one can see that the amplitude of the initial saccade to the moving target was consistently reduced following the MT lesion<sup>14,15</sup>. Both the pursuit deficit and the saccade deficit suggest that the monkey underestimated the speed of the moving target following the MT lesion. In contrast, the monkeys made accurate saccades to stationary targets at all locations in the visual field, including those for which the pursuit response to moving targets was impaired. As with the perceptual data described above, the eye movement data indicate that lesions of MT selectively damage a visual pathway that provides motion inputs to the oculomotor

system while leaving intact other pathways that supply information concerning the static position of visual targets.

#### A directional pursuit deficit

The visually derived pursuit deficit described above consistently occurred after lesions in peripheral portions of MT where neuronal receptive fields did not include the fovea. A qualitatively different pursuit deficit resulted from chemical lesions of the foveal representation of MT or of an adjacent visual area, MST, in which many receptive fields are directionally selective and include the fovea<sup>17,18</sup>. This deficit, illustrated in Fig. 5, differed from the previously described initiation deficit in two important respects. First, pursuit speed was reduced for the entire duration of the trial as opposed to an initial interval of

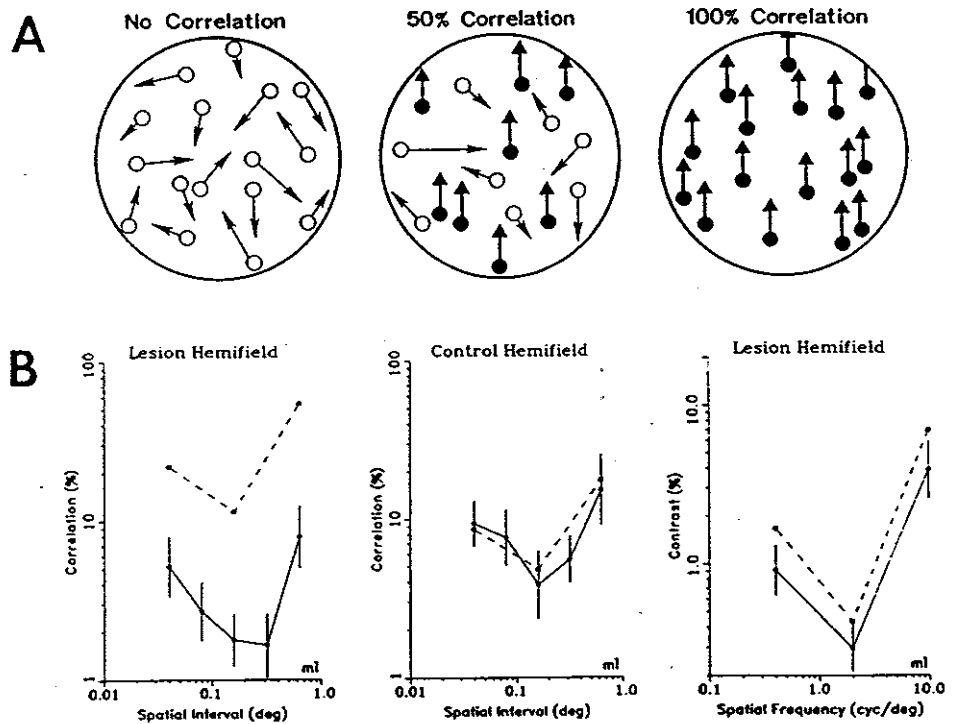


Fig. 3. (A) A schematic representation of the random dot stimulus used to measure motion discrimination thresholds. Dots are plotted individually and in rapid succession at random locations on a CRT screen. Each dot lasts for a brief interval after which it disappears and is replaced by another randomly placed dot. The operator may specify that a certain percentage of the dots be replotted with a fixed spatial and temporal offset from their partner dots. This subset of dots provides a net motion signal that is embedded within a masking motion noise. The panel on the left depicts a condition in which all dots are plotted randomly (no correlation, or 0% correlation). There is no net motion signal although there are many local motion events resulting from fortuitous associations among the stream of randomly plotted dots (arrows). In the panel on the right each dot is replotted with a fixed offset so that the motion of each dot is identical to that of the entire pattern (100% correlation). The center panel depicts an intermediate display in which 50% of the dots constitute a 'correlated' motion signal while the other 50% of the dots comprise a masking motion noise (50% correlation). Psychophysical thresholds were determined as the minimum correlation value for which the monkey could successfully discriminate upward from downward motion. (B) The psychophysical effects of an ibotenic acid lesion of MT. In each panel, the solid line and SD bars represent the mean pre-lesion threshold and so for each condition tested. The dashed lines indicate post-lesion thresholds obtained 24 h after the MT injection. The panel on the left shows motion thresholds for five different spatial intervals in the test (contralateral) hemifield (the temporal interval was held constant at 45 ms). The injection caused threshold increases of 400–800% in this hemifield. The center panel demonstrates that motion thresholds in the control (ipsilateral) hemifield were unaffected by the lesion. The panel on the right illustrates contrast thresholds for three different spatial frequencies in the test hemifield. The injection caused little, if any, elevation of contrast thresholds. (Adapted from Ref. 12.)

