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Single-neuron activity in the dorsomedial frontal cortex during smooth-pursuit eye movements to predictable target motion

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Abstract

A region of dorsomedial frontal cortex (DMFC) has been implicated in planning and executing saccadic eye movements; hence it has been referred to as a supplementary eye field (SEF). Recently, activity related to executing smooth-pursuit eye movements has been recorded from the DMFC, and microstimulation here has been shown to evoke smooth eye movements. This report documents neuronal activity present in smooth-pursuit tasks where the predictability of target motion was manipulated. The activity of many neurons in the DMFC reached a peak when a predictable change in target motion occurred. Furthermore, the peak activity of some cells was systematically shifted by manipulating the duration of the target event, indicating that the network these neurons were in could learn the temporal characteristics of new target motion. Finally, the activity of most neurons tested was greater when target motion was predictable than when it was unpredictable. The results suggest that the DMFC participates in planning smooth-pursuit eye movements based on past stimulus history.

Keywords: Monkey, Premotor, SEF, Eye movements

Introduction

Smooth pursuit is a voluntary eye movement that is used to follow moving objects. Like pursuit, saccades are voluntary, but they can be used to move the eyes to moving as well as stationary objects. Saccades can be made easily without a visual object present; however, it is usually necessary that the object be present and moving for the pursuit system to respond. The most notable exception to pursuit without direct motion input occurs when an object moves in a predictable fashion. Normally, the human smooth-pursuit system responds with an approximate 130-ms delay to a moving object. However, as first suggested by Dodge et al. (1930), when object motion is predictable, the smooth-pursuit system attempts to generate eye movements that are in synchrony with and which often precede the motion of the object.

Many paradigms have been used to assess predictive eye movements. The classic experiments on oculomotor prediction were done with targets that moved horizontally in a sinusoidal fashion (e.g. Westheimer, 1954; Stark et al., 1962). However, multiple mechanisms can be used to pursue sinusoidal stimuli, complicating our efforts to understand how predictive eye movements are generated (Deno et al., 1994). Predictive mechanisms have been hypothesized to be of at least two types, short-term and long-term. Short-term prediction involves estimating future target position by performing calculations on changes in current target motion. The brain could do this by determining the Taylor series which describes the sinusoid, or alternatively by computing the first and second derivative of target position plus a proportional (Deno et al., 1994). Long-term prediction on the other hand makes use of information that has been acquired through previous experience with repetitive target motion. For example, sinusoidal motion could be predicted by learning the timing or the spatial course of a single cycle of the target's path (Robinson, 1981; Deno et al., 1994). It may be possible to dissect further the mechanism underlying long-term prediction. During pursuit of a series of discrete and repetitive constant velocity target motions, eye movements can anticipate both the start of target motion (Kowler & Steinman, 1979) and the end (Kowler et al., 1989). The substrate used to generate predictive eye movements of periodic stimuli has been hypothesized to sum these two components to create the unified response (Boman & Hotson, 1992).

In humans, predictive eye movements comprise a substantial portion of the pursuit response, and can be difficult if not impossible to eliminate even with the most rigorous randomization (Kowler, 1990). Why then have no neurophysiological investigations of prediction been done? One possible reason is that prediction does not dominate smooth pursuit in the monkey the way that it does in humans (Fuchs, 1967), and a vast majority of the literature on the neurophysiology of smooth pursuit is based on monkey data. However, monkeys can and do predict well when the proper parameters are used (Deno et al., 1994).

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The dorsomedial aspect of frontal cortex (DMFC) is an area involved in eye movement control, but also in higher order aspects of movement planning. Saccade-related activity has been recorded in the DMFC (Schlag & Schlag-Rey, 1987; Schall, 1991), and saccades have been evoked here with microstimulation (Schlag & Schlag-Rey, 1987; Tehovnik & Lee, 1993). Because of these results, a region of the DMFC has been called a supplementary eye field (SEF). Neuronal activity related to orbital position has also been observed here (Schlag & Schlag-Rey, 1987; Lee & Tehovnik, 1995). Neurons in the DMFC display visual activity during pursuit (Schall, 1991; Schlag et al., 1992; Heinen, 1995*a*), and microstimulation here can evoke smooth eye movements (Tian & Lynch, 1995). More recent investigations have attempted to elucidate how the DMFC participates in higher order functions of motor control such as planning or motor set in preparation for saccades (Mann et al., 1988; Schall, 1991). In this report, we show that the activity of neurons in the DMFC can be influenced by varying the predictability of stimulus motion during oculomotor tasks.

Methods

Preparation and recording

Each of three monkeys (two *Macaca fascicularis*, one *Macaca mulatta*) was implanted with a coil of Teflon-coated stainless-steel wire under the conjunctiva of one eye (Judge et al., 1980) to record eye movements. A stainless-steel chamber was stereotaxically positioned on the midline of the skull of each animal. Two small stainless-steel tubes were mounted transversely to stabilize the head during experiments. For the smaller 3–4 kg monkeys, the chamber was placed at Horsley-Clark coordinate AP = 19, and for the larger 6-kg monkey, at AP = 24. All surgeries were performed with aseptic procedures under deep anesthesia (sodium pentobarbital 25 mg/kg, i.v.). Animals were anesthetized with ketamine (20 mg/kg, i.m.) and given atropine sulfate (0.05 mg/kg, i.m.) to suppress salivation 30 min before deep anesthesia was administered. Sutured incisions were treated with antibiotic ointments and penicillin was administered during the postsurgical recovery period. Following recovery from surgery, the monkeys were trained to sit in a custom-built Plexiglas® primate chair, and did so with their heads restrained during the experimental sessions (3–4 h/day). For five successive days each week, the animals received all of their water during recording sessions separated by two days of *ad-lib* water. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the California Pacific Medical Center and complied with the guidelines of the Public Health Service policy on Humane Care and Use of Laboratory Animals.

In daily recording sessions, single neurons were isolated with tungsten microelectrodes and windowed with a spike discriminator. Output of the discriminator could be monitored simultaneously on an oscilloscope and through an auditory speaker. A running average of single-neuron activity over trials could be viewed on a computer screen in histogram form to aid in determining the relationship between unit activity and eye or target motion. The program automatically sorts the histograms into separate speeds and directions on the screen, and allows them to be aligned on trial events such as target jump or target stop at any time during a block of trials. If a neuron exhibited task-related activity, discriminated spikes were written to disk for off-line analysis. A 486 PC was used to collect all data, as well as to display stimuli and manage real-time behavioral control.

Off-line, the resultant single-unit activity was convolved with a Gaussian to obtain a spike density function, i.e. a smoothed representation of instantaneous firing rate (Richmond et al., 1987). We used a σ of 50 ms for the Gaussian. Although the spike-density function is a noncausal filter, some distortion of the peak can nevertheless occur if the activity surrounding the peak is asymmetrical. Since we made some inferences based on the timing of peak activity, it was critical that we did not use a σ that was too large, as it could bias the peak toward an earlier time. However, given the sometimes erratic frequency of the cortical neurons we recorded, setting the σ too small could yield a false peak if several spikes occurred close together by chance. We empirically and carefully chose the 50 ms σ. However, to verify our choice independently, we simulated the ramp-like cell discharge by first creating a random array of spikes over a 1-s interval, and then biasing the probability that a spike would occur to be greater as time elapsed. We ran the simulation for 10 "trials" and looked for peak activity with our 50 ms σ, and also with a 20 ms σ, a standard width for histogram displays. On one trial, the 20 ms σ located a clearly different peak than that located visually. On the remaining trials, smoothing with the 50 ms σ resulted in a peak that was on average only 12.7 ms earlier than was produced when the 20 ms σ was used.

The time and amplitude of peak activity was assessed by determining the maximum of the spike density function in a given trial. In trials where we attempted to modify the timing of a neuron's response by changing the duration of the fixation period or the tracking period, the average peak activity in the first five trials of a block was compared with the average peak activity in the last five trials of the same block. In trials where the predictability of target motion was varied, activity was sampled at the time of the target event, i.e. at the instant the target started to move, or at the instant it stopped. For periodic responses, the peak was computed from neuronal activity that was cycle-averaged over 80 s of pursuit.

