UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Neurobiology of Choice: Responsibility of the Superior Colliculus for Making Pursuit and Saccade Target Selections

A dissertation submitted in partial satisfaction of the requirements

for the degree Doctor of Philosophy

in

Neurosciences

by

Christopher D. Carello

Committee in charge:

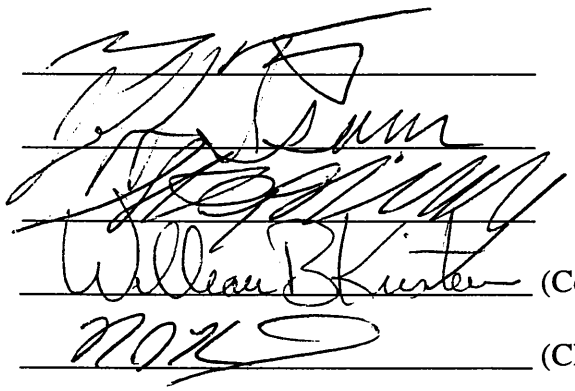
Professor Richard Krauzlis, Chair
Professor William Kristan, Co-chair
Professor Geoff Boynton
Professor Jeff Isaacson
Professor Steve Hillyard

2005

The dissertation of Christopher D. Carello

is approved, and it is acceptable in quality

and form for publication on microfilm:



(Co-chair)

(Chair)

University of California, San Diego

2005

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS AND DEDICATION

This work is dedicated to those who have traveled far away to fight a curious war in these uncertain times, including my brother Specialist Matthew R. Carello (WIA, Purple Heart), and to those who will soon continue to do so, including my father Sergeant David J. Carello. It saddens me that I was not, nor will not, be there to watch your backs; let my manuscript stand in my place and serve as the compass that leads you home.

I would also like to acknowledge my mother, Debra Carello, who raised us right and made me who I am; Old Gramma, Fontana Malena, who always watched over us and fed us as if we were starving; Gramma the Great, Dorothy Heath, who was always a pleasure to visit; Mary Alice Leclaire, my grandmother, to whom the last marshmallow will always belong; Mary Carello, my grandmother, whose love is an infinitely deep well; my grandfather Joe Carello who read to us the most intriguing stories, all from his imagination; grandfather Leclaire who took me on the best fishing trip of my life; Joanne, who makes my father very happy; my aunts and uncles, Betsy, George, Marc, Andy, Rick, Mike and Diane (who eventually became my surrogate godmother); my advisor, Rich Krauzlis and lab-mates, Dorion Liston, Laurent Madelaine, Nat Dill, Krista Kornylo, Leanne Chukoskie, Ziad Hafed, Garth Fowler, Lee Lovejoy and Sam Nummela, who collectively showed me how to do just about everything, over and over again; John Hildebrand, a true inspiration; Darien Hall, who's light I can no longer see; Mark

Meister, Rich Meister, Jeff Robinson, Jake Amberger, Marc McSavage, Brad Smith, Sam Fisher, Kelly Mattox, Andy McDonald, Eric Mullner, the SoCal Ghosts and others like them too numerous to list, all of whom made my life seem less like neuroscience (that's a good thing); Kevin and Vanessa Bender who trusted and honored me with the responsibility of performing their marriage ceremony; and Adams and Washington who both chose wisely, fifty-three thousand times. To those whose names remain conspicuously absent, may you continue to live in interesting times.

The material of Chapter One is based in part on, and contains material reprinted from, a publication of those results in the journal Neuron (Carello & Krauzlis, 2004) with permission from the copyright owner Elsevier. The dissertation author was the primary researcher and the co-author listed in this publication directed and supervised the research which forms the basis for this chapter.

VITA

2000	B.S., Biology & Psychology, University of Arizona
2003	M.S., Neurosciences, University of California, San Diego
2005	Ph.D., Neurosciences, University of California, San Diego

Publications

Carello, C.D. & Krauzlis, R.J. (2004). Manipulating Intent: Evidence for a Causal Role of the Superior Colliculus in Target Selection. Neuron 43 (4), 575-583.

Krauzlis, R.J. & Carello, C.D. (2003). Going for the Goal. Nature Neuroscience 6 (4), 332-333.

Krauzlis, R.J., Liston, D. & Carello, C.D. (2004). Target Selection and the Superior Colliculus: Goals, Choices and Hypotheses. Vision Research 44, 1445-1451.

ABSTRACT OF THE DISSERTATION

The Neurobiology of Choice: Responsibility of the Superior Colliculus for Making Pursuit and Saccade Target Selections

by

Christopher D. Carello

Doctor of Philosophy in Neurosciences

University of California, San Diego, 2005

Professor Richard Krauzlis, Chair

This dissertation is organized into a single chapter describing work that has contributed to our understanding of the role of the Superior Colliculus (SC) in the selection of visual stimuli as object-based goals for pursuit and saccade gaze orientations. The chapter is organized as a complete research report with its own abstract, introduction, results and discussion sections. In addition, the chapter is flanked by the general dissertation introduction and conclusion sections, which place the work into a more global perspective.

By applying microstimulation that was below the threshold for evoking a saccade to the intermediate layers of the SC while monkeys performed a visual discrimination and 2-alternative forced choice task, we were able to bias the monkeys' selection of targets in favor of those stimuli that appeared on contralateral side of the screen. Specifically, selection was biased toward targets that appeared within a location of the screen represented by the population of the SC in the vicinity of our stimulating electrode. Of

greatest significance was the fact that microstimulation biased target selection even when the resulting eye movement did not go toward the stimulated zone but instead traveled ipsiversive to the site of the electrode (as was the case during smooth pursuit trials). This finding suggests that the SC is responsible for selecting visual stimuli as targets for gaze orientation, regardless of the exact trajectory required to foveate a target. This replaces the long-held notion of the Superior Colliculus as a saccade machine with a more modern view of this brainstem structure as having a key role in the visuomotor decision network.

Introduction

In describing his own self-entanglement between two equal alternatives set before him during his ascent through paradise, Dante Alighieri remarked:

> *"Before a man bit into one of two*
> *foods equally removed and tempting, he*
> *would die of hunger if his choice were free;*
> *so would a lamb stand motionless between*
> *the cravings of two savage wolves, in fear*
> *of both; so would a dog between two deer;"*

His observation speaks of the seeming impossibility of making a choice, given two alternatives equal in every way; yet somehow, consciously or unconsciously, the balance is tipped in favor of one as we discard the alternative into the past. We are challenged, on a continual basis, with a self-perpetuating stream of decisions that lives between our senses and our actions. Each choice, and each subsequent action, calls forth a new set of sensory experiences, which in turn carry with them a new array of decisions. We navigate this meandering course deftly, scarcely aware of the currents and biases that tug from beneath the surface, or even the embankments that constrain us—our thoughts fixed steadily on the horizon. Except for those times when we introspect or find ourselves adrift, we seldom consider the hierarchy of moment-to-moment decisions that plot our course and define who we are.

Not all choices carry with them the same degree of consequence, thus every decision falls somewhere within a decision hierarchy. There are the high-level, life-defining decisions: What would I like to do when I graduate? With whom will I spend the rest of my life? Will I be a moral person? There are also mid-level decisions: Boxers

or briefs? Paper or plastic? Red wine or white? Finally, there are the decisions of the lowest order that play out the minutia of our lives: Darkness, sleep . . . lightness, awake. Blink now . . . and now . . . wait a moment . . . and, again, blink now. Look left . . . look right . . . look at the bug . . . watch it crawl. The higher-level decisions are the purview of philosophy, psychology, in some instances psychiatry, and literature. It is the domain of the quantifiable—the low level hierarchy—in which science is now capable of tuning its electrodes.

Our visual system, specifically the occulomotor division, is particularly well suited for the study of the neural basis of choice. From the primary visual area (V1) to extra-striate areas such as MT, the primate visual system and its properties are well mapped (Gattass, et al., 2005; Orban, Van Essen and Vanduffel, 2004). Additionally, unlike the complex outcomes of typical human behavior, eye movements are easily quantifiable. We scan our environment with a series of discreet ticks and jumps called saccades and, when circumstances permit, may smoothly pursue an object that moves across our visual field. As a result, the act of scanning and processing our visual environment is broken down into a sequence of decisions made at the rate of approximately three times per second.

There are a variety of factors that influence moment-to-moment gaze orientation decisions such as the salience of visual stimuli, predictions of locations of interest, inherent motor biases and sudden unexpected events. Though the choices are low-level, their outcomes may mean life or death for the organism. A creature in the woods, for instance, must scan its environment in continual search of predators and its own prey. It may have learned from past hunting success that its favorite quarry tends to hide amidst a

particular bush, therefore contributing an executive influence to search with particular fervor in those locations. However, a particular swath of color similar in pattern to its prey can override this urge, causing the hunter to look elsewhere along the forest floor. Likewise, a sudden, unexpected snap of a twig to the beast's periphery can reflexively ensnare its eyes—and full focus of attention—for fear of becoming the hunted.

Among the areas of the brain that have been implicated in the control of eye movements, the Superior Colliculus (SC) has long been regarded as a saccade machine. David Robinson was the first to rigorously and systematically chart the SC's highly ordered retinotopic map by noting the exact saccade trajectories produced during microstimulation (Robinson, 1972). Curiously, lesions of the SC produce very little saccade deficit after several weeks recovery (Schiller, Sandell and Maunsell, 1987), leaving one to wonder if the system is really critical for the production of saccades at all. A similar effect was also shown in the Frontal Eye Fields (FEF)—an area also implicated in the control of saccade and pursuit eye movements (Schiller, Sandell and Maunsell, 1987). Lesions to either area alone produced few lasting deficits, whereas lesions to both areas simultaneously resulted in a complete loss of the ability to make saccades. It is important to note that there was one substantial difference between the lesion effects of each individual area. Although able to make general saccades, SC lesion subjects lost the ability to make express saccades, which are a subset of very short latency saccades, made to a highly predictable target (such as a target that always appears in the same location) in the absence of any competing visual signals (including a fixation spot). FEF lesions, on the other hand, resulted in a deficit in subjects' ability to make anti-saccades in which the subject must suppress the reflexive saccade to a visual stimulus and instead make a

saccade to an empty region of space opposite the visual target. These differences suggest that the SC and FEF are not entirely redundant systems.

Recent work has been designed to elucidate the exact roles each area has in producing eye movements. Of particular note, activity in the SC has been shown to correspond not only to saccade movements, but to the online control of smooth pursuit as well (Krauzlis, 2003; Krauzlis et al., 1997, 2000, 2002). Furthermore, the steadily-rising so-called "buildup" or "prelude" activity that precedes the saccade-related burst of single neurons in the intermediate and deep layers of the SC has been shown to predict upcoming target choice, thus implicating the SC in the task of target selection (Krauzlis and Dill, 2002). The objective of the work contributing to this dissertation was to directly manipulate activity in the SC by introducing a low level of electrical current that is below the threshold for producing saccades while monkeys performed a visually guided, 2-Alternative Forced-Choice (2AFC) task in order to accomplish the following specific aims:

1. Establish a causal role of the SC in target selection.
2. Determine if pursuit target selection can be affected as well and, in doing so, lend further evidence to the role of the SC in pursuit control.
3. Determine if selection is based on the movement vector or if the activity related to selection can earmark a particular target as the goal of foveation, irrespective of the resultant movement vector.

Chapter 1

Manipulating Intent: Evidence for a Causal Role of the Superior Colliculus in Target Selection

Abstract

The superior colliculus (SC) is well known for its role in the motor control of saccades. Recent work has shown that it also plays a role in the selection of saccades, but a causal role in the process of target selection has not been demonstrated. We applied subthreshold microstimulation to the SC while monkeys performed a task requiring them to select a stimulus as the target for a pursuit or saccade movement. Stimulation increased the proportion of selections toward the stimulus that appeared contralateral to the site of stimulation and also decreased their latencies. For pursuit, this stimulation-induced contralateral response bias was with respect to the initial target location and not the direction of eye movement, demonstrating a causal effect on target choice distinct from any effect on motor preparation. These results show that the SC helps decide the object of the next movement, beyond its traditional responsibility of saccade production.

1.1 Introduction

The superior colliculus (SC) has long been regarded as part of the mechanism responsible for specifying the timing and endpoints of saccades. Microstimulation in the SC can evoke saccades, the amplitudes of which are largely determined by the position of

the electrode within an ordered topographical map of saccade endpoints (Robinson, 1972; Stryker and Schiller, 1975). Subthreshold stimulation can alter the trajectory of visually guided saccades due to an averaging of the visual saccade vector with the vector of the stimulated region (Glimcher and Sparks, 1993). Local inactivation of the SC can also alter the latency and the metrics of saccades (Hikosaka and Wurtz, 1985; Lee et al., 1988; Schiller et al., 1987). Single unit recording studies have documented the response fields of neurons in the SC corroborating the topographical architecture of this structure as well as its time-locked burst of activity several milliseconds prior to saccade onset (Sparks and Hartwich-Young, 1989; Wurtz and Albano, 1980).

More recent work supports the idea that the SC is involved not only in the motor production of saccades, but also in the selection of saccades. For example, several studies have shown that pre-saccadic activity in the SC, which can precede the movement by hundreds of milliseconds, is related to target selection for saccades (Basso and Wurtz, 2002; Horwitz and Newsome, 1999; Horwitz and Newsome, 2001; Krauzlis and Dill, 2002; McPeek and Keller, 2002a; McPeek and Keller, 2002b). Altering activity in the SC with microstimulation or pharmacological agents can also alter saccade trajectories and endpoints as well as the selection of saccade targets (McPeek et al., 2003; McPeek and Keller, 2004).

What remains unclear is whether the SC is causally involved in target selection itself, beyond its role in the selection and preparation of saccades. One approach to this problem is to examine the SC during smooth-pursuit eye movements. Recent studies have shown that SC activity is linked with the control of smooth-pursuit eye movements (Krauzlis, 2003; Krauzlis et al., 1997; Krauzlis et al., 2000; Krauzlis et al., 2002) and, in

particular, that premotor activity in the SC can predict target choice for pursuit as well as for saccades (Krauzlis and Dill, 2002). Unlike saccades, pursuit is primarily driven by stimulus motion rather than stimulus location, making it possible to dissociate target selection from movement preparation. For example, if a subject chooses and makes a saccade to a stationary target located to the left, target selection and the eye movement are both directed leftward. However, if that same target moves smoothly to the right, target selection remains leftward but the eye movement is now directed rightward. If the SC plays a causal role in target selection, then manipulating SC activity with weak microstimulation should increase the proportion of choices toward stimuli that appear in the hemifield contralateral to the site of stimulation, independent of the direction of eye movement required to acquire the target. We tested this hypothesis by microstimulating in the intermediate/deep layers of the SC, using currents that were subthreshold for evoking saccades, while the monkeys selected one of two stimuli as a target for pursuit or saccade eye movements in a 2-alternative-forced-choice task.

1.2 Methods

Animal preparation

We collected data from two adult rhesus monkeys (*Macaca mulatta*) that were 5 years of age and weighed 9–12 kg. All experimental protocols for the monkeys were approved by the Institutional Animal Care and Use Committee and complied with United States Public Health Service policy on the humane care and use of laboratory animals. The monkeys were prepared and studied using standard techniques for microstimulation,

single-neuron recording, and eye movement recording that have been described previously (Basso et al., 2000; Krauzlis, 2003).

Recording and stimulating procedures

Single-neuron recordings and microstimulation were performed in the intermediate and deep layers of the SC (1–3.5 mm below the surface), and electrode tracks were guided by structural MR images. For microstimulation, biphasic currents (10-30μA, 100-200Hz) were applied through tungsten microelectrodes (Frederick Haer) with impedances between 0.1 and 3.5 MΩ measured at 1 kHz, using a Grass S11 stimulator and PSIU6 isolation units (Astro-Med, Inc.). To determine the characteristic saccade vector associated with each SC site, we applied microstimulation for a duration matching that of the upcoming experiment (360 ms for Monkey A and 460 ms for Monkey W) immediately after a fixated spot stimulus was extinguished. Staircases of saccades were typically evoked with 10-15 μA applied at 200-250 Hz. Figure 1.1 shows the distribution of stimulation-evoked saccade vectors obtained from both monkeys for this study. A few sessions involved saccade amplitudes greater than 10 degrees and are therefore not visible on this plot. To determine the parameters for subthreshold microstimulation, the strength of applied current was systematically reduced (10-30μA, 91-200Hz) until we no longer evoked saccades characteristic of the site. At some sites, saccades much smaller than the characteristic saccade were observed during stimulation, but these comprised fewer than 30% of the trials (the stimulation parameters in these cases resulted in few or no saccades during the actual experimental task).

Behavioral paradigms

After the stimulation parameters for a given site were set, tests of the effects of stimulation on target selection began. At the beginning of each experimental trial, the monkey fixated a small spot stimulus (0.2^{o} diameter) that appeared at the center of the display for a randomized duration (2 – 2.5 s) (Figure 1.2). During this fixation interval, a centrally located 0.4°x0.4° square pre-cue appeared 1 – 1.5 s before the two target stimuli appeared and lasted for 600 ms; its luminance (either white or gray) indicated the identity of the upcoming target. At the end of the fixation period, two 0.2°x0.4° stimuli appeared (one white and one gray) on opposite sides of the extinguished fixation point at a fixed eccentricity (1°-15° horizontal, 0.3°-8° vertical), which varied from session to session depending on the electrode location. On half the trials the stimuli remained stationary (saccade trials) and on the other half (pursuit trials) the stimuli moved toward the midline of the screen at a fixed speed (9°/s - 46°/s, one speed per session based on the stimulus onset eccentricity for that session). The stimulus parameters for pursuit were practiced during behavioral training sessions prior to the beginning of the stimulation experiments, so that the pursuit responses during any given session were quite regular and reproducible, with minimal corrective saccades during pursuit initiation (see supplementary information). The monkey was given a small juice reward for tracking the stimulus that matched the luminance of the pre-cue. The onset locations for pursuit and saccade stimuli were adjusted so that one of the two appeared at a position in the visual field matching (or in the vicinity of) our stimulation site. Microstimulation was applied on half of the trials as described above beginning 100 ms prior to target and distractor onset and lasting 360 ms for Monkey A and 460 ms for Monkey W (durations were

adjusted based on monkeys' eye movement latencies and sensitivity to stimulation-evoked saccades). Each session consisted of approximately 1200 trials.

Data analysis

The occurrence of saccades was detected using eye velocity and acceleration criteria (Krauzlis and Miles, 1996). The onset of pursuit was estimated from traces of eye velocity on individual trials using a linear regression technique described previously (Adler et al., 2002). To confirm that this technique provided reliable estimates of pursuit onset, it was corroborated by a second test. We compared the mean velocity during pursuit onset (the first 100 ms after the estimated latency) to the mean velocity during fixation (a fixed 100-ms window starting 100 ms prior to target onset). We accepted the latency estimate only if the mean velocity during pursuit onset was significantly greater than that during fixation (t-test, $p < 0.05$).

Although stimulation-evoked saccades did occasionally occur, it is unlikely that these influenced our results. First, when present, stimulation-evoked saccades occurred on only about 10% of the trials. Second, these saccades were easily identified based on their very small amplitudes (0.5°-1°) and their short and stereotyped latencies; all such saccades were excluded from our calculations of percent correct. Third, the visual consequences of such small saccades were relatively minor. Because the saccades were very small, they brought them no more than 1° closer to either stimulus. Fourth, control experiments simulating the visual effects of such displacements showed no change in performance. In these control sessions without microstimulation (n=2), all objects on the screen were displaced by 1° on randomly selected trials at a random time within a

temporal window matching the timing of stimulation-evoked saccades. The visual displacement occurred on 25% of the trials – a frequency much higher than the actual occurrence of stimulation-evoked saccades during any experimental session. These control experiments showed no effect on the monkey's choice behavior.

To test the significance of the difference in performance on trials with and without microstimulation, we performed a one-tailed t-test using the binomial distribution to compute the standard error ($p < 0.05$).

