



Effects of electrical microstimulation in monkey frontal eye field on saccades to remembered targets

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Abstract

Spatially selective delay activity in the frontal eye field (FEF) is hypothesized to be part of a mechanism for the transformation of visual signals into instructions for voluntary movements. To understand the linkage between FEF activity and eye movement planning, we recorded neuronal responses of FEF neurons while monkeys performed a memory-saccade task. We then electrically stimulated the same sites during the memory-delay epoch of the task. The stimulation currents used were subthreshold for evoking saccades during a gap-fixation task. Microstimulation resulted in changes in the spatial and temporal components of saccade parameters: an increase in latency, and a shift in amplitude and direction. We performed a vector analysis to determine the relative influence of the visual cue and electrical stimulus on the memory-saccade. In general, the memory-saccade was strongly weighted toward the visual cue direction, yet the electrical stimulus introduced a consistent bias away from the receptive/movement field of the stimulation site. The effects of sub-threshold stimulation were consistent with a combination of vector subtraction and averaging, but not with vector summation. Vector subtraction may play a role in spatial updating of movement plans for memory-guided saccades when eye position changes during the memory period.

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1. Introduction

Many prefrontal cortical neurons, including those in the frontal eye field (FEF), are activated during tasks that require a maintained representation of a spatial location in working memory (Baddeley, 1986; Barborica & Ferrera, 2003; Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971; Fuster, Bauer, & Jervey, 1982; Goldman-Rakic, 1995a, 1995b, 1996; Kubota & Niki, 1971; Miller & Cohen, 2001; Miller & Asaad,

2002; Robins, 1996; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999). Several groups have found that neurons throughout dorsolateral prefrontal cortex have sustained firing during the delay interval of a memory-guided saccade task (MGS) and this activity is selective for the remembered location of the target (Constantinidis, Franowitz, & Goldman-Rakic, 2001; Funahashi et al., 1989; Funahashi, Bruce, & Goldman-Rakic, 1991; Goldman-Rakic, 1995b; Sommer & Wurtz, 2001). Spatially-selective delay activity has been regarded as a neural correlate of spatial working memory and is hypothesized to be part of a neural mechanism for the association and transformation of visual signals into voluntary movements (Courtney, Ungerleider, Kell, & Haxby, 1997; Funahashi et al., 1989; Miller, Erickson, & Desimone, 1996; Sweeney et al., 1996; Wallis &

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Miller, 2003). Similar delay activity has been identified in parietal cortex (Chafee & Goldman-Rakic, 1998; Gnadt & Anderson, 1988), thalamus (Wyder, Massoglia, & Stanford, 2003) and superior colliculus (SC; Mays & Sparks, 1980) and has been interpreted in terms of motor planning or a motor error signal. To better understand how delay activity relates to movement planning, we attempted to perturb spatial memory with subthreshold electrical stimulation of the frontal eye field.

The goal of these experiments was to shed light on the computational mechanism for translating FEF delay activity into saccades. Effects of stimulation in other areas, namely MT, have been characterized as a “winner-takes-all” (WTA) competition between electrical and visual signals (Salzman & Newsome, 1994) or as a weighted vector average (Groh, Born, & Newsome, 1997; Nichols & Newsome, 2002). These outcomes may depend on specifics of the behavioral task, e.g. Salzman and Newsome (1994) found evidence of WTA when the monkey was given discrete choices, but Nichols and Newsome (2002) found evidence for weighted vector averaging when the chosen direction was allowed to vary continuously. The computation performed may also depend on the type of eye movement made. Groh et al. (1997) found that stimulation at the same site in MT could have different effects on smooth pursuit and saccades. Hence, the “read-out” mechanism revealed by microstimulation may not correspond to a fixed computation, but rather a range of possible outcomes. The results may also show a mixture of effects, such as weighted averaging or a combination of vector averaging and subtraction.

In the present experiments, we searched for sites in the anterior bank of the arcuate sulcus where saccades could be evoked with electrical stimulation (Bruce & Goldberg, 1985; Robinson & Fuchs, 1969), and where neurons with spatially tuned delay activity could be recorded (Funahashi et al., 1989). These sites were located within or nearby the physiologically-defined Frontal Eye Field (FEF; Bruce & Goldberg, 1985), which projects to SC and to oculomotor regions of the brainstem (Helmski & Segraves, 2003; Segraves & Goldberg, 1987; Segraves, 1992; Sommer & Wurtz, 1998, 2000, 2001; Stanton, Goldberg, & Bruce, 1988), and contains a map of saccade amplitude and direction (Bruce, Goldberg, Bushnell, & Stanton, 1985). A previous study of subthreshold FEF microstimulation during memory saccades (Burman & Bruce, 1997) found that stimulation during movement execution tended to delay the production of saccades directed away from the movement field of the stimulation site, but did not investigate the effects of stimulation during the memory interval.

In the present study, we found that electrical stimulation in FEF during the delay period of a memory saccade task had weak but consistent effects on the direction, amplitude and latency of voluntary saccades.