Both horizontal and vertical eye position were measured with a magnetic-field search-coil system (Robinson, 1963), which has a sensitivity of 0.25 deg and a bandwidth of 1 kHz. Eye velocity was obtained directly by analog differentiation, and both eye position and velocity were sampled at 500 Hz by the computer. Saccades were excised from the records using an algorithm that finds epochs of time where eye acceleration first exceeds and then falls below a threshold (4200 deg/s^2). However, for the movement to be considered a saccade, the absolute value of eye *deceleration* then has to rise above and fall below the same threshold. The saccade epoch is then excised from the velocity record and replaced with a line that connects the average of several points preceding the saccade to several points following it in a fashion similar to algorithms used in the past (e.g. Keller & Kahn, 1986; Krauzlis & Lisberger, 1994). Eye velocity signals were filtered digitally using a noncausal Butterworth filter (2 pole, cutoff = 50 Hz). Eye acceleration was obtained by digital differentiation of eye velocity records. A second filter (cutoff = 25 Hz) was used to produce acceleration traces. Although the filters were noncausal, it should be noted that smoothing by definition distorts a trace, and latency is the pursuit parameter most susceptible to smoothing. Therefore, filter parameters were chosen carefully to minimize latency distortion, but to still remove most of the 60 Hz contamination of the signal. All filtering and other data processing were done using Matlab analysis software. To determine how the behavior related to neuronal responsiveness during pursuit initiation in learning experiments, eye acceleration was measured in a 20-ms bin centered at either 30 or 90 ms after pursuit onset.

Behavioral paradigms

To correlate neuronal discharge with smooth-pursuit eye movements, the animals were trained to fixate and then smoothly track a small (0.25-deg diameter) moving spot of light generated by an oscilloscope projector (spot luminance = 2 cd/m^2). The spot was back-projected onto a 90 × 90 deg tangent screen located 50 cm in front of the animal. Liquid reward was given when the animal kept its eye within a small, software-controlled window (usually ±5 deg) surrounding the position of the target. For some experiments, the motion of the target was sinusoidal and had a frequency of either 0.3 or 0.5 Hz (Fig. 1). The amplitude of target excursion was either 10 or 20 deg. However, since sinusoidal target motion provides both short-term and long-term predictive cues, we used repeated step-ramp stimuli for most experiments, which provide only long-term cues (Rashbass, 1961) (Fig. 1B). Researchers that were studying visually guided pursuit switched from sinusoidal motion to the step-ramp stimulus because it provided additional information about motion onset. Likewise, the step-ramp stimulus provides additional information about prediction of motion onset that cannot be gleaned from studying periodic pursuit. In the step-ramp paradigm, the animal fixates a stationary target which is then displaced transiently (step) in one direction before being moved smoothly back across where the animal fixated and then into the periphery (ramp). The size of the step can be set to eliminate catch-up saccades that normally accompany pursuit initiation. The step-ramp stimuli were then presented in blocks of trials between which the inter-trial interval was a fixed duration (usually 500 ms) to make the sequential trials essentially periodic. Early research suggested that monkeys could not generate eye movements that predicted target motion (Fuchs, 1967). However, recent evidence has shown that monkeys predict well under the appropriate stimulus conditions (Deno et al., 1994). Monkeys can generate anticipatory eye velocity before target motion when the target is turned off briefly before the target moves (gap paradigm) (Fig. 1B), but usually not if it is left on. It is important to note that we used the stubbornness of monkeys to predict to our advantage in experiments where we wanted to dissociate the internal predictive state from the actual movement command by *not* extinguishing the target before it moved, and thereby suppressing predictive eye movements.

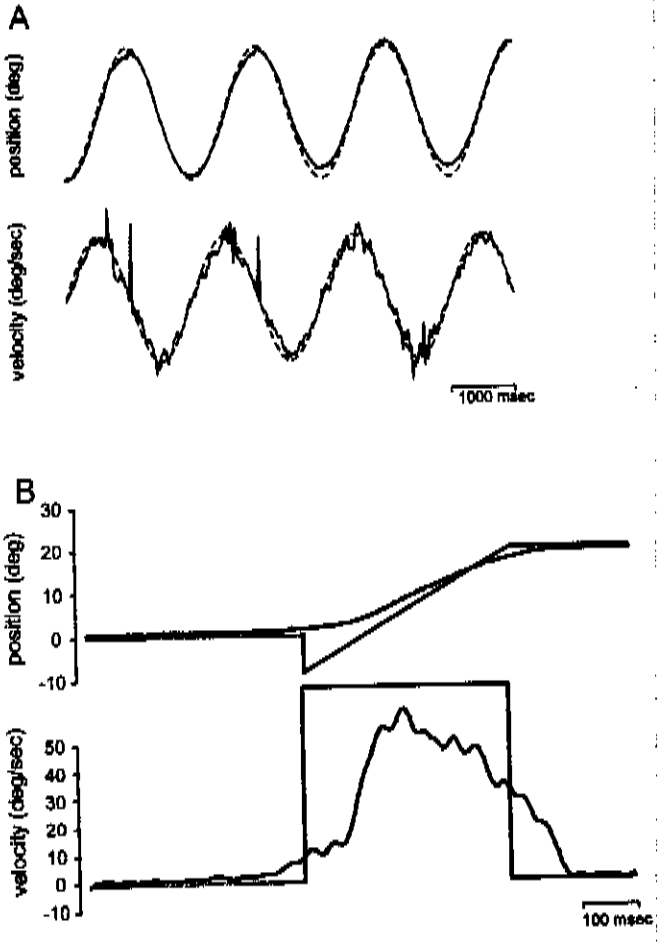

Fig. 1. Predictive smooth-pursuit paradigms. (A) Sinusoidal stimulus motion. Horizontal target (dashed line) and eye (solid line) position are at top. Horizontal eye and target velocity are at bottom. Spikes in the velocity trace are saccades. The eye and target are almost exactly in phase, indicating the monkey is predicting the motion well. (B) Step-ramp stimulus motion. Here the target steps to the left 7 deg, and moves at 70 deg/s to the right. The eye starts to move before the target, and slows down before even reaching target velocity, indicating prediction of the motion. The target is off during the shaded period. This "gap" facilitates anticipatory eye movements. Infinite negative target velocity during target step not shown. Other details are as in (A).

To determine if the activity of a neuron that accompanied a predictable event was related to prediction and not dynamics of the eye movement or visual motion, experiments were done with the individual neurons in which the predictability of the target timing was varied systematically in different blocks of trials. For example, the animal might pursue in a block of trials where the fixation period was always 500 ms, i.e. 100% predictable. In the next block of trials, the fixation period would be randomly set at either 500 or 1000 ms. Therefore on any given trial, the chance of the animal seeing a 500-ms fixation period was only 50%. The activity of the neuron was then quantified at the time of the target event, i.e. when the target started to move or stopped. The range of fixation durations used was 200–1000 ms. Similar manipulations were made with the duration of target motion during pursuit. The range of motion durations used was 500–1500 ms.

To assess the capability of a neuron to readjust the timing of its peak activity, the timing of either the fixation period or the motion of the target was changed systematically in different blocks of 20 trials. For example, the animal might be familiarized with a fixation period of 200 ms in the first 20-trial block. In the subsequent block the fixation period would be extended to 500 ms on the first trial, at which time the learning process could begin, and remain fixed at 500 ms for the entire block. Likewise, the target motion timing could be adjusted from, for example, 500 ms in the first block of trials, to 1000 ms in the next block. The range of target motion durations used was 500–1500 ms. Peak firing and relevant eye movement measures of the first five and the last five trials in the second block where computed and averaged to characterize the learning process, as described above.

