Comparison of Saccades Perturbed by Stimulation of the Rostral Superior Colliculus, the Caudal Superior Colliculus, and the Omnipause Neuron Region

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[1]*Graduate Group in Bioengineering, University of California, San Francisco 94143;* [2]*Graduate Group in Bioengineering, University of California, Berkeley 94720; and* [3]*The Smith-Kettlewell Eye Research Institute, San Francisco, California 94115*

Gandhi, Neeraj J. and Edward L. Keller. Comparison of saccades perturbed by stimulation of the rostral superior colliculus, the caudal superior colliculus, and the omnipause neuron region. *J. Neurophysiol*. 82: 3236–3253, 1999. Over the past decade, considerable research efforts have been focused on the role of the rostral superior colliculus (SC) in control of saccades. The most recent theory separates the deeper intermediate layers of the SC into two functional regions: the rostral pole of these layers constitutes a fixation zone and the caudal region comprises the saccade zone. Sustained activity of fixation neurons in the fixation zone is argued to maintain fixation and help prevent saccade generation by exciting the omnipause neurons (OPNs) in the brain stem. This hypothesis is in contrast to the traditional view that the SC contains a topographic representation of the saccade motor map on which the rostral pole of the SC encodes signals for generating small saccades (<2°) instead of preventing them. There is therefore an unresolved controversy about the specific role on the most rostral region of the SC, and we reexamined its functional contribution by quantifying and comparing spatial and temporal trajectories of 30° saccades perturbed by electrical stimulation of the rostral pole and more caudal regions in the SC and of the OPN region. If the rostral pole serves to preserve fixation, then saccades perturbed by stimulation should closely resemble *interrupted saccades* produced by stimulation of the OPN region. If it also contributes to saccade generation, then the disrupted movements would better compare with *redirected saccades* observed after stimulation of the caudal SC. Our experiments revealed two significant findings: *1*) the locus of stimulation was the primary factor determining the perturbation effect. If the directions of the target-directed saccade and stimulation-evoked saccade were aligned and if the stimulation was delivered within approximately the rostral 2 mm (<10° amplitude) of SC, the ongoing saccade stopped in midflight but then resumed after stimulation end to reach the original visually specified goal with close to normal accuracy. When stimulation was applied at more caudal sites, the ongoing saccade directly reached the target location without stopping at an intermediate position. If the directions differed considerably, both initial and resumed components were typically observed for all stimulation sites. *2*) A quantitative analysis of the saccades perturbed from the fixation zone showed significant deviations from their control spatial trajectories. Thus they resembled redirected saccades induced by caudal SC stimulation and differed significantly from interrupted saccades produced by OPN stimulation. The amplitude of the initial saccade, latency of perturbation, and spatial redirection were greatest for the most caudal sites and decreased gradually for rostral sites. For stimulation sites within the rostral pole of SC, the measures formed a smooth continuation of the trends observed in the saccade zone. As these results argue for the saccade zone concept, we offer reinterpretations of the data used to support the fixation zone model. However, we also discuss scenarios that do not allow an outright rejection of the fixation zone hypothesis.

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INTRODUCTION

The superior colliculus (SC) has long been implicated as a critical neural structure in controlling saccades –fast, conjugate eye movements that realign the visual axis to objects in the periphery. Traditionally, the SC has been thought to participate strictly in the generation of saccades (see Sparks and Hartwich-Young 1989 for a review) and, more generally, gaze shifts. Microstimulation of SC during fixation evokes a fixed vector saccade (FVS) in the head-restrained animal or an eye-head coordinated gaze shift in the head-unrestrained animal, and the amplitude and direction of the stimulation-induced movement depend on both the site and parameters of stimulation (Freedman et al. 1996; Paré et al. 1994; Robinson 1972; Schiller and Stryker 1972; Stanford et al. 1996). Suprathreshold stimulation in the head-fixed preparation elicits small saccades from rostral SC sites and larger eye movements from more caudal regions, whereas stimulation of medial and lateral areas of the SC generates saccades with upward and downward components, respectively. In agreement with the saccade motor map defined by the simulation studies, the locus of neural activity in the deeper layers of SC encodes the optimal saccade vector (McIlwain 1975; Schiller and Stryker 1972; Sparks et al. 1976; for head-free gaze, see Freedman and Sparks 1997). On the basis of these studies, the topography in the deeper layers is believed to consist only of a uniform *saccade zone* (Fig. 1*A*) (Robinson 1972) that is in spatial register with the retinotopic organization of the superficial layers (Cynader and Berman 1972).

This long-held view recently has been questioned by studies that have reported a subset of neurons that discharge vigorously during fixation and show a pause in activity during most saccades (Munoz and Guitton 1989, 1991; Munoz and Wurtz 1993a; Peck 1989). These cells, which have been called fixation neurons, are located within the deepest portion of the intermediate layers of an estimated 0.72 mm of the rostral SC (Munoz and Wurtz 1995b), a region that has been referred to as the *fixation zone* or the *rostral pole of the SC* (Guitton 1991; Munoz and Istvan 1998; Munoz and Wurtz 1995b; Munoz et al. 1993). Neurons within the dorsal intermediate layers of the

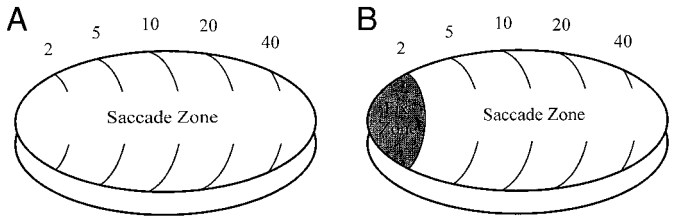

FIG. 1. Schematic of the two rival hypotheses attributed to the deeper intermediate layers of the superior colliculus (SC). *A*: traditional view (Robinson 1972; Schiller and Stryker 1972) that each site encodes a saccadic displacement (i.e., the entire SC is a saccade zone). *B*: more recent idea (Guitton 1991; Munoz and Guitton 1989, 1991; Munoz and Wurtz 1993a,b, 1995a,b; Munoz et al. 1991, 1993) that the rostral SC is involved in fixation (fix zone; shaded region) and the remainder of the SC is the saccade zone. Numbers on *top* represent the iso-amplitude meridians on the motor map.

rostral SC as well as all intermediate layer neurons in the remaining caudal SC participate in saccade generation as in the traditionally accepted saccade zone hypothesis. Figure 1*B* represents a schematic of the deeper intermediate layers, in which the saccade zone is defined as the region caudal to a discrete fixation zone (also see Fig. 13 of Munoz and Wurtz 1995b). Hence, the fixation zone is composed of fixation neurons and the saccade zone constitutes of burst and buildup neurons (Munoz and Wurtz 1995a). These electrophysiological and additional stimulation and lesion studies in the rostral pole of the SC (Munoz and Wurtz 1993b) have led to a developing notion that two functions and regions exist in the SC motor map: one encoding fixation and the other saccade generation (Munoz and Guitton 1991; Munoz and Istvan 1998; Munoz and Wurtz 1995a,b; Munoz et al. 1991, 1993).

The fixation neurons are hypothesized to exert their saccade prevention role by projecting to and exciting the omnipause neurons (OPNs) found in the nucleus raphe interpositus on the midline within the paramedian pontine reticular formation in the brain stem (Büttner-Ennever et al. 1988). Like fixation neurons, the OPNs stop firing during *all* saccades (Cohen and Henn 1972; Evinger et al. 1982; Keller 1974; Luschei and Fuchs 1972) and also discharge tonically during fixation. Functionally, the OPNs are thought to gate the saccade burst generator: activity in OPNs results in fixation and absence of discharge leads to a saccadic eye movement (Keller 1974). On the basis of similarities in activity and on known electrophysiological (King et al. 1980; Raybourn and Keller 1977) and anatomic connections (Langer and Kaneko 1984, 1990), an excitatory projection from the fixation neurons of the SC to the OPNs was hypothesized to control the saccade-related discharge characteristics in the latter neuronal group (Munoz and Guitton 1989; Munoz and Wurtz 1993a,b; Munoz et al. 1991). Indeed, collicular projections to the OPN region since have been shown to originate predominantly, but not exclusively, from the rostral pole (Büttner-Ennever and Horn 1994; Gandhi and Keller 1997; Paré and Guitton 1994).

Although the fixation zone hypothesis has gained widespread acceptance, a closer examination of the data provided in its support casts doubt on at least its most rigid interpretation and therefore motivates a reevaluation of this theory. Several observations noted in the papers of Munoz and Wurtz (1993a,b), who routinely are credited for establishing the role of the primate rostral superior colliculus in fixation, and in other reports also can be interpreted to support the traditional uniform saccade zone concept or a theory of multiple functionalities for the rostral pole of the SC (see DISCUSSION). Most importantly, as mentioned earlier, fixation neurons suppress activity during *most* saccades. But they also discharge a significant burst for small contraversive saccades (e.g., Figs. 10 and 11 of Munoz and Wurtz 1993a; Fig. 1 of Krauzlis et al. 1997; Fig. 3 of Anderson et al. 1998), strikingly similar to the burst expected from a neuron in the saccade zone coding for an eye movement. Then do these neurons in the proposed fixation zone encode saccades of small vectors and form the continuation of the saccadic motor map? Or do they function like the OPNs and act to preserve fixation?

Spatiotemporal trajectories of saccades perturbed by microstimulation

We addressed these questions by examining the effects of stimulation of different SC sites on ongoing saccades. Previous studies have explored the interactions between visually guided and SC-stimulation evoked saccades where the stimulation was applied to either the posited fixation zone (Chaturvedi and Van Gisbergen 1999b; Munoz and Wurtz 1993b) or the saccade generation region (Chaturvedi and Van Gisbergen 1999a; Schlag-Rey et al. 1989; Sparks and Mays 1983). (For stimulation studies in the head-free cat, see Pélisson et al. 1989, 1995.) However, effects on saccades disrupted by stimulation of the fixation zone have not been compared with the perturbations induced by stimulation of more caudal regions of the SC. The general approach in these past studies has been as follows: a persistent or briefly flashed visual target is presented in the periphery, and the monkey is required to make a saccade to the target location. Before the large eye movement, a *target-activated* response arises within an ensemble of neurons in the caudal SC. At various intervals around the onset of the saccade, different sites within the deeper intermediate layers of the SC are stimulated, producing an interaction between the *stimulation-induced* and target-activated population responses, which then is reflected in the eye movement behavior. Because of the hypothesized functional difference between the fixation and saccade zones, stimulation of the SC in these two regions during ongoing saccades makes different predictions on both the collicular interactions and the resulting eye movement.

In the traditional saccade zone concept (Fig. 1*A*), stimulation of the SC during a target-directed saccade should change, at least momentarily, the metrics of the encoded movement. The new, desired goal may be, for example, a weighted vector average of the saccades coded by the stimulation-induced and target-activated population responses (Chaturvedi and Van Gisbergen 1999a; Robinson 1972; Van Opstal and Van Gisbergen 1989). Alternatively, it also could be equivalent to the saccade retinotopically coded by the stimulation site but updated by a lagged change in eye position from the beginning of the targeted movement; the combined effect of the target-directed saccade and the stimulation-evoked movement has been termed the *colliding* saccade (Schlag and Schlag-Rey 1990; Schlag-Rey et al. 1989). Or a combination of these and other hypotheses may be implemented. Whatever the exact mechanism, the ongoing saccade curves and deviates in direction from its normal trajectory, and we shall refer to this movement as a *redirected* saccade. The eye movement then stops, usually well short of the desired goal. Often another

saccade then is generated to bring the eyes near the original target location.

To assign general terminology, we shall refer to the combination of the ongoing movement and the component perturbed by the stimulation as the *initial* saccade, the ensuing period when eyes have stopped in the orbits as the *interruption duration*, and the subsequent movement as the *resumed* saccade. If a resumed saccade is not observed, the eye movement is considered a *truncated* saccade.