The amplitude and direction changes were consistent with a combination of visually-weighted vector averaging and vector subtraction. Vector averaging is a possible mechanism for normalizing movement amplitude in the presence of multiple targets (Lisberger & Ferrera, 1997). The vector subtraction effect suggests that subthreshold microstimulation may initiate a spatial updating of the memory-guided saccade plan (Balan & Ferrera, 2003; Duhamel, Colby, & Goldberg, 1992; Goldberg & Bruce, 1990; Quaia, Optican, & Goldberg, 1998; Salinas, 2004; Umeno & Goldberg, 1997) or its rotational equivalent (Henriques, Klier, Smith, Lowy, & Crawford, 1998; Smith & Crawford, 2001). We speculate that subthreshold stimulation may cause the oculomotor system to behave as if the monkey had made a small saccade in the direction of the movement field of the stimulation site just prior to the memory-saccade. A preliminary version of these results has been presented in abstract form (Opris & Barborica, 2001).

2. Methods

Experiments were performed on four subadult male rhesus monkeys (*Macaca mulatta*) weighing between 6 and 9 kg. All methods were approved by the Institutional Animal Care and Use Committee at Columbia University and the New York State Psychiatric Institute. Monkeys were prepared for experiments by surgical implantation of a post used for head restraint and a recording chamber to give access to the cortex. Eye position was recorded using a monocular scleral search coil (Judge, Richmond, & Chu, 1980). All surgical procedures were performed using aseptic technique and general (isoflurane 1–3%) anesthesia. Monkeys were trained to sit in a primate chair for the duration of the experiment with their heads restrained and perform the memory-saccade task. Correct performance of the task was reinforced by liquid reward.

2.1. Visual stimulation

Fixation targets were generated and controlled by a Cambridge Research Systems VSG2/3F video frame buffer. The output from the video board was displayed on a calibrated 27 in. color monitor (Mitsubishi) with a 60 Hz non-interlaced refresh rate. The monitor stood at a viewing distance of 30 in. so that the display area subtended roughly 40 deg horizontally by 30 deg vertically. The spatial resolution of the display was 1280 pixels by 1024 lines. Fixation targets were small (0.5 deg) white squares presented on a uniform gray/black background. The luminance of the fixation target was 65.0 cd/m², while the background was close to 0 cd/m² (below the photometer threshold). The frame buffer was programmed to send out digital pulses (frame sync)

for timing purposes at the beginning of each video frame in which a target was turned on or off. These pulses were recorded by the computer using a hardware timer (Lisberger Technologies), and stored together with the neuronal and eye movement data.

2.2. Neuronal recording and electrical stimulation

A recording chamber (20 mm diameter) was implanted on the intact skull overlying the *arcuate* sulcus. The recording chambers were positioned at stereotaxic coordinates 25A, 15L (Szabo & Cowan, 1984). At the start of each recording session, a hydraulic microdrive was mounted on the recording chamber. Recordings were made using platinum-iridium or tungsten electrodes with impedances of 0.1–2 M Ω @ 1 kHz. Signals from the microelectrode were amplified, filtered and monitored on an oscilloscope and audio monitor. A time-amplitude window discriminator converted extracellular action potentials into digital pulses (TTL) which were sampled by the computer with 0.01 ms time resolution. Units were isolated on the basis of waveform. When a unit was isolated, stimulus parameters such as target eccentricity were adjusted to optimize its response. Neuronal spike trains were collected and stored along with eye position and velocity records.

Sites in peri-arcuate cortex were stimulated through the same electrode used to record neuronal activity. The stimulation consisted of a train of 0.2 ms biphasic pulses at a rate of 350 pulses/s delivered by an optically-isolated pulse stimulator (AM Systems). The pulse waveform, duration and frequency were the same for all experiments. The output of the stimulator was gated by a computer-generated TTL level so as to be synchronized with other trial events. The current threshold for evoking saccades was determined by stimulating during a gap-fixation task with a 200 ms gap between fixation target offset and stimulus onset (Opris, Barborica, & Ferrera, 2001). The threshold was defined as the current level at which involuntary saccades were evoked on about half the stimulation trials (Bruce et al., 1985). Recording and stimulation sites were classified based on stimulation threshold as being within the low-threshold FEF if the threshold was less than 85 μ A (range: 10–85 μ A; mean: 43 μ A), and non-FEF peri-arcuate cortex (PAC) otherwise. This classification uses a higher threshold criterion than others have used (Bruce et al., 1985). However, we feel this is warranted as thresholds were measured during a fixation task which results in higher thresholds as compared to stimulation during free gaze (Goldberg, Bushnell, & Bruce, 1986).

The arcuate sulcus could be visualized transdurally during the recording chamber surgery. The position of the sulcus was confirmed by making long electrode penetrations (up to 10 mm below the cortical surface) during which action potentials characteristic of neuronal

cell bodies could be continuously recorded as the electrode advanced, indicating that the tip of the electrode remained in gray matter throughout the penetration. Electrical stimulation was applied at several depths along these penetrations and the elicitation of saccadic eye movements provided further confirmation that the electrode was in the arcuate sulcus. Fig. 1A shows a coronal MRI for one monkey (F) with an electrode track (*) clearly visible in the anterior bank of the arcuate sulcus. Fig. 1B shows saccades evoked during a fixation task by suprathreshold electrical stimulation at the site marked by the asterisk. Fig. 1C and D shows the microdrive coordinates for all penetrations (3 hemispheres) in monkeys A and C, and also indicates the stimulation threshold and evoked saccade vector for each site. The evoked saccades were generally contraversive and showed a mediolateral gradation of amplitudes (Bruce & Goldberg, 1985). In addition, we frequently observed a systematic rotation of the evoked saccade direction as the depth of the electrode changed. These features of the saccade amplitude and direction map are characteristic of the FEF.