200 ms. This chronic reduction in pursuit speed, clearly observable in the averaged eye-speed traces in Fig. 5B, made it necessary for the monkey to execute numerous 'catch-up' saccades during sustained intervals of smooth pursuit (Fig. 5A, lower traces). Secondly, this deficit was present for any pursuit eye

movement toward the hemisphere that sustained the lesion, regardless of the point of origin of target motion. Pursuit in the opposite direction was unaffected. The known physiological properties of neurons in foveal MT and MST do not provide a clear explanation for this directional deficit. Many neurons in these areas discharge in relation to smooth pursuit eye movements, but there is no striking asymmetry in the directional preferences of these neurons that could account for the directional pursuit deficit<sup>19-22</sup>. However, an eventual understanding of the mechanisms underlying this deficit is of particular interest, because the deficit is virtually identical to a pursuit deficit observed in humans following unilateral lesions of parieto-occipital cortex<sup>23</sup>. Comparative investigations of these deficits may permit identification of motion-related visual areas in the cortex of humans that are homologous to those being studied in monkey cortex.

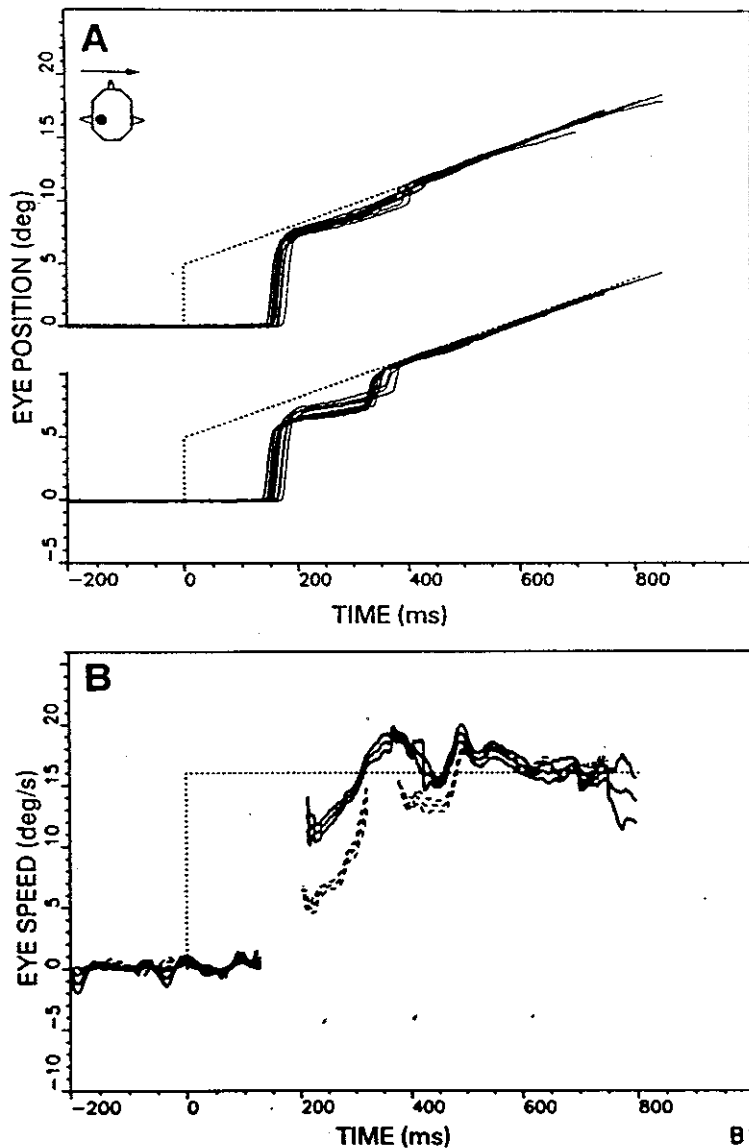
#### Recovery of function

Recovery of function is typically observed following each of the deficits we have described. With daily practice, recovery from the effects of small, subtotal lesions of MT is frequently complete within a week and almost always complete within two weeks. Longer-lasting<sup>17</sup> or even permanent<sup>12</sup> deficits are evident following larger lesions, but the permanent deficit is small relative to the acute deficit that immediately follows the lesion. The mechanisms that mediate the recovery of function are a matter of active investigation<sup>24</sup>. Plastic changes in topography or receptive field size within MT may play a role in the recovery from subtotal lesions. However, the substantial recovery observed after a complete unilateral lesion of MT indicates that other visual areas are capable of assuming the functional roles formerly played by MT neurons.

This finding is not surprising in light of the anatomical complexity that characterizes even a single cortical pathway such as that for visual motion. For example, higher level areas of the motion pathway, such as MST, receive a varied set of afferent inputs in addition to those from MT<sup>25</sup>. Behavioral recovery from the effects of MT lesions may reflect synaptic changes within higher level areas that permit greater reliance on alternative sources of afferent input. From this point of view, the complex web of anatomical connections between extrastriate visual areas can provide resistance to the deleterious effects of damage to any single area.