Histology

Before the animals were sacrificed, electrolytic marker lesions were made at selected sites by passing d.c. current at 40 μA for 40 s through the tip of a tungsten microelectrode. Animal behavior was monitored closely to insure that no discomfort was experienced when the lesions were made; however, this never occurred. Histological material was obtained after deeply anesthetizing the animal with pentobarbital and perfusing with buffered 10% formalin. Frozen serial sections (50 μm thick) were cut in the sagittal plane, and every other section was subsequently stained with cre-

syl violet. Electrode tracks were then reconstructed with the aid of recovered marker lesion sites.

Results

The location of the chambers placed almost all electrode penetrations anterior to the motor cortex, as confirmed by the absence of layer 5 giant pyramidal cells in histological sections, and posterior to the rostral granular cortex typical of prefrontal areas (Wise & Tanji, 1981). Many were further confined to the 8 × 12 mm area defined by microstimulation and single-cell recording that was originally defined as a SEF (Schlag & Schlag-Rey, 1987), but some extended slightly caudal (Fig. 2), which was more consistent with the area where neurons involved in saccade planning and execution have been found (Schall, 1991). Since the area recorded in by Schall (1991) and our area overlap both the SEF and the supplementary motor area (SMA), we will use the more topographical and general terminology of dorsomedial frontal cortex (DMFC) to describe the loci of recording in the current study.

Our investigation was concerned initially with characterizing neuronal activity in the DMFC during periodic target motion, since such motion has classically been used to characterize predictive pursuit; however, this approach was abandoned early for reasons explained below. Cells active during periodic pursuit usually displayed a ramp-like buildup in activity that peaked around the time that the direction of target motion reversed (Fig. 3). Following the peak in firing, the activity of the cell quickly returned to baseline. We did not feel that the cell was simply responding to orbital position or velocity of the eye since the response of the neuron was highly nonlinear, while the response of the eye was roughly sinusoidal during tracking of sinusoidal motion (see Fig. 1). Furthermore, the responses seemed not to be simply related to visual motion, since the peak occurred even in the absence of a visual target (Fig. 4) for the few cells that were tested in this fashion. Instead, the rhythmic nature of the ramp-like activity suggested that the cells might be involved somehow in timing the periodic motion of the target. Also, the phase relationship of peak activity to the reversal of the target in space seemed appropriate for a signal that could convey when the target would reverse, since 80% of the cells had peaks that occurred before the target reversed direction (mean lead time = 153 ms; standard error = 49 ms). The timing of the peak response for the sample of neurons that showed a peak during periodic pursuit is summarized in Fig. 5.

However, because of the inherent difficulty in dissociating short-term versus long-term aspects of a putative predictive response when sinusoidal stimuli are used (see Methods), we early on abandoned the sinusoidal motion and decided to restrict the stimuli in our investigation to step-ramp targets, which were made periodic by repeated presentation. A further advantage of the step-ramp motion is that the stimulus can be illuminated and remain stationary before it moves, ensuring that visual motion does not contaminate the neuronal response. Fig. 6 shows examples of single-unit activity that was recorded during trials using the step-ramp para-

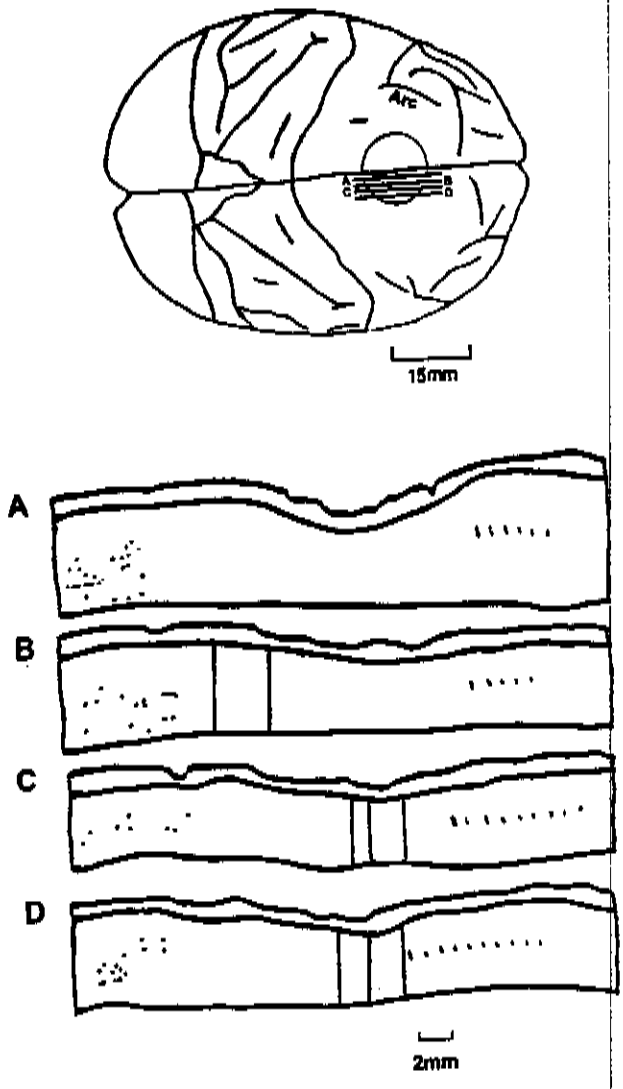

Fig. 2. Histology. The chamber location of one monkey is shown on a dorsal view of the brain. Sagittal sections (below) were obtained from the location of labeled lines beneath the chamber. The sections show a reconstruction of electrode penetrations, indicated by vertical lines. Dots are the locations of pyramidal cells; hatching indicates the anterior appearance of a granular layer. Arc: arcuate sulcus.

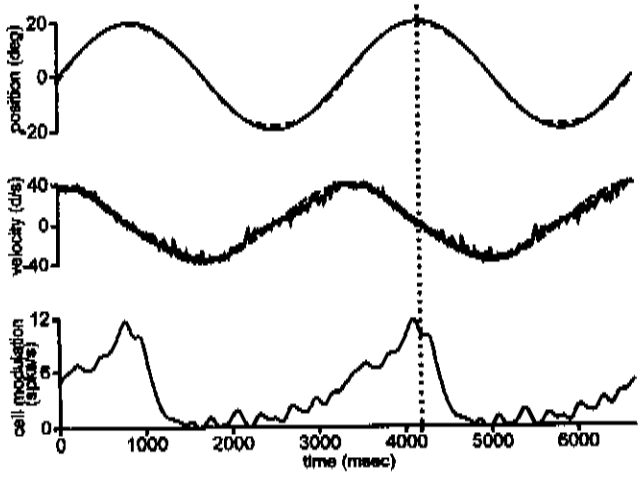

Fig. 3. Neuronal activity during sinusoidal tracking. The firing rate of the cell peaks around the time when the target reversed direction (vertical dotted line). Horizontal target position (dashed line) and eye position (solid line) are at top. Horizontal eye and target velocity are in the center. Activity is represented with a spike density function at the bottom. Activity and eye movements are averaged over 80 s. Two identical cycles are shown for ease of visualization.