According to the fixation zone hypothesis (Fig. 1*B*), microstimulation in the fixation zone triggered on saccade onset also produces a perturbed eye movement with initial and resumed components, but the initial saccade does not exhibit spatial deviation and therefore is not a redirected saccade. Instead the disruption would be similar to the interrupted saccade produced by stimulation of the OPNs (Becker et al. 1981; Keller 1977; Keller et al. 1996; King and Fuchs 1977). Artificial activation of fixation neurons is hypothesized to directly activate the OPNs (Munoz and Wurtz 1993b), which in turn briefly stops the saccade in place without any directional deviation from the original trajectory. After a variable duration, a resumed movement is generated to bring the eyes near the original location of the target. The reactivation of OPNs presumably does not change, instead only momentarily suppresses, the encoded metrics of the desired saccade because the target-activated population response in the SC is reduced significantly when stimulation is delivered to either the OPNs (Keller and Edelman 1994) or the fixation zone (Munoz et al. 1996).

Previous studies that stimulated the fixation zone during large saccades (Munoz and Wurtz 1993b; Munoz et al. 1996), however, did not analyze the spatial trajectories of the perturbed saccades to rule out nonfixation-zone mechanisms. Consequently, it is unknown whether the stimulation of the rostral pole produces redirected or interrupted saccades. In fact, no past reports, to our knowledge, have analyzed systematically the effects of SC stimulation site on the metrics of perturbed movements, much less differentiate between redirected and interrupted saccades. Nor has any study compared the results with those produced by stimulation in the OPN region in the same animal. In addition to the redirection of saccades, we also measured the endpoint accuracy of the movements, the amplitude of the initial component, the latency at which the stimulation effect is observed and the interruption duration. Although not all the metrics address the fixation- and saccade-zone issue, they do provide a quantitative and comparative description of the effects of stimulation site on ongoing saccades.

Uniformly sampled collicular sites along the rostralcaudal dimension of its deeper intermediate layers were stimulated during large ongoing saccades, using parameters subthreshold to those that produce a FVS. Similarly, the OPN region also was stimulated to produce interrupted saccades. The spatial trajectories and metrics of all perturbed saccades were quantified and, for the SC stimulation saccades, analyzed as a function of the stimulation site. The perturbations induced by stimulation of the fixation zone also were compared with the interruptions produced by stimulation of the OPN region. We found that stimulation of the rostral pole of SC produced significant deviation in the spatial trajectories of the ongoing eye movement, a result that resembled the redirected saccades induced from the caudal SC. These results suggest that the mechanisms by which stimulation of the fixation zone perturbs saccades are, at least partially, different from the pathways by which the OPNs interrupt saccades.

The data presented here have appeared previously in preliminary form (Gandhi and Keller 1995, 1998; Keller and Gandhi 1998).

METHODS

Three juvenile, male, *Macaca mulatta* monkeys were used for this study. The experiments involved recording eye movements and stimulating sites in the deeper intermediate layers of superior colliculi and the omnipause region to perturb ongoing saccades. All experimental protocols were approved by the Institute 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.

Surgical preparation

Surgery was performed under aseptic conditions. Heart rate, respiratory rate, body temperature, blood pressure, and oxygenation were monitored for the duration of the surgery. Four devices were implanted under isofluorane gas anesthesia in each monkey. *1*) A stainless steel chamber was placed stereotactically on the skull, slanted posteriorly at an angle of 38° in the sagittal plane and aligned normal to both colliculi. *2*) Another stainless steel chamber was mounted stereotactically on the skull, slanted laterally in the frontal plane at an angle of 25° and aligned on the OPN region. *3*) A head restraint consisting of two light, stainless steel tubes was positioned transversely. The chamber and the head bars were fixed to the skull with dental acrylic and small titanium bone screws. And *4*) a coil of Teflon-coated stainless steel wire was set under the conjunctiva of one eye using the method developed by Fuchs and Robinson (1966) and modified by Judge et al. (1980). After surgery, the monkeys were returned to their cage and were allowed to fully recover from surgery. Antibiotics (Ancef) and analgesics (Buprenex) were administered under the direction of a veterinarian during the postoperative period.

Training

Each monkey was trained to climb out of his cage into a primate chair and sit in it during the experiment. Training and subsequent experimental sessions were conducted four to five times a week. The monkey was given water or juice rewards for correctly executing behavioral paradigms and was allowed to work until satiation. Daily records were kept of the animal's weight and health status. Supplemental water was given as necessary, and unlimited access to it was provided on days when training or experimental sessions were not performed.

Experimental setup

Behavioral paradigms, visual displays, and data storage were under the control of a real-time program running on a laboratory PC system. The targets were presented via a computer controlled, analogue oscilloscope, which back-projected light spots on the 90 × 90° translucent screen placed 40 cm in front of the monkey (Crandall and Keller 1985). The targets were 15-min arc in diameter and 2 cd/m^2 in intensity against a diffusely illuminated dim homogeneous background illumination (0.05 cd/m^2).

The eye movement signals were obtained by placing the head-restrained animal with an implanted scleral coil in a pair of orthogonally aligned 20-kHz magnetic fields maintained electronically in temporal quadrature. The voltage induced in the coil was passed

through a phase detector, which separated the eye position signal into horizontal and vertical components with a sensitivity of 0.25°, zero drift and a bandwidth of 1 kHz (Robinson 1963). Horizontal and vertical eye velocity were obtained by analogue differentiation (with a cutoff frequency of 170 Hz) of the position signals yielding a root mean square velocity noise of ~1°/s. Horizontal and vertical eye position and velocity measurements were sampled by a 12-bit data acquisition card (Data Translation, DT-2831) at 1 kHz and stored on computer disk. Radial eye position and velocity were computed off-line by the Pythagorean theorem.

Behavioral paradigms

SC STIMULATION. Before each experiment, the SC chamber was opened and thoroughly cleaned under aseptic conditions. A double eccentric micropositioning device with a single, drilled hole, which allowed access for a microelectrode track at virtually any location within its 12-mm diam, was positioned in the chamber. A sharpened guide tube was placed in the hole and gently pushed through the dura. By means of a hydraulic drive system, a tungsten microelectrode (Frederick Haer; 0.5–1.5 MΩ impedance, tested at 1 kHz) was lowered through the guide tube into the superficial layers of the SC (identified by neural "swishes" on the audio amplifier as the monkey scanned the visual field). The microelectrode then was lowered an additional 2.0–2.5 mm to place its tip in the deeper intermediate layers of the SC. Neural activity was monitored during saccades tasks to confirm that the electrode tip was placed among fixation and buildup neurons (Munoz and Wurtz 1995a). For the remainder of the experiment, this site was stimulated to evoke as well as perturb saccades. Note that because the microelectrode penetrations were normal to the SC motor-map, only one site was typically stimulated on any given penetration.

The FVS for each SC site first was determined with the microelectrode now fixed as stated earlier. The monkey was required to fixate a centrally placed fixation spot for 500–900 ms before it was extinguished. Approximately 100–200 ms later, the SC site was stimulated by an analogue stimulator (Grass S88), set to produce symmetrical biphasic pulses of constant current (0.25-ms pulse widths for each pulse). Pulse frequency usually was fixed at 400 pps, and train duration was varied between 25 and 100 ms. Current intensity, controlled by an optical isolator (Tektronix model 2620 constant current stimulator) that delivered its output pulses across the microelectrode and the concentric guide tube, typically ranged from 25 to 35 μA. For each site, these parameters produced a FVS, thus providing a systematic approach to placing each microelectrode track on the SC motor map (Robinson 1972). For the tracks studied after the publication by Stanford et al. (1996), the stimulation duration was generally 100 ms to ensure that the FVS and site-specific maximum amplitude were equivalent. Because the stimulation duration was shorter, typically 50 ms, on previous tracks, we cross-referenced the FVS with the optimal retinal error vector, a value estimated from the most vigorous visual burst heard on the audio monitor when the electrode tip reached the surface of the SC during any given penetration. According to our book records, there was a general agreement between the two measures.

Next, the monkey was required to perform a memory/delayed saccade paradigm (Fig. 2). First, the fixation point was visually acquired for 500–900 ms. Next, a target appeared in the periphery for 300 ms. The fixation point remained illuminated for the duration of the target presentation, plus an additional randomly selected 0–300 ms. The cue to initiate saccades was fixation offset to guarantee that all eye movements were made to the remembered location of the target. Within a block of trials the target was presented at 30° eccentricity and in any of the four directions at integer multiples of 90° from the estimated direction of the FVS (see following text). Thus saccades were made in the preferred (FVS) direction, opposite direction, the direction 90° away such that the saccade encoded by the locus of target-activated response was in the same SC (sameSC90),

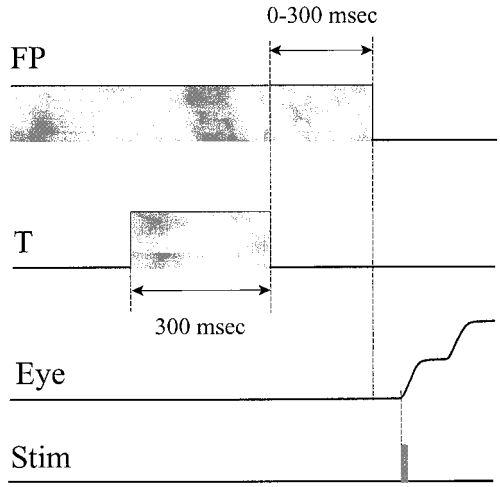

FIG. 2. Graphic representation of the memory/delayed saccade task used in the experiments. Monkey first visually acquired a fixation point (FP) for 500–900 ms. Next, a target (T) appeared in the periphery for 300 ms. Fixation point remained illuminated for the duration of the target presentation plus an additional, randomly selected 0–300 ms. Saccade cue was fixation offset to guarantee that all saccades were made to the remembered location of the target. Stimulation of SC sites was triggered on saccade onset on a randomly selected 50–75% of the trials.

and the other direction 90° away such that the locus of activity was in the opposite SC (oppSC90). This terminology, illustrated graphically in Fig. 3, was adopted for convenience.

Stimulation of SC sites was triggered on saccade onset on randomly selected 50–75% of the trials. Off-line inspection revealed that the trigger point occurred 5 ms (±2 ms) after the beginning of the eye movement. The stimulation parameters required to perturb ongoing saccades were always subthreshold with respect to the parameters used to produce the FVS. Stimulation currents and train durations to induce perturbations typically ranged from 10 to 25 μA and 10 to 35 ms, respectively. The stimulation frequency usually was kept constant at 400 pps.

Note that directions of the saccade target depended on the FVS direction determined on-line. Averaging the fixed vector saccades over many trials, when done off-line, often produced a slight discrepancy between the on-line estimation and the real FVS direction. The range of error in our direction estimate was rarely >20°.

OPN STIMULATION. The OPN chamber was cleaned under aseptic conditions and prepared for electrophysiological experiments using the same methods described for the SC chamber. A tungsten microelectrode was lowered through the guide tube via a hydraulic drive system until the center of the OPN region was encountered, a location determined by the unique discharge characteristics of these neurons during saccades (Cohen and Henn 1972; Keller 1974; Luschei and Fuchs 1972). In addition, the interrupted saccade paradigm was used to validate the electrode's location. This site then was stimulated for the remainder of the experiment (see following text). At least once in each monkey, the microelectrode was implanted, as described by Keller and Edelman (1994), and used to stimulate the OPN region for an extended period of time.

