JOURNAL OF NEUROPHYSIOLOGY
Vol. 69, No. 3, March 1993. Printed in U.S.A.

Effects of Low-Frequency Stimulation of the Superior Colliculus on Spontaneous and Visually Guided Saccades

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SUMMARY AND CONCLUSIONS

1. The first experiment of this study determined the effects of low-frequency stimulation of the monkey superior colliculus on spontaneous saccades in the dark. Stimulation trains, subthreshold for eliciting short-latency fixed-vector saccades, were highly effective at biasing the metrics (direction and amplitude) of spontaneous movements. During low-frequency stimulation, the distribution of saccade metrics was biased toward the direction and amplitude of movements induced by suprathreshold stimulation of the same collicular location.

2. Low-frequency stimulation biased the distribution of saccade metrics but did not initiate movements. The distribution of intervals between stimulation onset and the onset of the next saccade did not differ significantly from the distribution of intervals between an arbitrary point in time and the onset of the next saccade under unstimulated conditions.

3. Results of our second experiment indicate that low-frequency stimulation also influenced the metrics of visually guided saccades. The magnitude of the stimulation-induced bias increased as stimulation current or frequency was increased.

4. The time course of these effects was analyzed by terminating stimulation immediately before, during, or after visually guided saccades. Stimulation trains terminated at the onset of a movement were as effective as stimulation trains that continued throughout the movement. No effects were observed if stimulation ended 40–60 ms before the movement began.

5. These results show that low-frequency collicular stimulation can influence the direction and amplitude of spontaneous or visually guided saccades without initiating a movement. These data are compatible with the hypothesis that the collicular activity responsible for specifying the horizontal and vertical amplitude of a saccade differs from the type of collicular activity that initiates a saccade.

INTRODUCTION

As early as 1870, Adamuk recognized that electrical stimulation of the superior colliculus (SC) elicited conjugate movements of the eyes. Later work by Hess (1954) and Apter (1946) extended these findings, but it was Robinson's (1972) analysis of collicular stimulation that examined the topography of saccadic eye movements produced by stimulation at different locations throughout the colliculus. Robinson established that the stimulation of adjacent collicular regions at high frequencies (typically 500 Hz) produced short-latency, fixed-vector saccades of similar amplitudes and directions. One major conclusion drawn from this work is that stimulation of a discrete region of the SC produces a sequence of neural events that specifies the horizontal and vertical amplitude of a saccade (specification) and provides the signals necessary to initiate that movement (initiation).

Most current models of the saccadic system (e.g., Keller 1981; Van Gisbergen et al. 1981; Zee et al. 1976) require separate specification and initiation signals. According to these models, brain stem circuits use the movement specification signal to generate the pulse and step of neural activity required to produce a saccade and hold the eye in a new position. Saccades are initiated by a separate trigger signal that releases these pulse/step generators from tonic inhibition.

Sparks (1978) determined that the high-frequency burst characteristics of saccade-related burst neurons (SRBNs) in the SC satisfy the two criteria for an initiation signal: the onset of the burst is tightly coupled to saccade onset, and burst onset precedes the movement by an interval (18–20 ms) adequate to trigger the brain stem circuits that activate the eye musculature. In confirmation of earlier work (Wurtz and Goldberg 1972), it was also noted that the burst occurred only before saccades having particular horizontal and vertical amplitudes (the movement field of the cell) and that the burst was most vigorous before saccades to the middle of the movement field.

Further support for the separation of initiation and specification signals is found in the work of Sparks et al. (1987), who found that pontine stimulation can trigger, prematurely, impending visually directed saccades. Their findings suggest that for visually directed saccades, signals specifying the saccade metrics develop gradually over the 70- to 100-ms period that precedes saccade onset. The specification signals start to accumulate ≤80 ms before the burst of the SRBNs begins. Psychophysical analyses (Becker and Jurgens 1979; Stanford et al. 1990) of movement specification and initiation provide further evidence for a gradually developing specification signal that precedes the initiation of the movement.

Parallel electrophysiological studies have identified collicular signals other than the high-frequency burst that encode the metrical properties of an impending saccade but that are not linked to the initiation of the movement. Mays and Sparks (1980) found that the activity of quasi-visual (QV) cells encodes the horizontal and vertical amplitude of potential saccadic targets. They also noted that some SRBNs have a low-frequency prelude of activity that may precede the high-frequency burst by as much as several hundred milliseconds. In a more recent study, Glimcher and Sparks (1992) demonstrated that this prelude activity encodes the horizontal and vertical amplitude of an impending movement that has not yet been initiated.

One interpretation of these findings suggests that the high-frequency burst of the SRBNs, which is tightly coupled to saccade onset and precedes the movement by 18–20 ms, is primarily involved in the initiation of a saccade. According to this view, the metrics of the movement are encoded by signals that precede this burst, signals such as the low-frequency activity of prelude bursters and QV cells. The major goal of the experiments described in this paper was to test the hypothesis that collicular activation can participate in the specification of saccade metrics without initiating a saccade. This hypothesis was examined by determining whether low-frequency stimulation, subthreshold for movement initiation, influences the horizontal and vertical amplitude of spontaneous and visually guided saccades.

METHODS

Surgical and training procedures

Two adult female rhesus macaques (*Macaca mulatta*) served as subjects. Two sterile surgical procedures were performed on each animal under isoflurane anesthesia. In the first, a scleral search coil (Fuchs and Robinson 1966; Judge et al. 1980) and head restraint device were implanted. Four orthopedic surgical screws were placed in drilled and tapped openings in the skull (Zimmer ECT tools and screws). A stainless steel head restraint socket was attached to the skull and screws with orthopedic bone cement (Palacos). After 2–4 mo of training, a 15-mm diam craniotomy was performed and a stainless steel receptacle for a hydraulic microdrive was attached to the skull with orthopedic bone cement and four additional surgical screws. The receptacle was centered on the intersection of the midsagital plane and the interaural line. The receptacle was sealed with a replaceable sterile teflon plug, which maintained the sterility of the receptacle chamber.

After complete osteointegration of the surgical screws, 2–3 mo after the first surgery, animals were placed on water restriction and habituated to head restraint. They were then trained to perform several oculomotor tasks of increasing difficulty for a fruit juice or water reward. Correct oculomotor responses were reinforced on a VR 2 variable ratio schedule. A 750-ms noise burst served as the secondary reinforcer on all correct trials.

Stimulating and recording sessions

During experimental sessions, an animal was placed in two 23-kHz sinusoidally oscillating magnetic fields arranged in spatial and phase quadrature. The head was fixed, and the current induced in the scleral search coil by the magnetic fields provided a measure of horizontal and vertical eye position with a sensitivity >0.25° (Fuchs and Robinson 1966). During data collection, horizontal and vertical eye position signals were sampled at 500 Hz.

Tristate light emitting diodes (LEDs), which could be illuminated to appear red, green, or yellow, were used as visual stimuli to guide eye movements. LEDs were positioned on a tangent screen in front of the animals. A total of 500 LEDs was arranged on a grid of 20 rows and 25 columns, each separated by 2°. This array placed LEDs at target positions covering 50° horizontally and 40° vertically.

For stimulating and recording sessions a hydraulic microdrive was affixed to a Kopf *x-y* micropositioner mounted on the receptacle and used to advance electrodes into the brain. A 21-gauge syringe needle, into which the tungsten-steel parylene-insulated electrode (Microprobe) was withdrawn, was used to pierce the dura. Physiological signals were amplified and filtered (bandpass of 200–4,000 Hz) to exclude the signals of the magnetic field. Individual action potentials were discriminated from the electrophysiological signal by time and amplitude criteria (BAK window discriminator). The electrode was advanced until the activity of SRBNs was encountered.

Single-unit or multiunit activity was monitored while the monkey performed single-target trials in which the animal was rewarded for making a saccade from a central fixation stimulus to an eccentric target. These trials allowed the movement selectivity of burst neurons to be determined. This information was used to select visual target locations for other trials. All stimulation experiments were conducted at sites where saccade-related burst activity was observed.

The recording electrode, isolated from the amplifiers, was also used for monopolar electrical stimulation. The amplitude and direction of saccades produced by suprathreshold stimulation were determined using a series of 250-Hz, 50-μA cathodal stimulus trains. For testing the effects of low-frequency stimulation, 0.2-ms biphasic constant current pulse pairs of matched intensity were used. The cathodal pulse was delivered first and followed 2.0 ms later by the anodal pulse. Current intensities of 10–50 μA and pulse pair frequencies ranging from 10 to 80 Hz were delivered in trains of variable duration during the experiments.

