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RESEARCH NOTE

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Single neuron activity in the dorsomedial frontal cortex during smooth pursuit eye movements

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Abstract This report describes the behavior of neurons in the dorsomedial frontal cortex during smooth pursuit eye movements. Single neurons were recorded from monkeys while they tracked a small target that moved from the center of a screen outward. The firing rate of most cells was modulated during smooth pursuit eye movements, and often the activity peaked around pursuit initiation. Visual motion of the small target with the eyes fixed could activate pursuit neurons, but did not account for the total pursuit response. Neurons were also selective for the direction in which the animal was tracking, indicating that they were linked to the generation of the eye movements, and not to non-specific arousal effects. The results suggest that the dorsomedial frontal cortex participates in initiating smooth pursuit. It is proposed that the dorsomedial frontal cortex is part of a partial alternative path to the classic pursuit pathway that might be used to facilitate the initiation or control of eye movements beyond a simple reflexive response to retinal slip.

Key words Frontal cortex · Eye movements · Monkey

Introduction

Much effort has been devoted to establishing the brain circuitry that generates smooth-pursuit eye movements (for reviews, see Lisberger et al. 1987; Wurtz et al. 1990; Keller and Heinen 1991). However, there are still substantial gaps in our knowledge. Most notable is the lack of understanding of cortical pursuit control. The well-established brainstem/cerebellar smooth pursuit pathway (Suzuki and Keller 1988; Stone and Lisberger 1990) is considered to be dependent largely on the middle temporal area (MT) and the medial superior temporal area (MST) for its input (Glickstein et al. 1980). However, lesions of MT and MST merely degrade the initiation or maintenance of eye movements without totally abolishing them (Dürsteler and Wurtz 1988), and recovery is rapid (Yamasaki and Wurtz 1991).

Recently the dorsomedial frontal cortex (DMFC) has been implicated in oculomotor function. Neurons here have been shown to respond before, during, and after saccades, as well as in the presence of visual stimuli (Schlag and Schlag-Rey 1987; Schall 1991). Saccades have also been evoked here using microstimulation (Schlag and Schlag-Rey 1987). In fact, smooth pursuit-related responses of DMFC neurons have been anectodally described before (Schlag and Schlag-Rey 1987). It seems reasonable to suspect that the DMFC is involved in smooth pursuit. The DMFC lies just off the midline and just medial to the superior limb of the arcuate sulcus, coinciding with Vogt's area 6aβ. It is richly interconnected with other frontal regions including the FEF, and has its own inputs from MST and the parietal lobe (Huerta and Kaas 1990). It has been classified as a supplementary motor area because it is distinct from the primary motor area, and has its own somatotopic representation of body parts (Woolsey et al. 1952). This report documents basic characteristics of smooth pursuit-related activity in the DMFC.

Materials and methods

Each of two monkeys *(Macaca fascicularis)* was implanted with a coil of Teflon-coated stainless steel wire mounted 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. For the smaller (3 kg) monkey, the chamber was placed at Horsely-Clark coordinate AP=19, and for the larger (6 kg) monkey, at AP=24. The chambers were located histologically as on the midline, 5 mm anterior to the posterior bend of the arcuate sulcus in the small animal, and just behind the bend in the larger monkey. The location of the chambers placed almost all penetrations anterior to the motor cortex, as confirmed by the absence of giant layer 5 pyramidal cells in histological sections (see Wise and Tanji 1981), and most were further confined to the 8×12 mm area defined by microstimulation and single-cell recording to play a role in the generation of saccades

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(Schlag and Schlag-Rey 1987). All surgery was performed with aseptic procedures under deep anesthesia (sodium pentobarbital 25 mg/kg i.v.). Animals were induced with ketamine (20 mg/kg i.m.), and given atropine sulfate (0.05 mg/kg i.m.) to suppress salivation 30 min before induction. Sutured incisions were treated with antibiotic ointments, and penicillin was administered during the post-surgical recovery period. Following recovery from surgery, the monkeys were trained to sit in a custom-built Plexiglas primate chair and sat with their heads restrained during the recording sessions (3–4 h/day). For 5 successive days each week, the animals received all of their water during recording sessions, separated by 2 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.