The monkeys were trained to execute eye movements during the delayed saccade paradigm (Fig. 2). The target amplitude was usually 30°, typically directed in horizontal and oblique directions. On most blocks of data collection, stimulation of the OPN region was triggered on saccade onset on a randomly selected 50–75% of the trials. The ranges of stimulation current and duration were 10–30 μA and 10–25 ms, respectively. Stimulation frequency was kept constant at 400 pps. Fixation zone and OPN region stimulation sessions always were conducted in independent blocks. Further experimental details regard-

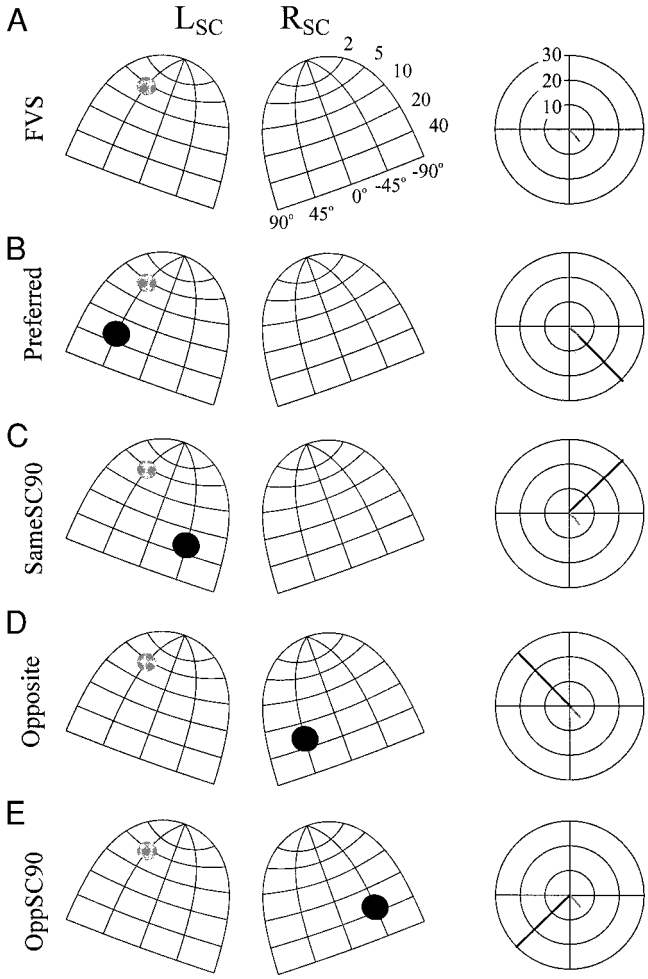

FIG. 3. Schematic to illustrate the target directions chosen for each SC track. Each row shows a model of the left (L_{SC}) and right (R_{SC}) colliculi and an equivalent polar plot representation of the visual field based on the formulae by Ottes et al. (1986) and Optican (1995). Numbers along the curvilinear trajectory in the R_{SC} model reflect the amplitude of the contralateral saccade coded by that meridian. Numbers along the bottom represent the direction of the encoded saccade. *A*: for illustration, stimulation of a site within the lateral region of the left SC (gray circle) produces a right-downward fixed vector saccade (FVS; gray line in polar representation). Direction of the FVS determined the directions of the target used in the delayed saccade task. Target amplitude was kept constant at 30°. In *B–E*, the locus of the target-activated (stimulation-induced) population response is represented by the black (gray) circle, and the equivalent vector of the saccade is schematized by a black (gray) line on the polar representation (right column). *B*: direction of the target is aligned with the FVS direction (*Preferred* direction condition). *C*: direction of the target is in the same hemifield but 90° away (*SameSC90* direction condition). *D*: direction of the target is in the direction opposite to the FVS direction (*Opposite* direction condition). *E*: direction of the target is in the opposite hemifield but only 90° away (*OppSC90* direction condition).

ing OPN stimulation to interrupt saccades have been published previously (Keller and Edelman 1994; Keller et al. 1996).

Data analysis

All off-line analyses were performed in Matlab (The Mathworks). The velocity signals, collected from the analog differentiator, were filtered digitally with a five-pole Butterworth filter in the forward and reverse direction to produce zero phase distortion. This signal then was differentiated, and a threshold criterion on the resulting acceleration signal was used to detect saccade onset. As this method sometimes erroneously marked the end of saccades particularly for large eye movements, which were often slow when made to remembered target locations (White et al. 1994), a velocity threshold criterion (typically 90°/s) was used to mark the endpoint of all saccades. In addition, all saccade onset and offset marks were checked by an operator and manually changed if necessary.

RESULTS

Forty-six sites in five colliculi of three monkeys (*monkey BA*: $n = 22$; *monkey BZ*: $n = 19$; *monkey HM*: $n = 5$) were stimulated at the onset of large saccades. The stimulation parameters applied during ongoing saccades were subthreshold to those used to produce the FVS or the site-specific maximal amplitude (Robinson 1972; Stanford et al. 1996). The saccadic target eccentricity was 30°, and the direction was either the preferred direction or any of other three directions at integer multiples of 90° away from it (Fig. 3).

The results will be presented in the following order: first, we focus on the type of saccadic perturbation induced by stimulation of SC sites along the rostralcaudal axis when the directions of the target-directed saccade and FVS are similar. These eye movements initially will be examined in the temporal domain (radial amplitude vs. time). This approach will demonstrate that the *apparent* interrupted saccade effect observed by stimulation of the fixation zone (Munoz and Wurtz 1993b) can in fact be induced from a larger region of the SC (Gandhi and Keller 1995). Second, we extend the qualitative assessment of the perturbations observed for saccades in several different directions and consider the effects of stimulation when illustrated as both spatial trajectories (horizontal component vs. vertical component) and temporal plots (radial amplitude as a function of time). These data will demonstrate that stimulation trials must be examined in both coordinate systems to accurately differentiate whether the perturbations are interrupted or redirected saccades. Third, we quantify several metrics of the perturbed saccades and report trends in the data as a function of stimulation site within the SC. Fourth, we compare the metrics of saccades perturbed from the fixation zone of the SC and the eye movements interrupted from the OPN region. Fifth, and finally, we briefly discuss the effects of stimulation parameters on the disrupted saccadic movements.

Site-specific perturbations (preferred direction)

SC sites uniformly sampled across the rostralcaudal dimension of the SC were stimulated at the onset of large, visually triggered saccades the directions of which were similar to the FVS evoked from each site. Figure 4 plots temporal representations of radial amplitude and velocity of ongoing saccades in the preferred direction for three sites chosen to span the rostralcaudal extent of the SC. For the two rostral sites (Fig. 4, *A* and *B*), one inside the fixation zone (FVS: 0.74@44°; amplitude@direction, the notation used henceforth) and the other outside (FVS: 9.23@21°), stimulation at each site stopped the saccade in midflight (—). The eye movements resumed shortly after stimulation offset and landed near the target location. In contrast, stimulation of a more caudal site (FVS: 19.34@336°) did not stop the ongoing saccades but, instead, slightly increased their peak velocity (Fig. 4*C*) compared with the averaged control saccade (- - -). These data suggest, albeit incorrectly, that the hypothesized functional

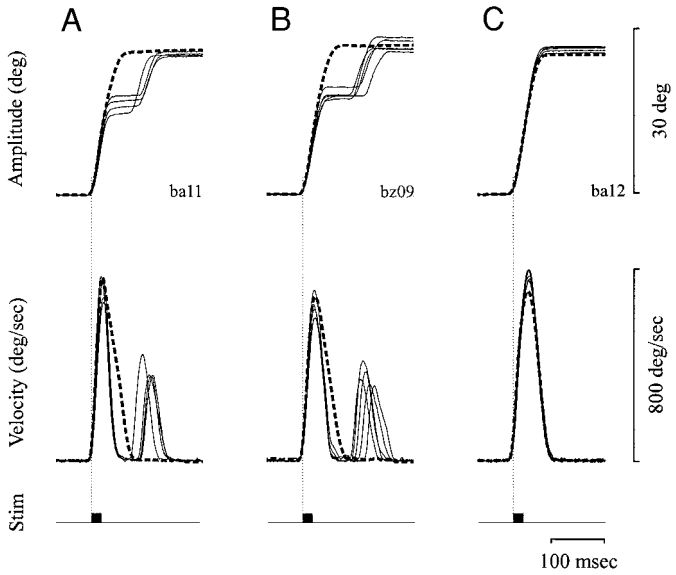

FIG. 4. Effects of stimulation site, analyzed in the temporal domain, during saccades in the *preferred* direction. Vectorial amplitude (*top*) and velocity (*middle*) traces for an averaged control (- - -) and several individual stimulated trials (—) are illustrated for 3 SC sites. *A*: stimulation was applied to a site within the fixation zone (FVS: 0.74@44°). *B*: stimulation of a site outside the fixation zone (FVS: 9.23@21°). *C*: stimulation of a site further caudal (FVS: 19.34@336°). In all cases, the stimulation was triggered on saccade onset (*bottom*). The dotted vertical lines indicate stimulation onset. Saccades in the preferred direction were stopped in midflight on stimulation of the 2 rostral sites (*A* and *B*), whereas the ongoing movement did not stop short of the target location on stimulation of the caudal site (*C*).

properties of the fixation zone extended beyond the rostral pole in our experiments.

Thus in examining the effects of stimulation on saccades in the preferred direction, a dichotomous observation that depends on the stimulation site was revealed. For each SC site, the stimulation either stopped the saccade momentarily (Fig. 4, *A* and *B*) or did not stop it at all (Fig. 4*C*). Figure 5 plots the location of the stimulation sites (based on the FVS) on a schematic of the saccade motor map (Ottes et al. 1986) and indicates whether stimulation at onset of 30° saccades resulted in either two saccades (open symbols) or a single eye movement (filled symbols). The spatial distribution indicates that stimulation of any SC site within the rostral ~2 mm (up to the 10° amplitude meridian) stopped the initial saccade short of the desired target, and a resumed component was executed to bring the eyes near the target location. Stimulation of sites caudal to this landmark did not stop the initial saccade, and it reached the desired goal with a single movement.

The effects of stimulation site also was considered during small saccades (<10°) in a pilot study (data not shown). The stimulation, triggered on saccade onset, had no noticeable effect on the saccade trajectory because the desired eye movement ended near the flashed target location. Apparently the initial saccade had completed before the effects of stimulation could be observed. Thus we did not further explore effects of stimulation site during small saccades.

Spatial trajectories versus temporal representations

Temporal representation of perturbed saccades in the preferred direction (Fig. 4) strikingly resembles saccades interrupted by OPN stimulation (see Fig. 1) (Keller et al. 1996). However, an examination of perturbed saccades in preferred and nonpreferred directions and as both *spatial trajectories* (horizontal component vs. vertical component) and *temporal plots* (radial amplitude as a function of time) demonstrates the danger of incorrectly classifying redirected saccades as interrupted saccades (Figs. 6–8). Data are presented for three SC sites that spanned the rostralcaudal extent of the SC and exhibited the battery of phenomena observed for all sites. In each figure, *A–D* illustrate temporal representations of individual stimulation trials (solid lines) and the average of control saccades (dashed line) to targets presented in the four directions. The equivalent spatial trajectories are shown in *subplot E*, while two traces of the FVS evoked by stimulation during fixation is presented in *F*.

Stimulation of a relatively caudal site (FVS: 13.21@345°) during saccades toward the preferred direction did not stop the eye movements in midflight and minimally altered their trajectories (quadrant IV, Fig. 6*E*), and the direction deviation is not obvious in the temporal representation (Fig. 6*A*). The spatial redirections are, however, emphasized during saccades in the other three directions. The temporal plot in Fig. 6*B*, for example, was very similar to a temporal representation of saccades interrupted by OPN stimulation (Fig. 1 of Keller et al. 1996) and fixation zone stimulation (Fig. 5 of Munoz and Wurtz 1993b). However, the spatial trajectories of these saccades (quadrant I, Fig. 6*E*) were clearly redirected, i.e., the instantaneous directions of stimulated saccades were altered dramati-

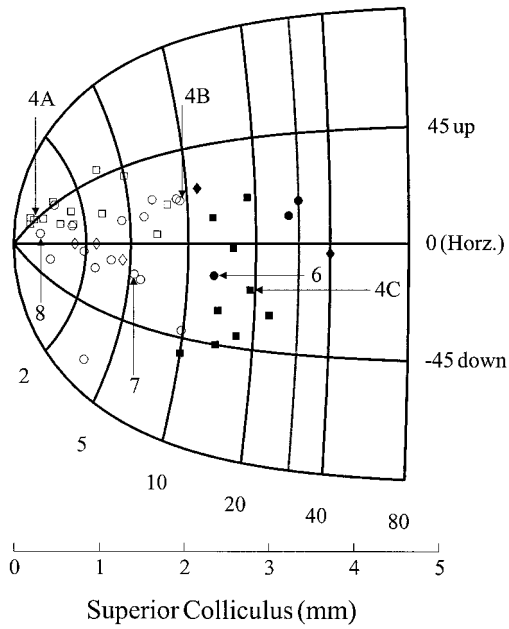

FIG. 5. Summary of effects of stimulation site during saccades in the preferred direction. As indicated in Fig. 4, stimulation of SC sites either temporarily stopped or continued ongoing saccades in the preferred direction. Distribution of the 2 effects as a function of stimulation site in indicated on the model colliculus. Location of each site was computed by converting the FVS metrics into colliculus coordinates (Ottes et al. 1986). Open symbols, sites that stopped large saccades in midflight; filled symbols, loci that did not stop the ongoing eye movements. Different symbol types represent the 3 different monkeys (squares, *monkey BA*; circles, *monkey BZ*; diamonds, *monkey HM*). Theoretical center of the target-activated response occurred along the 30° iso-amplitude meridian (gray line). Locations of the 3 sites represented in Figs. 4 are marked as 4*A*, 4*B*, and 4*C*. Similarly, the sites indicated as 6, 7 and 8 refer to the data illustrated in Figs. 6–8, respectively.