Experiment 1

Experiment 1 was designed to determine the effects of low-frequency electrical stimulation on the initiation and metrics of spontaneous saccades. On each trial, the direction and amplitude of spontaneous saccades occurring during a 1.0-s interval with no electrical stimulation were compared with the direction and amplitude of saccades made during a 1.0-s period with low-frequency stimulation. If low-frequency stimulation did not affect the specification of the metrics of impending movements, the distribution of saccadic amplitudes and directions observed under stimulated and unstimulated conditions would not differ.

BEHAVIORAL METHODS. Trial type 1 (Fig. 1*A*) consisted of a 2.0-s interval in which no visual targets were presented. Electrical stimulation did not occur during the first 1.0-s interval; low-frequency stimulation trains were delivered during the second 1.0-s interval. The horizontal and vertical amplitudes of all movements occurring during the trial were recorded. A randomly selected intertrial interval (1,000, 1,100, 1,200, 1,300, 1,400, or 1,500 ms) followed.

To eliminate visual feedback during electrical stimulation, room illumination was extinguished during type 1 trials. However, conditions of constant darkness reduce an animal's alertness and yield a dark-induced nystagmus. To prevent this, single-target trials, conducted under dim illumination, were randomly interleaved with type 1 trials and made up 15–25% of the trials presented to the animal. A 10- to 40-Hz xenon strobe was the source of the dim illumination. The strobe was used because its rapid offset allowed the room to be completely darkened virtually instantaneously (Guitton and Munoz 1991).

Type 1 trials were presented during a total of 10 sessions for each of the two animals. During five of these sessions, stimulation current was fixed (once each at 10, 20, 30, 40, and 50 μA) while frequency was varied systematically. Blocks of 150–200 trials were run at selected frequencies, ranging from a maximum of 80 Hz to a minimum of 10 Hz in descending steps of 10 Hz. A final block of trials reexamined the effects of the initial frequency and tested for nonspecific changes during the 2- to 3-h experiment. In the other five sessions, frequency was fixed (50–10 Hz) and current was stepped from high to low over a range of 80–10 μA.

DATA ANALYSIS. For all trials in which the same stimulation frequency and current were used, we measured the horizontal and

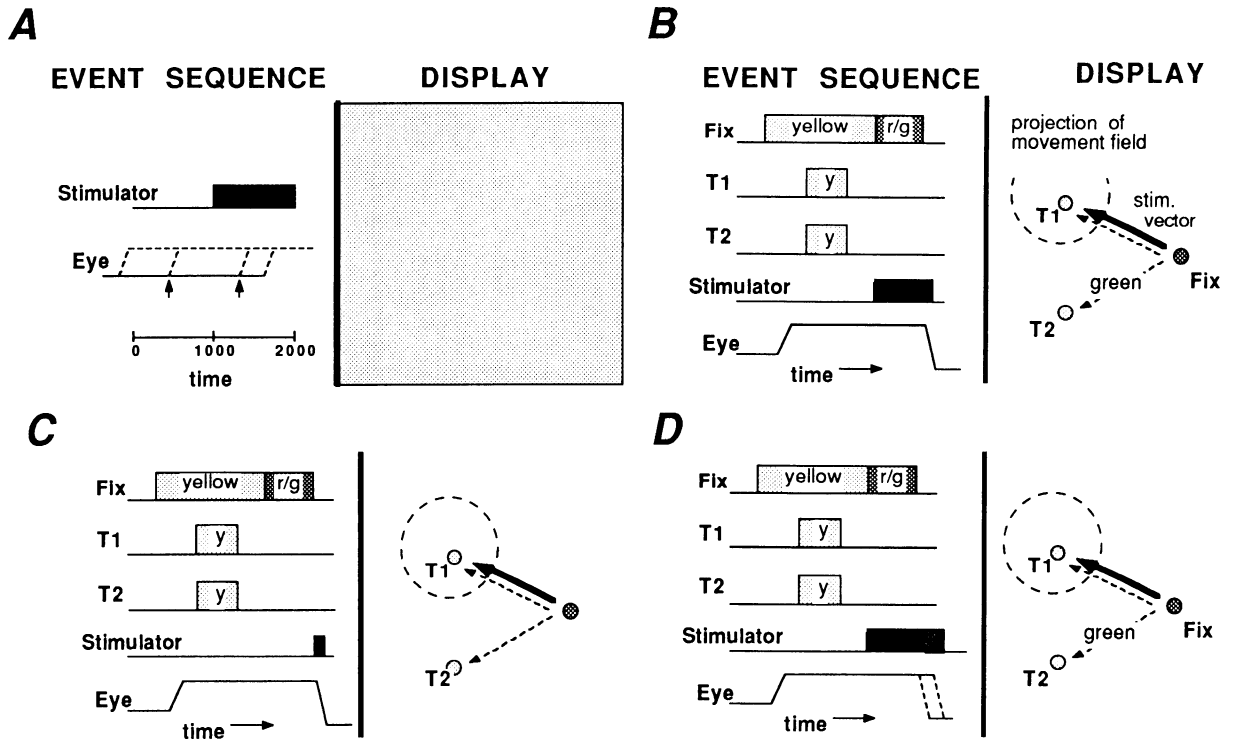

FIG. 1. *A*: trial type 1 was divided into two 1.0-s intervals. During both intervals, animals made spontaneous saccades in total darkness. During the 2nd interval, a train of biphasic stimulation pulses was delivered through an electrode in the intermediate layers of the superior colliculus. *B*: in trial type 2, a yellow fixation target was illuminated. The trial was terminated if a saccade to the fixation target failed to occur within 500 ms. After a fixation interval of 300–600 ms, 2 eccentric yellow potential targets (T1 and T2) were illuminated for 1,000–1,500 ms. The fixation stimulus remained illuminated during this interval. T1 and T2 were then extinguished, and the fixation light-emitting diode (LED) remained illuminated for an additional 400–600 ms. The fixation LED then changed color to either red or green, identifying the location of T1 or T2 as the saccadic goal. Red identified the remembered location of the upper LED as the impending saccadic goal, green identified the lower LED position as the goal. After 750 ms, the fixation LED was extinguished, indicating that a saccade to the remembered target must be completed within 350 ms to yield a reward. At the same time that the fixation target changed color, a low-frequency biphasic stimulator was activated. Three hundred fifty milliseconds after fixation target offset or after a saccade to the rewarded target was initiated (whichever was 1st), the stimulator was extinguished. *C*: trial type 3 was similar to trial type 2 except that the stimulator was not activated until the fixation target was extinguished. Three hundred fifty milliseconds later, or after a saccade to the rewarded target was initiated, the stimulator was deactivated. *D*: in trial type 4, the stimulator was extinguished 50, 100, 150, 200, 250, or 300 ms after the fixation LED was extinguished. The interval between stimulator offset and movement onset was computed for each movement.

vertical amplitudes of all first movements observed in the unstimulated interval. The first movements occurring in the stimulation intervals were measured separately. These values were used to compute the mean saccadic displacement of the eye during the first saccade of each interval using the following equation

$$= [((h_1 + h_2 + \cdots + h_n)/n)^2 + ((v_1 + v_2 + \cdots + v_n)/n)^2]^{1/2}$$

where h_1–h_n are the set of all horizontal component amplitudes, v_1–v_n are the set of all vertical component amplitudes, and n is the number of movements in the set. We refer to the resulting value as the mean saccadic displacement, a measure that permits the quantitative comparison of distributions of saccade metrics produced under stimulated and unstimulated conditions.

The resulting value will be near 0 if computed for a very large sample of movements that have random directions and amplitudes. However, if the low-frequency stimulation interacts with the specification of spontaneously generated saccades, then the computed value should shift toward that of the mean saccadic displacement produced by suprathreshold stimulation. The values obtained for the stimulated and unstimulated intervals should not differ significantly if low-frequency stimulation does not affect the metrics of spontaneous saccades.

For each interval, the time between the onset of the interval and the onset of the first saccade, the saccadic delay, was determined. Means for the distributions of these delays under stimulated and unstimulated conditions were also computed. If the low-frequency stimulation were ineffective in initiating a saccade, then the measures of saccadic delay obtained during the stimulation interval should not differ from those obtained during the unstimulated portion of the same trials.