Bias was calculated in units of d' assuming a constant criterion, based on methods from signal detection theory (Macmillan and Creelman, 1991). In brief, correct selection of a contralateral target was scored as a "Hit" and incorrect selection of a contralateral distractor was scored as a "False Alarm". Bias (c) was then defined as the sum of the z-transformed Hit rate (H) and False Alarm rate (FA) values, divided by –2:

$$c = -0.5[z(H) + z(FA)]$$

Similarly, sensitivity was measured in units of d' using the same Hit rate and False Alarm rate values. Sensitivity (d') was defined as the difference of the z-transformed Hit rate and False Alarm rate, divided by the square root of 2:

$$d' = [1/\mathrm{sqrt}(2)][z(H) - z(FA)]$$

Except where noted otherwise, all group comparisons between mean values of latency, percent correct, bias or sensitivity were tested for significance using 2-Way ANOVAs and post-hoc Tukey Tests of multiple comparisons.

1.3 Results

Behavioral paradigm and stimulation

We trained monkeys to select one of two small, gray-level bars as the target of a pursuit or saccade eye movement in a luminance discrimination task (Fig. 1.2). In a match-to-sample, 2-alternative forced choice design, a gray or white cue was presented during fixation to indicate the identity of the upcoming rewarded target. The two stimuli (one white and one gray) then appeared in opposite visual hemifields at a fixed eccentricity, which varied from session to session depending on our electrode location in the SC. The monkey was then rewarded for making a single saccade to the correct target during saccade trials or for smoothly pursuing the correct target during pursuit trials. The difference in luminance between the two gray and white stimuli was adjusted so that the monkeys were below asymptotic performance (~99% correct). During saccade trials (Fig. 1.2A), the two potential targets remained stationary after appearance throughout the duration of each trial. During pursuit trials (Fig. 1.2B), the two stimuli traveled horizontally toward the midline of the screen at a fixed velocity and then crossed into the opposing hemifields at the time of pursuit latency, giving rise to saccade-free pursuit (Rashbass, 1961). The pursuit target velocities were adjusted to the horizontal onset eccentricity for each session so that each target crossed the midline of the screen, close to the monkey's point of fixation, at approximately the latency of the monkey's reaction time for the task, thus giving rise to pursuit movements that were free of catch-up saccades. Daily pursuit target velocity settings did not scale linearly with eccentricity since monkey's reaction times were slower with more eccentric targets.

On half of the trials, we microstimulated at an intermediate or deep site in the SC with currents that were subthreshold for eliciting a saccade during free viewing. These currents were determined empirically prior to each session during a procedure designed to find the minimal stimulation parameters required to elicit a saccade during free viewing, which would be too weak to elicit saccades during the primary experimental task (see methods). A current and frequency that is just barely capable of evoking a saccade during free viewing will be largely insufficient to evoke a saccade during an active task (Burman and Bruce, 1997), as was the case in our experiment. We set the initial locations of the stimuli so that one of the two bars appeared at a position in the visual field matching that of our stimulation site in the SC. The saccade targets sometimes aligned more closely to the stimulation area than the pursuit targets due to the fact that we were limited in the extent to which we could adjust the pursuit target positions. A vertical displacement of the horizontally translating pursuit targets would have resulted in pursuit trials that were not saccade-free, as the monkeys would have been encouraged to make vertical saccades toward them. The monkeys were unable to predict the target color identities, location or required movement type as target identity (white/gray), target location (left/right), trial type (pursuit/saccade) and stimulation condition (with/without) were all randomly interleaved. Figure 1.3 provides a schematic example that shows the timing of events throughout a representative trial as well as the expected correct response as it would appear in horizontal eye position coordinates.

Raw data and percents correct

The raw data from six sample trials (3 each for both saccades and pursuit) is depicted in Figure 1.4. Upward deflections represent horizontal movement in the rightward direction and downward deflections represent horizontal movements in the leftward direction. The saccade data, plotted in degrees of horizontal displacement, illustrate an example of a rightward saccade, a leftward saccade and a double saccade in which the monkey initially selected the left target, then switched to the right (this last trial would be scored as a leftward choice). The pursuit data are plotted in velocity units of degrees per second. Because of the step-ramp design of our stimuli, moving targets that appear on one side of the screen give rise to pursuit movements in the opposite direction. Thus, the pursuit traces illustrate an example of a rightward pursuit velocity of approximately 15 degrees/sec. tracking a target that had initially appeared on the left side of the screen, and an example of leftward pursuit of a target that had initially appeared on the right side of the screen. The pursuit traces also illustrate an example of turnaround pursuit in which case the monkey began to track the rightward moving target, then made a catch-up saccade to the other target approximately 250 milliseconds later and began to pursue it in the leftward direction (this last example would be scored as rightward pursuit which indicates an initial selection of the target appearing on the left side).

The choice results from an entire representative session from the left SC can be seen in Figure 1.5. For saccade trials, we scored each selection by measuring the horizontal and vertical amplitudes of the first saccade. Each data point therefore represents the saccade endpoint and target selection of a single trial. When the saccade target appeared on the left side (i.e. ipsilateral to the site of stimulation), in the absence of

stimulation the monkey's percentage of correct leftward saccades was 93% (Fig. 1.5A, No Stimulation). The percentage dropped to 82% with stimulation (Fig. 1.5A, Stimulation). When the saccade target appeared on the right side (i.e. contralateral to the site of stimulation), in the absence of stimulation the monkey's percentage of correct rightward saccades was 82% (Fig. 1.5C, No Stimulation). The percentage rose to 99% with stimulation (Fig. 1.5C, Stimulation). In the above cases, the overall effect of stimulation trials was an increase in the number of saccades to the target on the right side of the screen (the contralateral target).

For pursuit trials, we scored the monkeys choices by measuring the eye velocity of the first 100 ms of pursuit. Each data point in this case represents the mean pursuit velocity during the 100 ms window, and therefore represents the monkey's pursuit selection during a single trial. Because the pursuit data are plotted in velocity coordinates, data points that appear on the right side of the graph represent the rightward pursuit of a target that initially appeared on the left side of the screen. The same logic applies to data points that appear on the left side of the screen. One must therefore remember that data points that appear on one side of the graph represent the selection of targets that originally appeared in the opposite hemifield. During the sample session illustrated in Figure 1.5, when a pursuit target appeared on the left side of the screen, in the absence of stimulation the monkey correctly pursued it (in the rightward direction) 90% of the time (Fig. 1.5B, No Stimulation). The percentage dropped to 65% with stimulation (Fig. 1.5B, Stimulation). When a pursuit target appeared on the right side of the screen, in the absence of stimulation the monkey correctly pursued it (in the leftward direction) 83% of the time (Fig. 1.5D, No Stimulation). The percentage rose to 91% with

stimulation (Fig. 1.5D, Stimulation). Thus, for this site, as was the case with saccades, there was an increase in percent correct during stimulation when the targets appeared contralateral to the site of stimulation and a decrease in percent correct when the targets appeared ipsilateral to the site of stimulation. Simply put, the monkey chose targets that appeared on the right side of the screen (the side contralateral to our electrode site) as objects for pursuit and saccades more often during stimulation.

We found similar effects across our sample of 35 sites (Fig. 1.6). Each data point represents the percent correct for each session, plotted separately for targets that appear contralateral to the site of stimulation and targets that appear ipsilateral to the site of stimulation, for saccades and for pursuit. In each plot, the percent-correct score for those responses in the presence of stimulation were plotted against the percent-correct score for those responses in the absence of stimulation. Points that appear above the major diagonal line represent sessions in which the percent-correct score was higher during the stimulated trials; those points below the major diagonal represent percent-correct scores that were lower during the stimulated trials. The cluster of data points that lay above the line for the two contralateral target graphs (Fig. 1.6A,B) indicates that stimulation induced an increased selection of contralateral targets for both pursuit and saccades. Likewise, the cluster of data points that lay below the line in the two ipsilateral target graphs (Fig. 1.6C,D) indicates a decreased selection of ipsilateral targets for both pursuit and saccades during stimulation. Recall that in the case of pursuit, there was a dissociation between the direction of eye movement and the initial stimulus location from which it derived, such that a contralaterally-appearing target gave rise to ipsiversive pursuit and vice-versa. Nevertheless, for both pursuit and saccades, the contralateral

increase in percent correct (and corresponding ipsilateral decrease) was with respect to target onset location, not the direction of the resulting eye movement. Specifically, stimulation resulted in a significant increase in the percentage of correct responses ($p<0.05$, assuming a binomial distribution) for contralateral targets in 26/35 sessions for saccades (filled circles, Fig. 1.6A) and 16/34 sessions for pursuit (Fig. 1.6B). Conversely, stimulation significantly decreased the percentage of correct responses for ipsilateral targets in 19 sessions for saccades (Fig. 1.6C) and 22 sessions for pursuit (Fig. 1.6D).

Saccade-free pursuit

In order for the pursuit trials to have any substantive meaning, they must be free of saccades during the initial selection period. The following results demonstrate that microstimulation did not have any appreciable effect on the corrective saccades that accompanied pursuit, or on the metrics of pursuit itself: First, by design, there were never any saccades of any size during a window surrounding pursuit onset, +/- 100ms. We chose target speeds that would minimize the occurrence of anticipatory or catch-up saccades during the onset of pursuit based on the monkeys' reaction times. Trials in which a saccade occurred during this phase were discarded from the analyses. We report a range of horizontal pursuit target step values (2°-15°) and speeds (9-46 deg./s) used in this study. The steps were tailored to match as closely as possible the site of the electrode in the SC; the speeds were adjusted to the monkeys' reaction times so that the target crossed their fovea during their response latency, giving rise to saccade-free, smooth pursuit. The target step and speed, once selected (based on prior behavioral training and

practice) , remained constant throughout the duration of a given session, giving rise to stable pursuit metrics. Figure 1.7 illustrates this point by showing the mean ipsiversive and contraversive pursuit velocity (+/- standard deviation) for two sessions by the same monkey, which differed in target step and speed. Data are aligned in these traces with respect to target onset. Mean velocity during stimulation has been superimposed onto the no-stimulation trace for each condition and indicates very little difference in pursuit metrics during stimulation other than a latency shift. Table 1.1 contains a comprehensive list of the characteristic saccade locations, target locations and speeds as well as stimulation parameters for every session.

Second, microstimulation did not change the frequency of saccades that occurred later, during the transition to steady state pursuit. Figure 1.8 documents the frequency of saccades that occurred during the half-second epoch beginning 100 ms prior to pursuit onset. Overall, there were saccades in about 1/3 of the trials; this proportion was not changed by microstimulation ($p > 0.05$ assuming a binomial distribution). In fact, microstimulation delayed saccades slightly (16 ms and 14 ms during ipsiversive and contraversive pursuit respectively, Mann-Whitney, $p > 0.05$). Importantly, the majority of these saccades occurred during sustained pursuit (at least 200 ms after pursuit onset) and could have no impact on the initial pursuit decision made 200 ms earlier. All of the corrective saccades that had accompanied pursuit occurred too late to influence the pursuit choice and were of small amplitude (figs. 1.9 and 1.10). Figure 1.7 illustrates that the metrics of pursuit during stimulation are indistinguishable from those in the absence of stimulation.

Third, microstimulation did not change the proportion of contralateral or ipsilateral saccades. Figure 1.9 shows saccade amplitude frequency histograms for ipsiversive and contraversive pursuit without stimulation (A,B) and with stimulation (C,D). Positive amplitudes represent contralateral saccades and negative amplitudes represent ipsilateral saccades. Stimulation did not result in a significant change in the frequency of either ipsilateral or contralateral saccades for either pursuit direction ($p > 0.05$ assuming binomial distribution). Though there was no change in directional saccade frequency, a Mann-Whitney test revealed a slight (0.25 deg.) increase in the median saccade amplitude of contralateral saccades during contraversive pursuit on stimulated trials (Fig. 1.9B,D "catch-up", $p<0.05$). This slight increase in median amplitude probably reflects the slight delay of catch-up saccades during sustained pursuit discussed in the previous paragraph.

It is possible that pooling data across all sessions has obscured otherwise significant saccade frequency trends within individual sessions. We therefore next analyzed the saccade frequency for each session individually. Only 5 out of 34 sessions showed a significant change in saccade frequency (3 had an increase, and 2 had a decrease in frequency). On the other hand, significant changes in pursuit choice were found for 17 sessions without changes in saccade frequency.

Further, because a different site within the SC was stimulated each session, the characteristic amplitude of the stimulation-evoked saccade differed on every session. One cannot entirely rule out the possibility that stimulation resulted in an increase in stimulation-evoked characteristic saccades by looking only at the raw amplitude frequency across many sessions representing different stimulation sites. We therefore

plotted the saccade frequency data after normalizing the saccade amplitudes to the amplitude of the characteristic saccade for their given session in Figure 1.10. Any normalized amplitude equal to 1 represents a saccade equal in direction and amplitude to the stimulation-evoked saccade for that session. Negative values represent saccades in the opposite direction (ipsilateral). The absence of a change in the frequency of saccades at or near 1 with stimulation indicates that the saccades were part of the monkeys' natural corrective behavior during sustained pursuit and were unaffected by stimulation.

Finally, since the amplitude of an stimulation-evoked saccade during an experiment could be less than the characteristic amplitude corresponding to a given site (due to subthreshold stimulation or averaging), we also compared the frequency of all normalized saccades that fell between a magnitude equal to zero and one. The frequency of these saccades was not changed by microstimulation ($p>0.05$ assuming binomial distribution).

Summary changes in percents correct

In order to see the collective ipsilateral and contralateral effect for each session, we plotted the two against each other as changes in percent correct. This has the advantage of collapsing separate ipsilateral and contralateral data into a single point for each session. As can be seen in Figure 1.11 (A,B), increases in percent correct for contralateral targets occurred concurrently with decreases in percent correct for ipsilateral targets during most sessions. Therefore the effect of microstimulation on pursuit and saccade choices was not simply a general increase or decrease in task performance, nor was it the result of having caused different types of effects at different sites. Instead, the

changes in percent correct were the result of the monkeys choosing the contralateral stimulus more often in the presence of stimulation, whether that stimulus was a target (resulting in a percent correct increase for contralateral targets) or a distractor (resulting in a percent correct decrease for ipsilateral targets).

The histograms in Figure1.11 further summarize the data by reporting the mean changes in percent correct found for contralateral and ipsilateral targets across all sessions for saccades (C) and pursuit (D). They also separate the data according to whether the target identity was white or gray. The mean data confirm that, throughout this experiment, contralateral targets experienced an increase in percent correct, whereas ipsilateral targets experienced a decrease in percent correct during stimulation. A 2-way ANOVA of the mean change in percent correct across all sessions confirms that the change in contralateral target percent correct was significantly different from the change in ipsilateral target percent correct for both saccades and pursuit (Tukey test, $p<0.001$). A closer examination reveals a difference between saccades and pursuit: the effects for contralateral targets were significantly bigger than those for ipsilateral targets for saccades (2-way ANOVA of the absolute value of the mean change in percents correct, $p=0.026$), whereas the opposite was true for pursuit ($p=0.002$). In other words, although the direction of effect is the same for both eye movement types, the region of greatest change was different: Saccades experienced a greater increase in contralateral percent correct, whereas pursuit experienced a greater decrease in ipsilateral percent correct. This difference might be due to the mismatch between stimulation site and stimulus location that emerged on pursuit trials, as the retinal position of the pursuit stimulus changed over time but the stimulation site remained fixed. This magnitude asymmetry

will be considered in much greater detail later in the discussion section. Although there was no significant difference in the effects based on target luminance for either saccades (2-way ANOVA, p=0.37) or pursuit (p=0.88), there was a trend that can be seen in the data. For both pursuit and saccades, and for both contralateral and ipsilateral target locations, the effects were always slightly larger when the target identity was gray. This is likely due to the fact that the white target was more salient than the gray and was therefore less easily overcome by our stimulation-induced bias.

Bias and sensitivity

The main point to be taken from Figure 1.11 (and this entire experiment) is that the combined contralateral and ipsilateral effects show stimulation to have increased the frequency of choices to objects that appear on the contralateral side of the screen, regardless of the target's identity. However, although it is initially intuitive and instructive to consider the effects in terms of percent correct changes in separate contralateral and ipsilateral locations, the spatial categorization can be cumbersome. Signal detection theory provides a compact way of quantifying the amount of spatial bias a monkey exhibits by comparing the proportion of hits and false alarms made to a particular location (Macmillan and Creelman, 1991). In a 2-alternative forced choice task, hits and false alarms are only scored in one of the two spatial locations (in the contralateral location, for instance). A hit is defined as any movement to the scored location when it contains the reward target. A false alarm is defined as any movement to the scored location when it contains the distractor. A bias score is related to the sum of hits and false alarms because they essentially represent how many times the monkey

selected the scored location over time, irrespective of the stimulus identity from trial to trial. It would be redundant to count the number of selections made to the opposite location (the ipsilateral location in this instance) because the number of movements made to that area (termed "misses" and "correct rejections") are inversely proportional to the number of hits and false alarms (a high rightward bias score necessarily implies a low leftward bias score). For simplicity, a single bias score is therefore calculated based on the number of hits and false alarms made with respect to a single location.

The same analysis can also be used to assess the monkeys' overall ability to discriminate the two stimuli (sensitivity, measured as d') (Macmillan and Creelman, 1991). Just like bias, sensitivity is measured using hits and false alarms from a single location. However, it is calculated based upon the difference between the number of hits and false alarms rather than their sum. The ability to discriminate well depends on the ability to acquire targets and avoid distractors, thus many hits and few false alarms results in a high sensitivity score. An abundance of both hits and false alarms, on the other hand, indicates a general proclivity to select the scored location, regardless of the stimulus identity, and thus represents a biased subject. In practical terms, bias and sensitivity measurements collapse ipsilateral and contralateral information into a single data point each, allowing one to see the overall effect for every session without having to compare data from two spatially disparate locations.

We used the constant criterion method for calculating bias (methods) and arbitrarily defined positive values as representing bias in the contralateral direction. Microstimulation resulted in an increase in bias toward the contralateral stimulus for both saccades and pursuit (Fig. 1.12A,B). Each point on those graphs represents the bias score

during stimulation for a single session plotted against the bias score without stimulation. A point that lays above the major diagonal line indicates a bias score that was higher during the stimulated condition and therefore represents an increase in bias for the contralateral stimulus. The sensitivity scores were plotted in a manner similar to bias (Fig. 1.12C,D)—each point on the graph represents the sensitivity score during stimulation vs. the sensitivity score without stimulation for a single trial. A point that lays above the major diagonal would represent a higher value of d' during stimulation, indicating a greater sensitivity for the task. The effect on sensitivity (d') differed between the two eye movement types: Saccade performance exhibited an increase in sensitivity during stimulated trials (Fig. 1.12C); pursuit tended to show a decrease in sensitivity (Fig. 1.12D). There was also an interesting indirect effect of microstimulation on the monkeys' bias. During saccade trials with no stimulation (abscissa, Fig. 1.12A), bias was negative for most sessions (28/35). Most data points are located to the left of zero and therefore favor the ipsilateral stimulus. This proportion was significantly different from that expected by chance if the monkey were unbiased ($c2$, $p = 0.023$). The monkeys did not show a consistent bias during the training sessions; this particular bias is unique in that it was a bias for the location ipsilateral to the electrode, which was placed in a different location or side of the colliculus from day to day. Though it seems counterintuitive that there should be any effect on the monkeys' choices during those trials in which stimulation was not applied, this effect might reflect a voluntary compensatory strategy. Because the monkeys were over-trained on the task, they became greatly accustomed to an equal number of leftward and rightward targets and may have responded to the increased number of stimulation-induced contralateral saccades during

an experimental session by developing a bias for ipsilateral objects or saccades during unstimulated trials. Pursuit showed a similar trend, although the proportion of sessions that showed a negative bias (20/34) was not significantly different from chance (χ^2, $p = 0.62$).