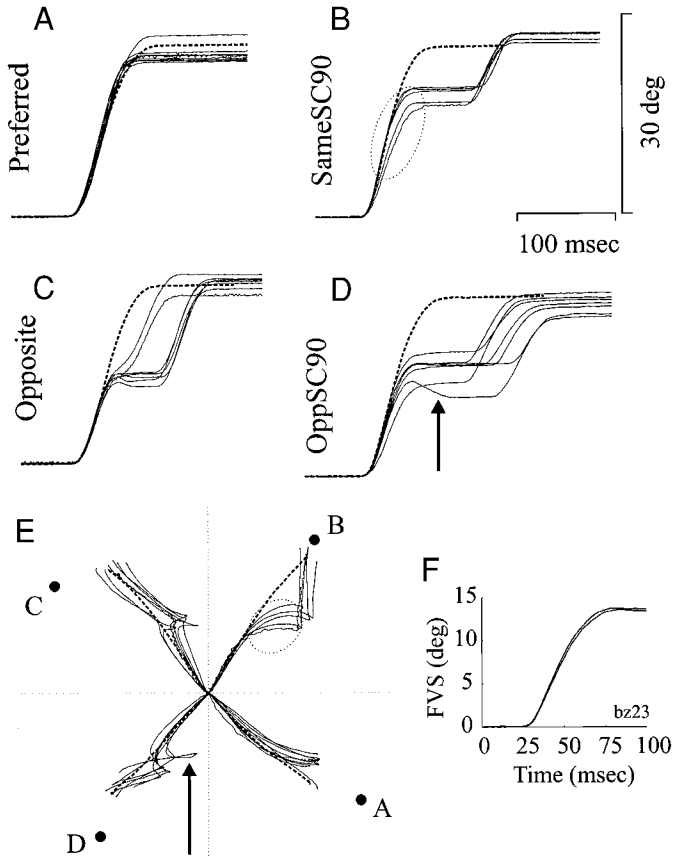

FIG. 6. Illustration in temporal and spatial domain of the saccade perturbations produced from a relatively caudal site (mean FVS: 13.21@345°). Temporal representation of individual stimulated trials (thin traces) and a mean control saccade (thick, dashed line) for the preferred, sameSC90, opposite and oppSC90 directions are plotted in subplots *A–D*, respectively. Corresponding spatial trajectories are shown in *E*, and 2 traces of the FVS evoked by stimulation during fixation are graphed in *F*. For the preferred direction (*A*), only 1 saccade was generated. For other directions, the stimulation produced redirected saccades, although most trials in the temporal representation fail to convey this point. Ovals in *B* and *E* encircle the corresponding parts of the eye movement. Note that during the stimulation induced direction deviation, the radial amplitude increases, albeit slower than for control saccades. This phenomenon makes it more difficult to differentiate between interrupted and redirected saccades based on an analysis of the temporal representation. If the direction of the stimulated saccade is reversed in midflight, both spatial and temporal representations can convey this information, as indicated by the arrow in *E* and *D*.

cally relative to control trials. Distinct deviations were not obviously detected in the temporal plots because the amplitude of the saccades increased, albeit more slowly, during the significant change in direction (see the ovals encircling the approximately corresponding regions in the 2 representations). The same observation also held for the other directions (Fig. 6, *C* and *D*). Note though that stimulation sometimes reversed the direction of the ongoing saccade, and this property was manifest as a decrease in the radial amplitude (see corresponding trial referred to by the arrow in Fig. 6, *D* and *E*). However, when the reversal was minor, only a subtle decrease in amplitude was evident.

Saccades perturbed from a more rostral site (FVS: 5.32@342°), but still outside the fixation zone, are illustrated in both spatial and temporal representations in Fig. 7. Stimulation of this site at the onset of saccades in the preferred direction (Fig. 7*A*) stopped the movements in midflight with minimal deviation in its spatial trajectory (quadrant IV, Fig. 7*E*). Shortly after the end of stimulation, resumed saccades occurred and brought the eyes near the location of the flashed target. In contrast, saccades in other directions were curved significantly, although the temporal representation often failed to illustrate this point (Fig. 7*D*, for example).

On the basis of the terminology presented in INTRODUCTION and observation of saccades in the preferred direction only, one could *incorrectly* conclude that stimulation of a site in the saccade zone can interrupt large saccades. An examination of both spatial and temporal representations for saccades in other directions also must be incorporated to establish that the stimulation redirected the eye movements. If the redirected saccades produced outside of the fixation zone appear as interrupted saccades produced by OPN stimulation, it is possible that the interrupted saccades reported to occur after stimulation of the fixation zone (Munoz and Wurtz 1993b) are in fact redirected saccades. Therefore it is crucial to consider whether saccades perturbed from the fixation zone also show a redirection in their spatial trajectories.

Figure 8 plots the spatial and temporal configurations of perturbed saccades from stimulation of a site with FVS (0.78@18°; see *F*) <2°. On the basis of the iso-amplitude marker that separates fixation and saccade zones (Munoz and Wurtz 1995b), the site illustrated in Fig. 8 was in the fixation

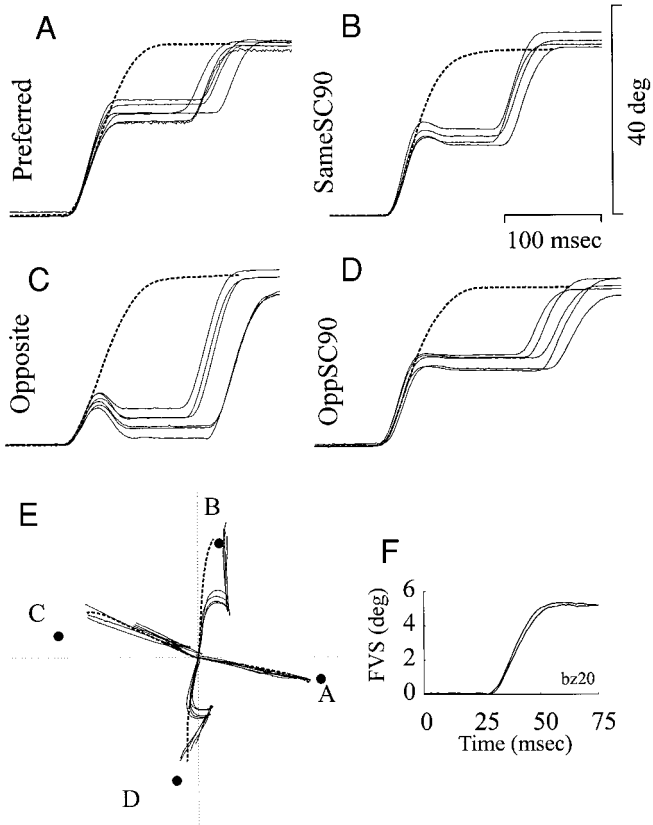

FIG. 7. Illustration in temporal and spatial domain of the saccadic perturbations produced from a SC site outside the fixation zone but more rostral than the site illustrated in Fig. 6. Mean FVS was 5.32@342°. Same format as that used in Fig. 6. Unlike the perturbations observed for the site in Fig. 6, stimulation of this site paused the ongoing saccades in the preferred direction in midflight.

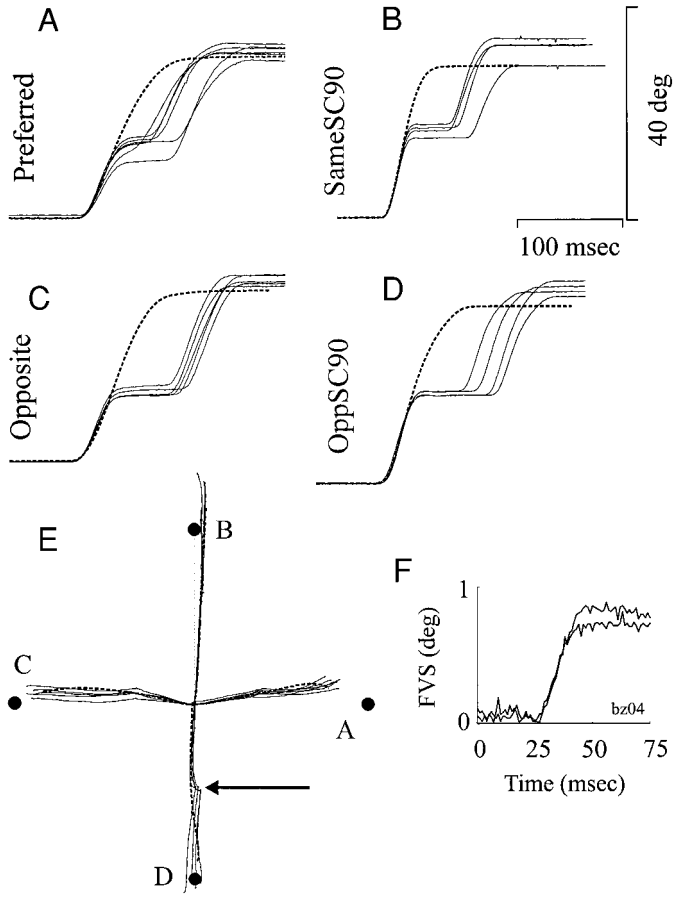

FIG. 8. Illustration in temporal and spatial domain of the saccadic perturbations produced from a SC site in the fixation zone. Mean FVS was 0.78@18°. Same format as that used in Fig. 6. Note that for this rostral site the redirection of saccades, particularly for nonpreferred directions, is considerably smaller but still present.

zone. Stimulation during saccades in the preferred direction (Fig. 8*A*) temporarily stopped the eye movements in midflight and minimally altered the direction of their spatial trajectories. For most saccades in other directions, the redirection of the trajectories were too small to be noticeable in the temporal representation (e.g., Fig. 8*D*) but still present in the spatial profiles (see Fig. 8*E*, ←). For some directions, however, the spatial deviation was not noticeable even in the spatial trajectories (upward saccades, Fig. 8*E*). Nevertheless, a quantitative analysis (to be presented in the next section) over all directions did indicate that the perturbations better resembled redirected saccades, not interrupted saccades.

Saccade metrics

We now provide a quantitative analysis of how the characteristics of perturbed saccades varied with stimulation site. A schematic of a saccade in both temporal and spatial representations along with the metrics quantified for our analyses is illustrated in Fig. 9. A description of each measure and how it was computed will be provided with the results.

Of the 46 tracks tested in three monkeys, sufficient data for quantitative analyses was collected for 32 sites from two (*BA* and *BZ*) monkeys. (The five tracks in *monkey HM* were used only to collect pilot data and, therefore, were not used for further study.) Stimulation was delivered during saccades in all four directions (see Fig. 3) in 19 of these tracks. For two sites, saccades were perturbed in all but the sameSC90 direction. Similarly, all but the preferred direction condition was fulfilled for one site. A total of six tracks contained data for only two directions (preferred and opposite: $n = 3$; sameSC90 and opposite: $n = 1$; sameSC90 and oppSC90: $n = 1$; preferred and sameSC90: $n = 1$). For the remaining four tracks, only the preferred direction was examined. In sum, the distribution of the number of sites stimulated for each of the four direction conditions are as follows: preferred, $n = 29$; sameSC90, $n = 23$; opposite, $n = 26$; oppSC90, $n = 23$.