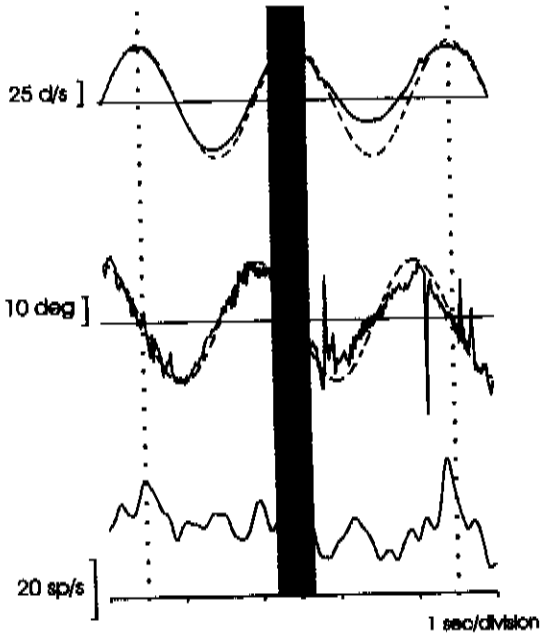

Fig. 4. Neuronal activity during target blanking. The neuron continues to show a peak of activity around the time when the target reverses direction during the blanking period (shaded area) despite the absence of visual motion. Note that the animal's behavior perseveres as well. Other details are as in Fig. 3.

digm. The data shown here are from neurons that were active during pursuit, a population that was composed of 60% of the cells that were tested with this paradigm. The activity of cells recorded when the step-ramp stimulus was used had a profile similar to that seen during periodic tracking, characterized by a ramp-like buildup of activity that rose to a peak and then dropped sharply. The peak could occur either at the end of the fixation period when the target

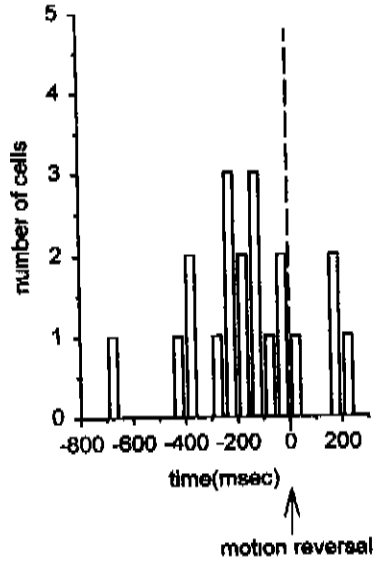

Fig. 5. Summary of peak activity time during periodic tracking. Data is shown as a frequency distribution with target reversal depicted by the dashed vertical line. Most neurons peaked before the target reverses direction.

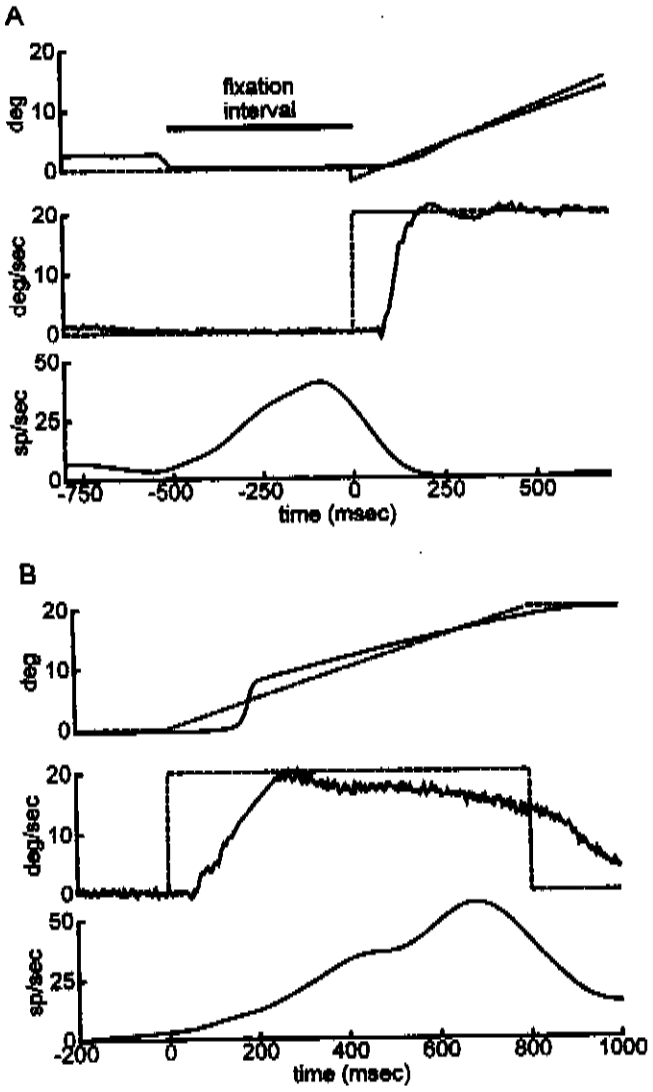

Fig. 6. Neurons that responded with the step-ramp tracking paradigm. (A) Activity begins to increase when the fixation point comes on, and builds up to a peak. The activity then begins to decline before the target moves (time zero). (B) Activity begins to increase when tracking starts, and builds up to a peak. The decline in activity now occurs before the target stops, indicated by the vertical dashed line. Infinite negative target velocity during target step in (A) not shown. Step is set to zero in (B). Each trace is an average of at least 10 trials. Other details are as in Fig. 3.

started to move, or near the end of the trial when the target stopped. For these studies, we concentrated on cells that peaked at or before one of these target events.

The response of the neuron in Fig. 6B is consistent with activity related to orbital position, i.e. it is maximal when the eye is 17 deg from the center. We did not test the activity of neurons exhaustively for an orbital position component, but typical activity for the few cells that we did test can be seen in Fig. 7. Here, when the monkey pursues upward from the center, the activity of the cell builds up to a maximum at about 20 deg. Without further testing, the activity here would be classified as an orbital position response. However, when the monkey pursues upward from 20 deg down to center, the peak occurs at the center instead.

Fig. 8 summarizes the results from a sample of 77 neurons that were active during smooth pursuit. As can be seen here, peak

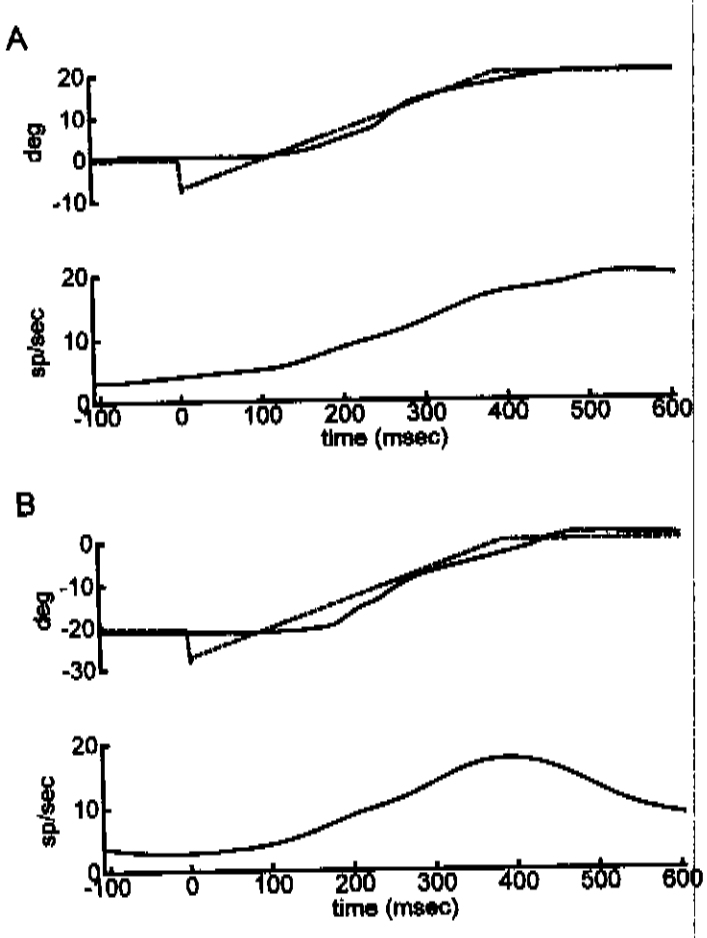

Fig. 7. Test of orbital position dependency. (A) Averaged traces during tracking a target that moved up from an initially central position. Eye (solid) and target (dashed) position are at top, cell activity at the bottom. The cell responds best when the eye is rotated 20 deg up. (B) The same cell, but here the target starts 20 deg down and moves to the center. The cell now responds best when the eye is approaching the center.

activity was clustered around the time that the target started to move or stopped. Since the peaks plotted in Figs. 8A and 8B are from the same sample of cells, we needed a way to specify more accurately the timing of the peak response with respect to either target motion onset or offset. We arbitrarily defined pursuit *initiation* neurons to be those with a peak response within ±500 ms of when the target started to move and pursuit *termination* neurons to be those with a peak response within ±500 ms of when the target stopped. In the sample of pursuit initiation neurons, 26% peaked before the eye moved, and 17% peaked before the target moved (mean lead time = 148 ms; standard error = 28 ms). In the sample of pursuit termination neurons, 67% peaked before the target stopped (mean lead time = 139 ms; standard error = 38 ms). Again, the timing of peak activity suggested that the response of many cells encoded the upcoming target event, i.e. the initiation or termination of target motion.