RESULTS. Figure 2 plots, for four blocks of trials, the horizontal and vertical amplitudes of each movement occurring during stimulated (*B*, *D*, *F*, and *H*) and unstimulated (*A*, *C*, *E*, and *G*) conditions. Stimulation current was fixed at 20 μA. Saccades occurring during the unstimulated interval displayed large variations in direction and amplitude (e.g., *A*). The metrics of saccades occurring during constant low-frequency stimulation (e.g., *B*), are shifted toward the movement elicited by high-frequency stimulation at this site, 12° leftward and 3° downward (−12, −3).

Low-frequency stimulation, unlike suprathreshold stimulation, biased the movement distribution but did not uniquely determine the amplitude and direction of each movement. The center of the distribution of movements made during stimulation was shifted toward the stimulation-specified saccade, but there was considerable variability in the metrics of individual movements. As frequency was decreased, the magnitude of the stimulation-induced shifts was reduced, as illustrated in *B*, *D*, *F*, and *H*.

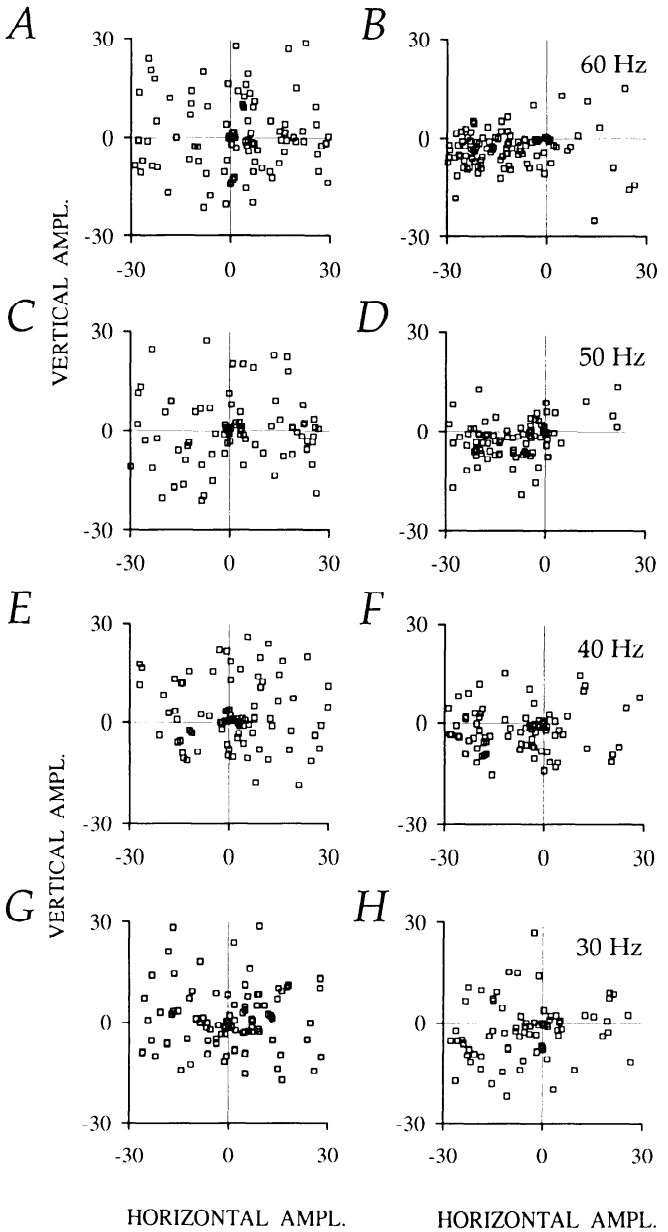

FIG. 2. Effects of low-frequency stimulation on spontaneous movements in 1 monkey (*M7337*). Each graph plots the horizontal and vertical amplitude of 130–180 movements. The panels at *right* plot movements made during low-frequency stimulation of 20 μA. The *left* panels plot movements occurring during the 1.0-s interval without stimulation. Suprathreshold stimulation at this site produced a movement 12° to the left and 3° downward (−12, −3). At higher frequencies (*top*), the distribution of saccade metrics is shifted toward the movement elicited by suprathreshold stimulation. At lower frequencies, this effect is diminished and the distribution of saccade metrics is similar to the unstimulated distributions. Adjacent panels (e.g., *A* and *B*) plot movements gathered during the stimulated and unstimulated portions of the same trials.

Figure 3 plots the effect of low-frequency stimulation on mean saccadic delay (±SD) for the same blocks of trials plotted in Fig. 2. Unfilled symbols plot the delay from the onset of the unstimulated interval to the onset of the first movement. Mean saccadic delays for stimulation intervals are plotted with filled symbols. Mean saccadic delay decreased at the highest frequency tested (which occasionally produced fixed-vector movements with a delay of 20–60 ms). At lower frequencies, which also biased the metrics of spontaneous movements, no effect of stimulation on saccadic delay was observed (Figs. 2–5).

Figure 4 summarizes the results obtained for each session for one monkey. The mean saccadic displacement (mean ± SE) is plotted against current or frequency. Each plot in the *left* column summarizes data from a session at a different stimulation site during which the frequency of stimulation was fixed but current was varied systematically. Movements made during both the stimulated (solid lines) and non-stimulated (dashed lines) portions of each trial are plotted for comparison. Data obtained during sessions in which current was fixed but frequency varied are summarized in the *right* column. These data clearly demonstrate that low-frequency stimulation biases the amplitude and direction of spontaneous saccades. Comparisons of data in different panels are inappropriate because a different stimulation site was employed for each session.

Figure 5 plots mean saccadic delays (±SD) for the same trials plotted in Fig. 4. The *left* column plots sessions in which frequency was held constant; the *right* column plots sessions in which current was held constant. Figures 4 and 5 illustrate the major findings of experiment 1: the directions and amplitudes of spontaneously occurring saccades are influenced by low-frequency stimulation which, for most of the frequencies and current levels tested, had no effect on movement initiation.

DISCUSSION. These data, which were replicated in the second animal, indicate that stimulation of the SC has independent effects on the specification and initiation of saccades. At currents and frequencies that have no effect on the mean saccadic delay, and thus on movement initiation, saccade metrics are biased.

The data presented here were gathered under conditions of total darkness. In pilot experiments, we found that low-frequency stimulation also biased the metrics of movements under conditions of constant dim illumination. But the magnitude of the stimulation-associated bias declined over the course of 200–500 trials, and after 500 trials, no effects of low-frequency stimulation were observed. Apparently, visual feedback allowed the animals to compensate for the stimulation-induced biasing of saccade metrics.

Experiment 2

Experiment 2 was designed to test the effects of low-frequency stimulation on visually guided saccades.

BEHAVIORAL METHODS. Fixation and target LEDs were presented during dim illumination, but all movements used for analysis occurred in total darkness. Three trial types were used. Trial

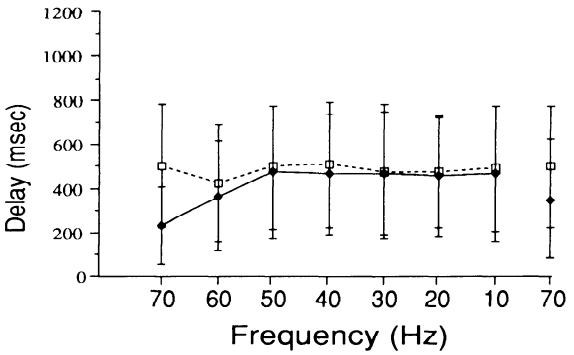

FIG. 3. Mean and standard deviation of the delay to 1st movement onset during stimulated (filled symbols) and unstimulated (unfilled symbols) segments of trial type 1. (The individual movements used in portions of this graph are plotted in Fig. 2.) There is no effect of stimulation on the distribution of delays under 50-, 40-, 30-, or 20-μA stimulation, although a shift in distributions of saccade metrics was observed (Fig. 2).