An important issue in evaluating the results we have reviewed is whether the conclusions are compromised by the transient nature of the deficits. We have argued that functional recovery is to be expected given the complexity of the motion pathway and the restricted extent of the lesions. The significance of the deficits rests not on their longevity, but on their specificity: the lesions impair performance of several motion-related tasks whereas performance of non-motion tasks is unaffected. The data indicate convincingly that neuronal activity in MT plays a major role in motion processing in the normally functioning cerebral hemisphere.

It is instructive in this respect to consider another case of recovery of function, that of saccadic eye movements following a lesion of the superior colliculus



**Fig. 4.** Effect of a chemical lesion of MT on the initiation of smooth pursuit eye movements. (A) Pursuit eye movements before (upper traces) and 24 h after (lower traces) a 1  $\mu$ l injection of ibotenic acid into MT. The schematic drawing in the upper left-hand corner indicates that the lesion was made in the left cerebral hemisphere and that motion of the pursuit target in this example was to the right. The dashed line represents target motion: following the fixation period, the target stepped 5 deg. to the right and moved smoothly to the right at 16 deg./s. The solid lines depict ten superimposed eye movement responses before and after lesion. (B) Mean speed of the pursuit eye movements shown in A. The dotted line shows target speed, the solid lines depict the speed of the pre-lesion pursuit movements (mean and SE), and the dashed lines indicate the speed of the post-lesion pursuit movements (mean and SE). The interruption of the eye speed traces resulted from excision of the saccade during data analysis. The primary effect of the lesion on pursuit eye movements was a reduction in eye speed during the initial 200 ms of the pursuit response. The deficit was evident only when target motion originated in a portion of the visual field that corresponded topographically to the location of the lesion in MT. (Modified from Refs 14 and 15.)

lus. The physiology of collicular neurons suggests a prominent role for this structure in the generation of saccades. On the day after an electrolytic lesion of the colliculus, however, monkeys have nearly normal saccadic amplitudes and lengthened saccadic latencies that recover within weeks<sup>26</sup>. Schiller and co-workers<sup>27</sup> have shown that simultaneous lesions of the superior colliculus and frontal eye fields permanently reduce the amplitude of visually guided saccades while lesions of either structure alone result in only transient deficits. Clearly, these structures act in parallel in mediating saccadic eye movements, and it would be a mistake to conclude from the transient nature of the collicular deficits that the superior colliculus is not involved in the generation of saccades. Indeed, major deficits have now been observed immediately following chemical lesions of the colliculus before compensatory mechanisms can be activated<sup>28</sup>. Therefore, in the analysis of complex neural systems, it can be important to assess the magnitude and selectivity of behavioral deficits immediately after perturbations of individual structures. The chemical lesion technique appears well suited for this task since it is minimally invasive: the lesions can be created in alert animals and behavioral testing can be resumed without delay.