If the neurons that we recorded in the DMFC were truly involved in the process of predicting target events, their activity should vary according to the predictability of the task. To test this assumption, we monitored the activity of neurons that remained isolated long enough as we varied the predictability of either the fixation period or the period of ongoing target motion. We found that the activity of a given neuron was higher when the timing of target motion was totally predictable than when it was random (Fig. 9). The differential activity of the cells could not have been related to motion of the target since target motion in both predictable and random conditions was the same on the trials that were compared. Furthermore, when the predictability of the fixation period was varied, activity was assessed at the instant that the target began moving, before it could have had any effect on the activity of the cell. We computed a ratio of neuronal activity during trials when target motion onset/offset was predictable to when it was unpredictable. The mean ratio was 1.46. A student *t*-test verified that this number was higher than the null case of 1.0 ($t = 2.18$; $P < 0.04$). In these experiments, the random blocks were composed of trials in which one temporal parameter was chosen from a fixed set of times. However, the conditional probability of encountering each of the "random" trial parameters was not equal as the chance of a longer duration parameter would greatly increase when one of a known shorter duration had elapsed. We compared the spike discharge for the shortest and longest target motion onset/offset intervals during the *random blocks only* (Fig. 10). For most cells, the response was higher for the longest interval. This pattern of activity is consistent with the cells encoding the conditional probability of the fixation/pursuit intervals. Two cells showed an opposite trend. This is interesting because the longest intervals in the blocks of trials that these neurons were recorded were much longer than those that the monkey experienced in daily training. It could be that the network of neurons was unfamiliar with those intervals, making encoding the longer time more difficult.

To predict the time when the trajectory of a moving target will change, the brain must have had past experience with the trajectory to have learned that time. We wanted to know whether neurons in the DMFC that peaked before predictable target events could readjust the timing of their firing activity to reflect learning of a new

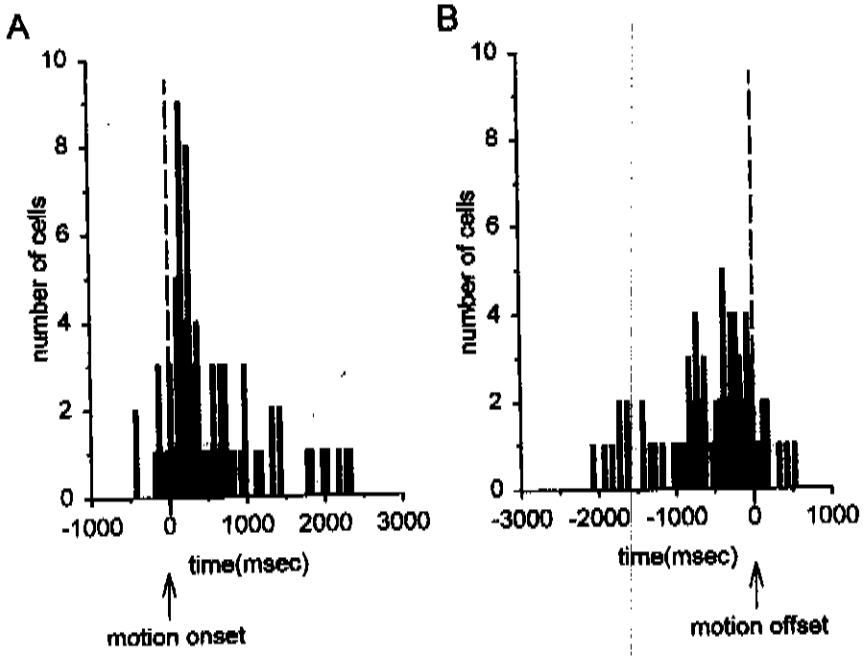

Fig. 8. Frequency distributions of peak activity time during step-ramp tracking. (A) Time of peak activity with respect to when the target started to move. (B) Time of peak activity with respect to when the target stopped. Dashed lines indicate target motion onset and offset in (A) and (B), respectively.

target trajectory. In fact, the time that peak activity of the neurons occurred could be readily altered when the animal was presented with a tracking task that involved a different duration fixation period or ongoing target motion time (Fig. 11). For cells with a peak of activity that occurred around the time when the target *started to move* in one block of trials, shortening the fixation period in a subsequent block of trials resulted in a shift of the peak towards an earlier time, and lengthening the fixation period in a subsequent block of trials resulted in a shift of the peak towards a later time. For cells with a peak of activity that occurred around the time when the target *stopped moving* during pursuit in one block of trials, shortening or lengthening the target trajectory in a subsequent block of trials yielded similar results. The results are summarized in Fig. 12. To test the significance of the result, we performed a correlation analysis on the data and verified that the correlation was different from zero ($t = 3.07$; $P < 0.01$). Note that the distributions overlap well, suggesting that a similar mechanism is involved in timing target onset and offset.

How does oculomotor behavior reflect learning the new trajectory? Eye acceleration was analyzed in blocks of trials in which we assessed changes in peak activity of neurons related to changing the timing of the fixation period (Fig. 13). Initial eye acceleration was low after fixation duration was changed, regardless of the magnitude of duration shift. However, the acceleration increased as the block progressed, suggesting that the animal's knowledge of when the target would move was facilitating pursuit. Interestingly, eye acceleration was modified only in the early period of pursuit initiation (at 30 ms) and not in the later period (at 90 ms). No change might be expected in the late period since it is thought to be visually guided (Krauzlis & Lisberger, 1994), and the visual motion was identical from trial-to-trial within a block of trials.

Discussion

We found that the activity of a population of neurons in the DMFC built-up in a ramp-like fashion to a peak during smooth pursuit trials. During sinusoidal pursuit, the peak of the activity occurred around the time that the target reversed direction. During constant-velocity pursuit, the peak of activity occurred around the time when either the target started to move or stopped. The timing of peak activity could be shifted systematically by changing the duration of either the fixation period, or the period during which the target moved. Furthermore, activity was greater when the duration of either period was made predictable by keeping it fixed in a block of trials, than when the duration was randomized.

DMFC involvement in oculomotor control

The area that we have referred to as the DMFC lies just off the midline and medial to the superior limb of the arcuate sulcus, coinciding with dorsal area 6 of Brodmann (1909). Our penetrations were concentrated in an area that included the SEF, but extended slightly more caudal than the area ordinally defined by Schlag and Schlag-Rey (1987), and included a portion of the SMA where saccade-related activity has been found (Schall, 1991). The SEF has been implicated in the control of saccades by several researchers. Both single-unit studies (Schlag & Schlag-Rey, 1987; Schall, 1991) and studies where saccades were elicited by electrical microstimulation (Schlag & Schlag-Rey, 1987; Tehovnik & Lee, 1993) have supported a role for the DMFC in the execution of goal-directed saccades. However, the studies with potentially the most relevance to SEF (and SMA) function were those performed using the go–nogo paradigm (Mann et al., 1988; Schall, 1991). The strength of this paradigm is that it allows one to tease out aspects of neuronal activity that are related to planning the movement from those related to its execution. Activity recorded that accompanies a saccade to a simple flashed target could be a conglomerate signal related to both planning and execution. With the go–nogo paradigm, the activity that is related to planning can be isolated from the conglomerate response, because in some trials (nogo) the movement is withheld despite all other elements of the task being the same. These workers found that a substantial portion of DMFC cells continued to fire in the nogo trials, whereas others were active only for the saccade.