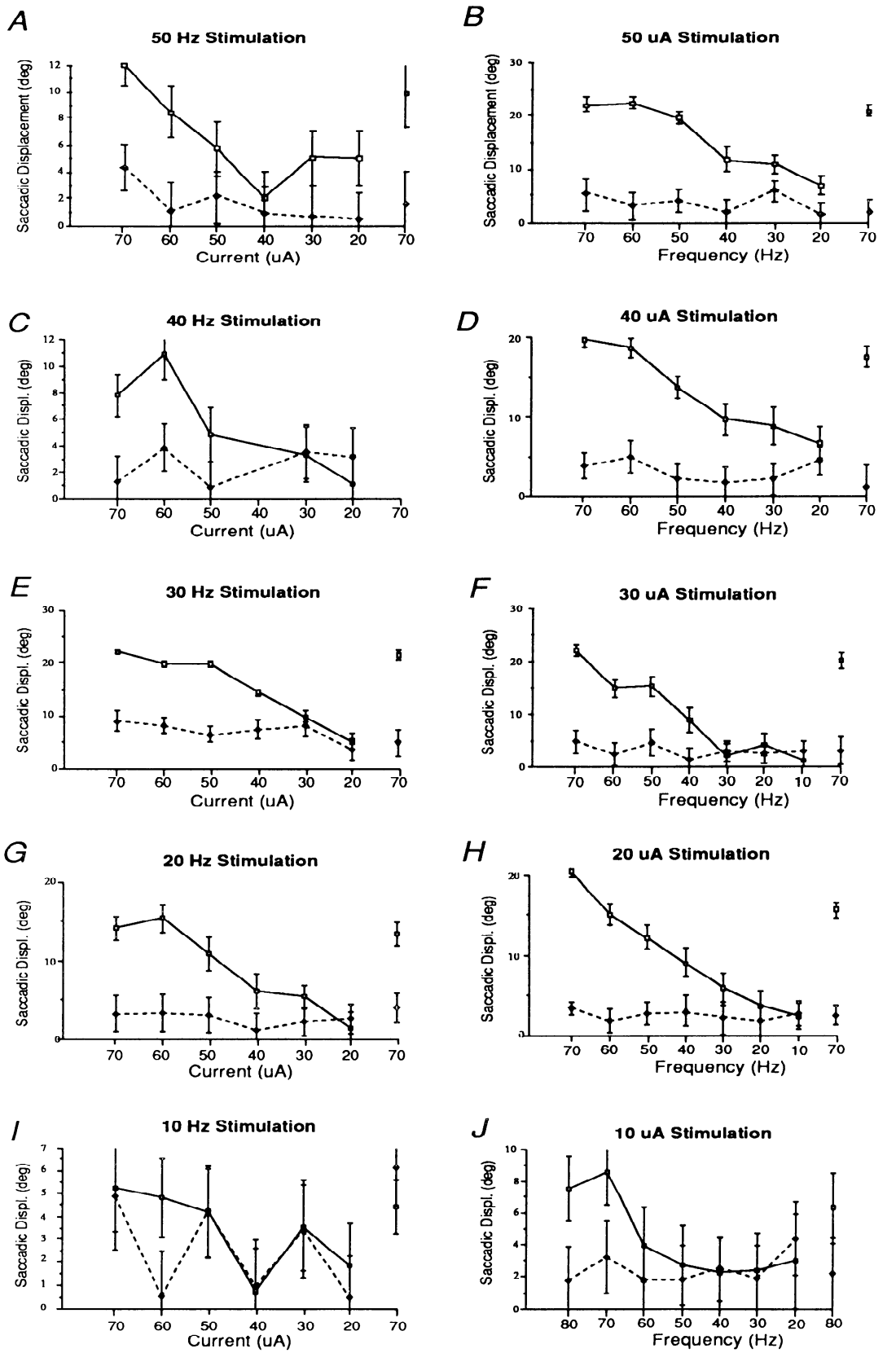

FIG. 4. The effects of stimulation on saccade metrics are plotted for all type 1 trials completed by 1 monkey (*M7337*). Each plotted point represents the mean saccadic displacement (see text). Solid lines connect points computed from the 1st movements occurring during the stimulation interval. Dashed lines connect points computed for 1st movements that occurred during the unstimulated interval. Error bars plot the standard error, computed as $[(\text{SE of horizontal mean})^2 + (\text{SE of vertical mean})^2]^{1/2}$. Each point plots a block of 60–160 movements gathered during blocks of 100 or 200 trials.

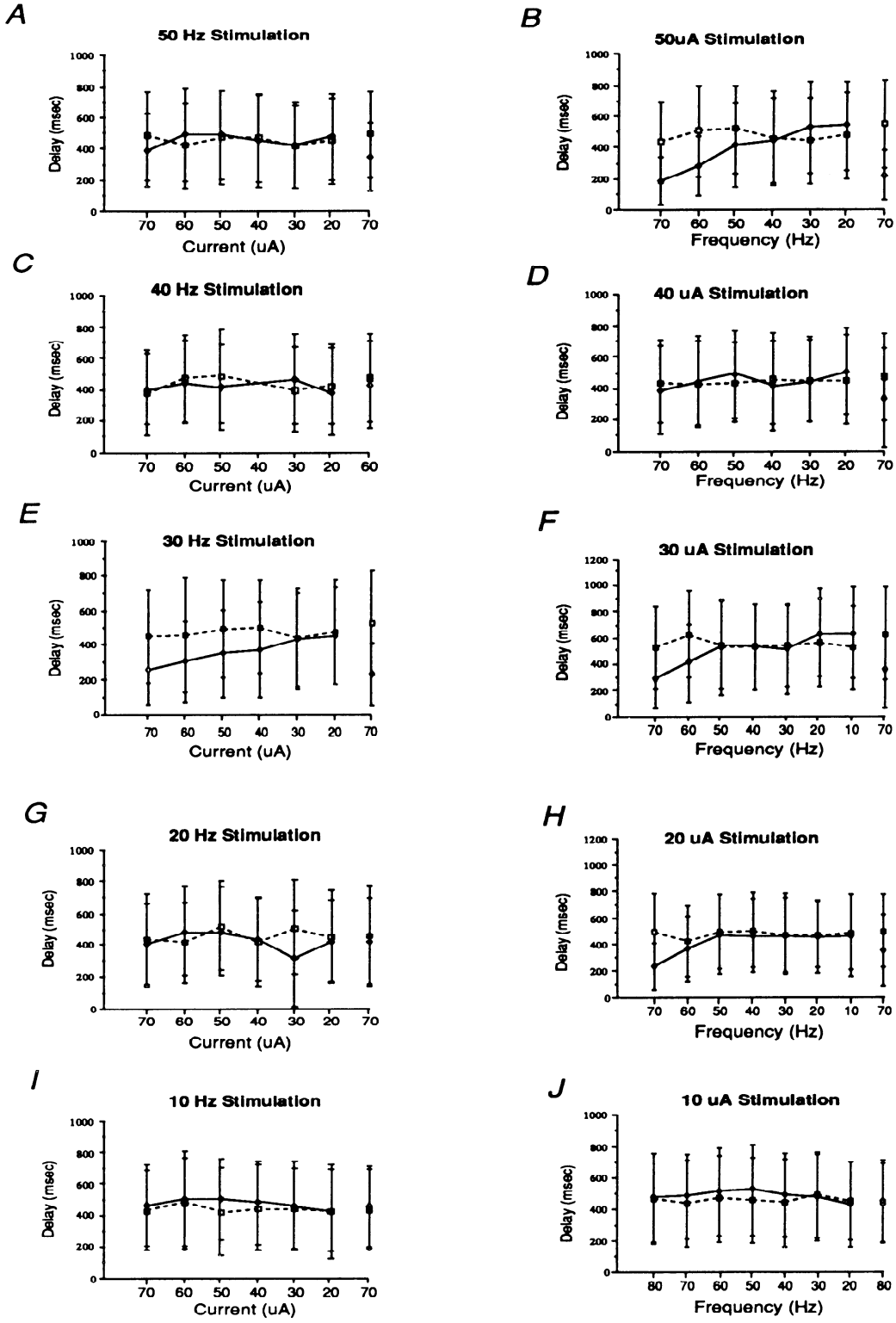

FIG. 5. Mean and standard deviation of delays to the 1st movement onset for the same data plotted in Fig. 4. *Left*: sessions during which frequency was held constant while current was varied in blocks. *Right*: sessions in which current was held constant while frequency was varied in blocks. Data from stimulated (——) and unstimulated (- - -) conditions are plotted.

type 2 (Fig. 1*B*) began with the illumination of a yellow fixation LED. If the animal fixated the target within 500 ms and maintained fixation for a variable interval (300–600 ms), two potential target LEDs, T1 and T2, were illuminated (yellow) for 1,000, 1,100, 1,200, 1,300, 1,400, or 1,500 ms. T1 and T2 were then extinguished and, after a delay of 300, 400, 500, or 600 ms, the fixation LED switched color randomly from yellow to either red or green. Green indicated that when the fixation light was extinguished, a saccade to the remembered location of the lower target would be rewarded; if the fixation LED was switched to red, the upper LED location was the saccadic target. T1 was positioned to elicit a saccade identical to the saccade produced by suprathresh-

old stimulation of the electrode site being tested. T2 was placed at an identical horizontal eccentricity, but at a vertical eccentricity that placed it across the horizontal meridian from T1.