Figures 10–14 summarize the metrics of saccades perturbed by stimulation of SC sites. All figures contain four subplots, each representing a different target direction relative to the direction of the FVS—recall from Fig. 3 that target directions were at integer multiples of 90° with respect to the direction of the FVS. If stimulation at onset of a large saccade in the *preferred direction* stopped the initial saccade well short of the desired goal, the stimulation site was marked with an open symbol (□ for *monkey BA* and ○ for *monkey BZ*). If the stimulation did not stop the ongoing saccade, the stimulation site was indicated by ■ and ● for the two monkeys. This symbol convention also was used for the distribution plotted in Fig. 5. It is worthwhile to reemphasize that stimulation of caudal sites at onset of saccades in nonpreferred directions did not produce single saccades but usually evoked a redirected saccade followed by an interruption period, when the eyes were fixed, and then a resumed movement which ended near the target location (Fig. 6). Nevertheless, these caudal sites will be represented by ■ and ● for all directions in Figs. 10–14. Linear regression fits were applied to the data plotted in Figs. 11−14, and only the statistically significant trends (slope significantly >0; $P < 0.05$, 1-tailed *t*-test) are superimposed on the plots. Statistical measures (Student's *t*-test) were performed on the mean final error (Table 1) and on the slope measure of all other metrics (Table 2).

FINAL ERROR (E1). An error measure (E1) was defined as the difference between the final amplitude of perturbed and control saccades. Using the convention of Keller et al. (1996), negative values of E1 indicated that the stimulated saccade fell short of the average amplitude of control saccades (hypometria); consequently, positive values of E1 implied that the stimulated saccade overshot the control behavior (hypermetria). Figure 10 shows the distribution of E1 as a function of SC stimulation site. The subplots show that perturbed saccades tended to be hypermetric compared with control saccades. The mean overshoot, however, was $<1°$ for all direction conditions and was significantly different from zero only for directions orthogonal to the FVS direction (Table 1).

As the majority of the perturbations were followed by a resumed saccade, which repositioned the eyes close to the flashed target location, trials without a resumed component, except preferred direction saccades perturbed from the caudal SC (see following text), were not included in the endpoint accuracy analysis. But for some sites and certain directions, trials with a resumed saccade were not always present within our database. Consequently, the number of tracks illustrated in Fig. 10 is less than or equal to the number of tracks analyzed for each direction condition. As for preferred direction sac-

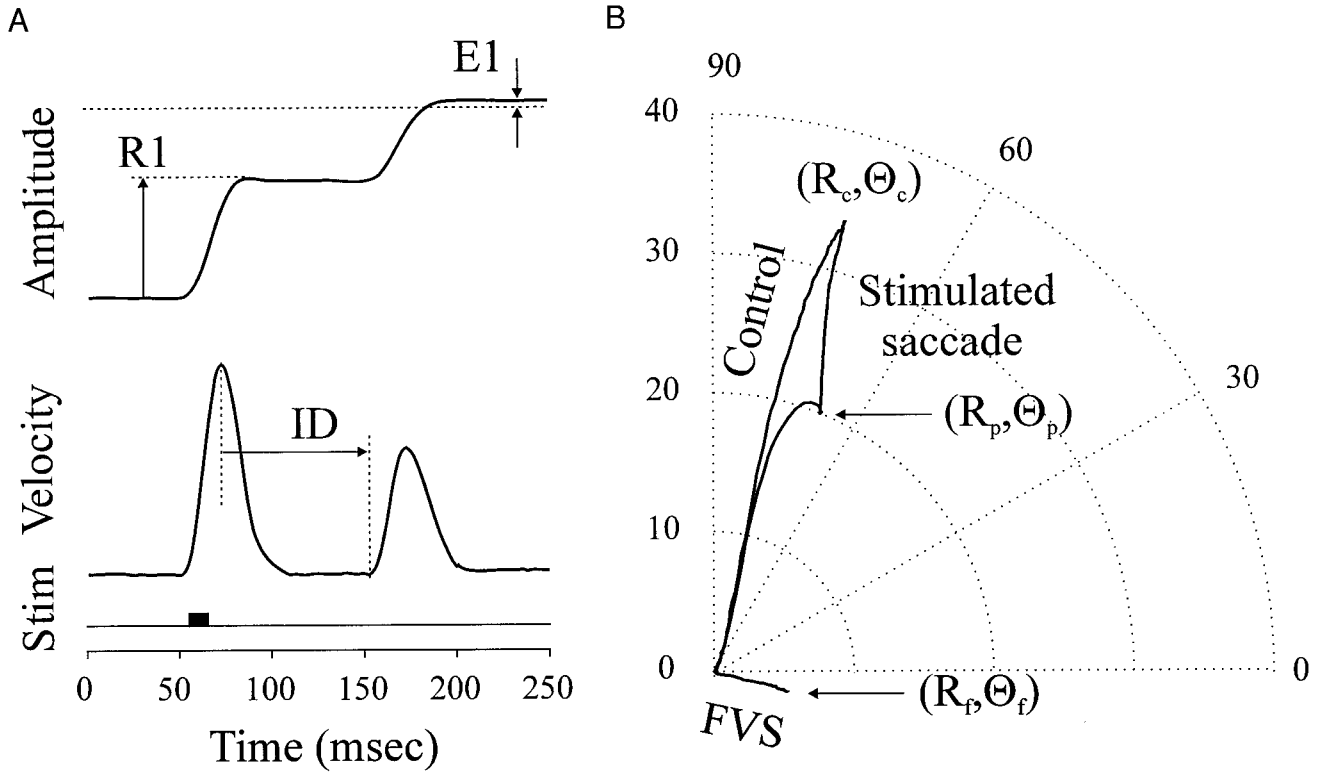

FIG. 9. Schematic to illustrate the parameters measured to quantify metrics of perturbed saccades. Representations in both temporal (*A*) and spatial (*B*) domains were used to mark the metrics of interest. *A*: radial amplitude, radial velocity, and the corresponding stimulation train are shown as a function of time. E1, final error with respect to average amplitude of control saccades (*top dashed line*); R1, maximum amplitude of the initial saccade; ID, interruption duration, measured as the time from peak velocity of the initial saccade to the onset of the resumed component. *B*: spatial trajectory of the same perturbed saccade shown as a polar representation, the eye movement trajectory labeled "stimulated saccade." For comparison, spatial trajectories of an averaged control saccade (upward and rightward) and a FVS (rightward and downward) also are shown. See text for the computation of direction deviation.

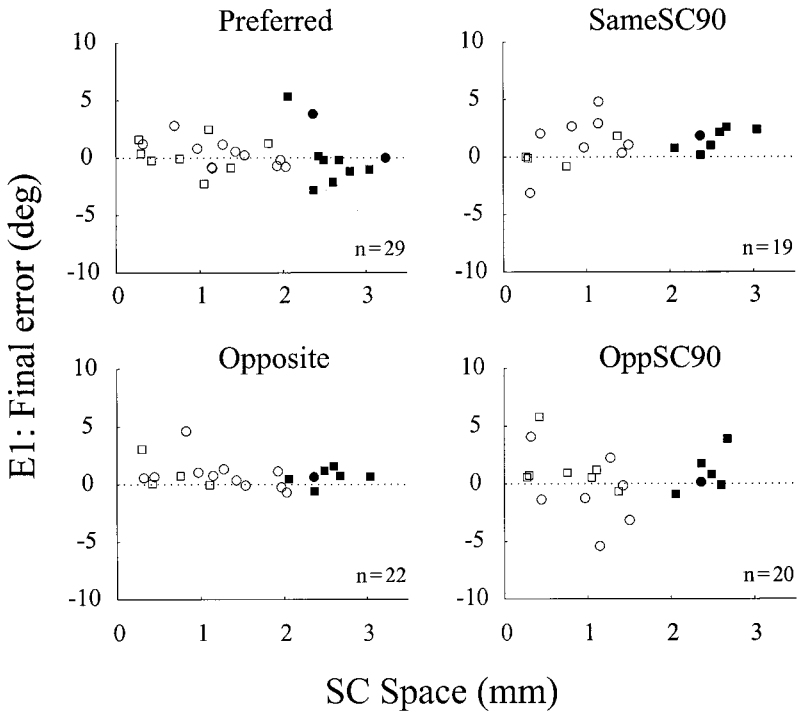

FIG. 10. Distribution of final error (E1) as a function of stimulation site. Four subplots refer to the 4 directions illustrated in Fig. 3. Abscissa, termed "SC Space (mm)," refers to the rostralcaudal component of the stimulation site, determined by converting the FVS into collicular coordinates. ○ and □, sites that stopped large saccades in the preferred direction in midflight. ● and ■, caudal sites that did not stop saccades in the preferred direction. *Monkey BZ*, ● and ○; *monkey BA*, ■ and □. - - -, 0 error. Number at the *bottom right corner* of each subplot denotes the number of stimulation sites included in the analysis.

TABLE 1. *Final error (E1) analysis*

	Direction	Mean, deg	*P* value
E1: final error	Preferred	0.4119 ± 2.1736	0.2200
	SameSC90	0.9507 ± 1.4921	0.0002*
	Opposite	0.2954 ± 1.2301	0.3022
	OppSC90	0.8254 ± 1.9637	0.0160*

Values are means ± SD for the four direction conditions for the vectorial final error analysis. A two-tailed *t*-test was performed to determine whether the mean E1 was significantly different from zero. SC, superior colliculus. *$P <$ 0.05.

cades perturbed by stimulation of the caudal SC sites, a resumed saccade was not necessary because the initial movement already had landed near the desired location; thus we included these trials.

INITIAL SACCADE AMPLITUDE (R1). The amplitude of the initial saccade (R1) was determined as the maximum radial displacement from the initial position achieved before the onset of a resumed component. In the case of stimulation of caudal sites during saccades in the preferred direction (sites marked by filled symbols in Fig. 5), the amplitude of the single eye movement was used for the initial amplitude. To minimize variability in saccadic accuracy, all initial amplitude measures were normalized by the average control saccade magnitude to the same target location. Figure 11 displays the normalized amplitude of the initial saccade as a function of stimulation site. Table 2 shows that the amplitude of the initial saccade increased as a function of stimulation site for all but the opposite direction conditions.

LATENCY OF PERTURBATION (L1). The time from stimulation onset to the point when the effect of stimulation was observed in the saccade trajectory was defined as the latency of perturbation (L1). Not all previous studies that have reported this measure explicitly mentioned how it was computed. For example, Munoz and Wurtz (1993b) stimulated the rostral SC at onset of large saccades and measured the latency from "stimulation onset to saccade alteration" (p. 581) without providing the computation details. Similarly, Miyashita and Hikosaka (1996) stimulated the SC during saccades and determined the equivalent latency measure by inspecting the velocity trace "by eye" (p. 189). Keller et al. (1996), on the other hand, computed L1 of saccades interrupted by OPN stimulation using two objective methods. They measured the metric as the time from stimulation onset to *1*) the time of eye velocity peak in the initial component and *2*) the epoch when the initial saccade's velocity trace separated >2 SE from the mean velocity plot of the nonstimulated saccades for the same target amplitude and direction and the same stimulation site. We compared the two sets of values for L1 obtained with each method and found that the values were similar. The same observation was reported by Keller et al. (1996) for saccades perturbed by stimulation in the OPNs. Only results from the latter technique will be presented here, unless noted otherwise.

Figure 12 plots the distribution of L1, computed using the standard error method, as a function of stimulation site for the four direction conditions, and the regression statistics are summarized in Table 2. The latency of perturbation increased significantly with stimulation site when the stimulation-induced and target-activated populations of neurons were present in the same SC (preferred and sameSC90 conditions). The slope was not significantly different from zero for the off axis and oppSC90 conditions.

DIRECTION DEVIATION. The method of computing the amount of redirection produced by stimulation of SC sites is detailed in Fig. 9*B*. For each target condition, the averaged control saccade direction (Θ_c) was measured. For stimulation trials, the direction of the eyes just before the onset of the resumed saccade was determined (Θ_p). Next, the absolute magnitude of the difference between the two directions ($\Theta_p - \Theta_c$) was computed. This value was marked positive if the redirection occurred in the direction of the FVS (as illustrated in Fig. 9*B*) and considered negative if the redirection was in the opposite direction. This final measure was labeled direction deviation (DD). For trials without a resumed saccade, the eye position when the ongoing eye movement stopped was used to compute Θ_p.