2.3. Behavioral tasks

Monkeys performed memory guided saccade (MGS) tasks during recording neuronal activity and microstimulation experiments (Fig. 2). At the beginning of each trial the monkey fixated a small white square in the center of the display. While he fixated, a small (0.5 deg) white peripheral cue was flashed at an eccentricity of 10 deg for 300 ms. The monkey was required to maintain fixation throughout the cue period and also throughout the subsequent delay period. At the end of the delay interval (1000 ms) the fixation target was extinguished and the monkey was rewarded for making a saccade to the remembered location of the cue. The task used in this experiment is similar to that used by Goldman-Rakic and colleagues (Funahashi et al., 1989, 1991). For neuronal recording (Fig. 2A), there were eight target positions, equally spaced (45 deg) around the clock face. This allowed us to estimate the receptive/movement field of the neuron. Neuronal activity was analyzed in three trial epochs; cue (30 ms after the onset of the visual cue until cue offset), delay (100 ms after the offset of the cue until the end of the delay) and presaccade (100 ms ending with the onset of the memory-saccade). A visually-guided saccade task without delay was also used to map neuronal responses as a function of target direction and eccentricity.

For stimulation experiments, the MGS task was the same as that used for neuronal recording except that only four cue locations were used (Fig. 2B). Stimulation trials were randomly interleaved with non-stimulation trials (50%/50%). Electrical microstimulation in the MGS task was delivered during the entire 1 s delay epoch and only

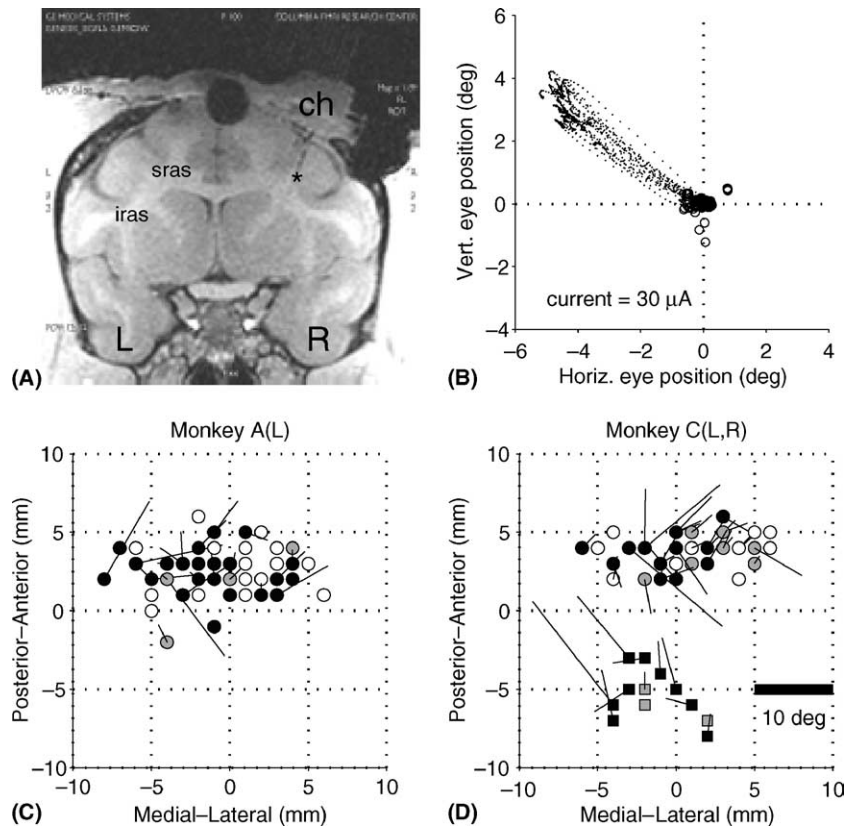


Fig. 1. Reconstruction of recording/stimulation sites. (A) Coronal MRI at the level of the arcuate sulcus; left and right hemispheres are labeled. “iras” and “sras” are the inferior and superior rami of the arcuate sulcus, respectively. “ch” is the recording chamber in the right hemisphere. Asterisk indicates electrode track. (B) Contraversive saccades evoked by suprathreshold stimulation at the site in (A) indicated by “*” (threshold was 25 μA). (C) Microdrive coordinates for electrode penetrations in monkey A, left hemisphere. Filled circles indicates stimulation thresholds $\leq 50 \mu\text{A}$, gray circles 50–100 μA , and open circles $> 100 \mu\text{A}$. Lines indicate electrically-evoked saccade vectors. (D) Microdrive coordinates for monkey C, left hemisphere (circles) and right hemisphere (squares). Coordinates for right hemisphere were shifted 5 mm posterior for display purposes. Same conventions as (D).

during the delay while the monkey maintained fixation on the visible fixation mark in the center of the display. The stimulating current varied between 5 μA and 90 μA depending on the stimulated site threshold, in accord with other studies (Butovas & Schwarz, 2003; Groh et al., 1997). The stimulation pulse frequency was 350 Hz and the current level was set at 50% of threshold except for sites that were tested with multiple current levels. Control experiments were performed using other current levels, up to a maximum of 100 μA , to determine if the effects depended on the intensity of stimulation. Monkeys were reinforced on stimulation trials with a probability commensurate with their performance on non-stimulated trials (75–95% of the trials).