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) spot of light as it either moved at a constant velocity out from the center of the screen, or stepped away from where the fixation point had been before smoothly moving back across the center and then out. The speed and direction of target motion were usually randomized over a discrete set of values in successive trials to minimize anticipation (speed range 1–60 deg/s). Most neurons were tested for a visual response by moving the target in a similar fashion while the monkey fixated. Tracking targets were generated with an oscilloscope projector system, and visual stimuli were projected onto a pair of orthogonally mounted, galvanometer-driven mirrors. Both were back-projected onto a translucent screen placed in front of the monkey.

Single neurons were isolated with tungsten microelectrodes. Single-unit discharge was convolved with a Gaussian to obtain a spike density function, i.e., a smoothed representation of instantaneous firing rate (Richmond et al. 1987). Horizontal and vertical eye position and velocity were sampled at 1 kHz. Eye velocity was obtained directly by analog differentiation (with a cutoff frequency of 170 Hz) of the position signal yielding an RMS velocity noise of about 1 deg/s. Behavior paradigms, visual displays, and data acquisition were controlled by a laboratory PC system.

Results

The firing rate of neurons in the DMFC often increased during smooth pursuit, and occasionally, although rarely, decreased. We will refer to such activity as a 'pursuit response', although conceding that it may not always have been related to a pure motor command. Of 158 neurons

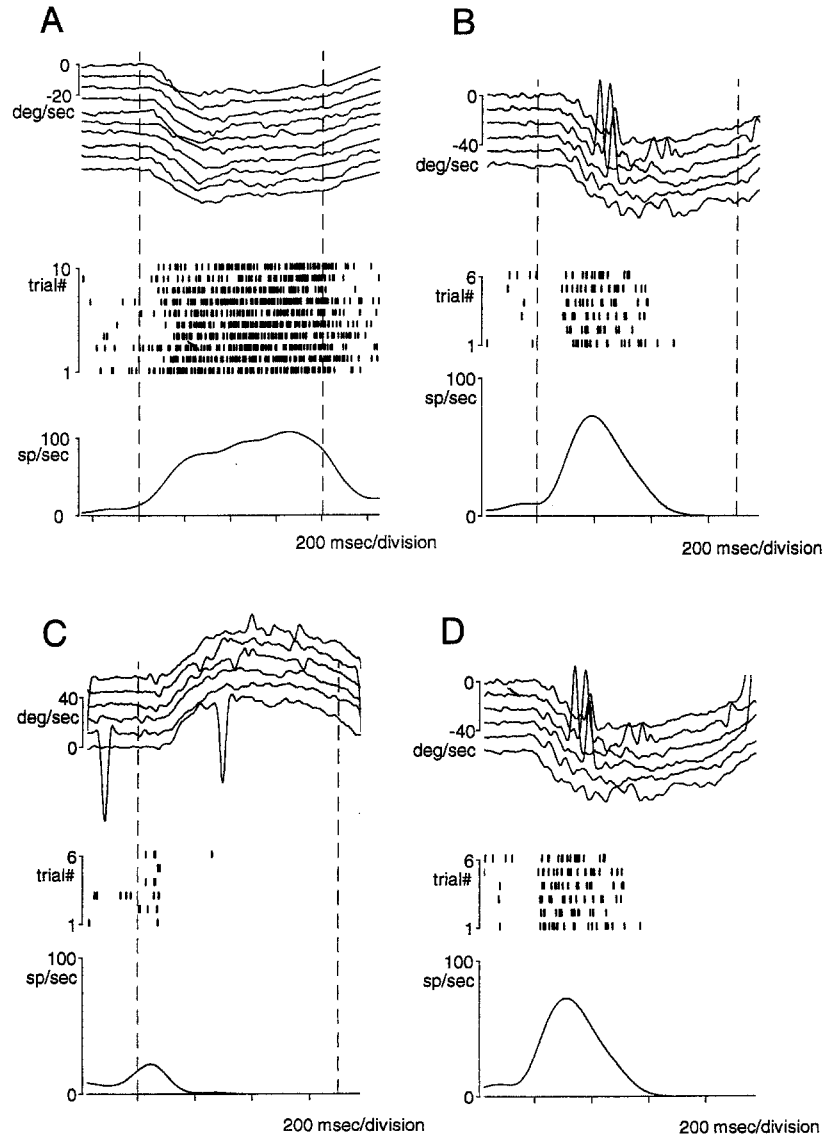

Fig. 1A–D Examples of single neuron activity in the DMFC. **A** A neuron responds vigorously while the monkey tracks 20-deg/s spot motion. **B** Strong activity of a different neuron during pursuit initiation to 40-deg/s spot motion of the left aligned on target motion onset and **C** less activity when the monkey pursues the spot moving at the same speed to the right. **D** Record shown in **B,** now aligned on pursuit onset, to demonstrate a better relationship with the eye movement. In all graphs, eye velocities from individual trials are shown at *top* (desaccaded in **A**), individual trial spike rasters in the *middle,* and average spike density function over all trials at *bottom. Vertical dashed lines* mark beginning and end of spot motion