Figure 13 illustrates the direction deviation as a function of stimulation site for the four sets of target directions. For preferred and opposite directions, no significant trend was present as a function of stimulation site. For target-directed saccades orthogonal to the FVS (sameSC90 and oppSC90 conditions), the direction deviations increased as more caudal stimulation sites were stimulated (Table 2).

INTERRUPTION DURATION. The interruption duration (ID) was computed as the time from the peak velocity of the initial component to the onset of the resumed component. The time of peak velocity was chosen instead of the end of the initial saccade because the initial component often did not come to a complete stop (velocity does not reach 0) before the second component resumed (Keller et al. 1996), particularly for smaller stimulation parameters in the OPN region. Because a resumed component must be present to compute ID, the analysis excluded tracks and direction conditions for which the database included only truncated or single saccades. Figure 14 plots the distribution of ID as a function of stimulation site for the four direction conditions. A weak positive trend was present only in the preferred direction (Table 2).

TABLE 2. *Statistics of the linear regression analysis*

Metric	Direction	*P* Value	*r*
R1: initial saccade amplitude, deg	Preferred	0.0001*	0.8404
	SameSC90	0.0009*	0.6121
	Opposite	0.0634	0.3071
	OppSC90	0.0065*	0.5098
L1: latency of perturbation, ms	Preferred	0.0021*	0.5148
	SameSC90†	0.0124*	0.5127
	Opposite	0.1334	0.2475
	OppSC90	0.3775	0.0745
DD: direction deviation, deg	Preferred	0.7334	0.1206
	SameSC90	0.0007*	0.6291
	Opposite	0.3413	0.0842
	OppSC90	0.0207*	0.4287
ID: interruption duration, ms	Preferred	0.0425*	0.4055
	SameSC90	0.0659	0.3585
	Opposite	0.8895	0.2718
	OppSC90	0.9328	0.3466

The statistics refer to the metrics plotted in each subplot of Figs. 11–14. A linear regression was applied to the appropriate metric as a function of stimulation site. Each *P* value indicates whether the slope of each regression was significantly greater than zero. The correlation coefficient (*r*) for each regression fit also is listed. * Slope is significantly greater than zero ($P < 0.05$; 1-tailed *t*-test).

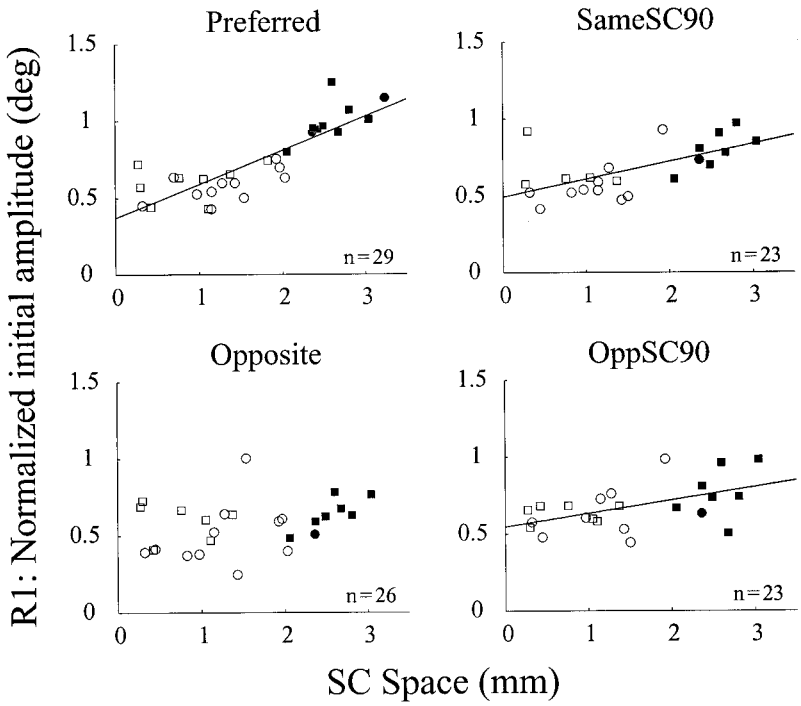

FIG. 11. Distribution of the normalized initial saccade amplitude (R1) as a function of stimulation site. Same format as that used in Fig. 10. Furthermore for each subplot, a linear regression fit was applied through the data points. Only the statistically significant trends are plotted on the corresponding subplot. See Table 2 for statistical significance of all trends and for correlation coefficients.

Comparison with saccades interrupted by OPN stimulation

The results presented thus far—that, for most directions, the metrics computed from stimulation of the rostral pole formed a continuum with the corresponding measure obtained from stimulation of the caudal SC—suggest that the perturbations induced by stimulation of the posited fixation zone resemble the redirected saccades commonly attributed to occur after stimulation of the saccade zone of SC during ongoing saccades. We further tested this point by comparing significant differences between perturbations produced by stimulation of the rostral pole of the SC and saccades interrupted by stimulation of the OPN region.

Eight (*monkey BA*: $n = 5$; *monkey BZ*: $n = 3$) of the 32 total sites stimulated in the SC of the two monkeys evoked FVS $<2°$ and, therefore, were considered as loci located within the hypothesized fixation zone. Omnipause neuron region stimulation data were collected from 13 experiments, 4 from *monkey BA* and 9 from *monkey BZ*. Because OPN stimulation induced interruptions do not depend on saccade direction (Keller et al. 1996), data from all directions were pooled together for each

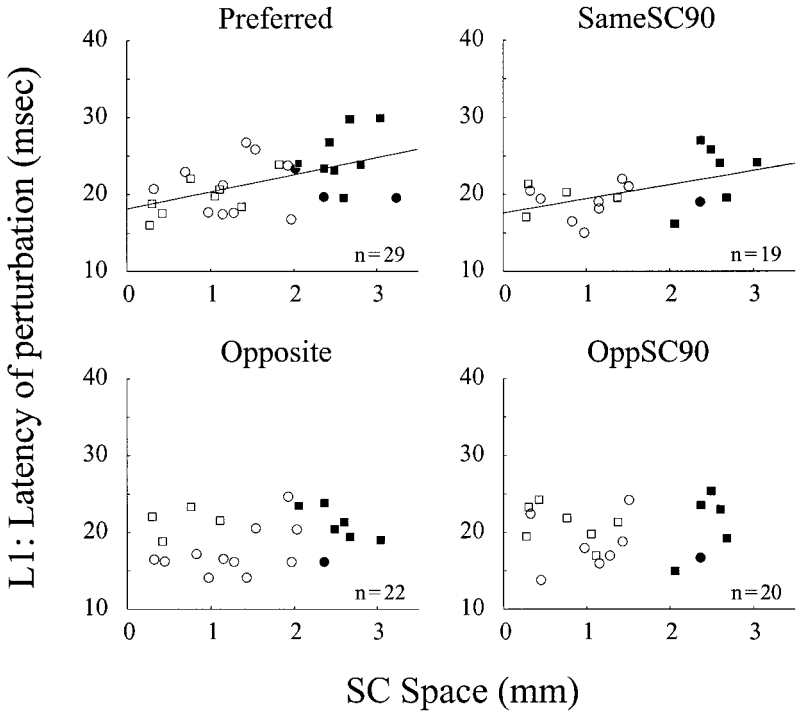

FIG. 12. Distribution of latency of perturbation (L1) as a function of stimulation site. Same format as Fig. 11.

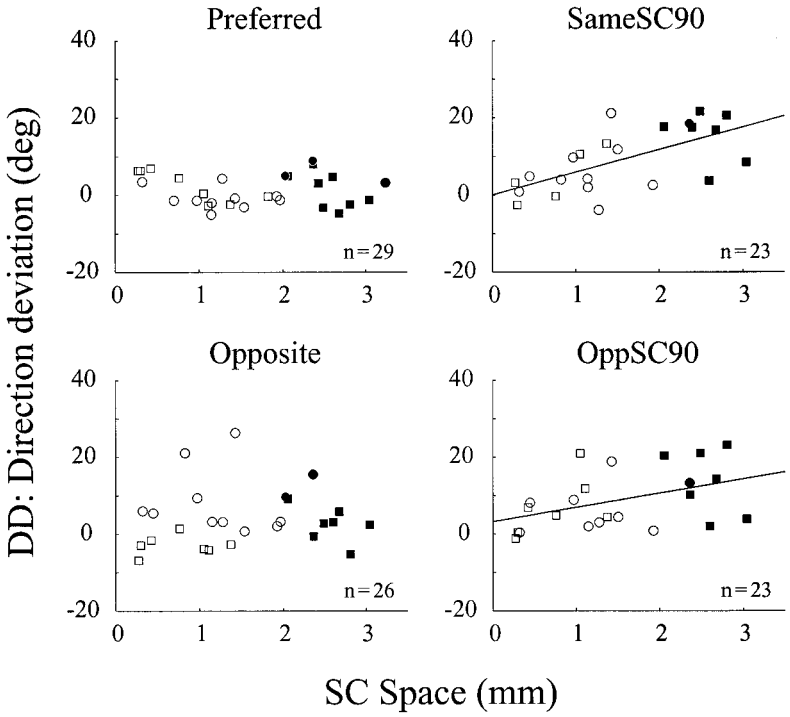

FIG. 13. Distribution of direction deviation (DD) as a function of stimulation site. Same format as Fig. 11.

stimulation site. In accordance with the fixation zone hypothesis, all four direction saccades perturbed by stimulation of each rostral pole site were combined as well. The metrics illustrated in Fig. 9 then were computed for each saccade and averaged to yield a mean value of each measure per stimulation site. Each mean value then was averaged over all stimulation sites within the rostral pole of SC or the OPN region, and the results are summarized in Table 3.

The final amplitude of saccades disrupted by stimulation of both rostral pole of SC and OPN region tends to slightly overshoot the control behavior, although the final error (E1) was significantly different from zero for rostral pole stimulation only ($P = 0.0189$; 2-tailed t-test); for OPN region stimulation, $P = 0.1469$. However, the mean final error produced by stimulation of the rostral pole of SC and OPN region were not significantly different ($P = 0.1413$; 2-tailed t-test). Regardless, the hypermetria was small, suggesting that the local feedback system compensated for the perturbations. The mean normalized amplitude (R1) for the rostral pole stimulation, although slightly greater, was not significantly different from the mean

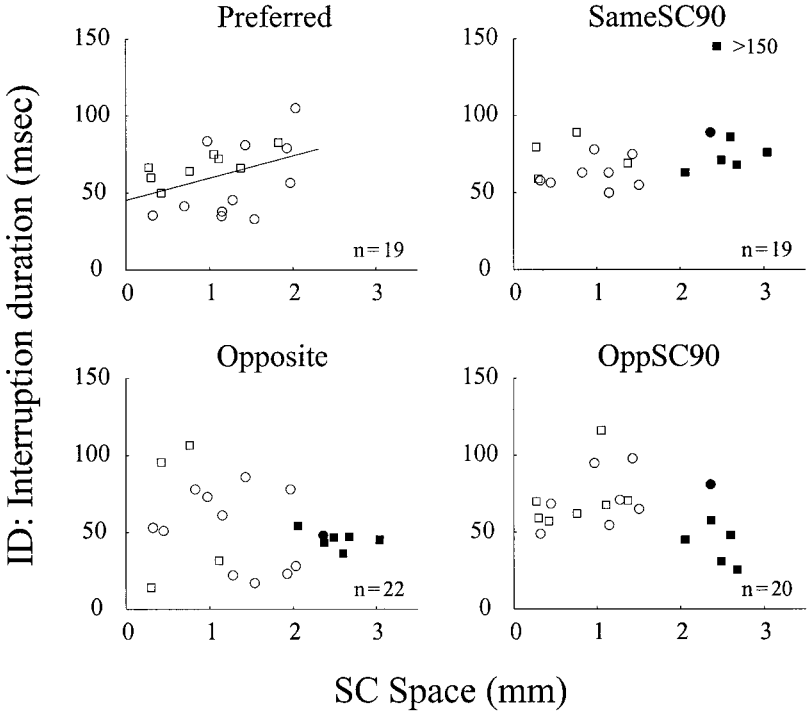

FIG. 14. Distribution of interruption duration (ID) as a function of stimulation site. Same format as Fig. 11.