The stimulation train began when the fixation stimulus changed from yellow to red or green. After a delay of 750 ms, the fixation LED and the stroboscopic room illumination were extinguished, cueing the animal to look to the remembered location of the target. If the animal began a saccade before this time, the trial was aborted. The stimulation train ended when a saccade to within 6° of the correct target location occurred, or after 350 ms, whichever was first. If the animal failed to make a saccade to the correct location within 100 ms after stimulator offset, a 1,500-ms timeout followed, after which the correct target was reilluminated. The animal was rewarded for making a saccade to the target.

In all rewarded type 2 trials, a minimum delay of 750 ms separated stimulation onset and movement onset. Therefore, the low-frequency stimulation trains used in experiment 2 could affect the direction and amplitude of visually directed saccades but could not initiate a saccade during the first 750 ms in which the stimulator was active.

Trial types 3 and 4 were designed to determine the effects of varying the temporal characteristics of low-frequency stimulation on visually guided saccades. Trial type 3 (Fig. 1*C*) was identical to trial type 2 except that the stimulator was not activated until the fixation LED was extinguished. This tested the hypothesis that stimulation can exert effects on visually guided saccades if presented after the visual cue for saccade initiation occurs. Trial type 4 (Fig. 1*D*) was designed to determine how long the effects of stimulation persisted after the stimulator was turned off. In this variant of task 2, the stimulator was activated when the fixation target switched to red or green and inactivated 50, 100, 150, 200, 250, or 300 ms after the fixation target was extinguished. Saccades occurred 100–400 ms after the offset of the fixation stimulus. Thus movements occurred before, during, or after the offset of the stimulator. By plotting the end points of saccades as a function of the interval between stimulation offset and saccade onset, it was possible to determine how long the effects of stimulation persisted.

During stimulation trials on which a saccade to target T2 was rewarded, low-frequency stimulation biased movements toward T1. Thus during the 50% of trials in which T2 was the correct target, stimulation reduced the incidence of a correct movement and, therefore, the frequency with which the animal was rewarded. During stimulation trials in which T1 served as the target of a rewarded saccade, stimulation might be expected to have the opposite effect, slightly increasing the frequency with which the animal was rewarded.

When large numbers of stimulation trials were run sequentially, the animal made a large number of errors and often aborted the trials before completion. For this reason, type 2, 3, or 4 trials on which the stimulator was not activated and single-target trials (described earlier) were randomly intermixed with the trial type under study. Type 2, 3, or 4 trials made up only 30–40% of the trials in a session. Only data obtained from the trial type under study when a saccade to target T2 was correct were used for the analysis that follows.

Trial types 2, 3, and 4 were not intermingled during a single experimental session. Each trial type was presented in separate experimental sessions. For each animal, type 2 trials were presented during four sessions with stimulation current fixed at 20, 30, 40, or 50 μA. At each current level, stimulation frequency was varied in sequential blocks of 60–200 trials from a maximum of 80 Hz to a minimum of 10 Hz in descending steps of 10 Hz. A final block of trials retested the highest frequency examined.

Type 3 trials were presented during two sessions with each animal. Stimulation current was fixed at 40 μA, and frequencies from 70 to 10 Hz were sampled in descending order. The highest frequency examined was then retested.

The analysis of type 4 trials required a large number of trials at a fixed frequency and current. Stimulation frequency was fixed at 40 Hz. Stimulation current was adjusted so that in type 2 trials, saccadic end points were approximately midway between T1 and T2.

RESULTS. *Trial type 2.* Figure 6 plots the effects of low-frequency stimulation on saccades to a target located 12° to the left and 2° below the fixation stimulus (−12, −2). Suprathreshold stimulation at the collicular site under investigation elicited a movement with a 12° leftward and a 14° upward component (−12, 14). The metrics of saccades occurring on two trials with 70-Hz stimulation were similar to the metrics of movements produced by suprathreshold stimulation. As frequency was systematically reduced (*B–G*), the saccade metrics shifted toward the visually specified movement. At frequencies <30 Hz (*F* and *G*), saccade metrics were indistinguishable from those produced on identical interleaved trials without stimulation.

The stimulation-induced bias in saccade metrics did not result from the sequential combination of two different saccadic trajectories. As illustrated in Fig. 7*A*, on stimulation trials, the movement trajectories were approximately straight lines with velocity

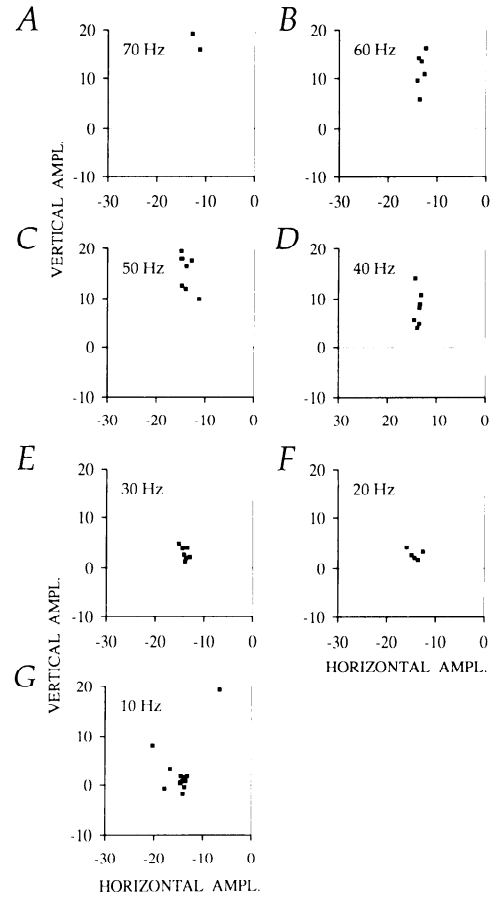

FIG. 6. Effect of low-frequency stimulation on visually guided movements. The visual target was located 12° to the left and 2° below the fixation point (−12, −2). Suprathreshold stimulation at this site produced a movement to −12, 14. During 70- and 60-Hz stimulation, the metrics of saccades clustered near −12, 14. As the frequency of stimulation was reduced, saccade metrics shifted continuously toward the metrics of saccades on trials without stimulation (visual target at −12, −2). The trials plotted are from a single session (*M7337*). [Note that movements directed to remembered targets above the horizontal meridian were hypermetric and those directed below the horizontal meridian were hypometric. This is normal for movements directed toward remembered targets and has been examined previously by Gnadt et al. (1991). Similar effects of memory intervals on saccadic accuracy can be seen in Figs. 8, 10, and 11].

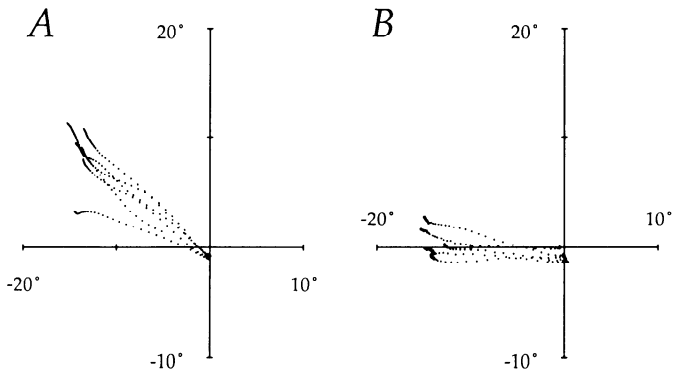

FIG. 7. Movement trajectories for (*A*) 5 type 2 stimulated trials (30 μA, 40 Hz) that were interleaved with (*B*) 5 unstimulated trials. Low-frequency stimulation, which biases saccade metrics, does not alter the normal trajectory/velocity profile of saccades.

profiles that peak once between movement origin and saccadic end point. Panel *B* plots movements during interleaved nonstimulation control trials. The movements plotted in *A* are the same movements plotted in Fig. 6*D*.

Figure 8 plots, for each session, the mean vertical saccadic end point for each frequency and current level tested for one monkey (*M7340*). Stimulation biased the metrics of visually guided saccades in a continuous frequency-dependent manner. In Fig. 8*D*, for example, 70-Hz stimulation produced a movement that is similar in amplitude and direction to the movement produced by suprathreshold stimulation at this same site. As the stimulation frequency was reduced, the magnitude of the stimulation-induced specification was reduced. Only the vertical end point is plotted in these graphs because the horizontal components of visually guided and suprathreshold stimulation-induced saccades were the same and unaffected by low-frequency stimulation. These results were replicated in the second monkey (*M7337*).