Figure 1.13 summarizes the effects of microstimulation on the average changes in bias and sensitivity across all sessions. Both pursuit and saccades showed an increase in bias for stimuli that appeared on the contralateral side during microstimulation, as indicated by the positive values for each. Although sensitivity differs in sign between pursuit and saccades, the relative magnitude of effects between them was not significantly different from each other for either bias or sensitivity measures (t-test, $p = 0.91$ for bias, $p = 0.79$ for sensitivity). In other words, the effects of microstimulation were statistically the same for pursuit and saccades. The sign difference in sensitivity can be deduced from the earlier percent correct measurements by the fact that saccades experienced a disproportionately large increase in contralateral percent correct whereas pursuit experienced an equally large decrease in ipsilateral percent correct. The spatial asymmetry in the amount of change in percents correct between the two is what gave rise to the apparent differences in sensitivity. Although the effects were the same for both pursuit and saccades (Fig. 1.13A compared to B), the increase in bias was significantly stronger than the change in sensitivity for each (2-way ANOVA, $p < 0.001$), indicating that the largest effect of microstimulation for both movement types was on bias, not sensitivity. Essentially microstimulation increased the likelihood that the monkeys would select the stimulus that appeared on the contralateral side of the screen as an object for a

saccade or pursuit, irrespective of whether that stimulus was a distractor, a target, white or gray.

By comparing the gray bars to the white bars in Figure 1.13, one can see that the changes in bias and sensitivity showed no significant differences based on the luminance of the target (2-way ANOVA, $p = 0.42$ for saccades, $p = 0.45$ for pursuit), nor were there any consistent trends based on these measurements (unlike the percent correct measurements which calculate each of the two spatial locations separately). From the perspective of bias and sensitivity, performance was equivalent for both gray and white targets, for both pursuit and saccades, with bias showing the strongest effects. Because the effects of stimulation were the same whether the target was white or gray, the results are not likely due to the introduction of a visual luminance increment (or decrement) onto the contralateral stimulus as has been seen from stimulation of cortical areas (Girvin et al., 1979). In such a case, one would expect opposite effects for the two target colors (a luminance increment would make a white target more discriminable, but a gray target less discriminable). However, to further address the possible influence of visual stimulus alterations (or phosphenes), we performed control experiments in which we stimulated in the superficial layers of the SC (which contain visual, but not movement-related, cells) during the same task. We confirmed our placement in the superficial layers by recording visual activity from single and multiple units prior to conducting these control experiments. There were no changes in percent correct, bias or sensitivity when we stimulated the superficial visual layers ($n = 4$ sessions), thus ruling out the possibility that our effects were due to visual artifacts or distractions.

In addition to the summary effects that can be seen in Figure 1.13, we chose to plot the change in sensitivity as a function of the change in bias on a session-by-session basis in order to ascertain if the two measures co-varied. It would make sense that large changes in bias would accompany large changes in sensitivity considering the fact that each is a product of hits and false alarms. There is no certainty, however, that this is the case; it is possible, for instance, that conditions which are optimal for affecting bias may differ from those that most strongly affect sensitivity. Figure 1.14 shows the changes in sensitivity plotted against the changes in bias for each session for both pursuit and saccades. Although the correlation is loose, ($r^2 = 0.32$ for saccades, $r^2 = 0.38$ for pursuit) one can see that sessions exhibiting strong effects on bias tended to also exhibit strong effects on sensitivity. This suggests that, although the sensitivity effects differed in sign between pursuit and saccades, they arose as a causal effect of stimulation (in addition to bias) as opposed to a pattternless deviation. The differences in sign therefore reflect a true difference between the monkeys' ability to discriminate saccade vs. pursuit targets in the presence of stimulation. This may be due to the effects of stimulation on latency, which may have had a particularly disrupting effect on the monkeys' ability to discriminate and select from two moving targets.

Spatial Specificity

The effect of microstimulation did show some degree of spatial specificity. Our pre-experimental, suprathreshold stimulation procedure allowed us to determine which part of the screen was represented by the area of the colliculus in which the electrode was placed. During some sessions the contralateral target was located very close to or within

this stimulated region; during other sessions the contralateral target was located further away by varying degrees. Figure 1.15 plots the proportion of sessions in which microstimulation resulted in a significant change in percent correct for both ipsilateral and contralateral targets. These sessions are grouped according to the distance between the location on the screen corresponding to our area of microstimulation and the actual placement of the contralateral stimulus. Nearly 70% of the saccade sessions resulted in a significant change in ipsilateral and contralateral percents correct when the stimulated area and the contralateral target were within one degree of each other. As the distance between the stimulated area and contralateral target increased, the percentage of sessions within each distance category exhibiting significant effects decreased. For instance, the proportion of significant sessions in which the stimulated area and contralateral target were 2-3 degrees away from each other dropped to 10%. The same pattern held true for pursuit as well. The only category for which this pattern did not hold was that in which saccade targets were greater than 3 degrees away from the stimulated area (approximately 60% of which had significant changes), and may be due to a low number of sessions that contributed to this group.

Latency

A simple explanation for our results is that microstimulation shifted SC activity toward response threshold at the stimulated location. If so, one might expect not only changes in bias or percent correct, but also changes in latency, because the shift in activity would alter the time it takes to reach threshold (Asrress and Carpenter, 2001; Carpenter, 1981; Carpenter and Williams, 1995; Hanes and Carpenter, 1999; Logan,

1994; Logan et al., 1984; McGarry et al., 2003; Osman et al., 1986). Figure 1.16A schematically illustrates the level of net activity between the left and right SC. In this example, an upward deflection represents a gradual increase in net activity for an impending contralateral response. The point at which the activity reaches that threshold determines the response latency. A downward deflection represents an impending ipsilateral response. The black line represents the net SC activity during unbiased trials in which monkey eventually selects a contralateral or ipsilateral target. The dotted drop line in this case indicates the eye movement latency (labeled "b" on the timeline). The second trace, colored gray in the schematic and labeled "with stimulation", represents net SC activity during trials in the presence of microstimulation. The effect of stimulation is to push the net SC activity closer to the contralateral response threshold, thus making a response to a contralateral target more likely. Because the biased trace begins closer to the contralateral response threshold during such trials, it should take less time for the rising signal to reach it. Therefore, contralateral responses would be expected to have shorter latencies (as indicated by the latency labeled "a" on the timeline). Conversely, for the net SC activity to ultimately reach the ipsilateral response threshold during a stimulation trial (downward deflection), the activity trace would have to travel a greater distance in order to compensate for the initial bias in activity for a contralateral response. Therefore, ipsilateral responses should have longer latencies (as indicated by the latency labeled "c" on the timeline). The primary consequences of this model are that unbiased, unstimulated trials should have similar latencies for both contralateral and ipsilateral saccades, whereas trials with stimulation should have shorter latency contralateral saccades and longer latency ipsilateral saccades. These values could be influenced by a

variety of factors including any inherent spatial bias the monkey may have, target and distractor signal strength and rate at which a signal in the SC rises toward threshold.

As predicted, the effect of stimulation on pursuit and saccade latency depended on whether the eye movement was made to a contralaterally or ipsilaterally appearing stimulus. Figure 1.16 shows the mean latency for saccades (B,D) and pursuit (C,E) for those sessions that exhibited a significant change in percent correct. The data were plotted separately for each monkey since their inherent latencies differed appreciably. The latency interaction between stimulation and the hemifield in which the selected stimulus appeared was significant for both movement types and both monkeys (2-way ANOVA, $p<0.001$). Selections made to stimuli appearing on the ipsilateral side (open circles) during stimulation having longer latencies than unstimulated trials. Conversely, selections made to stimuli that appeared on the contralateral side (filled circles) had shorter latencies during stimulation compared to unstimulated trials, except for monkey W's contralateral saccades, which had similar latencies in the presence or absence of stimulation. Even though the latency of his contralateral saccades did not decrease during stimulation, they were still considerably shorter in latency than ipsilateral saccades, which were greatly delayed. Monkey W's deviation from the model during contralateral saccades in the presence of stimulation is hard to explain, but may be due in part to an interaction between some of the other factors (mentioned earlier) that influence latency. It is also worth noting that Monkey W's latency values as a whole were noticeably longer than Monkey A, which is perhaps indicative of Monkey W's proclivity against a hasty response. However, these results show that, in general, eye movements evoked by objects at locations that matched the site of stimulation (i.e., appeared

contralateral) had shorter latencies, whereas eye movements evoked by objects at discordant locations (i.e., appeared ipsilateral) had longer latencies.

In addition to the primary effects of stimulation, there was also a saccade latency difference of the opposite sign during unstimulated saccade trials. The rise-to-threshold latency model predicts that ipsilateral and contralateral eye movements should have the same latencies during trials in which there is no stimulation (Fig. 1.16A). Notice, however, that the two are not the same during unstimulated saccade trials (Fig. 1.16B,C, no-stim). Contralateral saccades had a significantly longer latency than ipsilateral saccades for both monkeys (Fig 1.16B,D) during those trials in which we did not stimulate (independent t-test, $p<0.001$). This is most likely a consequence of the compensatory ipsilateral bias that the monkeys adopted in the absence of stimulation (mentioned earlier). An inherent bias directed in the ipsilateral direction would presumably offset the net SC closer to the ipsilateral saccade threshold early on in the trial, thus resulting in shorter latency ipsilateral saccades. Pursuit showed the opposite effect, with acquisition of ipsilateral stimuli having a significantly longer latency than contralateral stimuli during unstimulated trials for Monkey A (Fig. 1.16C, $p<0.001$) and a similar but not significant trend for Monkey W (Fig. 1.16E, $p=0.097$).

1.4 Discussion

Main effect, bias

The main point to be taken from this experiment is that subthreshold microstimulation increased the frequency of choices to objects that appear on the

contralateral side of the screen, regardless of the target's identity and regardless of the required movement type (Figs. 1.11 and 1.13). This manipulation of the monkeys' choices indicates that the SC plays a role in choosing an upcoming gaze target, in addition to its well known role in the motor preparation and execution of saccades (Sparks and Mays, 1990; Wurtz and Albano, 1980). These results build upon a body of work over the past several years that has suggested a connection between premotor activity in the SC and target choice. Increasing the probability that a saccade target would fall within a neuron's response field by decreasing the number of potential target locations has been shown to increase premotor activity in the SC (Basso and Wurtz, 1998). During that study, maximal firing rate was achieved when a single target appeared on the screen in the receptive field of the neuron. That maximal, pre-selection, firing rate was steadily decreased for each additional target (or distractor) that appeared on the screen simultaneous with the object in the cells receptive field. The addition of numerous potential targets changed the probability that the object in the receptive field would be the rewarded target of choice on any given trial, thus lowering pre-selection activity. Premotor activity has also been shown to discriminate targets from distractors (McPeek and Keller, 2002a) and to predict saccade target choice (Horwitz and Newsome, 1999; Horwitz and Newsome, 2001). For example, Horwitz and Newsome presented two identical stimuli on a screen, one of which fell within a cells receptive field. A patch of partially coherent motion, located at the central fixation area and thus outside of the cells receptive field, provided the only indication of which stimulus was the rewarded target (based on the direction of motion). Nevertheless, the activity of individual cells was sufficient to predict which stimulus would become the target of an upcoming saccade.

The level of predictive activity was even modulated in accordance with changes in the percentage of coherence in the coherent motion display (and thus reflected information on target probability). It has also recently been demonstrated that inactivation of the SC produces striking deficits in saccade target selection (McPeek and Keller, 2004). However, the saccade results alone, in the present study and others, cannot eliminate the possibility that premotor activity in the SC is related to motor preparation, rather than target selection. During traditional saccade tasks, the target location and saccade endpoint completely overlap, so it is impossible to tell if pre-saccade activity is related to a selection of a target or the subsequent motor plan. Because target location largely determines the saccade endpoint, premotor activity in the SC might represent a partially formed plan for a saccade, rather than an evolving decision about the target. Only if the region of target selection is dissociated from the direction of movement can we rule out one mechanism in favor of the other.

Effects on target choice, not motor trajectory

The effects of stimulation on pursuit target choice are particularly important for concluding that the SC has a role in target selection *per se*, because they provide a clear dissociation between the location of the stimulus and the metrics of the eye movement. These results complement our previous findings that the selection of targets for pursuit is associated with changes in the activity of SC neurons (Krauzlis and Dill, 2002; Krauzlis, 2003). As in the current results, those earlier experiments employed a step-ramp paradigm (Rashbass, 1961) in which the target appeared in one visual hemifield before moving smoothly toward and into the opposite hemifield. Neurons in the SC increase

their activity when the initial step is into their response field (i.e., contralateral) even when the subsequent pursuit moves the eyes in the opposite direction. Similarly, we found that microstimulation introduced a response bias for the stimulus contralateral to the SC site, even though this choice for pursuit resulted in an eye movement directed away from the initial target location. Thus, microstimulation of the SC manipulated the monkeys' choices based on the location of the target, not the direction of the pursuit eye movement used to acquire the target. This allows us to reject the notion that stimulation merely accelerated motor preparation for a particular eye movement vector, in favor of the idea that it instead marked a particular (contralateral) object for an upcoming movement.

Saccade-free pursuit

In order for the pursuit trials to have any substantive meaning, they must be free of saccades during the initial selection period. Taken together, our analyses indicate that stimulation had very little effect on saccades during pursuit (Figs. 1.7-1.10). There was no increase in contralateral saccades as one might expect if stimulation had facilitated saccade production. The saccades that did occur were too late to have any influence on pursuit choice. Changes in pursuit target choice were therefore not artifacts of saccade selection, but were instead directly due to the influence of microstimulation on target selection.

Latency effects

In addition to biasing the monkeys' choices, microstimulation also changed the latencies of pursuit and saccades, providing additional evidence that the SC plays a causal role in target selection. The mechanism of selection is not yet fully understood, but models of reaction time generally assume that some internal signal varies over time and that the movement is triggered when this signal reaches a threshold value (Carpenter and Williams, 1995; Link and Heath, 1975; Ratcliff et al., 1999; Reddi and Carpenter, 2000; Schwarz, 1993). If microstimulation biased this internal signal toward the contralateral stimulus, then the latencies for contralateral stimuli should be decreased and the latencies for ipsilateral stimuli should be increased (Fig. 1.16A). Overall, that is exactly what we observed, with the exception of one monkey's contralateral saccades (Fig. 1.16D, filled circles); this exception may reflect the fact that microstimulation is a coarse technique that disrupts, as well as displaces, the normal pattern of neuronal activity.

Another likely explanation for the difference in contralateral saccade latencies may be due to a difference in target alignment for the two monkeys. As was noted previously, the effects of stimulation were greatest when contralateral stimulus onset location overlapped closely with our zone of stimulation (Fig. 1.15). Many of the instances of close correspondence between the two occurred with Monkey A, resulting in the predicted decrease in contralateral saccade latency. Monkey W, on the other hand, experienced a larger proportion of sessions in which the contralateral stimulus did not overlap with the microstimulated area quite as closely. As a result, the neural population representing a contralateral target had to compete with the buildup activity of a yet another population (the neural population in the immediate vicinity of the stimulating

electrode) in addition to that of the competing distractor. Although this regional stimulation evidently increased the number of contralateral responses (just not quite as effectively as during sessions with tight overlap), it may not have been close enough to induce a faster response, instead creating a bit of latency interference or delay. Nonetheless, the effects of microstimulation on latency corroborate the previous findings that the latencies of saccades and pursuit are related to the firing rates of neurons in the SC (Basso and Wurtz, 1998; Dorris et al., 1997; Krauzlis and Dill, 2002; McPeek and Keller, 2002a).

Sensitivity effects

In addition changes in bias, microstimulation also had an effect on the target-selection sensitivity (d'). These changes were more variable and differed between pursuit and saccades which make them on the surface harder to explain. Though the term "sensitivity" caries with it a connotation of "attention", "general perception" or overall visual discriminability, it is important to consider the values from which the measure is derived. It is merely a measure of the proportion of hits vs. false alarms, which are themselves subject to more than the effects of visual acuity alone. In order to understand the seeming idiosyncrasy of our sensitivity results, one must consider at least three factors that will affect a subject's sensitivity toward a target in the midst of a distractor: Stimulus-based discriminability, spatial bias (induced and inherent), and the latency taken to make a selection. A sensitivity score is only equivalent to general discriminability when there are no biases present and when latency is held constant. In our task all three factors summed to influence the final behavioral choice.

The stimulus signal, by definition, always favors the correct answer (i.e. the target that matched the pre-cue). However, the signal strength of the rewarded target did vary between two values, with the white targets being more salient than the gray. For this reason, our effects on bias were slightly weaker when the target was white, since our induced bias signal had to compete with a slightly more salient target. Our stimulation-induced bias held had a proportionately greater influence when the intended target was the slightly less salient gray. The activity in the SC produced by the stimulus signal will either compete or cooperate with any biases in the system, depending on the spatial location of the target. These biases may derive from an inherent spatial bias (if a monkey prefers making rightward saccades for example), compensatory biases (as was seen during the unstimulated trials of our experiment, Figs. 1.12 and 1.16) and the microstimulation-induced bias supplied by our electrode, which favors the contralateral target.—all of which sum as a bias in the net SC activity which may alternatively overlap with or lay discordant to the target stimulus.

Latency is the third factor that contributes to the final decision—and its effects may differ for pursuit and saccades. There is a speed/accuracy tradeoff in which a longer response latency will afford a longer accumulation of sensory information, thus promoting an increased ability to discriminate the target from the distractor (Liston and Krauzlis, 2003). Longer latency saccades tend to be more accurate, but pursuit is complicated by the fact that the potential targets are not stationary. A subject must time a pursuit eye movement carefully in order to acquire a moving target without having to rely on catch-up or anticipatory saccades. For this reason, any manipulation that alters pursuit latency may accompany a decrement in performance. An increase in latency may induce

errors as the two targets slide closer together throughout the delay and nearly overlap. Rather than providing additional time to accumulate luminance information, a pursuit delay may instead result in more errors due to the crowding effects of two targets in close proximity moving in different directions. A shortening of pursuit latency may also hurt performance due either to a disruption in the timing movement itself, or due to the shorter amount of time allowed to make a sensory discrimination.

Considering the above-mentioned issues, the outcome of an interaction between stimulus signal, bias and latency depends on the spatial location of the target and the eye movement type for each trial. That is why the effects of stimulation on sensitivity are of a different sign for pursuit and saccades and why the percent-correct results are spatially asymmetric. Stimulation resulted in a net increase in saccade sensitivity because the contralateral increase in percent correct was greater than the ipsilateral decrease. Conversely, stimulation resulted in a net decrease in pursuit sensitivity because the decrease in ipsilateral percent correct was greater in magnitude than the increase in contralateral percent correct. Thus, the overall effect was of the same type for pursuit and saccades but differed in magnitude, spatially. The spatial asymmetry can be explained by simply tallying the relative influence of stimulus signal, bias and latency toward errors or correct responses (Table 1.2). Whenever the induced bias and latency promoted different answers (ipsilateral saccades and contralateral pursuit), the effects were modest. Whenever the induced bias and latency promoted the same answer (contralateral saccades and ipsilateral pursuit), the effects were large. When the spatially asymmetric effects are collapsed into the SDT calculation of sensitivity, the measure exhibits a difference in sign for pursuit and saccades, which could be mistaken for a

fundamental difference in the influence of microstimulation on discriminability. This difference in sign, however, more accurately represents different spatial magnitudes of the same basic effect.