TABLE 3. *Comparison of metrics produced by stimulation of the rostral pole of SC and the omnipause region*

Metric	Stimulation Site		
	Rostral SC	OPN Region	*P* Value
E1: final error, deg	1.14 ± 1.06‡	0.43 ± 1.01	0.1413
R1: normalized initial saccade amplitude, deg	0.54 ± 0.11	0.47 ± 0.11	0.2032
L1: latency of perturbation, ms	20.26 ± 4.84	16.69 ± 1.97	0.0400*
DD: direction deviation, deg	2.71 ± 3.16†	−0.48 ± 3.01	0.0391*
ID: interruption duration, ms	52.68 ± 8.61	30.92 ± 7.90	<0.0001*

Values are means ± SD averaged over all sites within rostral SC stimulation and omnipause neuron (OPN) region. A two-tailed *t*-test was performed to determine whether the two distributions had significantly different means. n = 8 and 13 sites for rostral SC and OPN region, respectively. * The means of both distributions are significantly different from each other ($P < 0.05$; 2-tailed *t*-test). † The mean is significantly greater than zero ($P < 0.05$; 1-tailed *t*-test). ‡ The mean is significantly different from zero ($P < 0.05$; 2-tailed *t*-test).

value yielded for the OPN region stimulation ($P = 0.2032$; 2-tailed *t*-test). On the other hand, the ID was significantly longer for SC stimulation compared with OPN region stimulation ($P < 0.0001$; 1-tailed *t*-test). Similarly, the latency of perturbation (L1) for fixation zone stimulation trials was consistently longer by ~3 ms relative to OPN stimulation induced interrupted saccades ($P = 0.0400$; 2-tailed *t*-test).

For the eight fixation zone stimulation sites, the latency of perturbation values, determined using the 2 SE and the peak velocity methods, were 20.26 ± 4.84 ms and 19.08 ± 2.39 ms, respectively, and these means were not significantly different ($P = 0.5481$, 2-tailed *t*-test). For the 13 OPN stimulation tracks, the L1 measures were 16.69 ± 1.97 ms and 16.46 ± 2.21 ms for the SE and peak velocity approaches, respectively, and these means were also not significantly different ($P = 0.8038$, 2-tailed *t*-test). Thus for saccades perturbed by stimulation of the rostral pole of SC and the OPN region, these two methods to determine the latency of perturbation, when the stimulation is triggered on saccade onset, produced equivalent results.

For all stimulation data, the direction deviation (DD) was determined as the difference between the direction just before resumed saccade onset and the direction of the average control saccade to the same target location. For the rostral pole stimulation condition *only*, this measure was made positive if the deflection occurred toward the FVS direction and negative otherwise. The mean DD averaged over all rostral SC sites was significantly greater than zero ($P = 0.0318$; 1-tailed *t*-test). For OPN stimulation condition, the mean DD was not significantly different from zero ($P = 0.5754$; 2-tailed *t*-test). Furthermore the mean DD produced by rostral SC stimulation was significantly different from mean DD computed for OPN region stimulation ($P = 0.0391$; 2-tailed *t*-test; Table 3).

Because the DD parameters for rostral SC and OPN region stimulation were not computed in the same way, the statistical comparison documented in Table 3 may be inappropriate. Therefore the DD metric for the OPN stimulation condition, as computed in the preceding text, was modified further as done for the SC stimulation analyses. We arbitrarily selected a reference direction and the magnitude of the difference between the direction just prior to resumed saccade onset and the direction of average control saccade was made positive (or negative) when the spatial redirection was toward (or away) from the reference direction. With this implementation, the mean ± SD for OPN stimulation condition was −0.51 ± 2.99°, which was not significantly different from zero ($P = 0.5532$, 2-tailed *t*-test). However, the mean DD produced by rostral SC stimulation was still significantly different from the mean DD computed for OPN region stimulation ($P = 0.0371$; 2-tailed *t*-test).

Note, however, that saccades interrupted by stimulation of the OPN region also were redirected, as indicated by a SD of ~3° (Table 3). This value is comparable with the variability observed for saccades perturbed by stimulation of the rostral pole of SC. The similarity might provide insights into the intrinsic variability present in the saccadic system. Nevertheless it is important to reemphasize that the mean direction deviation induced by stimulation of the rostral SC and the OPN region was significantly different.

Effects of stimulation parameters

The crucial factors determining the metrics and type of saccadic perturbation were the site of stimulation and the direction of the initial saccade relative to the direction of the FVS. A minor, secondary effect was produced by the choice of stimulation parameters. To minimize damage produced by repeated stimulation, we did not systematically vary the stimulation parameters to study their effects on saccadic trajectories. However, various stimulation current (10–30 μA) and duration (10–50 ms) parameters (frequency was kept constant at 400 pps) typically were used for most SC sites, allowing a qualitative treatment.

For stimulation of SC sites within the rostral 2 mm during saccades in all directions, an increase in the stimulation parameters increased the interruption duration. Further increase in stimulation parameters, typically outside the range used in our experiments, raised the proportion of truncated saccades. For sites caudal to the 2-mm region, stimulation at onset of large saccades in the preferred direction did not stop or alter the ongoing saccade. Instead, a minor increase in peak velocity was observed. Stimulation of such caudal sites often increased the peak velocity of the ongoing saccade, but this measure was only weakly related to the stimulation parameters (see Munoz et al. 1991; Stanford et al. 1996). Unlike for saccades in the preferred direction, saccades in the nonpreferred directions did not show an increase in the peak velocity. For lower stimulation parameters, the saccades usually paused in midflight and slightly altered their spatial trajectories. An increase in the stimulation parameters emphasized these effects.

DISCUSSION

The experiments and analyses reported in this manuscript quantified the perturbations produced in ongoing saccades by electrical stimulation in the SC. Our approach was to stimulate sites along the rostralcaudal axis of the SC at onset of large saccades in several directions and to measure changes in the metrics of the saccadic perturbations as a function of stimulation site. The metrics computed from stimulation of the posited fixation zone formed a continuum with the trend observed for stimulation of more caudal sites (Table 2). For comparison, saccades also were interrupted by stimulation of the OPN

region, and most of their metrics were found to differ significantly from the measurements of saccades perturbed by stimulation of the fixation zone (Table 3).

Rostral SC function: fixation, saccade generation, or both?

Munoz and Wurtz (1993a,b) hypothesized that fixation neurons in the rostral pole of the SC function to prevent saccade generation by exciting the OPNs. They stimulated the region of fixation neurons during saccades and interpreted the perturbations to occur via the same mechanisms that interrupt saccades on stimulation of the OPNs. This claim was based on temporal domain (radial amplitude and velocity as a function of time) analyses of rightward and leftward saccades. In our study, we reanalyzed saccades perturbed by stimulation of the fixation zone by examining their spatial trajectories (Figs. 6–8 and 13). Our results indicate that these perturbations more closely resembled redirected saccades, particularly when the target-directed saccades were orthogonal to the FVS, and that their mean direction deviation was significantly different from the average redirection observed for saccades interrupted by stimulation of the OPN region. Thus our results provide evidence contrary to the fixation zone hypothesis; however, they do not unequivocally refute it.

Munoz and Wurtz (1993a) reported finding visuomotor burst neurons just dorsal to the fixation neurons they recorded in the rostral pole of the SC. As these cells exhibit a movement field (i.e., they discharge a burst during small saccades), it is possible that the current from stimulation of the more ventral intermediate layers of SC had spread to this dorsal region and/or the saccade zone, both in our study and in the experiments of Munoz and Wurtz (1993b). In other words, activation of neurons that discharge a burst during small eye movements could have produced the redirected saccades. If so, fixation neurons are equally likely candidates to contribute to redirecting the spatial trajectories because most of these cells also discharge a burst for small contraversive saccades (Fig. 10 and 11 of Munoz and Wurtz 1993a; Fig. 1 of Krauzlis et al. 1997; Fig. 3 of Anderson et al. 1998). How is it possible, then, that fixation neurons are "critical for maintaining active visual fixation and suppressing the generation of saccades" (Munoz and Wurtz 1993a, p. 567) when "for most contraversive saccades, most [fixation] cells showed an increase in discharge" (Munoz and Wurtz 1993a, p. 565)? The fixation zone hypothesis and the saccade-related discharge characteristics of fixation neurons clearly suggest that these cells have at least two seemingly contradictory functions—saccade generation and saccade prevention. Although Munoz and Wurtz (1993a,b) never explicitly stated that fixation neurons are not involved in the generation of small saccades, they offered no explanation to resolve the paradox.

Further studies are required to investigate how the saccadic system parses the two opposing signals from the same neuron, and we contribute to this research effort by suggesting a conceptual model. A simple scheme that would preserve saccade initiation and termination is mutual inhibition between the OPNs and the excitatory burst neurons (EBNs) in the paramedian pontine reticular formation (PPRF). Well before saccade onset, the ensemble SC response is a low-frequency discharge from the fixation and buildup neurons that are concentrated within the rostral SC (see population response figures in Anderson et al. 1998; Munoz and Wurtz 1995b). The activation of OPNs prevails because the net excitation of the EBNs is below threshold. Closer to saccade onset, intracollicular and/or extracollicular processing causes a subset of SC neurons to discharge a high-frequency burst, and this excitatory input surpasses the threshold of EBNs causing them to burst rigorously and inhibit the OPNs (indirectly) (see Moschovakis and Highstein 1994).

For large saccades, the locus of the high-frequency burst in SC occurs in a caudal region of the contralateral SC. Inhibitory interactions within distant regions of the same SC (Meredith and Ramoa 1998; Munoz and Istvan 1998) reduce activity in rostral SC neurons, which suppress the facilitatory input to the OPNs and thus aid in shifting the balance of activity from the OPNs to EBNs (see Gandhi and Keller 1997). For small contraversive saccades, however, the rostral SC neurons do not exhibit a pause but, instead, many discharge a high-frequency burst, suggesting that they project to both the OPNs and EBNs (see Scudder et al. 1996). Again, the small eye movement is triggered when the net excitation of EBNs reaches threshold, but the total excitatory input required to overcome the increased excitatory input to the OPNs may also be greater. A superposition of the population buildup neuron response for 2.5 and 25° saccades (Fig. 15 of Anderson et al. 1998) qualitatively supports this hypothesis.

To place validity on the fixation zone theory, as defined by Munoz and colleagues, the functional importance of rostral SC projections to the OPNs must be demonstrated, at least for large saccades during which the SC neurons exhibit a pause in activity. In particular, the fixation neurons are expected to modulate the discharge properties of OPNs. However, a quantitative analysis, based on extracellular recordings, has revealed that OPN activity does not consistently follow the temporal evolution of fixation neuron discharge (Everling et al. 1998b). Also for large saccades perturbed by stimulation of the rostral pole of SC, the resumption of OPN activity does not occur at monosynaptic latency but, furthermore, is *delayed* even more than during control trials (Gandhi and Keller 1999). These studies suggest that collicular projections to the OPNs provide at most a minor functional contribution to fixation (also see Kaneko 1996).

Therefore the *primary* function of SC neurons, including the so-called fixation neurons located deeper within the intermediate layers in the rostral pole of the SC, may conform to the hypothesis of a saccade zone across the motor map even though the distribution of connections to OPNs and EBNs may vary systematically across the map from caudal to rostral SC. Then how does this theory explain the evidence used to support the fixation zone theory? In the text that follows, we reinterpret the data originally used to support the fixation zone hypothesis (Munoz and Wurtz 1993a,b) in terms of the saccade zone hypothesis.

NEURAL ACTIVITY. As argued in the preceding text, neurons in the deeper intermediate layers of the rostral SC discharge a burst of action potentials for most contraversive saccades. Although Munoz and Wurtz (1993a) emphasized the tonic prelude response and linked it to fixation, the lack of pause during these saccades make them equally qualified to contribute to saccade generation.