#### Concluding remarks

Our knowledge of visual cortical organization has greatly increased in recent decades. The newly discovered extrastriate visual areas are sufficiently formidable in number and complexity to raise doubts of our ultimate ability to understand their functional roles in vision. However, current physiological data are encouraging in that the extrastriate areas appear to be organized into a small number of pathways that process relatively distinct aspects of the visual image. We need experimental approaches by which the physiological properties of neurons in these pathways can be linked to the perceptual and behavioral capabilities of the animal. Discrete chemical lesions placed in identified visual areas have now provided one such link for the motion pathway. The technique can be further exploited to ask more refined questions concerning the perceptual and behavioral contributions of neuronal processing in this pathway. We are optimistic that this approach can also be used for a behavioral analysis of function in other extrastriate pathways.

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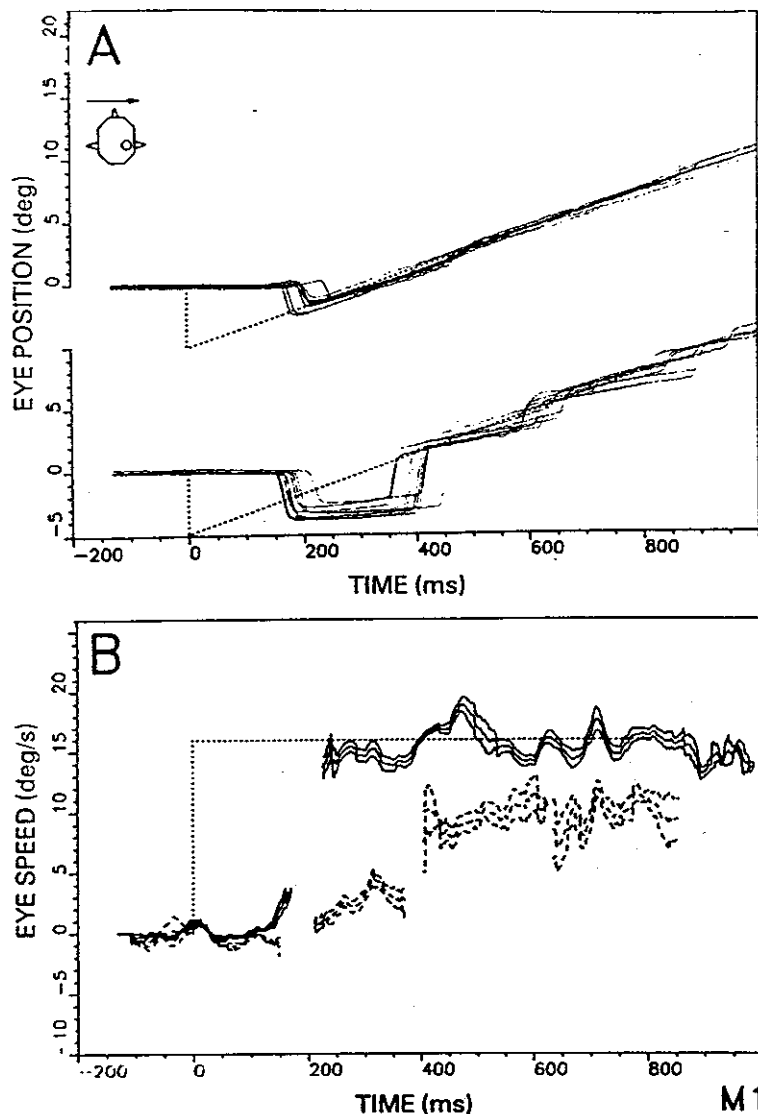


Fig. 5. A directional pursuit deficit that followed injection of ibotenic acid at the border of foveal MT and MST. The lesion was in the right hemisphere, as indicated in the schematic drawing in the upper left-hand corner. The target stepped 5 deg. to the left and then moved to the right at 16 deg./s. (A) Pursuit eye movements made before (upper trace) and 24 h after (lower trace) the MT-MST lesion. The dashed line represents target motion, and the solid lines depict ten superimposed pursuit responses for each case. (B) Mean speed of the pursuit eye movements shown in A. The dotted line shows target speed, the solid lines depict the speed of the pre-lesion movement (mean and se), and the dashed lines indicate the speed of the post-lesion pursuit movements (speed and se). Unlike the deficit illustrated in Fig. 4, pursuit speed was reduced throughout the trial when the lesion involved MST or the foveal region of MT. This deficit was evident for all pursuit movements toward the hemisphere containing the lesion (to the right in this example) regardless of the point of origin of the target motion. (Modified from Ref. 17.)

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