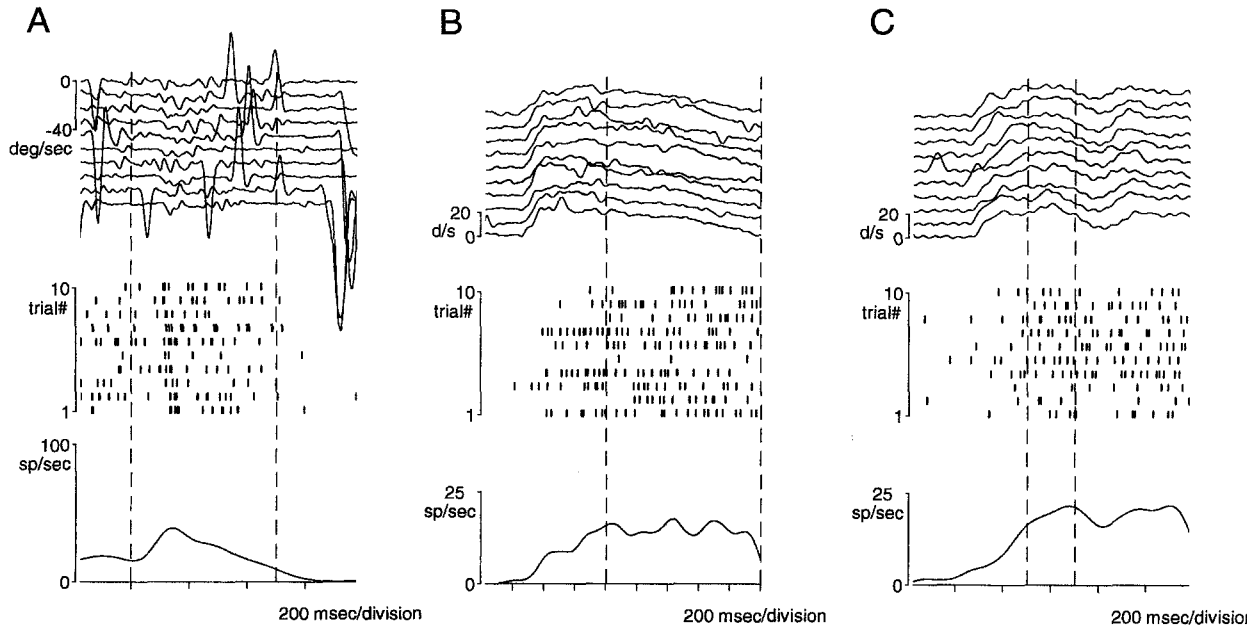

Fig. 2A–C Dissociation of visual from extraretinal neuronal response. **A** The same cell shown in Fig. 1B–D responds less when the animal fixates and the spot is swept across the visual field to the left at 40 deg/s. **B** Response of a neuron when the target was stabilized on the retina during pursuit (stabilization occurs between *dashed lines*). **C** Response when the target was blinked off for 200 ms (between *dashed lines*). In both **B** and **C**, the response perseveres in the absence of target motion

recorded in the DMFC, 60% had a pursuit response. The response was sometimes similar to that described for MT and MST neurons during pursuit (Newsome et al. 1988) in that it was relatively homogeneous over the duration of the eye movement (Fig. 1A). Since MST projects to the DMFC, a response with this character might be expected. Our goal though was to ascertain the further contribution of the DMFC to the generation of pursuit eye movements.