2.4. Eye movement recording

Eye position was monitored using a monocular scleral search coil system (CNC Engineering). Separate horizontal and vertical eye position signals were fed through an analog differentiator (low pass, -3 dB at 25 Hz) to yield horizontal and vertical eye velocity, which were then dig-

itally sampled by computer at 1 kHz/channel and stored on disk for further analysis. Eye position and velocity records were used to estimate saccade latency and final eye position. First, polar eye velocity (R') was computed as the Pythagorean sum of horizontal (H') and vertical (V') eye velocity. Then, polar eye velocity was differentiated to yield polar eye acceleration (R''), and saccade onset was computed using an acceleration criterion ($R'' > 500 \text{ deg/s}^2$). The end of the saccade was found using the complementary criterion ($R'' < 500 \text{ deg/s}^2$), and the final eye position was obtained by taking the average eye position in a 20 ms window triggered on the end of the saccade. Saccade latency was computed for each trial as the onset time of the saccade relative to the end of the delay interval.

To determine if subthreshold microstimulation during the MGS task affected ocular fixation stability, we calculated radial eye position during the delay interval for stim vs. no-stim trials for all experiments. Within each condition, trials were combined and within-session eye position distributions were constructed by binning the samples. The within-session distribution was nor-

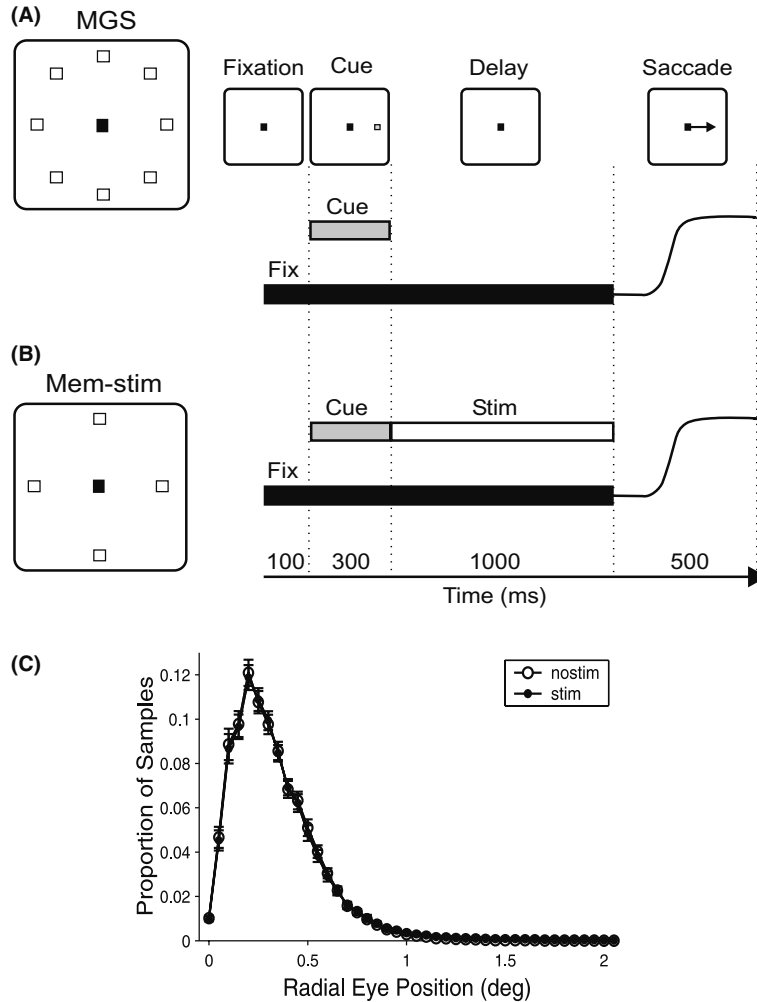


Fig. 2. Schematic description of the microstimulation paradigm. (A) Memory guided saccade task (MGS). The leftmost panel represents the visual display with eight target positions equally spaced (45 deg) around the clock face. The bars show the successive time epochs corresponding to fixation, cue presentation, delay and the saccadic response. A saccade towards the remembered location of the visual cue is depicted by the eye position trace. (B) Memory stimulation task. Electrical stimulation was delivered during the entire delay epoch (1000 ms) of the MGS task (panel a) at four target positions, 0, 90, 180 and 270 deg. (C) Fixation accuracy for stimulated (open circles) and non-stimulated trials for all experiments. Error bars are ± 1 s.e.m.

malized by the total number of samples for that session. The average distribution was constructed by computing the mean \pm s.e.m. for each bin, and is shown in Fig. 2C. (Note that the eye position window was ± 2.0 deg but fixation precision was typically better than 0.5 deg) The fact that the distributions do not peak at zero reflects the fact that radial eye position is necessarily positive and does not indicate any systematic bias. There was no significant difference between the distributions for stim and no-stim trials (t -test, samples paired by bin number, $p > 0.9$).