Even the tonic activity, which can be sustained during the

blink paradigm (Munoz and Wurtz 1993a), can be interpreted as a prelude signal preparing, but not necessarily executing, small eye movements, including miniature saccades. These latter eye movements tend to be several minutes of arc and are produced when a subject tries to maintain fixation (Steinman et al. 1973). The 0.1° resolution of the magnetic search coil technique (Fuchs and Robinson 1966; Munoz and Wurtz 1993a) may not have detected the miniature saccades corresponding to the elevated response during the blink period. It is worth emphasizing that both miniature saccades and fixation neurons serve to hold fixation but the neural mechanisms used to maintain it are completely different. In the former case, miniature eye movements small enough to maintain target representation on the fovea are generated, whereas in the latter scheme, fixation neurons increase the excitation to the OPNs to prevent any saccade generation.

A similar reasoning also can explain the observation that rostral pole neurons display greater activity during fixation before antisaccades than prosaccades (Everling et al. 1998a). The antisaccade task may require extra effort to suppress the natural tendency to look at the presented target and may accomplish it by making more miniature saccades, corresponding to a higher prelude response.

Alternatively, the tonic response observed in rostral pole neurons may not be linked exclusively to the saccadic system, but also may code information about vergence eye movements (cf. Chaturvedi and Van Gisbergen 1999b). Indeed, neural activity selective for disparity and disconjugate eye movements has been recorded in neurons rostral to the SC (Mays et al. 1986) as well as in the rostral pole of the SC (Dias et al. 1991; Jiang et al. 1996).

REVERSIBLE CHEMICAL INJECTIONS. Munoz and Wurtz (1993b) showed that inactivation (activation) of the rostral SC by small injections of muscimol (bicuculline) reduced (increased) the latency of large saccades. This observation was used to support the idea of a fixation zone because a decrease (increase) in the fixation function expedited (delayed) the motor preparation and initiation of saccades. In other words, the weights of a mutually inhibitory circuit between the rostral SC (which is active because a fixation target is present before saccade onset) and the caudal SC (which is active because a saccade target is presented in the periphery) were altered by the injections. Inactivating (activating) the rostral SC, for example, decreases (increases) the processing time required to produce a high-frequency burst in the caudal SC.

However, inhibitory collicular interactions are not limited between rostral and caudal ends of the SC–medial and lateral regions within a colliculus also mutually inhibit each other (Munoz and Istvan 1998). That the observed changes in latency after a reversible lesion of the rostral SC (Munoz and Wurtz 1993b) is a property of inhibitory collicular circuitry, not of the fixation zone, may be demonstrated by a saccade paradigm in which the rostral SC neurons discharge minimally or sporadically (such as during spontaneous saccades) (Munoz and Wurtz 1993a) and two different populations of neurons caudal within the same SC burst maximally [for example, by flashing 2 targets at equal eccentricities but 45° apart in direction (e.g., Edelman and Keller 1998)]. Consider the following experiment: train the animal to make saccades to a specific color target (red, for example). After training, locate a SC site encoding large saccades with a significant vertical component (for instance, 20@315°). Microinject small volumes of muscimol at this SC site. Allow the animal to make spontaneous saccades in the dark. After the end of certain spontaneous saccades, flash two different color targets (red and green, for example), one at 20@315° and the other at 20@45°, and require the animal to make the eye movement to the red target. Assuming the two targets activate distant ensemble of neurons, the mutual inhibition model would predict that the latency of saccades to the top (bottom) target would decrease (increase) compared with a preinjection distribution of reaction time. This prediction is similar to the observation produced by inactivation of the rostral SC, but in this case, the lesion does not compromise the hypothesized fixation zone. Note that it may be essential to inject very small volumes because the fixation zone lesion results were not replicated with larger doses (Aizawa and Wurtz 1998).

STIMULATION OF THE ROSTRAL SC. The rostral SC has been stimulated during fixation, just before saccade onset, and during large, ongoing eye movements (Munoz and Wurtz 1993b; present study), and all the results can be interpreted in terms of the uniform saccade zone hypothesis. The data from stimulation *during saccades* already have been discussed in terms of redirection of the spatial trajectories.

The *inset* in Fig. 8 shows that stimulation of the rostral pole *during fixation* can produce a FVS $<2°$ in amplitude. Because both visuomotor neurons and fixation neurons burst for contraversive saccades, the FVS is most likely due to activation of both cell types and not as a consequence of current spread to neurons caudal to the fixation zone (Munoz and Wurtz 1993b).

Low-frequency and long-duration stimulation of the fixation zone *before onset of contraversive saccades* reduces their gain and increases their latency (Fig. 4, B and C, of Munoz and Wurtz 1993b). The hypometria can be a weighted average of the saccades coded by the stimulation-induced and target-activated population of SC neurons. The increase in latency may reflect intracollicular inhibition increasing the processing time necessary to produce the high-frequency discharge in SC burst neurons and hence the EBNs in the PPRF. Note that the change in latency cannot strictly be a consequence of an increased excitability of OPNs because the contraversive saccades typically were triggered before the offset of stimulation. Furthermore the latency shift may decrease to zero as the stimulation site is moved caudal (Munoz and Wurtz 1993b; for a related psychophysical result, see Walker et al. 1997) perhaps because the efficacy of projections from SC neurons within the stimulation-induced population to the EBNs increases (Moschovakis et al. 1998).

Low-frequency, long-duration stimulation of the fixation zone *before onset of ipsiversive saccades* delays movement onset until stimulation offset without compromising the amplitude (Fig. 4, A and D, of Munoz and Wurtz 1993b). The SC projections from the stimulation-induced and target-activated sites, because they are in different colliculi, may excite EBNs (Chimoto et al. 1996; Moschovakis et al. 1998; Raybourn and Keller 1977) on both sides of the midline. We speculate that mutual inhibition between right and left reticular brainstem regions and intercollicular inhibition prevents neurons on either side from reaching threshold, thereby increasing the latency. The end of stimulation nulls the stimulation-induced

activity and removes the excitatory input to the corresponding (contralateral) EBNs. Consequently, an orthometric saccade coded by the target-activated ensemble of neurons is executed.

Mechanisms of saccadic perturbations

In our experiments, we observed that whenever the target-directed saccade and stimulation-evoked saccade were separated by ≥90°, the ongoing saccade was noticeably redirected from its spatial trajectory and then stopped in midflight. Frequently a resumed saccade was generated to bring the eyes near the (flashed) target location. If the directions of the initial large saccade (to a target at 30° eccentricity) and FVS were roughly aligned, the initial and resumed saccade combination was observed when the stimulation site was within the rostral ~2-mm region. Stimulation of more caudal sites appears to accelerate the initial saccade, which ends when the desired goal is reached.

We hypothesize that stimulation of any SC site during large saccades activates a population of neurons which interacts through local circuit connections with the ensemble of SC cells, which are already active and are coding the ongoing movement. Thus when the stimulation-induced and target-activated populations of neurons overlap or are near neighbors, they excite each other and the ongoing saccade does not stop. If the two populations are more distant, they have inhibitory influences on each other such that the initial saccade is stopped well short of the desired goal. This hypothesis suggests that the influence of a neuron on its neighbors follows a Mexican hat function: excitation of proximal cells and inhibition of distant neurons, including those in the opposite colliculus.

These hypothesized interactions between local excitation and distant inhibition also may partly explain the trend observed for the latency of perturbation metric (L1; Fig. 12). When the stimulation-induced and target-activated mounds of activity are as far away as possible (in our experiments, the rostral pole and the 30° site, respectively), they have inhibitory influences on each other and the initial saccade stops with a specific L1. As the stimulation electrode is placed more caudally, the two ensembles of locally excited neurons begin to overlap, which, we speculate, increases the time required for the inhibitory network to overcome the excitatory one. Consequently, the value of L1 increases as a function of the caudal distance of the stimulation site. When the locally excited populations of neurons overlap substantially, the intracollicular inhibition is ineffective, and only a single saccade is generated to reach near the target location.

The range of stimulation sites sampled in our study allows us to approximate the extent of the excitatory zone. Because all sites rostral to approximately the 2-mm site (<10° amplitude meridian) stopped all 30° saccades, the distance in SC coordinates between the most caudal open symbol in Fig. 5 and the site encoding the control saccade was considered a conservative estimate of the minimal distance necessary to observe intracollicular inhibition. Using the formulae to transform visual space into SC coordinates (Optican 1995; Ottes et al. 1986), the extent of local excitation is ~1.3 mm, a value smaller than the 1.5 mm reported by McIlwain (1982) in the cat. Our smaller estimate, however, may be due to subthreshold stimulation parameters (for a review on stimulation induced current spread, see Tehovnik (1996). In addition, the dendritic and axonal arborizations of SC neurons, which typically extend ≤2 mm (Behan and Kime 1996; Ma et al. 1990; Moschovakis et al. 1988), suggest a large excitatory span for these neurons. The anatomic organization of SC neurons thus constrains the region of SC capable of stopping ongoing saccades in the preferred direction to ~2 mm in the head-fixed preparation. Perhaps a similar effect can be produced from a broader region for larger saccades or head-unrestrained gaze shifts.

The local excitation and distant inhibition weighting of SC neurons also have been suggested by neural network models (Arai et al. 1994; van Opstal and van Gisbergen 1989) and electrophysiological experiments (Lee et al. 1997; Meredith and Ramoa 1998; Munoz and Istvan 1998; Pettit et al. 1999). Note that the distant inhibition is not exclusively between the rostral pole and the caudal region. In fact, stimulation of sites within the caudal SC also inhibits activity at sites within other, distant caudal regions of the same and opposite SC (Munoz and Istvan 1998). Our finding that stimulation of the caudal SC during large saccades in an orthogonal direction (sameSC90) stops the saccade in midflight is in accordance with suppression of the target-activated discharge.

Assessment of the metrics

The perturbations induced by stimulation of either the entire SC or the OPN region typically were followed by a resumed saccade that brought the eyes near the location of the flashed target. The resumed movements tended to slightly overshoot the control behavior independent of stimulation site, but the hypermetria compared with control (unstimulated saccades) was statistically significant only for the rostral SC (Table 3) and the orthogonal directions across the entire SC (Table 1). Nevertheless the magnitude of the mean final error was <2° even for these sites and directions, suggesting that the local feedback system for the saccadic system can compensate effectively for these extreme spatiotemporal perturbations in saccade trajectory.

The initial amplitude increased as a function of stimulation site for nearly all direction conditions (Table 2). This trend is expected if the stimulation momentarily replaces the desired goal by the FVS or by a weighted average of the saccade vectors coded by the stimulation-induced and the target-activated regions, as discussed in the previous section. Vector averaging also has been reported by psychophysical studies that varied the placement of distractors to perturb the saccades (cf., Walker et al. 1997).

The latency of perturbation values measured in our study are significantly greater than those documented in previous reports (<10 ms, Miyashita and Hikosaka 1996; ~12 ms, Munoz and Wurtz 1993b). One possible cause for the discrepancy is the measurement methods (see RESULTS). Yet another, and we believe, more likely explanation is the timing of the microstimulation. As both collicular and reticular burst neurons discharge more vigorously near saccade onset than around saccade end, the effects of stimulation may be observed with a longer latency in the former case.

The mean latency of perturbation was also greater by ~3 ms for saccades perturbed from the rostral pole of the SC than from the OPN region. This value suggests that, relative to stimulus-induced activation applied directly to the OPNs, the stimulation train delivered to the SC needs to travel across one

or more synapses to inhibit activity in the MBLNS, and one obvious candidate would be the projection from fixation neurons to the OPNs. However, if the mechanisms of perturbation are different, a 3-ms difference does not necessarily imply extra synapses for the signal to cross. The latency of perturbation is on the order of 20 ms, which also could reflect processing at a network level, leading to inhibition of the saccadic burst generator. That the mean interruption duration is significantly different for stimulation of the rostral pole and the OPN region (Table 3) also supports the notion that the perturbations may manifest via partially nonoverlapping mechanisms. In particular, the inhibition appears more potent when the stimulation is applied to the SC.

We thank Drs. L. M. Optican and L. Goffart for commenting on an earlier version of this manuscript.

This work was funded by National Institutes of Health Grants 5 T32 GM-08155 (University of California, San Francisco and Berkley, Graduate Groups in Bioengineering) and R01 EY-06860 (E. L. Keller) and a UCSF Regents Fellowship (N. J. Gandhi).

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Received 24 May 1999; accepted in final form 17 August 1999.

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