Low-frequency stimulation shifts the saccadic end point away from the visually specified saccadic target. On some trials, animals corrected for this displacement by producing a second saccade that brought the point of gaze closer to the actual location of the target. To examine these secondary saccades, a subset of trials in which stimulation altered the visually guided movement were further examined.

For each current tested using trial type 2, one frequency of stimulation produced movements that, on average, terminated approximately halfway between the visually specified and the stimulation-specified end points (see Figs. 8, *C* and *D*). These trials were used to analyze the latencies, trajectories, and probabilities of occurrence of secondary saccades. (Secondary saccades were defined as movements following the initial saccade by ≤550 ms that bring gaze closer to the target location.) The error of primary, or initial, and secondary saccades from these trials is plotted in Fig. 9. Panel *A* plots the vertical error, distance from the visually specified target, for all primary saccades. Panel *B* plots, for the same trials, the saccadic error remaining after secondary saccades: clearly, on average, the direction of gaze was closer to the location of the visual target after the secondary saccades. Panel *C* plots the interval between primary and secondary movements when they occurred. Secondary saccades, when they occurred, compensated for the effects of stimulation on the current position of the eye. This indicates that some record of the animal's original saccadic objective is retained after low-frequency collicular stimulation biases saccadic eye movements.

Trial type 3. In trial type 2, stimulation occurred during the interval when the change in the color of the fixation stimulus specified which of the two eccentric LEDs was the target. Trial type 3 determined the effects of shorter periods of stimulation, immediately preceding the movement, on saccades to visual targets.

Effects observed on type 3 trials were similar to those observed on type 2 trials. Figure 10 plots trials in which suprathreshold stimulation elicited a movement 10° upward while the visually specified target was located 10° below the horizontal meridian. At higher frequencies, saccadic amplitudes and directions were similar to those for suprathreshold stimulation. As the stimulation frequency was reduced, the saccade end point shifted regularly toward the visually specified goal.

Type 4 trials. Trial type 4 was used to examine the duration of the effects of low-frequency stimulation. Figure 11 plots the vertical amplitude of saccades as a function of the interval between the offset of the stimulation train and movement onset. As observed in type 2 trials, movements occurring before the stimulation terminated (negative latencies) were biased toward the movement produced by suprathreshold stimulation. At positive intervals (stimulation terminates before the movement begins), the stimulation had no effect and movements terminated near T2, the visually specified goal.

DISCUSSION

Experiments 1 and 2 demonstrate that low-frequency stimulation of the SC can alter the metrics of spontaneous and visually guided saccades without affecting the time at which the movements are initiated. These results are discussed in the context of behavioral data indicating that movement specification is a gradual process and that it is separable from movement initiation. Also considered are

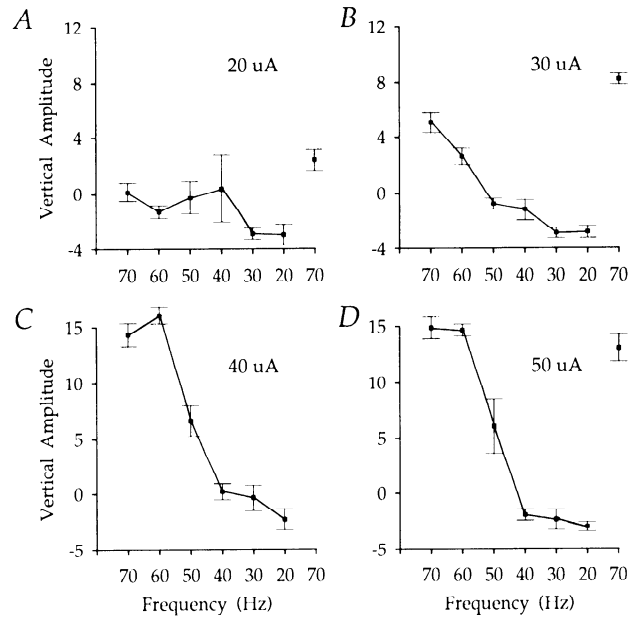

FIG. 8. Vertical saccadic amplitude (mean and standard error) plotted as a function of stimulation frequency for 4 blocks of type 2 trials in 1 monkey (*M7340*). Each graph plots data obtained from a session in which a single current level was used. Each point represents the mean of 5–25 movements. *A*: suprathreshold stimulation at this site produced a movement with an 8° upward component (+8). An 8° downward component (−8) was the visually specified goal. *B*: suprathreshold stimulation at this site produced a movement to +8; −8 was the visually specified goal. *C*: suprathreshold stimulation at this site produced a movement to +10; −10 was the visually specified goal. *D*: suprathreshold stimulation at this site produced a movement to +10; −10 was the visually specified goal.

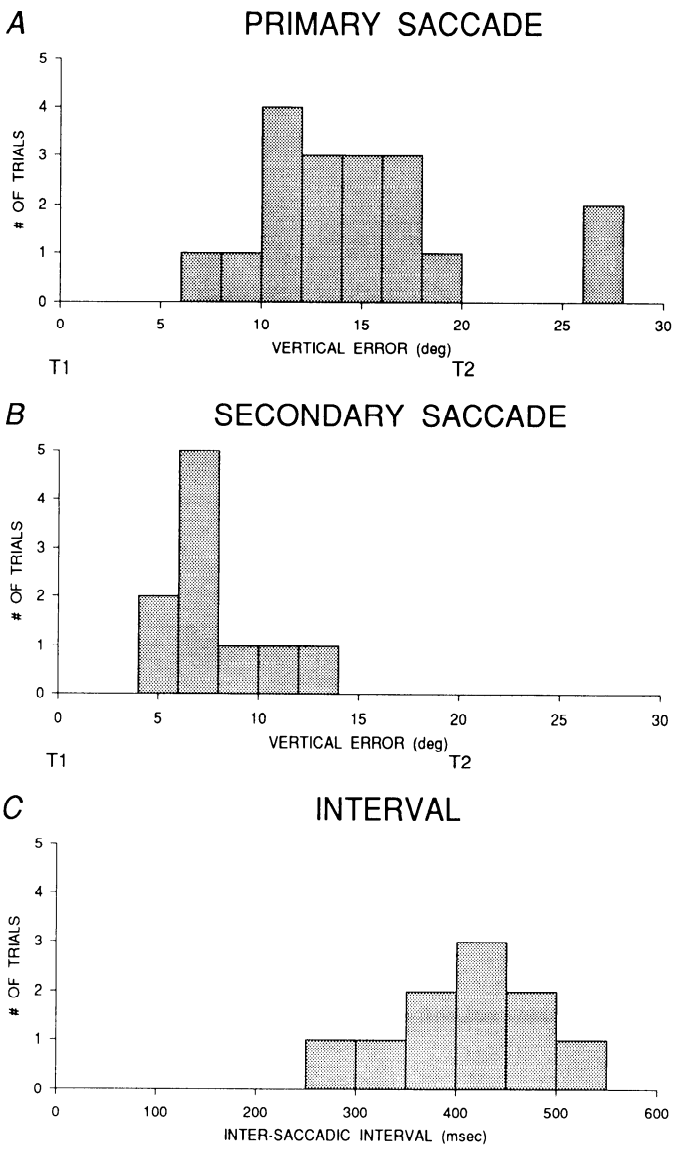

FIG. 9. *A*: vertical error remaining after primary saccades. (Movements are those plotted in the 50 Hz/40 μA and 50 Hz/50 μA blocks of trials shown in Fig. 8.) *B*: vertical error remaining after secondary saccades occurring within 550 ms of the cue to initiate the primary saccade. These movements were effective in reducing vertical error. *C*: plot of the interval between the end of the primary saccade and the beginning of the secondary saccade.

physiological data that identify neural signals appropriate for the metrical specification of saccades and for the initiation of saccades.

Evidence for separate specification and initiation

Becker and Jurgens (1979) instructed human subjects to make saccades to a visual target. Shortly before the saccade was initiated, the target was abruptly displaced to a secondary location. In an important finding, Becker and Jurgens noted that the target displacement altered the amplitude of the initial saccade. The magnitude of this amplitude shift increased as a continuous function of the interval between target displacement and movement onset. When the target displacement occurred just 50–75 ms before the movement began, the second target exerted a barely discernable influence on the amplitude of the saccade. The influence of the second target gradually increased with longer intervals until at 200 ms the amplitude of the saccade was appropriate for the secondary target position. These data support the hypothesis that movement specification is a gradual process requiring a significant time for completion.