2.5. Data analysis

2.5.1. Neuronal responses

Neuronal responses were collected while monkeys performed a memory-guided saccade task. The mean fir-

ing rate (f) during the delay and presaccadic intervals were used to assess the strength of the prefrontal neuronal activity involved in saccade planning and initiation. The optimal direction for neuronal activity and the corresponding tuning vector were estimated using an array of eight spatial locations for visual cues having the same eccentricity but equally spaced polar directions. The tuning vector was computed as a vector sum:

$$\mathbf{V} = \sum (\mathbf{u}_i * f_i) \quad (1)$$

where \mathbf{u}_i is a unit vector pointing to the i th target and f_i is the firing rate associated with that direction. To determine the systematic modulation of neural activity during relevant time epochs we calculated a tuning index TI defined by:

$$\text{TI} = (f_{\max} - f_{\min}) / (f_{\max} + f_{\min}) \quad (2)$$

where f_{\max} and f_{\min} are max firing rates at the preferred location (in the response field), and min firing rates at the opposite (null) location, respectively. This index ranges between 0 (equal response to best and null locations) and 1.0 (no response at null location).

2.5.2. Behavioral responses

The interaction between electrically injected and visually-evoked memory signals can be modeled as a combination of two vectors. In each stimulation trial, the saccade vector \mathbf{R} is expressed as a weighted combination of the visual (\mathbf{V}) and electric (\mathbf{E}) vectors. The visual vector is identical to the cue vector, which we assume to be represented as a visual memory or saccade plan. The possible outcomes for the subthreshold stimulation experiment are shown in Fig. 3. The stimulation effect was characterized in terms of the difference vectors (\mathbf{D}_i) between the memory saccade endpoint in the absence of stimulation (\mathbf{V}_i) and in the presence of stimulation (gray circles). We considered six distinct outcomes: (1) Visual “winner-takes-all” (WTA; Fig. 3A) implies that there is no difference between the memory saccades with or without stimulation (i.e. no effect). (2) Electric WTA (Fig. 3A) implies that the monkey saccades to the RF/MF of the stimulation site regardless of the visual cue. (3) Vector averaging (Fig. 3A) represents a compromise between visual and electric WTA and may be weighted toward one or the other. (4) Vector summation (Fig. 3B) occurs when the visual and electric

vectors add. (5) Vector difference (Fig. 3C) is the opposite of vector summation. (6) Finally, Fig. 3D shows a linear combination of vector subtraction and averaging.

The outcomes illustrated graphically in Fig. 3 can be formalized using two-dimensional vector analysis. The first step is to compute four vectors ($\mathbf{V}_1, \dots, \mathbf{V}_4$) each of which represents the average memory-guided saccade vector for one of the four cue locations in the absence of stimulation. The signal introduced by electrical stimulation is described by a vector (\mathbf{E}). It is then possible to express the saccade vector (\mathbf{R}_i) for each stimulation trial as a linear combination of the component vectors (\mathbf{V}_i, \mathbf{E}):

$$\mathbf{R}_i = w_v \mathbf{V}_i + w_e \mathbf{E} \quad (3)$$

where, w_v and w_e are weights for visual and electric vectors, respectively.

In general, \mathbf{E} is not known (although it is presumably related to the preferred location of neurons at the stimulation sites and/or the saccades evoked by electrical stimulation, if any) and therefore it is impossible to solve for w_v and w_e exactly. One solution proposed by Groh et al. (1997) is to assume that the sum of the weights, $w_v + w_e = 1$, allowing one to use a single parameter g ($w_e = g, w_v = 1 - g$). The gain parameter can then be estimated by a linear regression equation:

$$\mathbf{R}_i - \mathbf{V}_i = \mathbf{C} - g \mathbf{V}_i \quad (4)$$

with $\mathbf{C} = g \cdot \mathbf{E}$ being a constant vector (Groh et al., 1997). Pure vector averaging (VA) is described by $g = 0.5$, while the extreme situations $g = 0$ and 1 correspond to visual and electrical winner-take-all (WTA) mechanisms, respectively (Fig. 3A).

The single-parameter model works best when the \mathbf{R} vectors lie near the line that connects the tips of the \mathbf{V} and \mathbf{E} vectors. This line includes the VA and WTA outcomes, but does not include vector summation or subtraction. Groh et al. (1997) suggested a work-around for these latter possibilities. However, we have chosen a different analysis that provides a direct estimate of the direction of the \mathbf{E} vector. This analysis is valid when the weight of the visual vector, \mathbf{V} , is close to 1.0, as it indeed turned out to be in nearly all experiments (see Section 3). In this alternative analysis, we calculated for each stimulus location the difference between the saccade vector (averaged over trials) in the absence of stimulation and the saccade vector in the presence of stimulation. This resulted in four difference vectors (Fig. 3, gray arrows labelled \mathbf{D}_i), where

$$\mathbf{D}_i = \mathbf{R}_i - \mathbf{V}_i \quad (5)$$

From Eq. (3), it can be seen that if w_v is close to 1.0, then the \mathbf{D}_i vectors approximate a scaled version of the \mathbf{E} vector. The condition that $w_v \approx 1.0$ is satisfied for visual WTA ($w_v = 1.0, w_e = 0.0$), vector summation ($w_v = 1.0, w_e = 1.0$) and vector subtraction ($w_v = 1.0, w_e = -1.0$). Even if w_v is not close to 1.0, the sum of