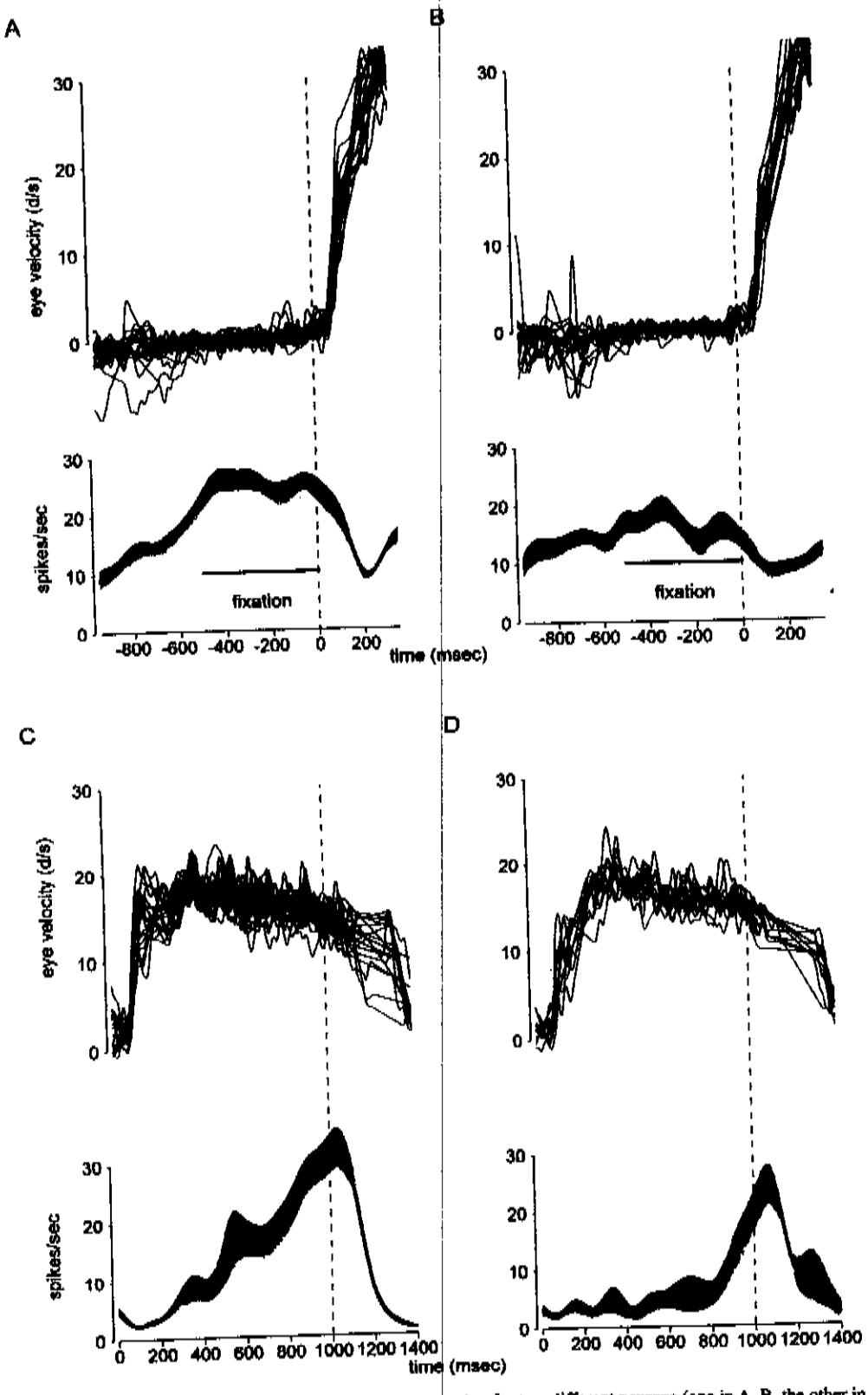

Fig. 9. Neuronal activity for predictable and unpredictable target motion for two different neurons (one in A–B, the other in C–D). (A) In this block of trials, the target always started to move (vertical dashed line) 500 ms after it appeared. At top are individual eye velocity traces during fixation and pursuit initiation. At bottom is mean cell discharge (thick line) and standard error of the mean (shaded area). (B) In this block of trials, the target started to move either 500 or 1000 ms after it appeared with random presentation, but only 500-ms trials are shown. The neuron is more active in trials where the animal can know when the target will start to move. (C) The target always moved for 1000 ms. (D) The target moved for 500, 1000, or 1250 ms with random presentation, but only 1000-ms trials are shown. Dashed line is the time when the target stopped. The neuron is more active during trials in which the animal can know when the target will stop.

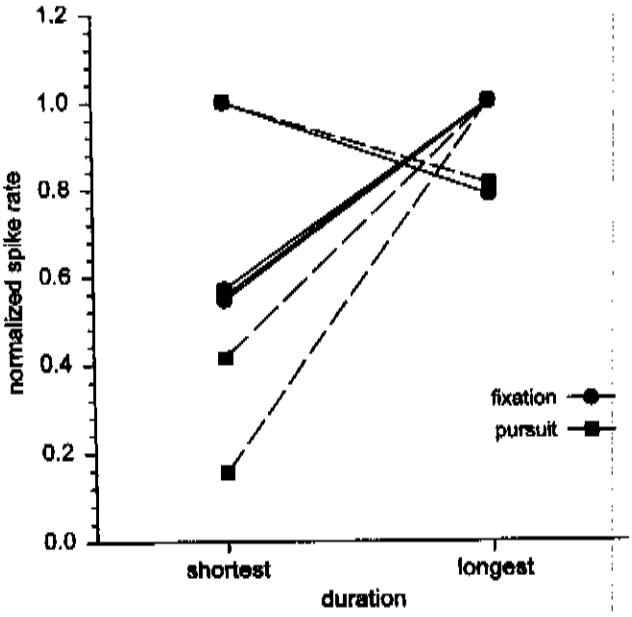

Fig. 10. Neuronal activity during the shortest and longest fixation and pursuit intervals. Activity is normalized with respect to the interval with the highest spike rate. Activity is usually higher for the longer interval, consistent with an encoding of increasing conditional probability of a longer interval after the shorter interval had elapsed. Note that two neurons showed an opposite trend. In both cases, the intervals were much longer than those that the monkey typically experienced in daily training (1000-ms fixation, 1500-ms pursuit).

We used a different approach to characterize the component of neuronal activity related to planning. The go–nogo paradigm only allows one to say that the activity of a given cell *is related* to a certain behavior, but not *how* that activity participates in controlling that behavior. In our experiments, manipulation of trial parameters was done to tease out the specific manner in which the planning activity might be used by the animal to perform the task. We found that systematically changing the timing and randomization of target motion changed the timing and amplitude of the activity. These results are important because they could elucidate the type of processing that networks of neurons in the DMFC use for planning smooth pursuit.

The existence of saccade-related activity in the DMFC suggests another interesting problem. Do the same networks that participate in pursuit planning also participate in the planning of saccades? Although not the focus of the present study, a neuron was occasionally isolated long enough to test the relationship of its activity in saccade paradigms. DMFC neurons that responded near the time of target motion onset in pursuit trials would often respond in a similar fashion for saccades. Furthermore, the activity in pursuit trials was not merely related to the saccades which often accompany pursuit initiation since the activity occurred in pursuit trials when saccades were absent (Heinen, 1995*a*). This is consistent with the idea that planning-related computations performed by the DMFC may not be specific to a particular motor system, as has been suggested before (Goldberg, 1985).