In fact, we found that the pursuit response of DMFC cells was usually much less sustained than that of MST neurons, commonly displaying a prominent peak. Most often, a neuron tested with our constant velocity paradigms showed peak activity that occurred around the time that the target began to move (Fig. 1B–D). Specifically, 38% of the peaks were within 250 ms of target motion onset. Mean peak latency to target onset of this population of cells was 97.2 ms (SE 22.3 ms). The early activity of DMFC neurons occurred either in isolation or superimposed on the sustained increase in firing rate. One might suspect the activity was related to initial acquisition saccades, since the DMFC is known to play a role in saccade generation (Schlag and Schlag-Rey 1987; Schall 1991). To test for the possibility of saccade-related discharge, we had the monkey track spot motion in the step/ramp paradigm. The step/ramp paradigm minimizes the occurrence of saccades, as the animal can catch the target more easily since it initiates a smooth pursuit eye movement in the direction of target motion before the target crosses the fovea. Careful inspection of the record in Fig. 1 reveals that the activity persisted in the absence of saccades. In fact, the firing frequency of ten pursuit cells analyzed with the jump ramp paradigm was almost the same in trials where an initiation saccade was present (43.2 spikes/s, SE=4.2 spikes/s) as when one was not (44.2 spikes/s, SE=4.5 spikes/s).

An early response could be due to visual input, since the target moves rapidly across the retina to initiate pursuit trials. Therefore, time permitting, cells were tested for a visual motion component by having the animal fixate while the spot was moved outward from the center of the visual field (Fig. 2A). The small spot activated pursuit cells 92% of the time, although the response was usually smaller than that seen during pursuit. The preferred direction of spot motion for the cell was almost always the same as the preferred tracking direction; however, a few cells interestingly showed a preference for the opposite direction. During pursuit, there was often significant activity beyond the peak, which allowed us to quantitatively assess the magnitude of the visual contribution to the response. For a sample of cells, the spot was blinked off briefly (200–300 ms) or stabilized on the retina during ongoing pursuit soon after the animal acquired the target to determine the remaining response in the absence of visual motion (Fig. 2B–C). Stabilization was achieved by electronically adding the eye position signal to the target position signal after smooth pursuit had been successfully initiated. We then determined the mean firing rate of the neuron in a 50-ms interval centered 200 ms after the blink or stabilization was initiated and compared it to the mean firing rate over the same interval during normal pursuit. Computing a simple ratio of the activity of a neuron during blink/no-blink and stabilization/no-stabilization paradigms (Newsome et al. 1988) yielded mean values of 0.58 and 0.96, respectively. The amount of discharge remaining in the absence of visual motion indicated a significant extraretinal contri-

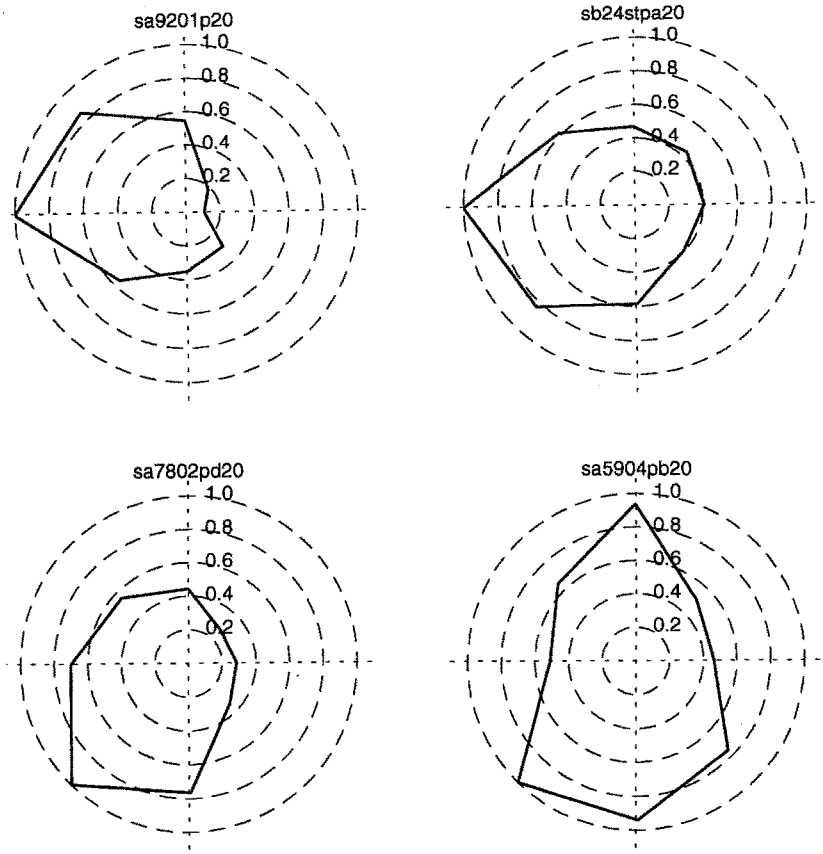

Fig. 3A–D Polar plots of the responses of four different neurons; in each case for eight directions of tracking. **A–C** These neurons were tuned to one direction of tracking. **D**, This neuron responded more for vertical than for horizontal tracking (axis tuning). The magnitude of each response has been normalized with respect to the preferred direction of a given neuron

bution to the response of DMFC neurons, as is the case in MST. Interestingly, the ratios computed for DMFC neurons are close to the middle of the range documented for cells there. In MST, stabilization, in general, also produced larger ratios than did blinking the spot off.