Other evidence that signals specifying the metrics of a saccade develop gradually comes from the recent experiments of Stanford and colleagues (1990). Human subjects were trained to synchronize saccades to the fourth in a series of equally spaced tones. Visual targets appeared at one of two locations at a variable interval before the onset of the tone that cued the movement. Because the saccade was synchronized to the fourth tone, this protocol permitted control of the interval during which the location of the target could be used for response specification. Results indicate that signals specifying the direction and amplitude of the saccade develop gradually during the 50–100 ms after target presentation.

Evidence that specification and initiation signals can be dissociated comes from studies in which electrical stimulation of the paramedian pontine reticular formation was used to perturb the position of the eye in the orbit before the onset of a visually guided saccade (Sparks et al. 1987). Sparks and colleagues discovered that pontine stimulation can prematurely trigger saccades to visual targets before the visually guided response has been completely specified. When the pontine stimulation was delivered at target onset, the metrics of the eye movement produced by stimulation were specified entirely by the pontine stimulation. If, however, pontine stimulation began 50–125 ms after target onset, the resulting movement was a combination of the horizontal movement specified by pontine stimulation and a portion of the impending visually guided saccade. Longer delays typically produced movements including a large portion of the visually specified saccade, whereas shorter delays produced movements dominated by the stimulation-in-

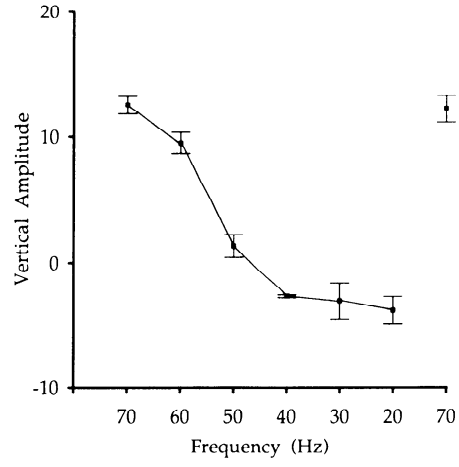

FIG. 10. Vertical saccade amplitude (mean and standard error) plotted as a function of stimulation frequency for a single block of type 3 trials in 1 monkey (*M7337*). Stimulation current was fixed at 40 μA. Suprathreshold stimulation at this site produced a movement with a 10° upward component, whereas a movement with a 10° downward component was the visually specified goal. (10–25 movements per point)

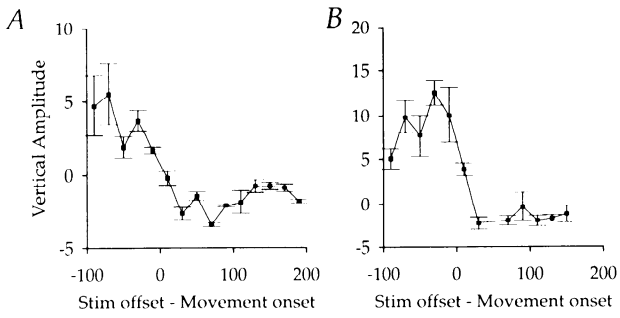

FIG. 11. Effect of stimulation on the vertical amplitude of saccades as a function of the interval between stimulator offset and movement onset. Means and standard errors were computed for 20-ms bins. *A*: 50-μA, 40-Hz stimulation in 1 monkey (*M7337*) was delivered at a site where suprathreshold stimulation produced a movement with a 6° upward component. An accurate movement to the visual target would have a 6° downward component. When movement onset followed stimulation offset (positive latencies), no effect on vertical amplitude was observed. *B*: 42-μA, 40-Hz stimulation in a 2nd monkey (*M7340*) at a site at which suprathreshold stimulation produced a 12° upward movement. A movement with a 6° downward component was the visually specified goal.

duced movement. At delays of >125 ms, the movement produced was a combination of the completely specified saccade to the visual target and the stimulation-induced movement.

These three experiments show that saccadic specification, and the neural processes that underlie it, occur gradually and may, in principle, be separated from the neural events that trigger the movement. These data are consistent with models of the saccadic system (Keller 1981; Van Gisbergen et al. 1981; Zee et al. 1976) that assume saccades are triggered by a signal differing from signals conveying information about the metrics of the movement. A description of the types of neural activity within the SC that may be involved in the initiation of saccades as well as the specification of the metrics of the movement follows.

Collicular signals for specification and initiation

There is compelling evidence, summarized in the introduction, that the high-frequency burst of SRBNs found in the SC has the properties required of a saccadic initiation signal (Keller 1979; Sparks 1978, 1986; Sparks and Mays 1981a,b). Moreover, SRBNs, but not other collicular cells with saccade-related activity, project to the region of the pons (Raybourn and Keller 1977) containing omnipause neurons, cells known to inhibit the brain stem pulse-step circuits.

The burst of SRBNs could be involved not only in the initiation of saccades but also in specifying saccadic direction and amplitude. The burst of SRBNs is unlikely to be the only source of a specification signal because of the evidence summarized above, evidence demonstrating that signals specifying saccade direction and amplitude gradually develop over a 70- to 125-ms period preceding saccade onset (Becker and Jurgens 1979; Sparks et al. 1987; Stanford et al. 1990). On the basis of these data, the process of specifying the metrics of an impending saccade begins 100–155 ms before the onset of the high-frequency burst of SRBNs.

Low-frequency collicular activity may be involved in the gradual specification of saccade metrics. Mays and Sparks (1980) found that the activity of QV cells encodes the metrics of a saccade well before the onset of the movement. These cells are visually responsive, but their activity does not depend on a specific region of the retina being activated. Instead, QV cells become active whenever a saccade with a particular direction and amplitude becomes relevant, even after the offset of a saccade target. Moreover, no component of QV cell activity is tightly linked to the initiation of a saccade.

Other low-frequency signals also exist that may play a role in target specification. Some SRBNs, for example, have a low-frequency prelude of activity that may precede the high-frequency burst by as much as several hundred milliseconds (Sparks and Mays 1981b). Glimcher and Sparks (1992) examined this prelude activity using an experimental paradigm designed to study the process of response selection. They found that when two potential saccade targets were presented, the prelude of low-frequency activity (30–100 Hz) began only after sufficient information became available to select the correct (to be rewarded) response. Prelude onset had no fixed temporal relationship to movement initiation. Thus the location of low-frequency prelude activity of SRBNs within the topographically organized motor map could encode the metrics of the impending movement. This activity would not be appropriate for movement initiation because it lacks a fixed temporal association with movement onset.

Collectively, the behavioral and electrophysiological studies summarized above are consistent with the hypothesis that low-frequency signals present in the colliculus are involved in the gradual specification of the metrics of a saccade. This hypothesis suggests that the initiation of these gradually specified movements is triggered by the high-frequency burst of collicular SRBNs (See Berthoz et al. 1986; Sparks 1986; and Sparks and Mays 1991 for other possible roles for the high-frequency burst of collicular SRBNs). Some of these findings formed the basis of an earlier suggestion that the type of collicular activity encoding saccade metrics differs from the signals representing the decision to make a saccade (Keller 1981).

Interactions between stimulation and visually guided processes

In experiment 1, low-frequency stimulation of the SC altered the metrics of spontaneous saccadic eye movements. These effects were observed in the absence of an effect on the initiation of spontaneous movements: the mean delay to movement onset was unaffected by low-frequency stimulation. In experiment 2, low-frequency stimulation was observed to affect visually guided saccades. On stimulation trials, the metrics of saccades initiated by visual stimuli were intermediate between the metrics of visually directed saccades in the absence of stimulation and the metrics of saccades produced by suprathreshold stimulation. Low-frequency stimulation affected the metrics of visually directed saccades but did not initiate short-latency eye movements. These findings are consistent with the suggestion that low-frequency collicular signals participate in specifying the direction and amplitude of an impending saccade (Glimcher and Sparks 1992).

Implicit in this argument is the assumption that the frequency of collicular stimulation and the frequency of neural activity elicited by this stimulation are monotonically related. Although a direct test of this assumption was beyond the scope of these experiments, the data presented do support this assumption. Figures 4 and 8 both show that the measured behavioral output, the stimulation-induced biasing of saccade metrics, was monotonically related to the frequency of stimulation.[1]

Also, it should be noted that the relationship between specification and initiation signals is measured under slightly different conditions in experiments 1 and 2. Experiment 2 employed trial types in which a fixation target was visible during the first 750 ms of the stimulation train. Sparks and Mays (1983) reported that the threshold current for eliciting a saccade with collicular stimulation increases when the animal is fixating a target. Thus, it is likely that the thresholds for evoking a saccade by microstimulation were higher in experiment two than in experiment one.