The results of previous studies provide evidence that neurons in the DMFC code orbital position (Schlag et al., 1992; Lee & Tehovnik, 1995). The profile of activity in some of the records that we presented is consistent with an orbital position signal. Although we do not dismiss the presence of such activity in the DMFC, our data suggest that neurons here can exhibit more complex behavior. The length of the experiments that we performed prohibited an exhaustive test for position dependency on every cell. However, the response of a few cells was tested explicitly for a position component. In one block of trials these cells could exhibit what appeared to be classic orbital position sensitivity. However, having the animal track along a different vector produced a response with a similar temporal profile, despite the fact that the position of the eye in time was entirely different. Furthermore, our results when target duration was explicitly manipulated resulted in a shift of peak activity. Such a shift is inconsistent with a simple orbital position signal. However, it could be that the neurons were encoding *relative* target (or eye) position in this situation. Although this explanation might hold for activity recorded while the target was moving, it cannot account for the similar profile of activity recorded during fixation. Finally, we performed experiments where differences in target predictability yielded different profiles of activity. Here, a given cell could have markedly different behavior despite the fact that orbital position was the same.

DMFC involvement in movement planning

The DMFC has been shown to participate in higher order motor control by other investigators. The readiness potential, one of the most thoroughly investigated scalp-recorded potentials, is thought to emanate from the SMA. This potential has a similar profile to cells we have recorded in that it builds up in a ramp-like fashion, and then drops before the movement (Deeke & Kornhuber, 1977). It is not only observed in conjunction with a movement, as it still occurs when the movement is withheld (Libet et al., 1982*a*). Furthermore, the time course of the potential is shorter when the movement is spontaneous rather than when it is timed by an external signal (Libet et al., 1982*b*). Although the readiness potential has been usually recorded accompanying finger movements, it has also been measured in the DMFC before saccades (Becker et al., 1972; Evdokimidis et al., 1992).

The SMA also participates in processing sequences of movement. Early work documented cerebral blood flow in the SMA during finger presses of a spring (Roland et al., 1980). A simple spring press caused blood flow to increase in the primary motor and sensory cortices, but only during sequences of spring presses did activity extend to the SMA. However, during mental rehearsal of those sequences, only the SMA was active. The SMA has also been shown to be activated during sequences of learned saccades and alternating self-paced saccades (Petit et al., 1993), as assessed by positron emission tomography (PET). Furthermore, damage to the SMA can impair sequences of learned saccades (Gaymard et al., 1990). Single-unit work has pointed to a population of neurons in the SMA that are only active for a specific sequence of movements such as the "turn-pull-push" of a manipulandum, but not a "turn-push-pull" (Tanji & Shima, 1994).

A role for the DMFC in oculomotor prediction?

Smooth pursuit is a voluntary eye movement that is used to follow moving objects. However, because of the processing time needed to convert the visual motion signal to an eye movement, theoretically the velocity of the eyes would never match the velocity of an object once it began to move. Predictive eye movements circumvent processing delays to achieve more effective tracking. The classic predictive eye movement is a reversal in the velocity of the eyes that matches or precedes a reversal of the velocity of a sinu-

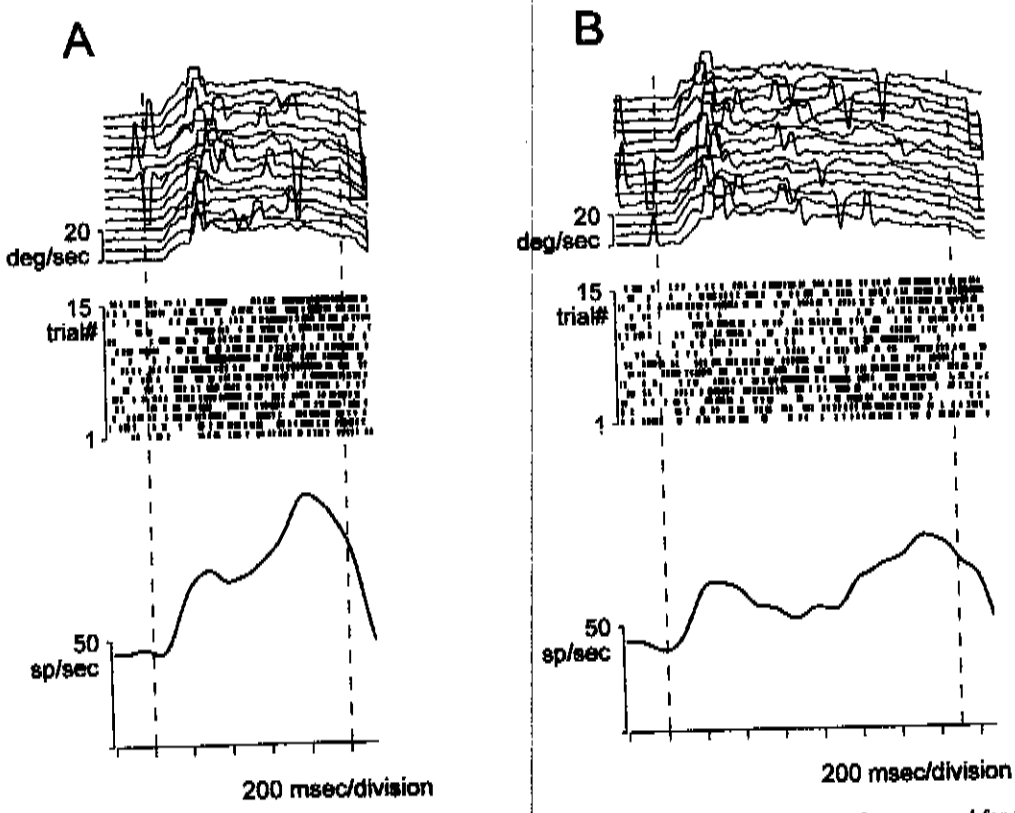

Fig. 11. Modification of peak activity timing. (A) The animal tracked in a block of trials where the target always moved for 1000 ms. Average eye velocity at top, raster of neuronal activity during individual trials in the middle, and average neuronal activity at the bottom. The peak began to decline before the target stopped. The smaller peak is probably related to pursuit initiation or saccades, evidence that this neuron participated in several functions. (B) The target now moves for 1500 ms. Here, only the last five trials are shown in the average. Note that the peak shifted in time to again precede target motion offset.

soidally moving target (Westheimer, 1954; Stark et al., 1962). Anticipatory pursuit has been described more recently to occur before a target starts to move (Kowler & Steinman, 1979), or before it stops (Kowler et al., 1989). Predictive pursuit is thought to be a sum of these two anticipatory components (Boman & Hotson, 1992). In our study, we found that the activity of neurons in the DMFC often reached a peak around the time that a sinusoidally moving target reversed direction, or a constant-velocity target either started or stopped.

Could the DMFC be involved in predictive or anticipatory smooth pursuit? The anatomy is sufficient to allow interactions with the smooth-pursuit system. The DMFC could receive pursuit signals from the FEF, which is involved in pursuit (Huerta et al., 1987), from MST (Huerta & Kaas, 1990), or from other parietal areas that participate in motion processing and pursuit control (Huerta & Kaas, 1990; Barbas & Mesulam, 1985). The DMFC could send output to brain-stem areas involved in pursuit generation either indirectly through the FEF (Huerta et al., 1987), or through direct projections to the nucleus reticularis tegmenti of the pons (NRTP), which is involved in dynamic control of pursuit (Suzuki et al., 1991).