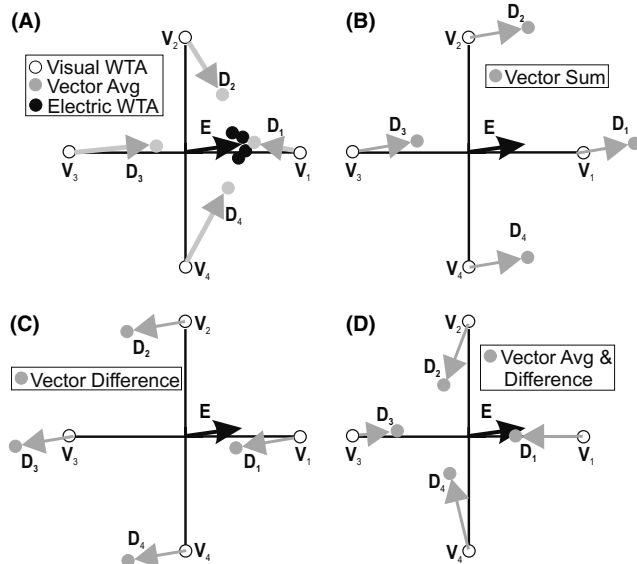


Fig. 3. Schematic description of vectorial computations for readout algorithms. (A) Groh-Born-Newsome model. The interaction between the electric (\mathbf{E}) and visually (\mathbf{V}) elicited signals, results in one of the following possibilities: a winner-takes-all (WTA) vector for visual cue, a winner-takes-all vector for electric signal, or vector average. Open circles represent visual vectors \mathbf{V}_i and grey arrows stand for difference vectors \mathbf{D}_i . (B) Expected pattern of results for vector summation. (C) Expected pattern for vector subtraction. (D) Expected pattern for a combination of vector averaging and subtraction.

the \mathbf{D}_i vectors may still approximate the direction of the \mathbf{E} vector provided the stimulation effect is similar in magnitude (but not necessarily in direction) for all cue locations. We therefore took the sum of the four difference vectors to be an estimate of the direction of the \mathbf{E} vector. This analysis allows all possible outcomes, including vector summation and subtraction.

Statistical analysis. To determine the statistical significance of neuronal activity during the cue, delay and presaccadic intervals we compared the mean firing rate to firing during the fixation epoch using an unpaired t -test. We also tested each cell for a significant difference ($p < 0.05$) in mean firing rate across cue directions using a one-way ANOVA. To determine the statistical significance of the stimulation effects (differences in saccade amplitude, direction and latency between stimulated and non-stimulated trials), we performed a two-way ANOVA (factors: stimulation present/absent and cue direction; $p < 0.05$ level of significance). To calculate linear and circular correlation coefficients we used Matlab scripts for linear correlation algorithm (level of significance was $p < 0.05$) and a Rayleigh test for circular uniformity of angular distributions (Zar, 1999). The level of significance was $p < 0.05$ for both tests. Rayleigh's test determines whether the angles are uniformly distributed around a circle or have a unimodal non-uniform distribution. It returns the probability of the null hypothesis that the population is uniformly distributed (Zar, 1999).

2.5.3. Database and classification of neurons and stimulation sites

Based on previous work (Funahashi et al., 1989, 1991) we classified neuronal activity in our memory-guided saccade task as visual, memory or movement-related. We recorded the activity of 129 neurons (72 cells in monkey A, 51 cells in monkey C, and 4 cells in monkey D, 2 in monkey F). We stimulated at 177 sites. Trials were excluded if there were multiple saccades or if the memory-saccade latency was not in the range of 80–350 ms. A site was removed from the database if there were less than 4 valid repetitions of each trial type. Of the original 177, 146 sites (74 sites on monkey A, 60 sites on monkey C, 7 sites on monkey D and 5 sites on monkey F) met the selection criteria and 31 sites were excluded. Of the selected sites, 82 were classified as FEF based on stimulation threshold (see “electrical microstimulation”), and

Table 1
Number of cells with significant effects (ANOVA $p < 0.05$) of cue direction on neural activity during visual, delay, and presaccadic epochs

| Area | Visual | Delay | Presaccadic |
|-------|--------------|--------------|--------------|
| FEF | 37/70 (53%) | 44/70 (63%) | 42/70 (60%) |
| PAC | 24/59 (41%) | 23/59 (39%) | 25/59 (42%) |
| Total | 61/129 (47%) | 67/129 (52%) | 67/129 (52%) |

ANOVA (factor = cue direction; $p < 0.05$).

Table 2
Number of stimulation sites with significant effect of stimulation on saccade amplitude, direction and latency

| Area | Amplitude | Direction | Latency |
|-------|--------------|--------------|--------------|
| FEF | 33/82 (40%) | 31/82 (38%) | 31/82 (38%) |
| PAC | 26/64 (41%) | 27/64 (42%) | 19/64 (30%) |
| Total | 59/146 (41%) | 58/146 (40%) | 50/146 (34%) |

ANOVA (factor = stimulation present/absent; $p < 0.05$).