Etiology, intention

One of the goals of occulomotor research is to uncover the mechanisms by which gaze orientation decisions are made. The etiology of the effect that microstimulation had on target selection in the SC is unclear, but two types of mechanisms seem plausible. The first is based on a change in the intended target of gaze orientation without any changes in visual processing. This is most simply conveyed as a shift in the SDT decision criterion, which governs the system's level of bias for one object or spatial region over another. The decision space of a 2-AFC task can be represented by a two-dimensional plot with the salience of the contralateral stimulus on the abscissa and the salience of the ipsilateral stimuli on the ordinate (Fig. 1.17). Each point on the graph indicates the luminances of a pair of stimuli—the position of the point indicates the relative luminance of each, with points along the major diagonal representing equiluminance. The distribution of potential images in which the contralateral stimulus is the correct target (with an accompanying ipsilateral distractor) occupies a circular region or distribution cloud. The majority of that distribution will lay on the lower right quadrant of the graph since that is the region in which the contralateral stimulus is more salient than the ipsilateral. However, due to noise in the visual display or noise in the neural SC activity, some of this distribution may lay in the upper left quadrant as well, expressing those few trials in which the contralateral target is the correct answer despite

having a slightly lower signal. A second distribution, the majority of which lays in the upper left quadrant, describes those potential paired stimuli images when the ipsilateral stimulus is the rewarded target (with an accompanying contralateral distractor). The degree to which these two distributions overlap expresses the difficulty of the forced choice task, with the overlapping regions representing those trials in which the target and distractor pairs are ambiguously similar in luminance (Fig. 1.17A). Therefore the distance between the midpoints of these distributions is equal to the sensitivity (d') with which a subject can discriminate contralateral target trials from ipsilateral target trials. A greater separation of the two distributions, as is seen in Figure 1.17B, indicates a lesser degree of ambiguity and overlap, an easier target-distractor discrimination and, hence, a greater sensitivity (d'). But in order to make a selection, subjects must establish a criterion by which they respond to one stimulus over another. The decision criterion line designates a subject's proclivity to select one location over another. The subject will always respond with a contralateral selection during all trials in which the point on the stimulus distribution falls to the right of the decision criterion line; the subject will conversely make an ipsilateral response during all trials in which the point on the stimulus distribution falls to the left of the decision criterion line. A truly unbiased subject will have a criterion line that bisects the two overlapping distributions equally, giving rise to an equal number of contralateral and ipsilateral responses (Fig. 1.17A,B). A shift in the position of the criterion line illustrates s an inherent bias toward choosing a particular location. For example, the criterion line in Figure 1.17C has been shifted to the left; the majority of the overlapping distributions now lay to the right of this line, thus giving rise to an abundance of contralateral responses. The position of the criterion line

essentially describes the system's bias across numerous trials. Neurophysiologically, this bias is likely embodied as a level of net SC activity that begins closer to one of two response direction thresholds (Fig. 1.16A), and denotes the mounting intention of the system. By stimulating a particular region of the SC, we may have artificially boosted the net baseline activity of the SC toward the contralateral response threshold, effectively biasing the response output without overtly pushing the eyes (the supplied current was subthreshold for a saccade related burst) and without changing the attentional state of the subject. This change in selection or intent would be seen as a leftward shift in the SDT decision criterion (Fig. 1.17C).

Etiology, attention

Alternatively, microstimulation may have had in indirect effect by causing a shift in visual attention, consistent with the premotor theory of attention (Rizzolatti et al., 1987; Sheliga et al., 1995). The premotor theory of attention, as it applies to eye movements, postulates that impending eye movements are preceded by an obligatory shift of attention toward the location of the upcoming saccade endpoint. For example, the visual responses of neurons in the SC are enhanced when the stimulus is the target of a saccade (Goldberg and Wurtz, 1972; Robinson and Kertzman, 1995; Wurtz and Mohler, 1976), providing early suggestions of a link between visual attention and SC activity. It has also been shown that the "buildup" activity of saccade-related neurons is modulated by symbolic cues and stimulus probability, manipulations that also cause changes in reaction time (Basso and Wurtz, 1998; Kustov and Robinson, 1996). Additionally, a subset of SC neurons, the visuomotor cells, is active during covert shifts of attention (in

which the eyes do not move) evoked by spatially precise cues but not by symbolic cues (Ignashchenkova et al., 2004). Furthermore, the endpoints of saccades evoked by SC stimulation are modified by shifts of attention (Kustov and Robinson, 1996). Stimulation-evoked saccades normally have a stereotyped direction and amplitude. However, when Kustov and Robinson stimulated in the SC while monkeys performed a task that required them to covertly shift attention, the saccade vectors deviated toward the location in which the monkeys had diverted their attention. The results from all of these studies support the idea that the SC is part of a shared circuit for orienting attention and selecting targets for eye movements. Of course, such a circuit would not be restricted to the SC, and our stimulation results do not allow us to distinguish whether the selection signal arises within the SC or elsewhere. For example, an attentional effect has recently been demonstrated in another eye-movement related area – stimulation in the frontal eye fields increased the visual response of those V4 neurons that represent the stimulated area (Moore and Armstrong, 2003; Moore and Fallah, 2004).

In our experiment, the response bias introduced by microstimulation, as well as the effects on eye movement latency, could be explained by a shift of attention toward the contralateral stimulus at the expense of the ipsilateral stimulus. Such an attentional shift could have the same effects on performance as a change in the decision criterion (Macmillan and Creelman, 1991). Consider panel D of Figure 1.17: If attention were allocated away from the ipsilateral location and toward the contralateral location, the salience of all ipsilateral targets would be decreased and the salience of all contralateral targets would be increased. Both target/distractor salience distribution clouds would subsequently shift down and to the right, indicating a global increase in contralateral

target salience. Notice that, although the decision criterion line does not move in panel D (indicating a lack of spatial bias), the proportion of stimuli pairs that lay to the right of the criterion line is equal to that seen in panel C. The behavioral outcome of this shift in salience will be an increase in the number of responses toward contralateral stimuli—not because of a change in the monkeys' spatial bias as in panel C, but instead because of a change in the relative salience of the two targets.

After considering the logic of panels C and D from Figure 1.17, it should be apparent that each presents a valid mechanism through which we could obtain a contralateral response bias. By either shifting one's response criterion up and to the left (as in panel C) or by shifting the global salience of the stimuli distributions down and to the right (as in panel D) a greater proportion of trials fall into the contralateral response region. It is impossible to tell from hits and false alarms alone which mechanism is responsible, therefore the results from our experiment do not differentiate between the two types of selection mechanisms—spatial attention or response intention— because both are capable of producing a contralateral response bias. Nor are the two mutually exclusive. Regardless of the exact mechanism or place of origin of the selection, our results show that the SC applies the selection signal toward choosing eye movement targets, even in the absence of saccades. Thus, in addition to its traditional role in the motor control of saccades, the SC is also involved in the preceding step of selecting which object will become the target of an upcoming eye movement.

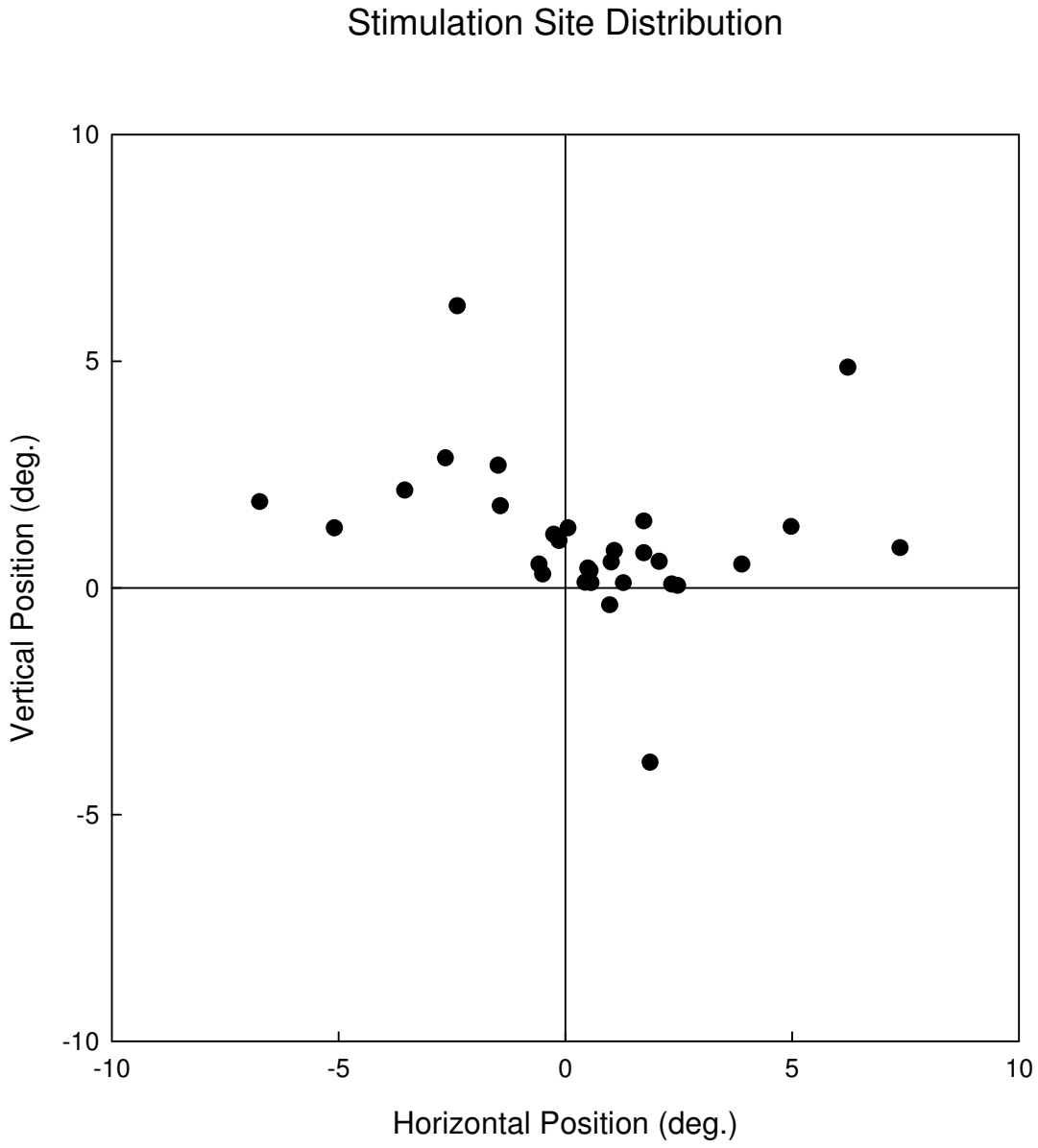


Figure 1.1. Stimulation site distribution
This figure shows, in Cartesian coordinates, the distribution of stimulation sites as defined by the characteristic stimulation-evoked saccade. Each point represents the location in 2-dimensional space that is represented by the population of neurons that were nearest to the stimulating electrode. These values were determined by stimulating the monkey with supra-threshold currents during free viewing and eliciting a staircase of saccades, all steps having equal vectors. The horizontal and vertical amplitudes of a single saccade step were then plotted here and used to place the visual stimuli on the computer screen.

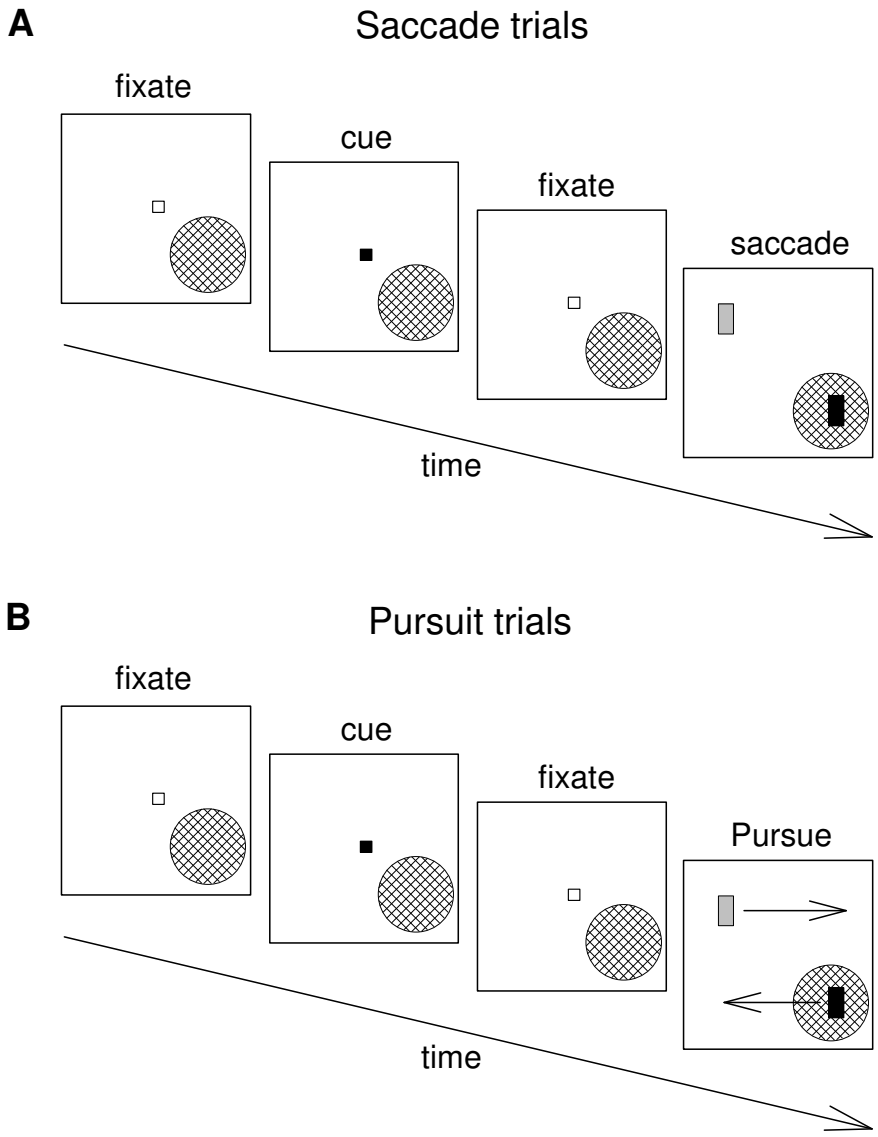


Figure 1.2. Sequence of events during saccade and pursuit trials
The monkey fixated the small central square and larger square cue before making an eye movement to the matching stimulus after the fixation square was extinguished. On saccade trials (A), target and distractor stimuli were stationary. On pursuit trials (B), stimuli moved at a constant speed (9-46^{o}/s) in directions indicated by the arrows. Crosshatched region represents the visual location corresponding to the site of stimulation in the SC.

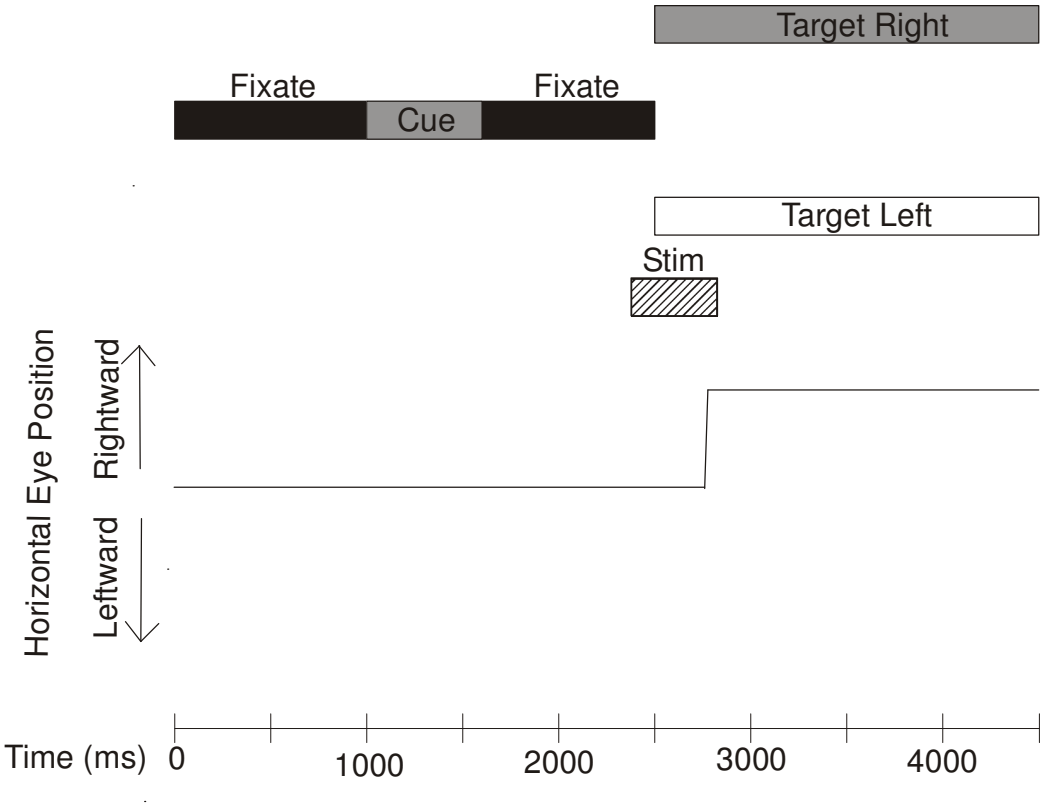
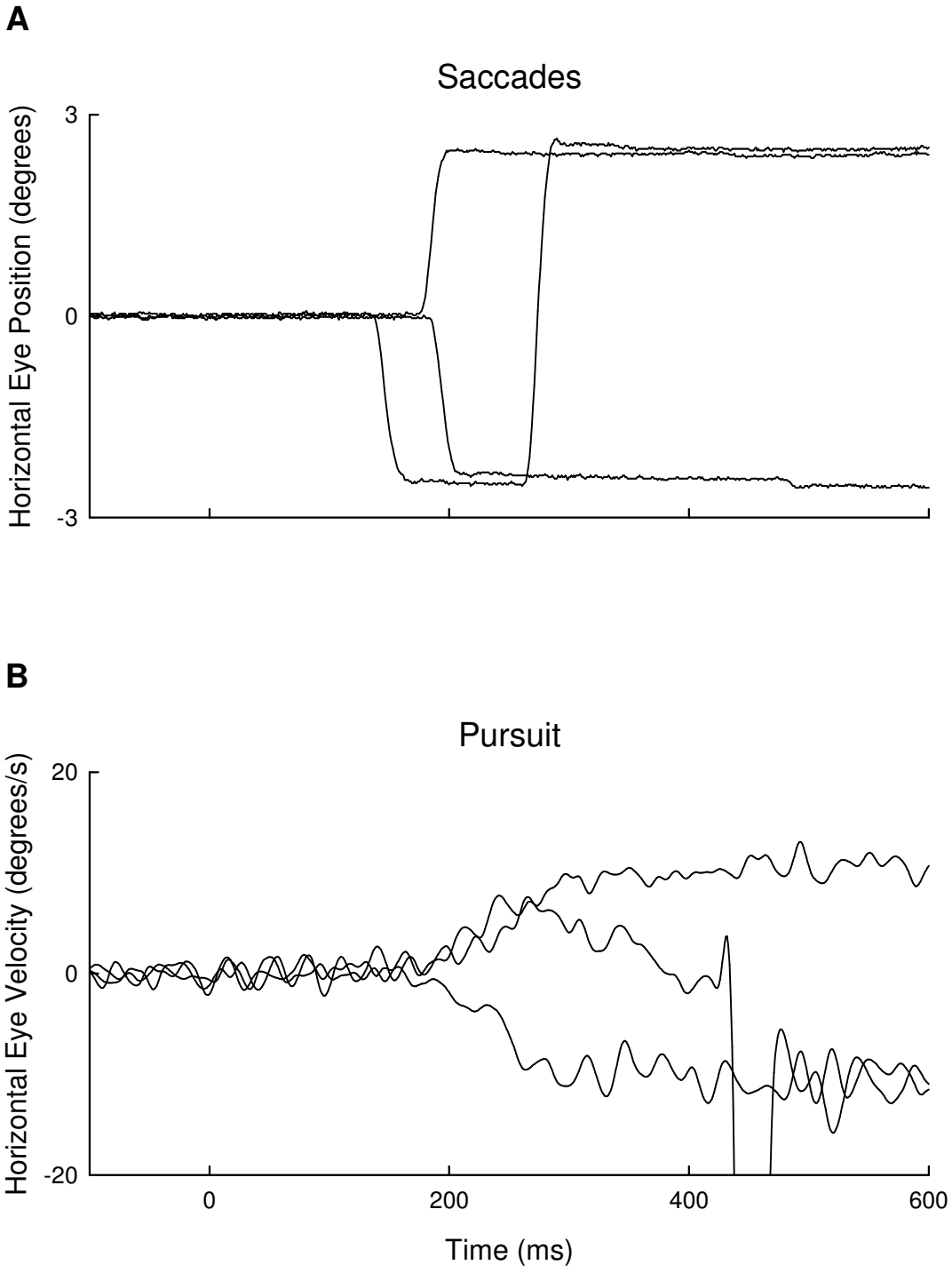


Figure 1.3. Sequential timing of visual events and stimulation
The fixation period, shown in black, spanned a variable duration from 2 – 2 ½ seconds (this example illustrates the longest duration of 2 ½ seconds). Within the fixation period, the central fixation cue changed color for 600 ms. The color of the cue matched the color of the upcoming rewarded target (gray in this example). Microstimulation, depicted in this figure as the diagonally-hatched box, was applied on ½ of the trials 100 ms prior to the onset of the two visual targets and lasted 360 – 460 ms, for the two monkeys respectively. The stimulation period overlapped with the target onset period, which began as soon as the central fixation point was extinguished. The schematic shows two targets—a gray target appearing on the right, which matches the color of the fixation pre-cue, and a white target appearing on the left, which serves as a distractor in this example. A schematic of the monkey's horizontal eye position appears below the event timing schematic. The trace shows an upward deflection 250 ms after the onset of the two targets thus represents a correct choice toward the gray target.