If a neuron responds better for one tracking direction than others, it is more likely to be involved in eye movement generation than in a more general process such as attention or arousal. As can be seen in Fig. 3, DMFC cells were often directionally tuned. Shown here are tuning curves obtained from the activity of four neurons that were rigorously tested for a directional preference. Directional selectivity was quantified by computing a directional index: DI = 1– (peak response in the non-preferred direction/peak response in the preferred direction). For a sample of 97 neurons, directional indices ranged from close to zero (no directional tuning) to 0.86, which represents a preferred to non-preferred response ratio of approximately 7:1. The mean of the distribution was 0.27 (standard error =0.02). Directional selectivity of DMFC cells is substantially poorer than that seen for MT neurons both in response to visual stimuli in anesthetized (Van Essen et al. 1981) and alert (Mikami et al. 1986) monkeys, and during smooth-pursuit (Erickson and Dow 1989). Since MST is closer in the stream of processing to the DMFC than MT, one would like to compare the directional indices of DMFC neurons directly to MST. Unfortunately, there is currently no such data for MST neurons.

Discussion

We found that the activity of a large percentage of neurons in the DMFC was modulated during smooth pursuit. A common property of DMFC neurons in our study was a predominant response at the beginning of the pursuit trial. Most pursuit cells also responded for visual motion, and were, as a population, directionally selective. How, then, might DMFC neurons participate in smooth pursuit eye movement generation?

Pursuit neurons have been found in other major cortical areas, namely PG (Robinson et al. 1978), the FEF (Bruce et al. 1985), and MST (e.g., Maunsell and Van Essen 1983; Newsome et al. 1988). The DMFC receives input from the parietal lobe, the FEF and other closely associated frontal areas, as well as MST (Huerta and Kaas 1990). It, in turn, projects to the nucleus reticularis/pontine nuclei complex (Huerta and Kaas 1990), brainstem areas known to participate in pursuit control (Suzuki et al. 1990), and could, therefore, ostensibly influence pursuit eye movements.

Let us consider some alternatives for where the DMFC might be in the functional smooth pursuit circuitry. Perhaps the first guess would be that it falls between MST and the brainstem control regions and merely continues to process or refine the pursuit signal that passes it. Another possibility is that the DMFC is part of a separate motion processing/pursuit path that originates in early visual areas (V1/V2) and goes through parietal areas

to the FEF and the DMFC. Anatomical connections are present that could subserve such a circuit (Huerta and Kaas 1990; Barbas and Mesulam 1985).

We think that the DMFC is actually a structure in a partial alternative path, receiving smooth pursuit-related input from MST and the parietal lobe. The DMFC could share processing with the FEF before sending output to the brainstem. The purpose of such an extra 'loop' on the classic pursuit pathway might be to facilitate the initiation or control of eye movements that would otherwise depend solely on retinal slip. Anticipatory and/or predictive eye movements could utilize a signal that occurred before target motion onset for example, and some evidence has been found for predictive neuronal activity in the DMFC (Heinen 1994). The DMFC could facilitate smooth pursuit, even in cases where no anticipation or prediction occurs, by issuing a preparatory or motor set signal. In other words, the DMFC might be involved in telling the eyes 'when' to move to boost performance (e.g., initial acceleration) beyond that which would occur due to simple anatomical latency constraints. Our finding that DMFC neurons are less selective for direction than MST/MT is consistent with this. Furthermore, preparatory activity here has been related to the time that a saccade is initiated (Hanes and Schall 1993), and might be expected to perform a similar function for pursuit. In any of these cases, MST inputs would only serve to calibrate or refine the predictive or set mechanism while still driving eye movements directly through pontine connections. Therefore, although neurons in the DMFC that are active during pursuit seem to have some properties similar to those of cells in MST, their other very different characteristics suggest a higher-level role in smooth pursuit generation.

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