64 as high threshold peri-arcuate cortex (PAC). The number of cells with statistically significant direction tuning and the number of stimulation sites with significant effects are shown in Tables 1 and 2.

3. Results

To test the hypothesis that spatially selective delay activity in dorsolateral prefrontal cortex is involved in the planning of memory-guided saccades, we recorded neuronal responses of neurons in FEF and adjacent peri-arcuate cortex of four monkeys as they performed a memory-saccade task. We then electrically stimulated the same sites with subthreshold current levels during the delay epoch of the task. Results for a typical experiment are shown in Fig. 4. Fig. 4A shows firing rate histograms for a single FEF cell and the tuning plot indicating its best direction vector (gray arrow). The preferred directions of the neuron for the delay and presaccadic intervals were in the lower-left hemifield. We also mapped the presaccadic activity as a function of target eccentricity using a simple visually-guided saccade task (Fig. 4A, lower central plot). The firing rate increased monotonically as a function of stimulus eccentricity up to 16 deg, even though the electrically evoked saccades for this site averaged only 4.5 deg.

Immediately after recording, the site was stimulated during the memory delay with 30 and 40 μA currents (Fig. 4B and C shows data for both current levels combined). The stimulation threshold for this site was 60 μA . To show the effect of microstimulation for each direction we plotted saccade endpoints for both STIM and NOSTIM trials. The delay period microstimulation had significant effects on saccade vector (Fig. 4B) and latency (Fig. 4C). For remembered targets near the preferred location, electrical stimulation biased saccades by deflecting them downward, as compared to non-stimulation trials (max difference ~ 3.0 deg; $p < 0.05$ t -test). Electrical stimulation also caused an increase in saccade latency of up to 36 ms. The latency increase was maximal for targets near the preferred location.

3.1. Physiological characterization of stimulation sites

Most prefrontal neurons have spatially tuned activity during the visual cue, delay and presaccade epochs of