Figure 1.4. Raw data from six sample traces
The two plots depict horizontal eye position for saccades (A) and horizontal eye velocity for pursuit (B). Upward deflections correspond to movements in the rightward direction and downward deflections correspond to movements in the leftward direction. The saccade plot shows traces from three representative saccade trials—a single rightward saccade with a latency of about 200 ms, a single leftward saccade with a latency of about 200 ms and a double saccade trial in which the monkey originally made a leftward saccade (175 ms) immediately followed by a corrective rightward saccade (250 ms). For the purposes of our analyses, we always focused on the monkeys' initial decisions, therefore this double saccade trial would have been scored as a leftward choice. The pursuit plot shows traces from three representative pursuit trials—a rightward pursuit trial, a leftward pursuit trial and a trial with turnaround pursuit, each with an onset of about 175 ms. In the turnaround pursuit trial, the monkey initially pursues the target moving rightward, but the velocity then slows at about 250 ms and reverses direction. The monkey also made a catch-up saccade in order to reach the steady-state velocity of the leftward target, as can be seen by the radical velocity spike that occurs at about 450 ms


A
Saccades
Horizontal Eye Position (degrees)
3
0
-3
B
Pursuit
Horizontal Eye Velocity (degrees/s)
20
0
-20
0
200
400
600
Time (ms)

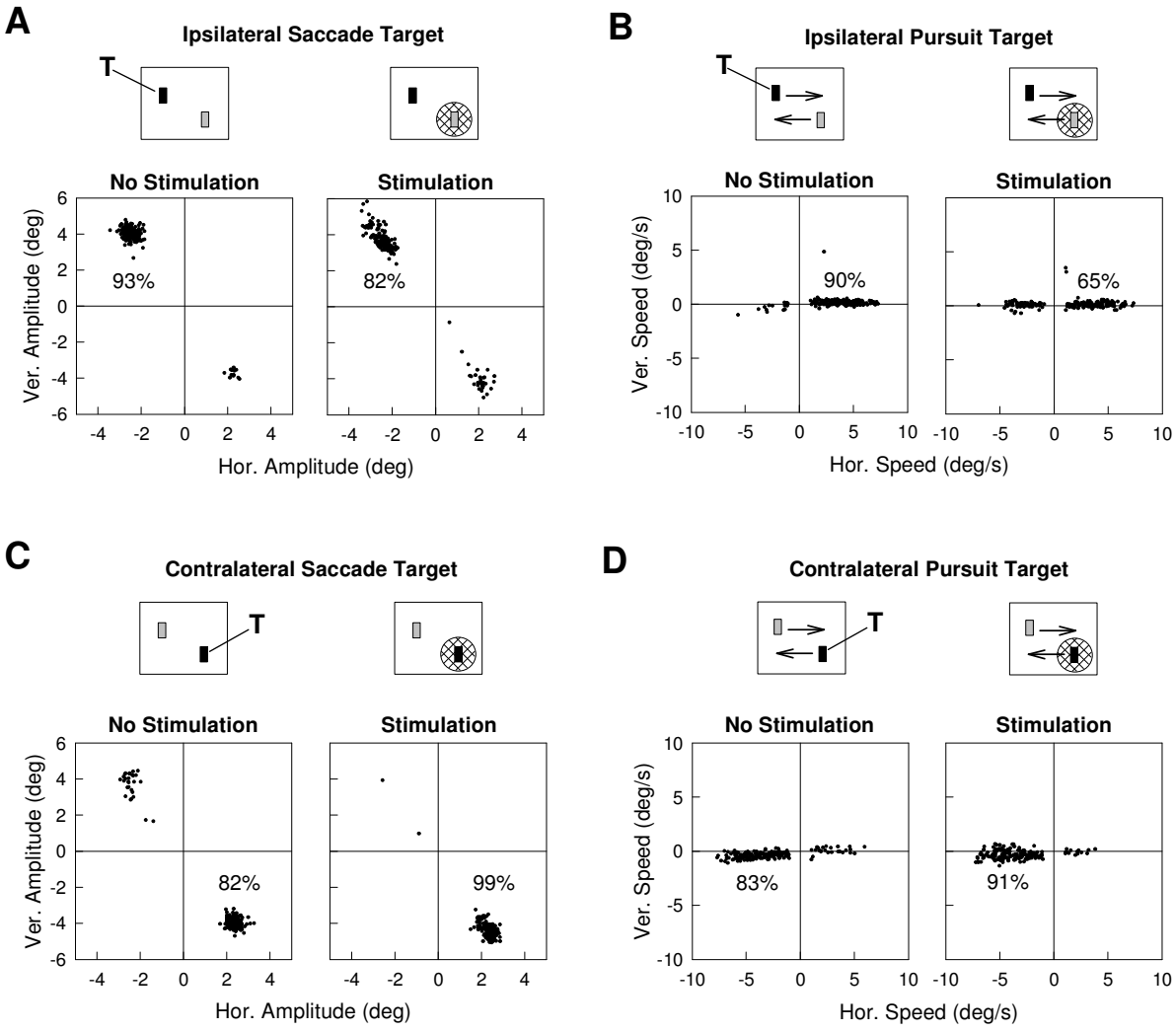


Figure 1.5. Changes in target choice caused by SC stimulation during a representative session
The experimental conditions are identified by the icons at the top of each panel: the black bar (labeled "T") represents the target onset location and the crosshatched region indicates the visual location corresponding to SC stimulation. For saccade conditions, the endpoints of the first saccade from every trial are plotted for targets appearing ipsilateral (A) and contralateral (C) to the site of SC stimulation. For pursuit conditions, the horizontal and vertical velocities over the first 100 ms of pursuit are similarly plotted for targets appearing ipsilateral (B) and contralateral (D). The pair of plots within each panel shows the results from trials with (right) and without (left) stimulation, and the inset values report the percentage of correct responses for each condition.

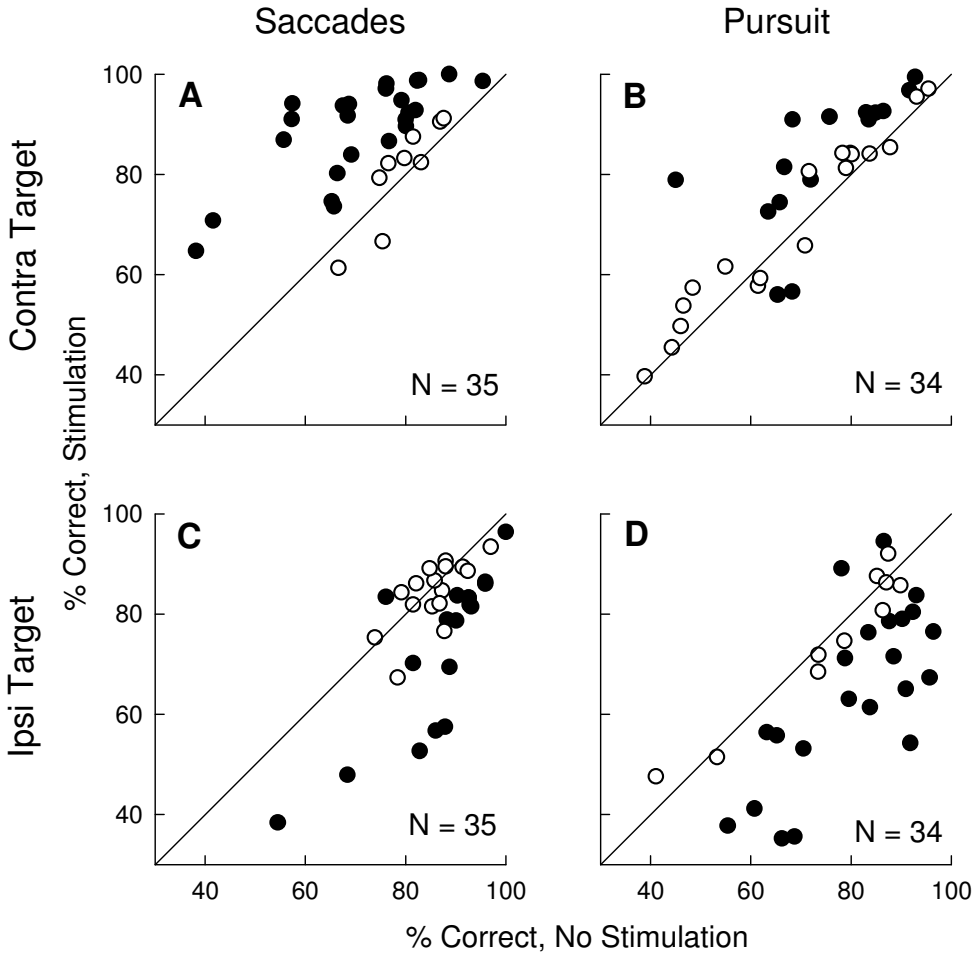


Figure 1.6. Changes in target selection caused by SC stimulation
The percentage of correct responses on trials with stimulation (% Correct, Stimulation) is plotted as a function of the percentage of correct responses without stimulation (% Correct, No Stimulation). Data are plotted separately for saccade (A, C) and pursuit (B, D) trials, and for targets initially appearing contralateral (A, B) and ipsilateral (C, D) to the site of SC stimulation. Each symbol shows data from a single session (n = 35 sessions; one session run as saccade-only). Filled circles indicate sessions for which stimulation caused a significant change in percent correct. A few data points are not visible, as they fell beyond the plot axes (percent correct < 40%).

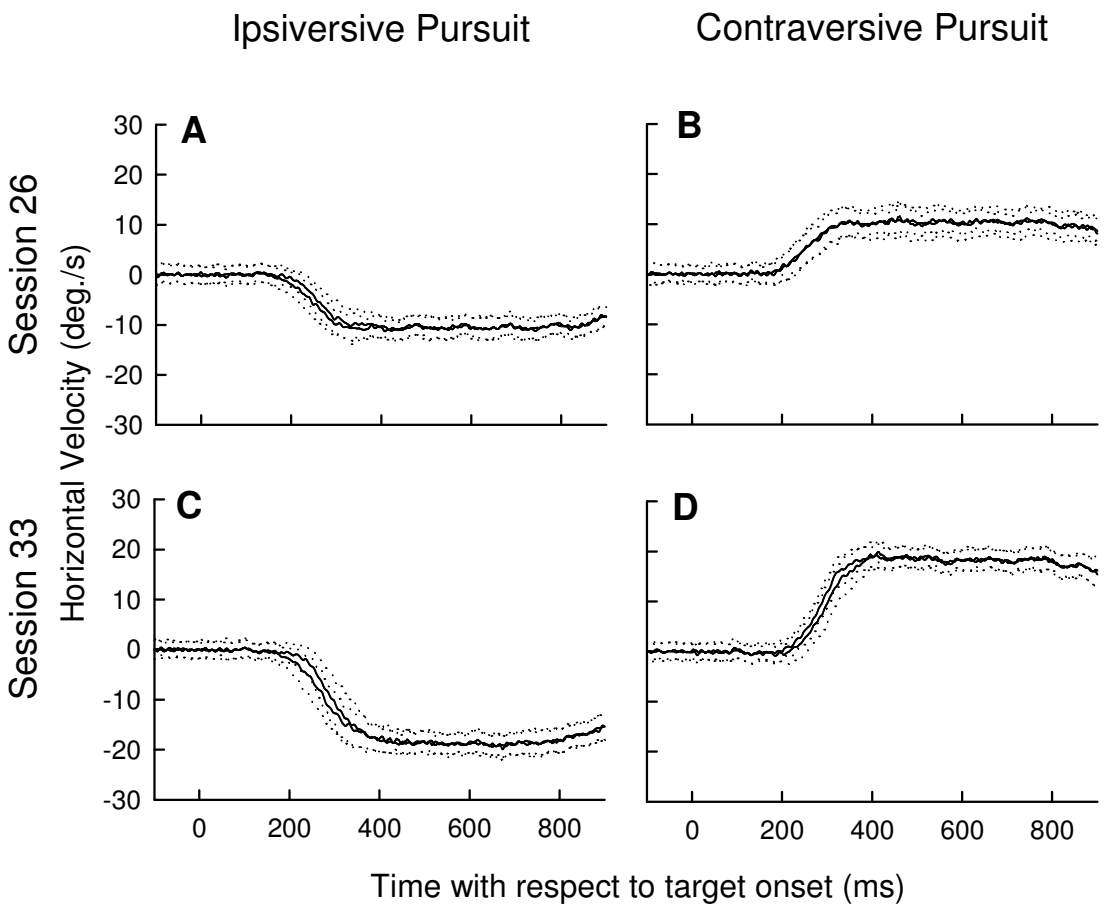


Figure 1.7. Mean pursuit eye velocity traces for two sessions with and without stimulation
Traces represent two sessions by the same monkey under different pursuit velocities. Mean horizontal eye velocity (+/- standard deviation) during ipsiversive and contraversive pursuit for session 26 (A,B) with a target pursuit velocity of 10 deg/s and session 33 (C,D) with a target pursuit velocity of 18 deg/s are aligned with respect to target onset. The two traces from each plot representing the monkey's mean pursuit velocity during stimulated trials and during trials without stimulation are superimposed and overlap very closely.

Table 1.1. Stimulation site, target location, target speed and stimulation parameters for all 35 sessions

Column one identifies each session by a number 1-35. Column two represents the stimulation site location by providing the horizontal (x) and vertical (y) coordinates of the evoked saccade during pre-experimental supra-threshold test trains. Column three lists the x and y coordinates of the saccade target closest to stimulated zone. Column four lists the x and y coordinates of the onset location for the pursuit target closest to stimulated zone. Column five lists the pursuit target speeds. Column six lists the stimulation current and frequency. Session 21 contained only saccade conditions.

Session	Stim site	Sacc. target	Purs. target	Purs. speed	Stim. params
1	(-0.5, 0.3)	(-3.5, 0.3)	(-4.0, 0.3)	15 deg/s	10 uA, 200 Hz
2	(0.4, 0.3)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	15 uA, 200 Hz
3	(0.5, 0.4)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 200 Hz
4	(1.0, 0.6)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	30 uA, 100 Hz
5	(1.7, 0.8)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 143 Hz
6	(1.1, 0.8)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 125 Hz
7	(-1.5, 0.7)	(-3.5, 0.3)	(-4.0, 0.3)	15 deg/s	15 uA, 167 Hz
8	(-0.1, 1.0)	(-3.5, 0.3)	(-4.0, 0.3)	15 deg/s	15 uA, 167 Hz
9	(-0.2, 0.2)	(-3.5, 0.3)	(-4.0, 0.3)	15 deg/s	15 uA, 167 Hz
10	(-1.4, 0.5)	(-3.5, 0.3)	(-4.0, 0.3)	15 deg/s	10 uA, 143 Hz
11	(0.1, 1.3)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	15 uA, 200 Hz
12	(2.1, 0.6)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 200 Hz
13	(-0.6, 0.5)	(-3.5, 0.3)	(-4.0, 0.3)	15 deg/s	10 uA, 167 Hz
14	(-3.5, 2.1)	(-3.5, 0.3)	(-4.0, 0.3)	15 deg/s	10 uA, 167 Hz
15	(0.6, 0.1)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 167 Hz
16	(7.4, 0.9)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 167 Hz
17	(1.0, -0.4)	(3.5, -0.3)	(4.0, -0.3)	15 deg/s	10 uA, 167 Hz
18	(5.0, 0.3)	(5.0, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 200 Hz
19	(3.9, 0.5)	(3.5, 0.3)	(4.0, 0.3)	15 deg/s	20 uA, 167 Hz
20	(2.5, 0.1)	(3.0, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 143 Hz
21	(1.7, 0.8)	(3.5, 0.3)	N/A	N/A	15 uA, 143 Hz
22	(2.3, 0.1)	(3.0, 0.3)	(4.0, 0.3)	15 deg/s	10 uA, 143 Hz
23	(1.3, 0.1)	(2.5, 0.3)	(2.5, 0.3)	9 deg/s	10 uA, 167 Hz
24	(6.2, 5.0)	(6.0, 0.3)	(6.0, 0.3)	22 deg/s	10 uA, 143 Hz
25	(0.5, 0.4)	(2.0, 0.3)	(2.5, 0.3)	9 deg/s	10 uA, 167 Hz
26	(1.9, -0.8)	(2.5, -0.3)	(2.5, -0.3)	10 deg/s	15 uA, 125 Hz
27	(13.3, 0.6)	(13.5, 0.3)	(13.5, 0.3)	42 deg/s	15 uA, 125 Hz
28	(-15.2, -7.4)	(-15, -8)	(15, -0.3)	46 deg/s	15 uA, 143 Hz
29	(-2.4, 0.2)	(-2.5, 0.3)	(-2.5, 0.3)	9 deg/s	15 uA, 111 Hz
30	(15.3, -0.7)	(12.0, -1.0)	(12.0, -0.3)	40 deg/s	15 uA, 125 Hz
31	(-6.0, -12.4)	(-5.5, -6)	(-5.5, -0.3)	20 deg/s	15 uA, 200 Hz
32	(-11.3, -4.5)	(-10, -4)	(-10, -0.3)	35 deg/s	15 uA, 143 Hz
33	(-5.1, 0.3)	(-5.0, 0.3)	(-5.0, 0.3)	18 deg/s	10 uA, 111 Hz
34	(-2.6, 0.8)	(-2.6, 0.8)	(-2.6, 0.3)	9 deg/s	10 uA, 100 Hz
35	(-6.7, 0.9)	(-6.7, 0.9)	(-6.7, 0.3)	25 deg/s	15 uA, 111 Hz

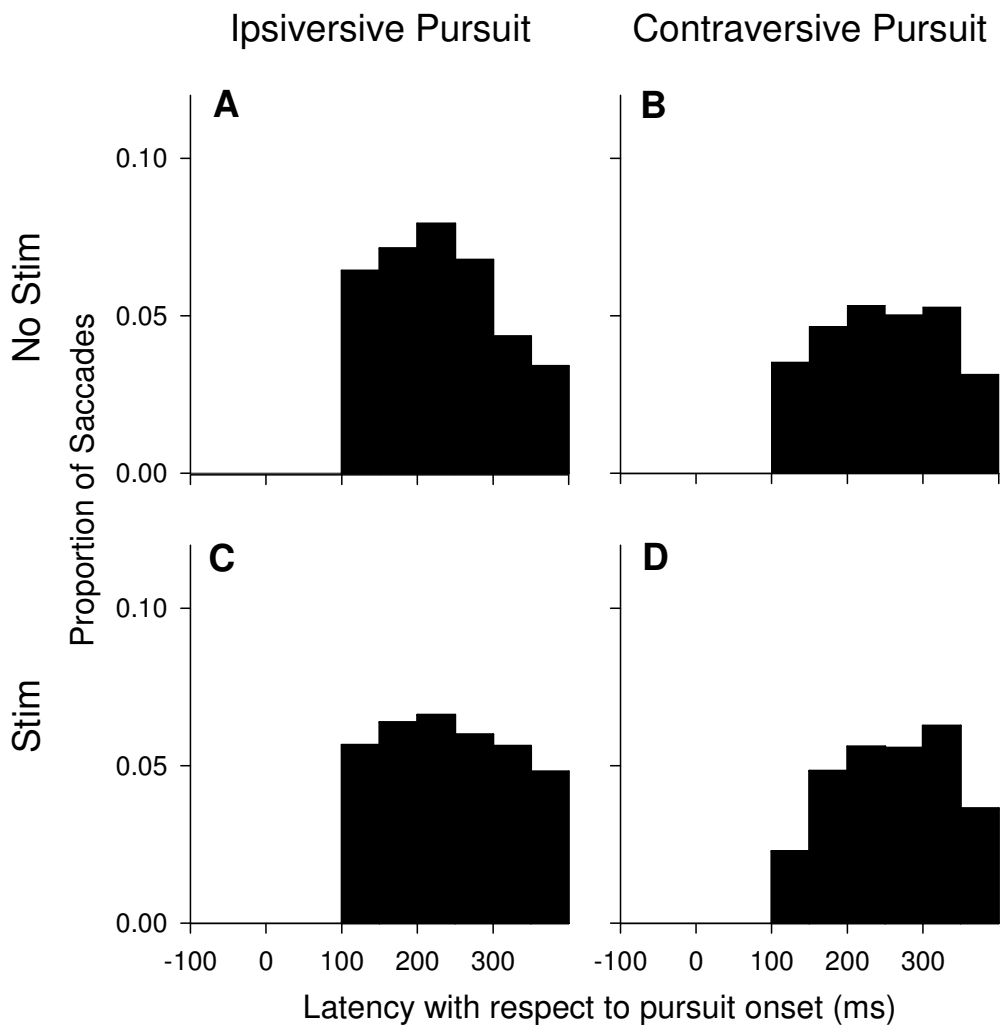


Figure1. 8. Frequency of saccades during pursuit with and without stimulation
Data are grouped into 50 ms latency bins with respect to pursuit onset (time 0); range is from 100 ms prior to 400 after pursuit onset. Panels include ipsiversive and contraversive pursuit in the absence of stimulation (A,B) and with stimulation (C,D). The overall saccade frequencies are 36% for ipsiversive pursuit, no-stim (A) and 35% stim (C); 27% for contraversive pursuit, no-stim (B) and 28% stim (D). The percent changes are not significantly different ($p > 0.05$).