Sparks and Mays (1983) observed a similar interaction between visually guided saccades and stimulation-induced movements. They reported that the direction and amplitude of saccades evoked by high-frequency stimulation of the SC were influenced by the location of a visual target to which a saccade had not yet been directed. The magnitude of the effect depended, in part, on how long the visual target was present before the onset of the stimulation train. Taken together, the findings of Sparks and Mays (1983) and those reported in this paper indicate that the specification of saccade metrics can be influenced by activity occurring over widespread regions of the SC. This conclusion is strengthened by the earlier report of Robinson (1972) that subthreshold high-frequency stimulation at one site in the SC influenced the direction and amplitude of movements produced by suprathreshold stimulation at another remote collicular site. Similar experiments have demonstrated that a stimulating electrode in the frontal eye fields can influence the metrics of a saccade elicited by collicular stimulation (Schiller et al. 1979). This raises the possibility that the interactions we have observed between collicular stimulation and visual targets may involve noncollicular eye movement systems.

Visually evoked neural activity and activity produced by low-frequency, subthreshold collicular microstimulation can interact to specify the metrics of a saccade. However, this interaction does not modify all records of the visually identified saccadic objective. As illustrated in Fig. 9, the modified movements that occurred on stimulation trials were followed, in many cases, by a secondary saccade that brought the direction of gaze closer to the location of the original, but no longer visible, visual target. Although the examination of secondary saccades was not a goal of the current experiments, the observation that they did occur is important because it demonstrates that stimulation had little or no effect on the process of identifying the location of a previously viewed visual target.

[1] If, over the system's dynamic range, the frequency of elicited collicular activity were not monotonically related to the frequency of collicular stimulation, then an additional nonmonotonic element (inversely matched to this hypothetical nonmonotonic property of the electrode-tissue interaction) would be required to explain the monotonic functions that were observed. This outcome, though possible, seems highly improbable.

Time course of stimulation effects

Experiment 2 also examined the time course of the effects of low-frequency stimulation. Stimulation trains that began when the animal was cued to initiate a movement were as effective in altering the metrics of saccades as were stimulation trains that preceded the initiation cue by 750 ms. Task 4 examined the temporal persistence of the stimulation-induced effects. Stimulation trains terminating at saccade onset were as effective as stimulation trains that continued for 60 ms after the saccade began. However, stimulation trains that ended 40–60 ms before the movement began had no effect on the end points of visually guided saccades. The stimulation-induced signals that modify movement specification persist for a very short time.

Conclusions

High-frequency stimulation of the SC can both specify and initiate a saccadic eye movement. The data presented here demonstrate that low-frequency stimulation of the SC can activate neural circuits that participate in movement specification without engaging neural circuits responsible for movement initiation. These findings are consistent with single-unit recording data indicating that low-frequency signals in the SC accurately encode movement metrics in advance of movement initiation (Glimcher and Sparks 1992), and with behavioral data suggesting that the specification of saccade metrics is a continuous process that precedes movement initiation and requires ≥50–200 ms for completion (Becker and Jurgens 1979; Stanford et al. 1990). Collectively, these data support the hypothesis that collicular activity involved in the metrical specification of impending movements can be separated from collicular activity involved in the initiation of these movements.

The authors express their gratitude to K. Pearson, J. Levine, and J. Groh.

This work was supported by a grant from the National Eye Institute (EY-01189) and a National Research Service Award to P. W. Glimcher (F32-EY06305).

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Received 10 June 1992; accepted in final form 16 October 1992.

REFERENCES

ADAMUK, E. Ueber die innervation der augenbewegungen. *Zentralbl. Med. Wiss.* 8: 65–67, 1870.

APTER, J. T. Eye movements following strychninization of cats. *J. Neurophysiol.* 9: 73–86, 1946.

BECKER, W. AND JURGENS, R. An analysis of the saccadic system by means of double step stimuli. *Vision Res.* 19: 967–983, 1979.

BERTHOZ, A., GRANTYN, A., AND DROULEZ, J. Some collicular efferent neurons code saccadic eye velocity. *Neurosc. Lett.* 72: 289–294, 1986.

FUCHS, A. F. AND ROBINSON, D. A. A method for measuring horizontal and vertical eye movement chronically in the monkey. *J. Appl. Physiol.* 21: 1068–1070, 1966.

GLIMCHER, P. W. AND SPARKS, D. L. Movement selection in advance of action in the superior colliculus. *Nature Lond.* 355: 542–545, 1992.

GNADT, J. W., BRACEWELL, R. M., AND ANDERSEN, R. A. Sensorimotor transformations during eye movements to remembered visual targets. *Vision Res.* 31: 693–715, 1991.

GUITTON, D. AND MUNOZ, D. P. Control of gaze shifts by the tectoreticulospinal system in the head-free cat. I. identification, localization and effects of behavior on sensory responses. *J. Neurophysiol.* 66: 1605–1623, 1991.

HESS, W. R. *Diencephalon; Autonomic and Extrapyramidal Functions.* New York: Grune & Stratton, 1954.

JUDGE, S. J., RICHMOND, B. J., AND CHU, F. C. Implantation of magnetic search coils for measurement of eye position: an improved method. *Vision Res.* 20: 535–538, 1980.

KELLER, E. L. Colliculoreticular organization in the oculomotor system. In: *Reflex Control of Posture and Movement,* edited by R. Granit and O. Pompeiano. New York: Elsevier/North-Holland, 1979.

KELLER, E. L. Brainstem mechanisms in saccadic control. In: *Progress In Oculomotor Research,* edited by A. F. Fuchs and W. Becker. New York: Elsevier/North-Holland, 1981.

MAYS, L. E. AND SPARKS, D. L. Dissociation of visual and saccade-related responses in superior colliculus neurons. *J. Neurophysiol.* 43: 207–232, 1980.

RAYBOURN, M. S. AND KELLER, E. L. Colliculoreticular organization in primate oculomotor system. *J. Neurophysiol.* 40: 861–878, 1977.

ROBINSON, D. A. Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res.* 12: 1795–1808, 1972.

SCHILLER, P. H., TRUE, S. D., AND CONWAY, J. L. Paired stimulation of the frontal eye fields of anesthetized monkeys during eye and head movement. *Exp. Brain Res.* 179: 162–164, 1979.

SPARKS, D. L. Functional properties of neurons in the monkey superior colliculus: coupling of neuronal activity and saccade onset. *Brain Res.* 156: 1–16, 1978.

SPARKS, D. L. Translation of sensory signals into commands for control of saccadic eye movements: role of primate superior colliculus. *Physiol. Rev.* 66: 118–171, 1986.

SPARKS, D. L. AND MAYS, L. E. The role of the monkey superior colliculus in the control of saccadic eye movements: a current perspective. In: *Developments in Neuroscience. Progress in Oculomotor Research,* edited by A. F. Fuchs and W. Becker. New York: Elsevier/North-Holland, 1981a.

SPARKS, D. L. AND MAYS, L. E. Movement fields of saccade-related burst neurons in the monkey superior colliculus. *Brain Res.* 190: 39–50, 1981b.

SPARKS, D. L. AND MAYS, L. E. Spatial localization of saccade targets. I. compensation for stimulation-induced perturbations in eye position. *J. Neurophysiol.* 49: 45–63, 1983.

SPARKS, D. L. AND MAYS, L. E. Signal transformations required for the generation of saccadic eye movements. *Annu. Rev. Neurosci.* 13: 309–336, 1991.

SPARKS, D. L., MAYS, L. E., AND PORTER, J. D. Eye movements induced by pontine stimulation: interaction with visually triggered saccades. *J. Neurophysiol.* 58: 300–318, 1987.

STANFORD, T. R., CARNEY, L. H., AND SPARKS, D. L. The amplitude of visually guided saccades is specified gradually in humans. *Soc. Neurosci. Abstr.* 16: 372.19, 1990.

VAN GISBERGEN, J. A. M., ROBINSON, D. A., AND GIELSEN, S. A quantitative analysis of the generation of saccadic eye movements by burst neurons. *J. Neurophysiol.* 45: 417–422, 1981.

WURTZ, R. H. AND GOLDBERG, M. E. Activity of superior colliculus in behaving monkey. III. Cells discharging before eye movements. *J. Neurophysiol.* 35: 575–586, 1972.

ZEE, D. S., OPTICAN, L. M., COOK, J. D., ROBINSON, D. A., AND ENGEL, W. K. Slow saccades in spinocerebellar degeneration. *Arch. Neurol.* 33: 243–251, 1976.