How might DMFC neurons participate in control of predictive pursuit? It could be that the neurons we recorded which exhibit peak activity before a transient target event are part of a network of cells that encode the time of an upcoming target event. Another interesting feature of the activity profile of these neurons was the ramp-like build-up of activity before the peak. The profile was

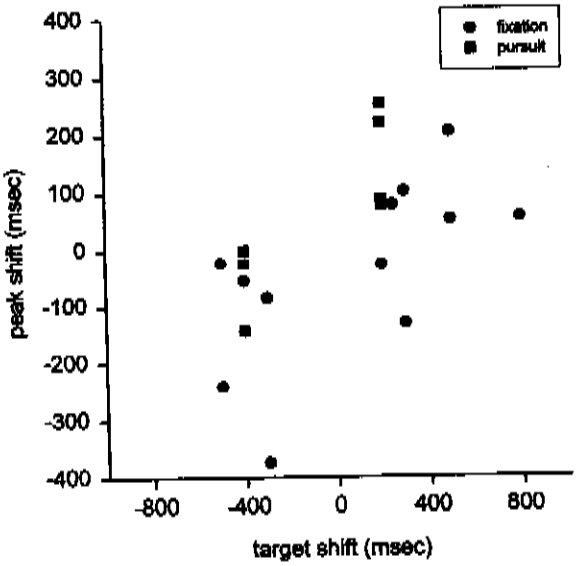

Fig. 12. Summary of peak activity modification for all neurons where the duration of either the fixation or tracking period was manipulated. Making either the fixation period, or the time that the target moved during pursuit longer, is considered a positive target shift. Making the fixation period, or the time that the target moved shorter, is considered a negative target shift. Note a shift in peak activity of the same sign, which is therefore in the proper direction to realign it with the target event.

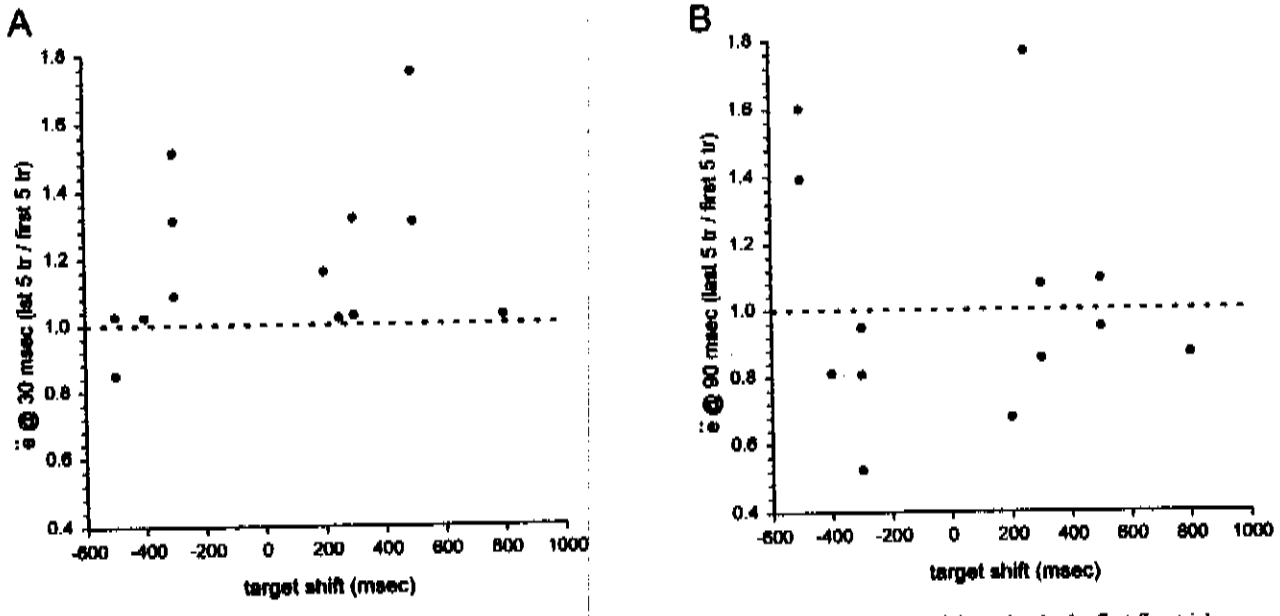

Fig. 13. Eye acceleration as a result of target shift. Shown is a ratio of acceleration in the last five trials to that in the first five trials following a shift in fixation period duration for (A) 30 ms into the pursuit movement, and (B) 90 ms into the movement. Early (30 ms) eye acceleration increases over the block of trials as the animal becomes more familiar with the motion, regardless of the magnitude of the shift, while late (90 ms) eye acceleration does not.

similar to that which might accompany an integrative process. Since the critical target events in all of our experiments could have been predicted by keeping track of elapsed time, one hypothetical system consistent with our results it that the network of cells is integrating time. This might be accomplished if the network integrated input from another pool of neurons that fired at a constant rate. A resetting of the activity level back to baseline (possibly by a thresholding mechanism) could signal that the event was about to occur.

We are suggesting that the activity of neurons we recorded was related to timing the movement, because it was sensitive to explicit manipulations of target timing. Timing is important for planning a movement, but knowledge of spatial location, sequencing, and other characteristics of target motion are undoubtedly used to facilitate predictive behavior. There is evidence that the DMFC codes for orbital position and participates in sequencing for complex behaviors (see earlier discussion). It could be that different populations of cells encode these different properties, or it could be that a single neuron is capable of encoding more than one characteristic itself, by "multiplexing" the different signals.

A cognito-motor interface?

Neurons that we recorded in the DMFC responded in a fashion consistent with anticipating when a target would start or stop moving. Past work has shown that this area participates in visually guided pursuit initiation as well (Heinen, 1995*a*). In the previous study, we concentrated on the discharge of neurons which peaked around movement onset. In the current study, we looked at neurons that peaked around target events; for initiation cells this meant that the peak occurred close to when the target started to move. However, the activity of initiation neurons recorded in each study was not cleanly different, in that the period it occurred in commonly overlapped.

Neurons that respond for preparatory and motor aspects of saccades have also been found in the DMFC (Schall, 1991). Apparently, networks of neurons in this region that participate in one function can overlap and share elements of networks that participate in a different, but related function. One could view this processing as a transformation of information from an internally generated target motion signal into a motor command, like the transform from a sensory motion signal to a motor command that occurs at the MT/MST border (Newsome et al., 1988).

The results of the current study raise the exciting possibility that neurons in the DMFC which are involved in anticipating when a target will move are coupled to neurons involved in visually guided pursuit. There is behavioral evidence that anticipatory and visually guided pursuit are subserved by the same mechanism. If the speed of a target is made predictable, anticipatory eye velocity and eye velocity during visually guided pursuit initiation increase in parallel (Kao & Morrow, 1994). The results supported the idea that anticipatory and visually guided pursuit eye movement generation were governed by a similar mechanism. Data from the current study is consistent with the conclusion of these authors in that early eye acceleration during visually guided smooth-pursuit initiation was correlated with neuronal behavior when target motion onset time was manipulated.

How is the coupling accomplished? Some models of pursuit place prediction in a separate loop in the basic system and incorporate a switch that allows the pursuit system to use either visually guided or predictive information to drive the eyes (Dallos & Jones, 1963; Barnes & Ruddock, 1972; Heinen, 1995*b*). The DMFC may be in this loop. Other researchers have suggested that there is a switch in the pursuit system also, but that it has a somewhat different purpose (Grasse & Lisberger, 1992; Goldreich et al., 1992). These researchers characterized the switch as being activated by the mere presence of a stimulus that will become the target of a pursuit eye movement. Furthermore, the pursuit "switch" is more readily activated when the stimulus is present for a longer time preceding pursuit initiation. The state of the switch is hypothesized to control the first 0–40 ms of pursuit, whereas the next 40–100 ms

period of pursuit is thought to be driven by visual inputs (Krauzlis & Lisberger, 1994). In the present study, neuronal activity was influenced by manipulating the duration of a familiar target trajectory. The change in target trajectory also influenced pursuit in the first 40 ms, but not the later period. We take this as evidence that the switch proposed by these workers may not be altogether different than the one that closes the predictive loop.

In summary, the DMFC appears to participate in higher order control of smooth pursuit. Neurons here can apparently learn the timing of familiar motion, and are more active when it is possible to predict upcoming motion. The results add to the growing body of evidence that the DMFC integrates information related to planning a movement with that involved in its execution.

Acknowledgments

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