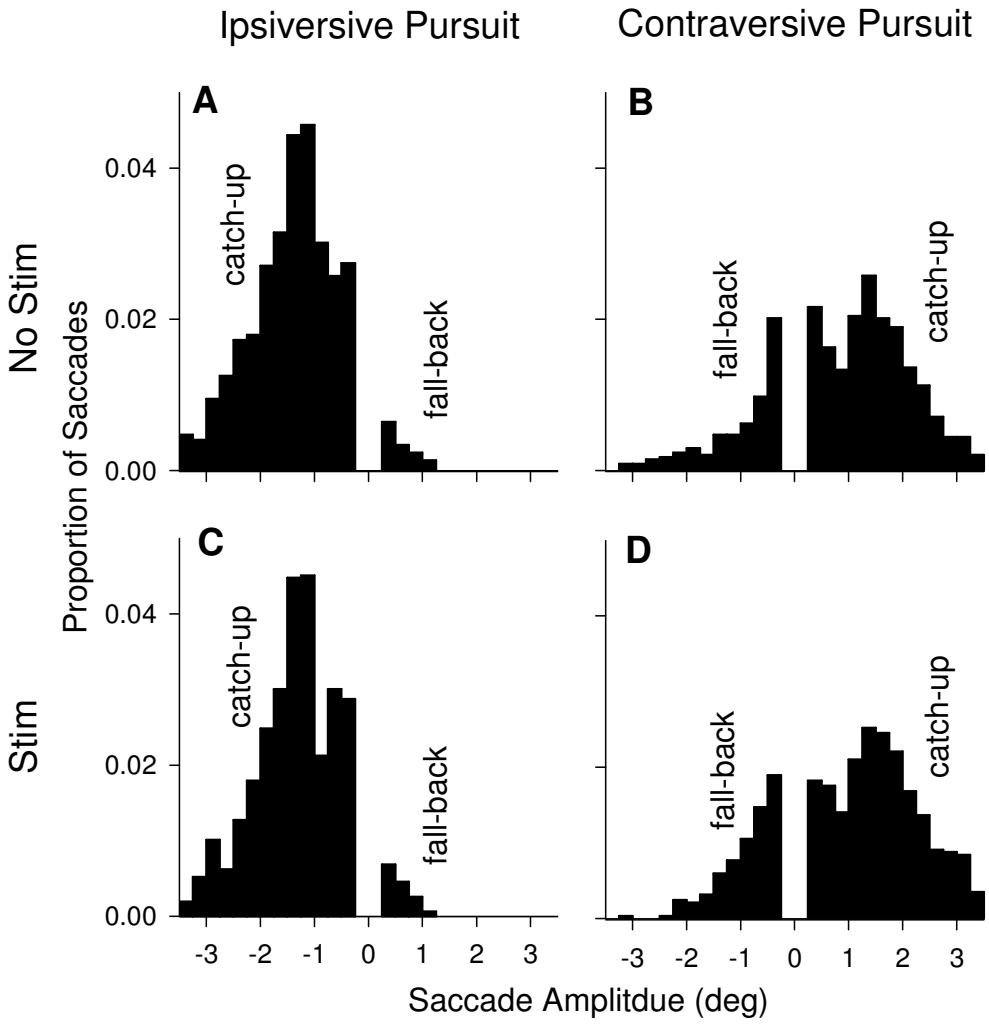


Figure 1.9. Frequency histogram of saccade amplitudes during pursuit with and without stimulation Data are grouped into 0.25° bins with positive amplitudes representing contralateral saccades and negative values representing ipsilateral saccades. The plotted range (-3.5° - 3.5°) contains most of the observed saccades; those occurring outside this range were included in the statistical analyses. Panels include ipsiversive and contraversive pursuit in the absence of stimulation (A,B) and with stimulation (C,D). Contralateral saccades during contraversive pursuit (freq. = 21% no-stim, 21.5% stim) and ipsilateral saccades during ipsiversive pursuit (freq. = 34% no-stim, 33% stim) have been labeled "catch-up", whereas ipsilateral saccades during contraversive pursuit (freq. = 6% no-stim, 6.5% stim) and contralateral saccades during ipsiversive pursuit (freq. = 2% no-stim, 2.5% stim) have been labeled "fall-back". The differences in percent correct between stimulated and unstimulated conditions are not statistically significant ($p > 0.05$ assuming a binomial distribution).

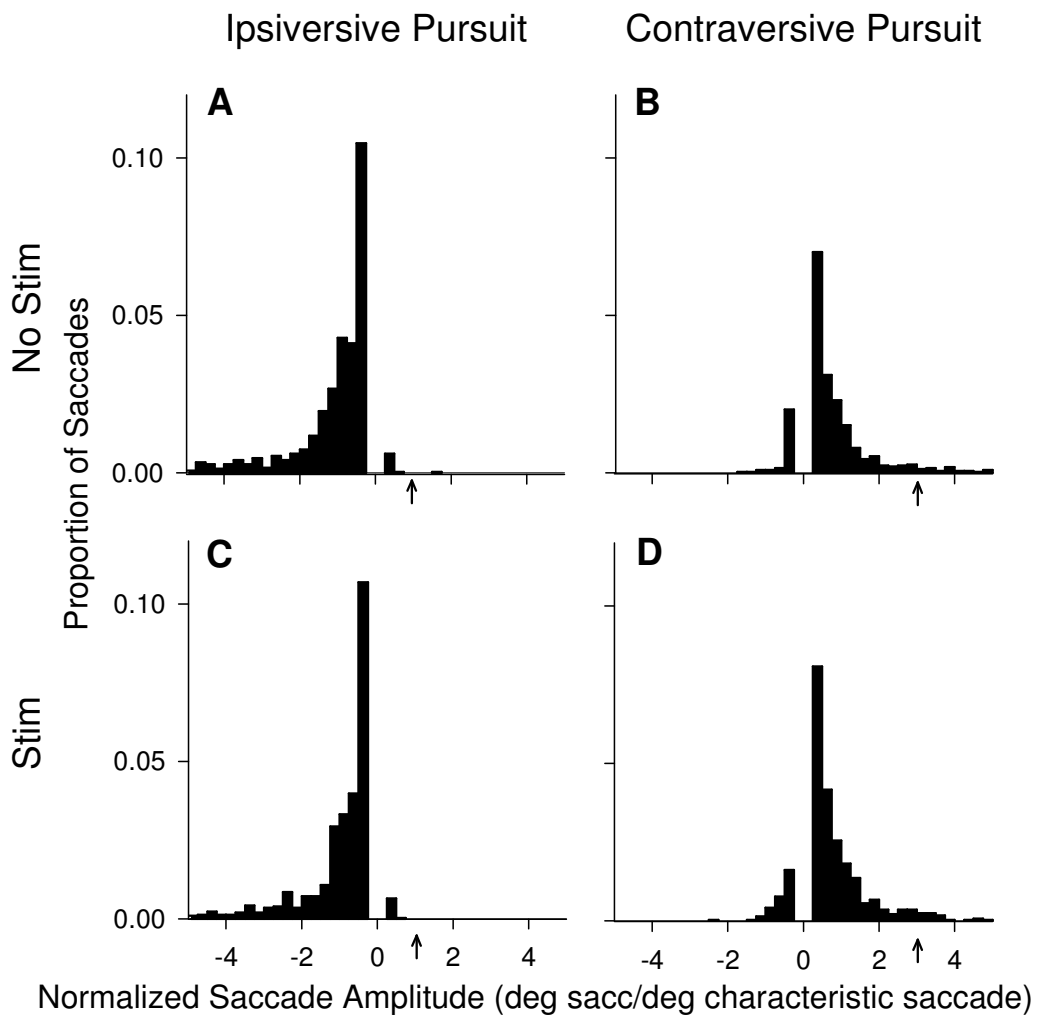


Figure 1.10. Frequency histogram of saccade amplitudes normalized to the amplitude of the characteristic saccade

Data are grouped into bin increments equal to 0.25 the magnitude of the characteristic saccade amplitude with positive amplitudes representing contralateral saccades and negative values representing ipsilateral saccades. Arrow indicates a magnitude value of one (equal to the amplitude of the characteristic saccade for a given session). The plotted range (-4.5° - 4.5°) contains most of the observed saccades; those occurring outside this range were included in the statistical analyses. Panels include ipsiversive and contraversive pursuit in the absence of stimulation (A,B) and with stimulation (C,D). The percentage of saccades that fall within a magnitude range between zero and one (which represent potential stimulation evoked or smaller amplitude stim-averaged saccades) during contraversive pursuit equals 14% no-stim, 15.5% stim, and during ipsiversive pursuit equals 0.5% no-stim, 0.5% stim. These differences are not statistically different ($p > 0.05$, assuming binomial distribution).

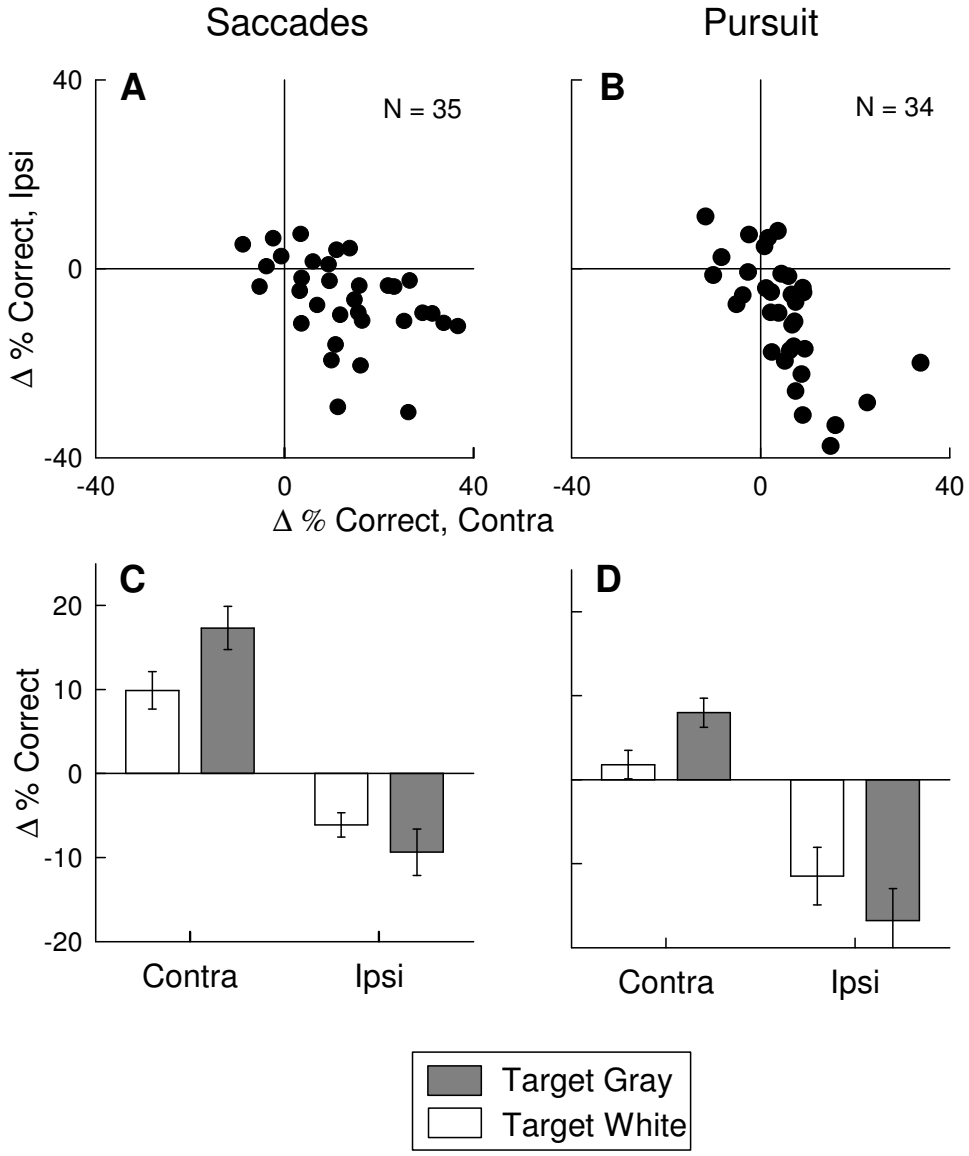


Figure 1.11. Comparison of changes in target selection for ipsilateral and contralateral targets Change in percent correct for ipsilateral targets is plotted as a function of change in percent correct for contralateral targets for saccades (A) and pursuit (B). Mean change in percent correct across all sessions for contralateral and ipsilateral targets for saccades (C) and pursuit (D). Gray bars represent trials on which the target identity was the darker of two stimuli; white bars represent trials on which the target identity was the lighter stimulus. Error bars indicate the standard error of the mean. 2-way ANOVA showed a significant main effect of target onset location (contralateral/ipsilateral) on change in percent correct ($p<0.001$) for both pursuit and saccades, but no effect of target luminance.

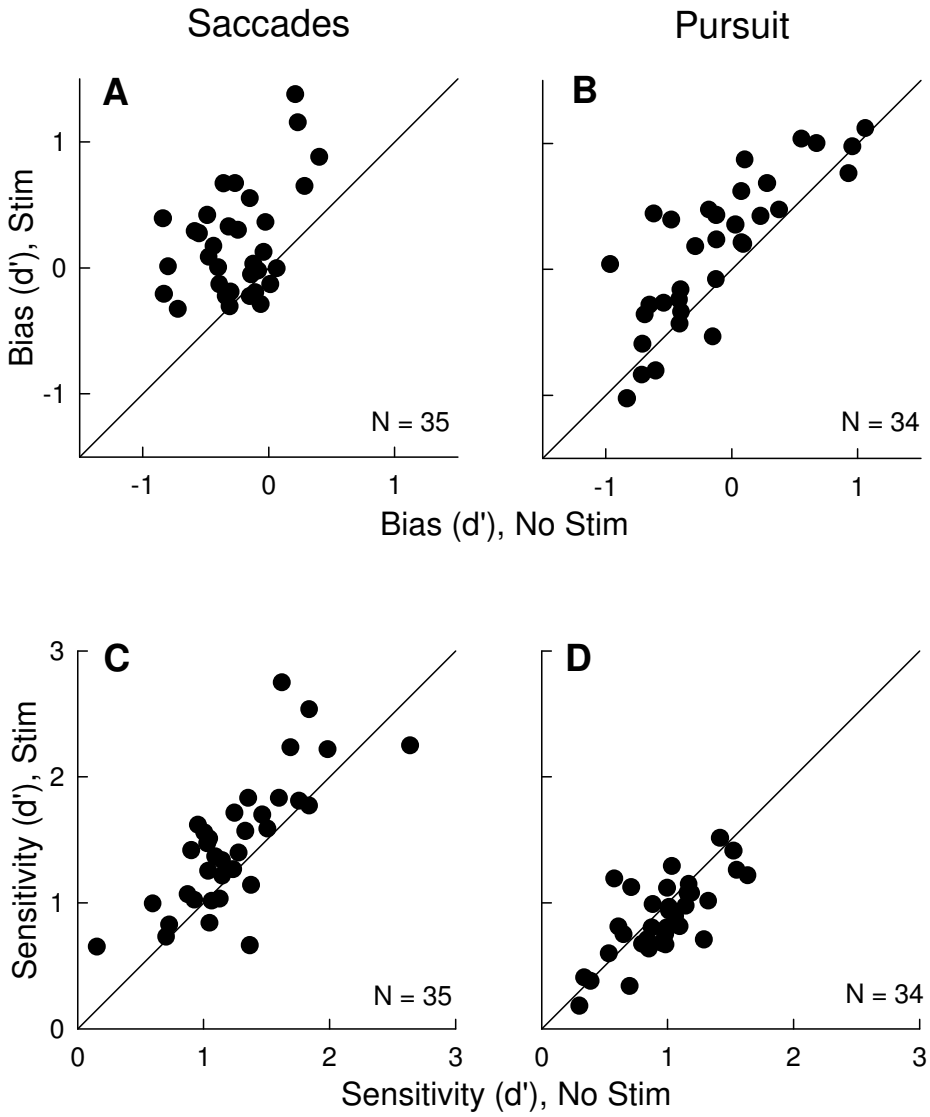


Figure 1.12. Changes in bias and sensitivity caused by SC stimulation
Bias (A, B) and sensitivity (C, D) on trials with stimulation are plotted as a function of the values obtained on trials without stimulation, separately for saccade (A, C) and pursuit (B, D) conditions. Each symbol shows results from a single session. Note that the axes for bias and sensitivity have different ranges but the same scale.

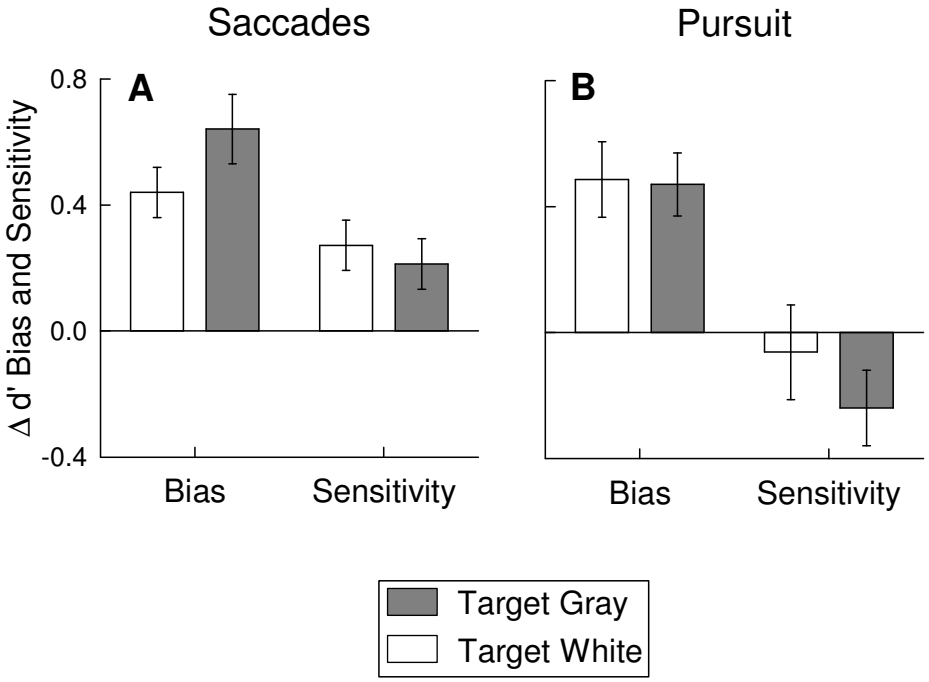


Figure 1.13. Mean changes in bias and sensitivity across all sessions for saccades and pursuit
Gray bars represent trials in which the target identity was the darker of two stimuli; white bars represent trials in which the target identity was the lighter stimulus. Error bars indicate the standard error of the mean. 2-way ANOVA reveals a significant difference between the magnitude of bias and sensitivity effects ($p<0.001$) for both pursuit and saccades. There was no significant difference based on target luminance.

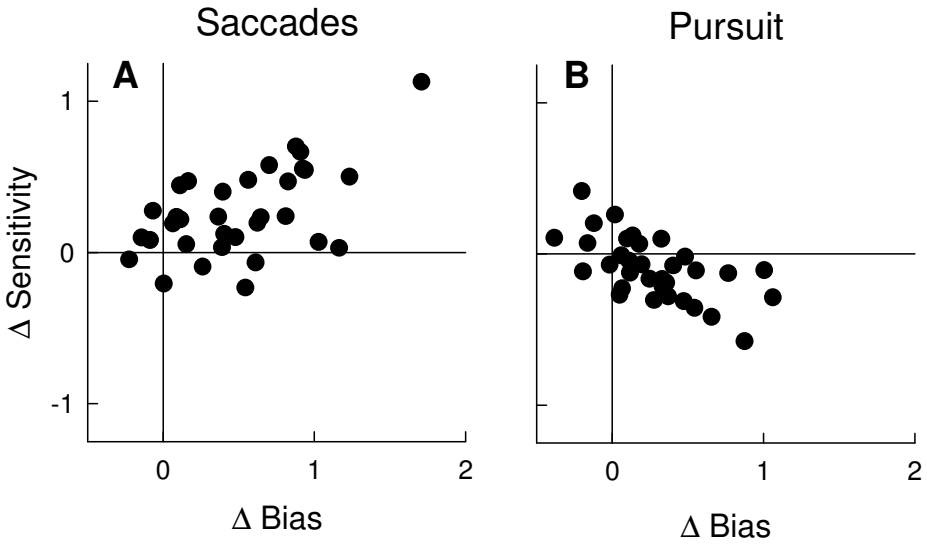


Figure 1.14. Changes in sensitivity as a function of changes in bias for each session
The purpose of this figure is to ascertain if there was a correspondence in the strength of bias and sensitivity effects for each session. Each point represents the change in sensitivity plotted against the change in bias for a single session. The saccade plot (A) shows a rough positive correlation—sessions that had a strong increase in contralateral bias tended to have a strong increase in sensitivity ($r^2 = 0.32$). The pursuit plot (B) shows a negative correlation—sessions that had a strong increase in contralateral bias tended to show a strong decrease in sensitivity ($r^2 = 0.38$). In both cases strong effects in one measure tended to accompany strong effects in the other.

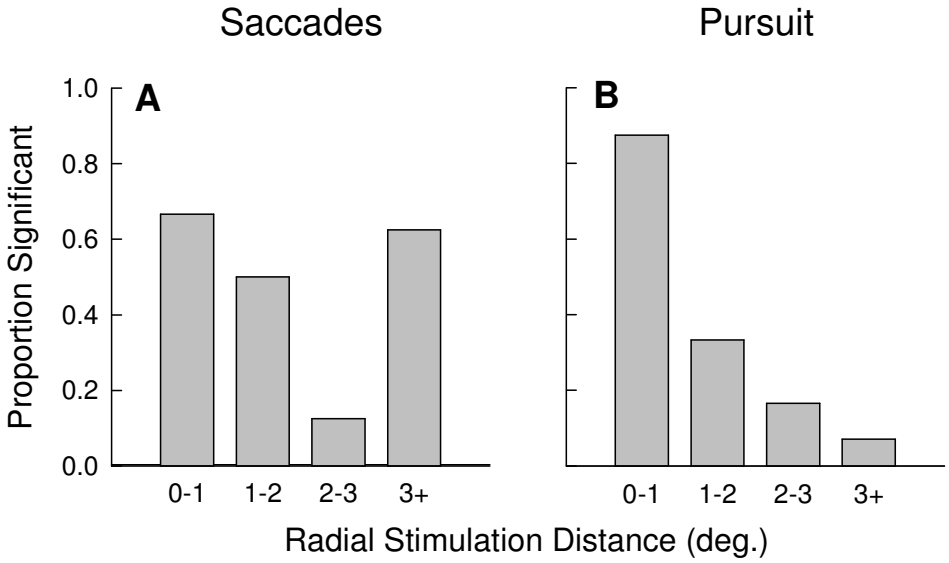


Figure 1.15. Strength of effect as a function of distance between stimulated area and target location The abscissa of both graphs marks the radial distance between the location of the stimulating electrode in the SC (as assessed by the vector amplitude of a stimulation-evoked saccade) and the location of the contralateral target on the computer screen. The distances are grouped into 1-degree bins, with the final bin representing all sessions in which the distance between stimulation site and stimulus location were greater than 3 degrees. The ordinate plots the proportion of sessions that exhibited a significant change in percent correct for each distance category. Generally, those sessions in which the stimulated zone and visual stimulus locations closely overlapped had a greater proportion of significant effects (~65% for saccades A, ~90% for pursuit B). As the separation between stimulated zone and visual stimulus location increases the proportion of sessions exhibiting significant effects decreases. The only exception to this pattern is the saccade category representing separations greater than 3 degrees (fourth column of the saccade plot A), which exhibits a high proportion of significant sessions (~60%). This may be due to chance occurrence as a result of the low number of sessions that contributed to this group.

Figure 1.16. Changes in saccade and pursuit latency caused by SC stimulation
(A) Schematic representing activity in the net SC during an impending contralateral response. The gray line represents a schematic response in the presence of microstimulation. The black line represents a similar trial in the absence of stimulation. (B-E) Latency measurements grouped according to the starting location of the stimulus that evoked a particular direction of eye movement. (B, D) Saccade latency is plotted as a function of stimulation condition (Stim, No Stim), separately for each monkey. Filled circles represent contralateral saccades; open circles represent ipsilateral saccades. (C, E) Pursuit latency is plotted as a function of stimulation condition. Filled circles represent pursuit of the stimulus appearing on the contralateral side; open circles represent pursuit of the stimulus appearing on the ipsilateral side. Error bars indicate the standard error of the mean. Stimulation increased the latencies of both saccades and pursuit for stimuli that appeared on the side ipsilateral to the site of SC stimulation ($p<0.001$) and decreased the latency for eye movements to stimuli that appeared on the contralateral side ($p<0.001$), except for Monkey W's contralateral saccades, which were slightly increased.

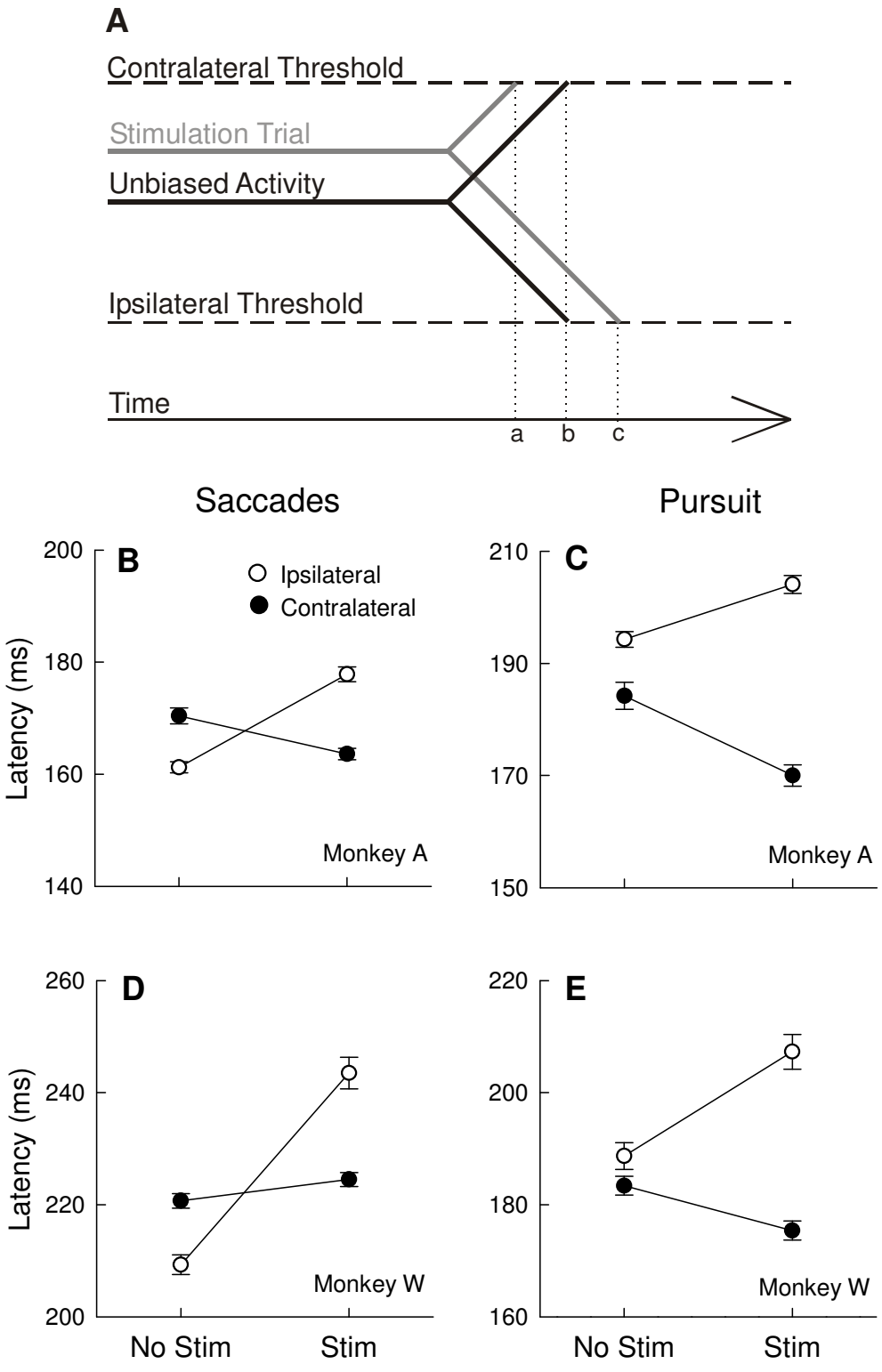

A
Contralateral Threshold
Stimulation Trial
Unbiased Activity
Ipsilateral Threshold
Time
a
b
c
Saccades
Pursuit
B
Ipsilateral
Contralateral
Latency (ms)
200
180
160
140
Monkey A
C
210
190
170
150
Monkey A
D
260
240
220
200
Monkey W
No Stim
Stim
E
220
200
180
160
Monkey W
No Stim
Stim

Table 1.2. The effects individual factors are expected to have on ipsilateral and contralateral pursuit and saccade movements

Three factors are considered in this table: The stimulus signal (i.e. whether a target or a distractor falls within a given location), the effects of microstimulation (whether stimulation would promote an error or correct response to a given area) and the expected effects of a latency shift (i.e. whether a disturbance in latency would enhance or disrupt the monkey's ability to choose the right target). The overall sign of effect one would expect for a given trial type (an increase or a decrease in errors) depends on the interplay of all three factors. Each column will be considered separately:

First column: When a saccade target appears on the side of the screen ipsilateral to the electrode we would expect the stimulus signal to promote a correct response (the stimulus signal always promotes a correct response because the stimulus signal is always 100% accurate). On the other hand, we would expect microstimulation to promote and error because microstimulation would promote a contralateral saccade which, in this case, would bring the monkey's gaze to the distractor stimulus. A latency shift may be expected to promote a correct response because the delay in response would give the monkey extra time to evaluate the two stimuli.

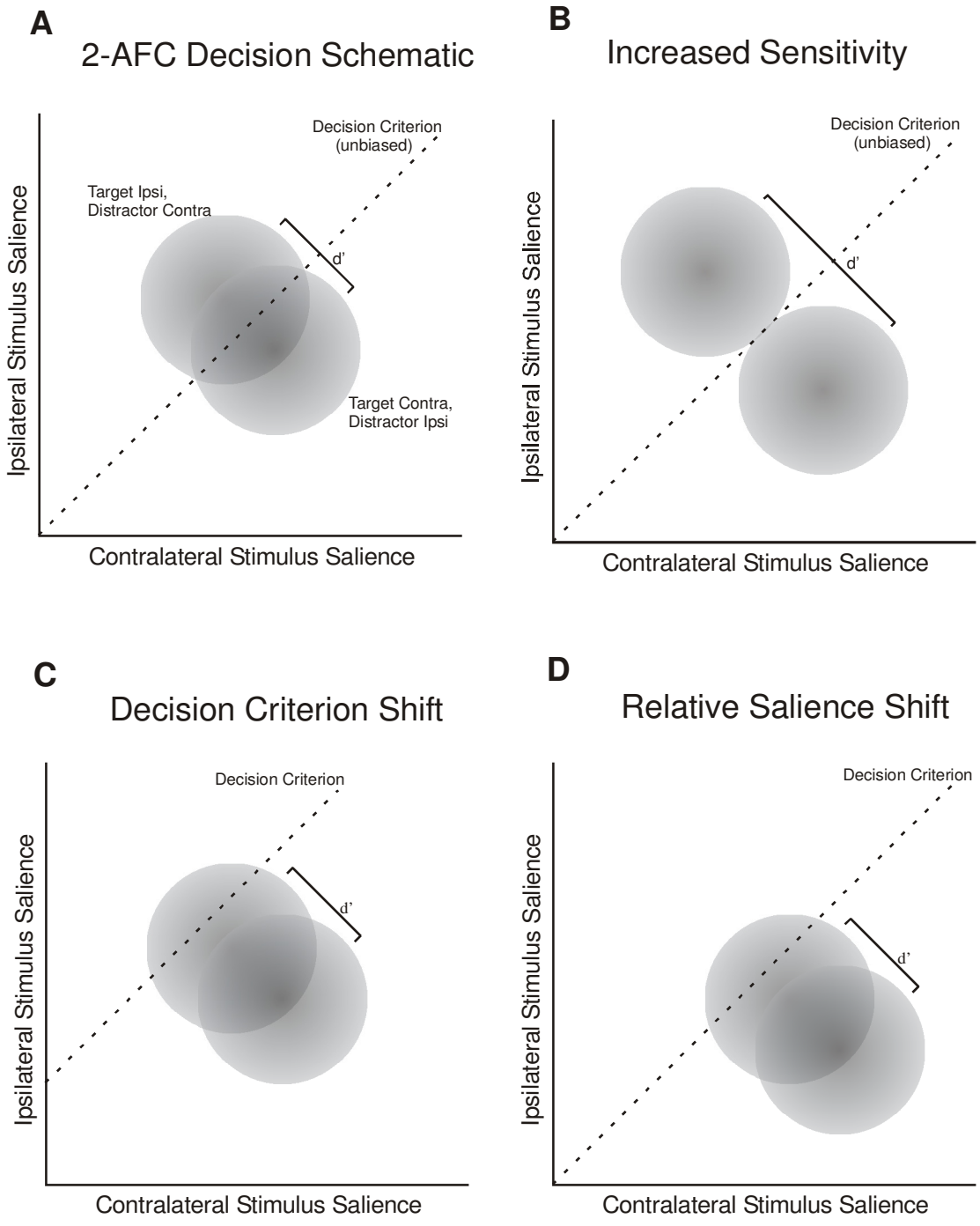
Second column: We would expect the stimulus signal to promote the correct response (the stimulus signal always promotes a correct response). We would expect microstimulation to promote a correct response because stimulation will promote a contralateral saccade which, in this case, would bring the eyes onto the target. The latency shift may have a variable response.

Third column: The stimulus signal always promotes a response toward itself (i.e. a correct response). Microstimulation would promote an error because it would promote selection of the contralateral stimulus which, in this case, is the distractor. Latency shifts always promote errors during pursuit trials because they disrupt the timing of the monkey's acquisition of a moving target.

Fourth column: The stimulus signal always promotes a response toward itself (i.e. a correct response). Microstimulation would promote a correct response because it would promote selection of the contralateral stimulus which, in this case, is the target. Latency shifts always promote errors during pursuit trials because they disrupt the timing of the monkey's acquisition of a moving target.

	Saccades		Pursuit	
	Ispi	Contra	Ispi	Contra
Stimulus Signal	promotes correct	promotes correct	promotes correct	promotes correct
Microstimulation	promotes error	promotes correct	promotes error	promotes correct
Latency Shift	promotes correct	(variable)	promotes error	promotes error

Figure 1.17. Signal detection theory schematic of bias, sensitivity, decision criterion shifts and salience shifts of a 2-alternative forced-choice task
Because all our stimuli occur in target-distractor pairs, a single point on this graph represents the salience of the ipsilateral target (ordinate) and the salience of the contralateral target (abscissa). The circular clouds represent all possible combinations of ipsilateral/contralateral stimuli pairs of varying saliences. A point that lays along the major diagonal would represent a pair of stimuli that are equally salient. There are two circles shown in each plot. One circle represents all of the stimuli pairs in which the contralateral stimulus is the target (and thus more salient); the other circle represents all of the stimuli pairs in which the ipsilateral stimulus is the target (and thus more salient). The distance between the centers of the two circles (d') represents how discriminable the two trial types are. When the task is difficult (panel A) the two circles overlap significantly, thus it is hard to differentiate target from distractor because their saliences will tend to be more similar on many trials. The resulting discriminability (d') is very low. When the task if very easy (panel B) the two circles are far apart from each other. As a result the target and distractor saliences are usually unambiguously different on a majority of trials (d' is large). The dotted line represents the monkey's decision criterion. He will respond to any point that falls to the right of that criterion with a contralateral choice. Any point that falls to the left of that line will result in an ipsilateral response. A line that divides the two distributions evenly represents an unbiased subject. Compare the location of the line to panel C. In this panel the stimuli are the same as panel A, but the criterion line has shifted in the upper-left direction. A greater proportion of trials now lay to the right of this line, which means the monkey will respond to a greater number of trials with a contralateral selection. In other words, shifts in the criterion line represent changes in a subject's bias. In panel D the criterion line remains in the original position, but the stimuli have now shifted in the lower-right direction. This represents a scenario in which the contralateral stimulus has become globally more salient. Because the majority of points now lay to the right of the decision line, the monkey will respond to a majority of the trials with a contralateral response. Therefore, either a shift in bias (panel C) or a shift in relative signal salience (panel D) can produce the same results. Panel C represents a hypothetical effect microstimulation could have directly on a monkey's bias. Panel D represents a hypothetical effect microstimulation could have on the monkey's attention (drawing attention toward the contralateral target, thus making it appear more salient).


A
2-AFC Decision Schematic
Decision Criterion
(unbiased)
Target Ipsi,
Distractor Contra
d'
Target Contra,
Distractor Ipsi
Ipsilateral Stimulus Salience
Contralateral Stimulus Salience
B
Increased Sensitivity
Decision Criterion
(unbiased)
d'
Ipsilateral Stimulus Salience
Contralateral Stimulus Salience
C
Decision Criterion Shift
Decision Criterion
d'
Ipsilateral Stimulus Salience
Contralateral Stimulus Salience
D
Relative Salience Shift
Decision Criterion
d'
Ipsilateral Stimulus Salience
Contralateral Stimulus Salience

The material of Chapter One is based in part on, and contains material reprinted from, a publication of those results in the journal Neuron (Carello & Krauzlis, 2004) with permission from the copyright owner Elsevier. The dissertation author was the primary researcher and the co-author listed in this publication directed and supervised the research which forms the basis for this chapter.

Conclusions and future directions

The ultimate effect of the work contained within this dissertation has been to place the SC in a new position on the visuomotor decision hierarchy. Once uniformly considered to be a simple motoric saccade machine, the SC is now regarded as a structure that contributes to the selection of objects for upcoming gaze orientations. Those selections are not limited to contralateral saccade trajectories, and do in fact frequently result in eye movements outside of the active population's receptive field—even movements that travel in the ipsiversive direction. The main conclusions of my dissertation work are summarized below to address the motivating questions given in the introduction. They are followed by a new set of questions, based on these findings, which will motivate future research on this topic.

1. The role of the Superior Colliculus in target selection is a causal one. Previous work has shown a correlation between so called "buildup" or "prelude" activity (found in cells of the intermediate and deep layers of the SC) that precedes the saccade related burst (SRB) event of single neurons and the subsequent choice of target (Krauzlis and Dill, 2002). By directly manipulating the activity of these cells using stimulation that was sub-threshold for triggering a SRB, we were able to bias the system toward selecting targets that appeared in the location of the visual scene represented by the stimulated population, thus establishing a causal relationship between SC activity and target selection.

2. The function of the SC is to select objects as goals for upcoming eye movements—not to simply compute contralateral saccade trajectories. This is an important distinction, supported by the pursuit results, that is not addressed in the preceding conclusion. The saccade results alone do not distinguish whether the effects were based on the selection of a visual target or a specific motor trajectory. During a traditional saccade task, both the visual stimulus and the motor trajectory endpoint occupy the same position in space. During pursuit trials, however, the target onset location and the eye-movement trajectory required to foveate the moving target are in opposite directions. If stimulation of the SC promoted a specific motor trajectory, we would expect to see an increase in the number of eye movements in the contralateral direction, regardless of the condition. Microstimulation during pursuit instead showed an increase in the number of eye movements in the ipsiversive direction—the trajectory of the visual stimulus that originally appeared in the stimulated region, thus revealing an object-based, goal-oriented role of the SC in target selection. The SC is responsible for selecting objects—not spatial positions—for gaze orientations.

3. The SC guides pursuit movements in addition to saccades. Long regarded strictly as a saccade machine, evidence has recently begun to reveal that the SC guides pursuit movements as well (Krauzlis, 2003; Krauzlis et al., 1997, 2000, 2002). The pursuit effect described in this dissertation implicitly identifies pursuit control as one of the SC functions, thus adding further evidence to that emerging story.

Future Directions

1. The SC is probably not the only brain area responsible for making target selection decisions. Other areas known to be involved in occulomotor control include the Frontal Eye Fields (FEF) and Supplementary Eye Fields (SEF) which are both involved in saccade and pursuit preparation particularly in relation to conditions that are more complex or contain a non-reflexive, cognitive component (Chen and Wise, 1995; Connolly et al., 2002; Everling and Munoz, 2000; Hanes and Wurtz, 2001), the Lateral Interparietal area (LIP), which has been implicated in assessing stimulus saliency and task relevance (Kusunoki, Gottlieb and Goldberg, 2000; Gottlieb and Goldberg, 1999) as well as other cortical association areas such as the Dorso-Lateral Pre-Frontal Cortex (DLPFC), which has been implicated in the processing of working memory important for coupling a visual event to a delayed motor response (Pierrot-Deseilligny, et al, 2005, 2003; Tsujimoto and Sawaguchi, 2004). The SC is presumably not a completely redundant system to those other areas and therefore likely has a functional specialization within the target selection complex. Its position on the brainstem, its direct retinal input and lesion studies (Schiller, Sandell and Maunsell, 1987) suggest that it may play a preferential role in making reflexive target selections to highly salient stimuli. It would be instructive to record from the SC as well as cortical occulomotor areas such as FEF while presenting stimuli that have both bottom-up and top-down features. The SC may provide a greater contribution to selections based on salient, bottom-up features whereas the FEF may provide a greater relative contribution when potential targets are discriminated based on a top-down feature such as a complex rule. Ideally, one would

observe differences in activity between these two areas, given identical stimuli but different bases for discrimination.

2. This dissertation has demonstrated that activity within the SC corresponds to selection of a target for an upcoming gaze orientation. As was shown with the pursuit effect, such activity does not necessarily correspond to the vector of that upcoming movement. Since the SC has long been regarded as the area responsible for computing such vectors, we must now ask where that computation takes place. There aren't many synapses between the SC and the ocular muscles, but perhaps the computation takes place in a particular region downstream from the SC such as the para-pontine reticular formation (PPRF). Or perhaps the computation is a property that is distributed across multiple areas such as the SC, FEF and the omni-pause neurons onto which those two areas synapse. It is also possible that all of the computation occurs within the SC, across different layers or cell types. A rise in activity in one region of the collicular map corresponding to the selection of an object may precede a rise in activity in a second region corresponding to the gaze trajectory. To answer these questions, one must record from those areas of interest while presenting subjects with targets that exhibit a mismatch between their initial location and final gaze endpoint (or path, in the case of pursuit). Smooth pursuit of moving targets is one way to address this issue, but it may also be possible to do so with saccade targets that translate to a new location before the eye movement is executed. With such a fractionated sequence of events (target presentation, target relocation, release of fixation), one may be able to resolve discrete neural events corresponding to the two components of the task—selection and vector computation.

3. There are two reasonable mechanisms that would explain the nature of the effect microstimulation had on target selection—that of attention or intention. Microstimulation may have affected attentional mechanisms by simply making the contralateral targets appear more salient, thus indirectly promoting their selection. This is certainly in register with the notion that the SC responds preferentially to salient, bottom-up features. Alternatively, microstimulation may have more directly influenced the mechanisms of selection itself—the intent of the system—without any indirect effects on the target's salience. If the mounting buildup activity of collicular neurons represents the probability that the system is going to select one target over another, microstimulation may simply have imposed a direct bias to that rising signal. The work contributing to this dissertation does not distinguish between the two alternative mechanisms. It would be very useful to conduct a study that can differentiate the two. The best way to accomplish this would be to design the stimuli in such a way that the direction of discrimination is orthogonal to the resulting eye movement direction. For example, one could place four stimuli on the screen. The subject must then make a sensory discrimination (not a saccade) between the two stimuli that lay along the horizontal axis. That discrimination will then reveal (through a previously learned rule) which of the two stimuli along the vertical axis is the appropriate target for a saccade (Fig. 0.1). While the monkey performed the task, one could microstimulate in a region of the SC that corresponds to the location of one of the two stimuli on the horizontal axis (the discrimination stimuli). If microstimulation produces a local attentional gain, we would expect the monkey to show a discrimination improvement and therefore correctly saccade

to the appropriate target along the vertical axis more often. If, instead, microstimulation produces a direct target selection, we would expect the monkey to make a saccade in error directly to the stimulus on the horizontal axis that falls within the area of stimulation.

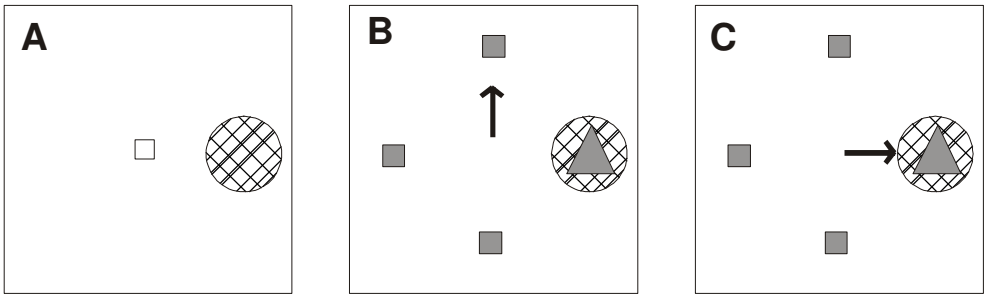


Figure 0.1. Four-AFC task
Panel A shows a central fixation point and the area on the screen that represents the zone of stimulation in the SC (crosshatch). Panel B shows the presentation of 4 stimuli and a hypothetical saccade response (arrow). The monkey must make discriminate between the two stimuli on the horizontal axis but is not supposed to make a saccade to either. Instead, based on that discrimination, he should make a saccade to one of the two stimuli on the vertical axis. The triangle represents a previously learned rule, which in this example instructs the monkey to make a saccade to the upper stimulus on the vertical axis. If microstimulation increased the monkey's attention to the stimulus that appears in the zone of stimulation, we would expect an improvement in the monkey's ability to discriminate and therefore an increase in correct saccade responses (in this case to the upper stimulus as is shown in panel B). However, if microstimulation instead imposes a bias for the selection of stimuli that fall within the stimulated zone, we would expect the monkey to make saccades directly to the triangle in error, as is shown in panel C.

The ultimate goal of biology is to fully explain how we function and why we behave the way we do. We continually look to the horizon, yet at some level remain vigilantly aware of the inches that lay before us, lest some hidden rock dash our vessel to splinters. The selection of minutia contributes to the choices of the mundane which in turn drive our most consequential decisions in a fractal hierarchy, whereby the lesser components imitate the whole, just as a stream's tributaries and inlets resemble the meander of its main channel. Perhaps—if we're lucky—so too does the brain exhibit such architecture, the mechanisms of morality and life-altering choice resembling the machinery that guides our eyes.

References

Adler, S. A., Bala, J., and Krauzlis, R. J. (2002). Primacy of spatial information in guiding target selection for pursuit and saccades. J Vis *2*, 627-644.

Asrress, K. N., and Carpenter, R. H. (2001). Saccadic countermanding: a comparison of central and peripheral stop signals. Vision Res *41*, 2645-2651.

Basso, M. A., Krauzlis, R. J., and Wurtz, R. H. (2000). Activation and inactivation of rostral superior colliculus neurons during smooth-pursuit eye movements in monkeys. J Neurophysiol *84*, 892-908.

Basso, M. A., and Wurtz, R. H. (1998). Modulation of neuronal activity in superior colliculus by changes in target probability. J Neurosci *18*, 7519-7534.

Basso, M. A., and Wurtz, R. H. (2002). Neuronal activity in substantia nigra pars reticulata during target selection. J Neurosci *22*, 1883-1894.

Burman, D. D., and Bruce, C. J. (1997). Suppression of task-related saccades by electrical stimulation in the primate's frontal eye field. J Neurophysiol *77*, 2252-2267.

Carello, C.D., and Krauzlis, R.J. (2004). Manipulating Intent: Evidence for a Causal Role of the Superior Colliculus in Target Selection. Neuron *44*, 575-583.

Carpenter, R. H. (1981). Occulomotor Procrastination. In Eye Movements: Cognition and visual perception, D. F. Fisher, R. A. Monty, and J. W. Senders, eds. (Hillside, NJ, L. Erlbaum Associates), pp. 237-246.

Carpenter, R. H., and Williams, M. L. (1995). Neural computation of log likelihood in control of saccadic eye movements. Nature *377*, 59-62.

Chen, L. L., and Wise, S. P. (1995). Supplementary eye field contrasted with the frontal eye field during acquisition of conditional occulomotor associations. J Neurophysiol *73*, 1122-1134.

Connolly, J. D., Goodale, M. A., Menon, R. S., and Munoz, D. P. (2002). Human fMRI evidence for the neural correlates of preparatory set. Nat Neurosci *5*, 1345-1352.

Dorris, M. C., Pare, M., and Munoz, D. P. (1997). Neuronal activity in monkey superior colliculus related to the initiation of saccadic eye movements. J Neurosci *17*, 8566-8579.

Everling, S., and Munoz, D. P. (2000). Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. J Neurosci *20*, 387-400.

Gattass, R., Nascimento-Silva, S., Soares, J. G., Lima, B., Jansen, A. K., Diogo, A. C., Farias, M. F., Botelho, M. M., Mariani, O. S., Azzi, J., and Fiorani, M. (2005). Cortical visual areas in monkeys: location, topography, connections, columns, plasticity and cortical dynamics. Philos Trans R Soc Lond B Biol Sci *360*, 709-731.

Girvin, J. P., Evans, J. R., Dobelle, W. H., Mladejovsky, M. G., Henderson, D. C., Abramov, I., Gordon, J., and Turkel, J. (1979). Electrical stimulation of human visual cortex: the effect of stimulus parameters on phosphene threshold. Sens Processes *3*, 66-81.

Glimcher, P. W., and Sparks, D. L. (1993). Effects of low-frequency stimulation of the superior colliculus on spontaneous and visually guided saccades. J Neurophysiol *69*, 953-964.

Goldberg, M. E., and Wurtz, R. H. (1972). Activity of superior colliculus in behaving monkey. II. Effect of attention on neuronal responses. J Neurophysiol *35*, 560-574.

Gottlieb, J., and Goldberg, M. E. (1999). Activity of neurons in the lateral intraparietal area of the monkey during an antisaccade task. Nat Neurosci *2*, 906-912.

Hanes, D. P., and Wurtz, R. H. (2001). Interaction of the frontal eye field and superior colliculus for saccade generation. J Neurophysiol *85*, 804-815.

Hanes, D. P., and Carpenter, R. H. (1999). Countermanding saccades in humans. Vision Res *39*, 2777-2791.

Hikosaka, O., and Wurtz, R. H. (1985). Modification of saccadic eye movements by GABA-related substances. I. Effect of muscimol and bicuculline in monkey superior colliculus. J Neurophysiol *53*, 266-291.

Horwitz, G. D., and Newsome, W. T. (1999). Separate signals for target selection and movement specification in the superior colliculus. Science *284*, 1158-1161.

Horwitz, G. D., and Newsome, W. T. (2001). Target selection for saccadic eye movements: prelude activity in the superior colliculus during a direction-discrimination task. J Neurophysiol *86*, 2543-2558.

Ignashchenkova, A., Dicke, P. W., Haarmeier, T., and Thier, P. (2004). Neuron-specific contribution of the superior colliculus to overt and covert shifts of attention. Nat Neurosci *7*, 56-64.

Keller, E. L., and Missal, M. (2003). Shared brainstem pathways for saccades and smooth-pursuit eye movements. Ann N Y Acad Sci *1004*, 29-39.

Krauzlis, R., and Dill, N. (2002). Neural correlates of target choice for pursuit and saccades in the primate superior colliculus. Neuron *35*, 355-363.

Krauzlis, R. J. (2003). Neuronal activity in the rostral superior colliculus related to the initiation of pursuit and saccadic eye movements. J Neurosci *23*, 4333-4344.

Krauzlis, R. J. (2004). Recasting the smooth pursuit eye movement system. J Neurophysiol *91*, 591-603.

Krauzlis, R. J., Basso, M. A., and Wurtz, R. H. (1997). Shared motor error for multiple eye movements. Science *276*, 1693-1695.

Krauzlis, R. J., Basso, M. A., and Wurtz, R. H. (2000). Discharge properties of neurons in the rostral superior colliculus of the monkey during smooth-pursuit eye movements. J Neurophysiol *84*, 876-891.

Krauzlis, R. J., Dill, N., and Kornylo, K. (2002). Activity in the primate rostral superior colliculus during the "gap effect" for pursuit and saccades. Ann N Y Acad Sci *956*, 409-413.

Krauzlis, R. J., and Miles, F. A. (1996). Release of fixation for pursuit and saccades in humans: evidence for shared inputs acting on different neural substrates. J Neurophysiol *76*, 2822-2833.

Kustov, A. A., and Robinson, D. L. (1996). Shared neural control of attentional shifts and eye movements. Nature *384*, 74-77.

Lee, C., Rohrer, W. H., and Sparks, D. L. (1988). Population coding of saccadic eye movements by neurons in the superior colliculus. Nature *332*, 357-360.

Kusunoki, M., Gottlieb, J., and Goldberg, M. E. (2000). The lateral intraparietal area as a salience map: the representation of abrupt onset, stimulus motion, and task relevance. Vision Res *40*, 1459-1468.

Link, S. W., and Heath, R. A. (1975). A sequential theory of psychological discrimination. Psychometrika *40*, 77-105.

Liston, D., and Krauzlis, R. J. (2003). Shared response preparation for pursuit and saccadic eye movements. J Neurosci *23*, 11305-11314.

Logan, G. D. (1994). On the ability to inhibit thought and action: A user's guide to the stop-signal paradigm. In Inhibitory processes in attention, memory and language, D. Dagenbach, and T. H. Carr, eds. (San Diego, CA, Academic Press), pp. 189-239.

Logan, G. D., Cowan, W. B., and Davis, K. A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychol Hum Percept Perform *10*, 276-291.

Macmillan, N. A., and Creelman, C. D. (1991). Detection Theory: A user's guide (New York, NY, Cambridge University Press).

McGarry, T., Chua, R., and Franks, I. M. (2003). Stopping and restarting an unfolding action at various times. Q J Exp Psychol A *56*, 601-620.

McPeek, R. M., Han, J. H., and Keller, E. L. (2003). Competition between saccade goals in the superior colliculus produces saccade curvature. J Neurophysiol *89*, 2577-2590.

McPeek, R. M., and Keller, E. L. (2002a). Saccade target selection in the superior colliculus during a visual search task. J Neurophysiol *88*, 2019-2034.

McPeek, R. M., and Keller, E. L. (2002b). Superior colliculus activity related to concurrent processing of saccade goals in a visual search task. J Neurophysiol *87*, 1805-1815.

McPeek, R. M., and Keller, E. L. (2004). Deficits in saccade target selection after inactivation of superior colliculus. Nat Neurosci *7*, 757-763.

Moore, T., and Armstrong, K. M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. Nature *421*, 370-373.

Moore, T., and Fallah, M. (2004). Microstimulation of the Frontal Eye Field and Its Effects on Covert Spatial Attention. Journal of Neurophysiology *91*, 152-162.

Orban, G. A., Van Essen, D., and Vanduffel, W. (2004). Comparative mapping of higher visual areas in monkeys and humans. Trends Cogn Sci *8*, 315-324.

Osman, A., Kornblum, S., and Meyer, D. E. (1986). The point of no return in choice reaction time: controlled and ballistic stages of response preparation. J Exp Psychol Hum Percept Perform *12*, 243-258.

Pierrot-Deseilligny, C., Muri, R. M., Nyffeler, T., and Milea, D. (2005). The role of the human dorsolateral prefrontal cortex in ocular motor behavior. Ann N Y Acad Sci *1039*, 239-251.

Pierrot-Deseilligny, C., Muri, R. M., Ploner, C. J., Gaymard, B., Demeret, S., and Rivaud-Pechoux, S. (2003). Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. Brain *126*, 1460-1473.

Rashbass, C. (1961). The relationship between saccadic and smooth tracking eye movements. J Physiol *159*, 326-338.

Ratcliff, R., Van Zandt, T., and McKoon, G. (1999). Connectionist and diffusion models of reaction time. Psychol Rev *106*, 261-300.

Reddi, B. A., and Carpenter, R. H. (2000). The influence of urgency on decision time. Nat Neurosci *3*, 827-830.

Rizzolatti, G., Riggio, L., Dascola, I., and Umilta, C. (1987). Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. Neuropsychologia *25*, 31-40.

Robinson, D. A. (1972). Eye movements evoked by collicular stimulation in the alert monkey. Vision Res *12*, 1795-1808.

Robinson, D. L., and Kertzman, C. (1995). Covert orienting of attention in macaques. III. Contributions of the superior colliculus. J Neurophysiol *74*, 713-721.

Schiller, P. H., Sandell, J. H., and Maunsell, J. H. (1987). The effect of frontal eye field and superior colliculus lesions on saccadic latencies in the rhesus monkey. J Neurophysiol *57*, 1033-1049.

Schwarz, W. (1993). A diffusion model of early visual search: theoretical analysis and experimental results. Psychol Res *55*, 200-207.

Sheliga, B. M., Riggio, L., Craighero, L., and Rizzolatti, G. (1995). Spatial attention-determined modifications in saccade trajectories. Neuroreport *6*, 585-588.

Sparks, D. L., and Hartwich-Young, R. (1989). The deep layers of the superior colliculus. Rev Oculomot Res *3*, 213-255.

Sparks, D. L., and Mays, L. E. (1990). Signal transformations required for the generation of saccadic eye movements. Annu Rev Neurosci *13*, 309-336.

Stryker, M. P., and Schiller, P. H. (1975). Eye and head movements evoked by electrical stimulation of monkey superior colliculus. Exp Brain Res *23*, 103-112.

Tsujimoto, S., and Sawaguchi, T. (2004). Properties of delay-period neuronal activity in the primate prefrontal cortex during memory- and sensory-guided saccade tasks. Eur J Neurosci *19*, 447-457.

Wurtz, R. H., and Albano, J. E. (1980). Visual-motor function of the primate superior colliculus. Annu Rev Neurosci *3*, 189-226.

Wurtz, R. H., and Mohler, C. W. (1976). Organization of monkey superior colliculus: enhanced visual response of superficial layer cells. J Neurophysiol *39*, 745-765.