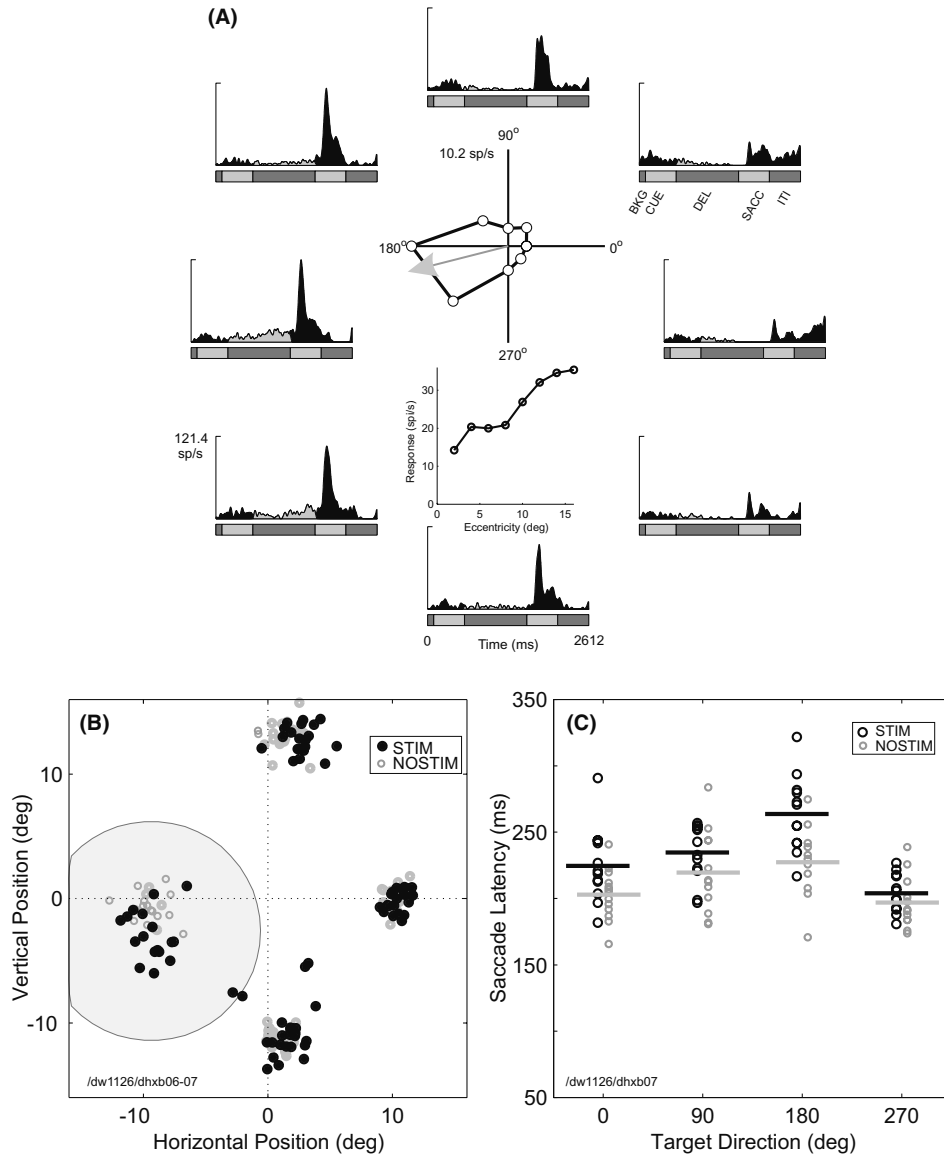


Fig. 4. Standard experiment performed at one FEF site. (A) Multigram showing the neuronal spiking activity in the MGS task. The peri-stimulus-time-histograms (PSTHs) aligned on cue onset are plotted for the eight target directions. The uppermost of the two central plots shows average delay activity as a function of cue direction. The gray arrow indicates the preferred direction (center-of-mass vector). The lower-central plot shows presaccadic activity as a function of target eccentricity. (B) Effect of sub-threshold electrical microstimulation. Saccade endpoints are depicted by black dots for STIM trials and for the NOSTIM trials by gray circles. The receptive/memory/movement field is gray shaded. (C) Latency plot showing the distribution of saccade onsets for STIM and NOSTIM trials. For the 180 deg target location, the latency difference between STIM and NOSTIM conditions was 36 ms. The average points for both types of trial blocks are depicted by small horizontal bars (black for STIM trials and gray for NOSTIM trials).

delayed saccade tasks. The relative strength of activity during these epochs can be used to classify cells as “visual”, “visual–movement”, or “movement” (Boch & Goldberg, 1989; Bruce & Goldberg, 1985; Funahashi et al., 1989; Wurtz & Mohler, 1976). To understand the effects of microstimulation, it is important to know which of these signals is dominant at the site of stimulation. Fig. 5A compares mean activity for the preferred direction during the visual cue and memory delay intervals for each neuron. In low-threshold FEF, the visual response was somewhat stronger than the delay activity

(based on regression slope $m = 1.14$), whereas in high-threshold PAC, the two responses were comparable ($m = 0.91$). Neural activity during visual and delay epochs was well-correlated ($r = 0.76$ for $n = 70$ FEF cells, and $r = 0.89$ for $n = 59$ high threshold PAC cells). Fig. 5B shows that delay and presaccadic activity were also correlated ($r = 0.45$ for FEF; $r = 0.84$ for PAC). However, in FEF, presaccadic activity was typically much more robust than delay activity ($m = 4.08$), whereas presaccadic and delay activity were comparable ($m = 0.94$) for high-threshold PAC.

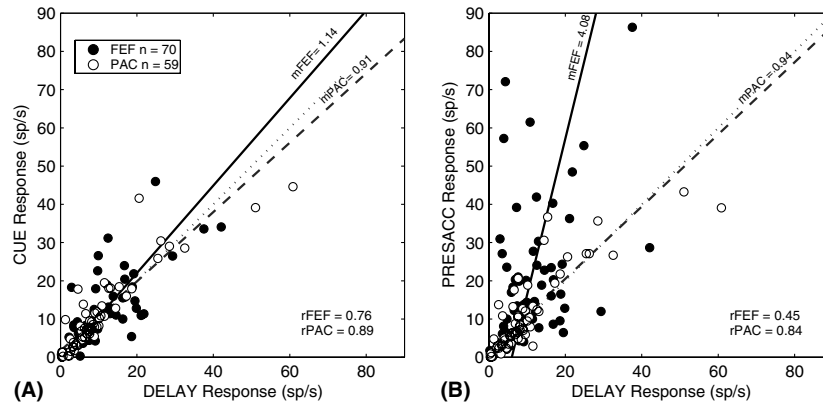


Fig. 5. Characterization of neurons recorded at stimulation sites. (A) Scatter plots showing the mean firing rate during visual cue vs. delay epoch for low threshold FEF cells (empty circles) and higher threshold peri-arcuate cells (PAC; filled circles). The number (n) and correlation coefficients (r) are shown for both sub-populations. Solid and dashed lines are linear regressions ($m = \text{slope}$). Dotted line is $x = y$. (B) Mean firing rate for presaccadic vs. delay activity. Same conventions as (A).

3.2. Subthreshold stimulation effects on saccade parameters

Each stimulation site was tested for statistically significant effects of subthreshold stimulation on saccade latency and saccade vector (amplitude and direction). From a total of 146 microstimulation sites, we found 59 sites with a significant effect on saccade amplitude (41%), 58 sites with an effect on direction (40%) and 50 sites with a shift in saccade latency (34%). Table 2 shows the breakdown according to low-threshold FEF and high-threshold PAC sites. The shift in saccade latency distribution at the population level is shown in Fig. 6A. For sites with a significant latency shift ($n = 50$; $p < 0.05$; ANOVA, shown in darker color) the latency difference was 16.4 ± 39.2 ms (mean \pm s.d.). Fig. 6B shows the distribution of saccade amplitude changes; for sites with significant amplitude change ($n = 59$), the amplitude change averaged -1.5 ± 1.5 deg

(mean \pm s.d.), i.e. there was a general decrease in saccade amplitude. On average, the amplitude of saccades evoked by suprathreshold stimulation during a fixation task (mean $6.74 \text{ deg} \pm 5.23$ s.d.) was smaller than the amplitude of voluntary memory-saccades during the MGS task ($11.24 \text{ deg} \pm 1.68$ s.d.). Hence, a subthreshold stimulation-induced reduction in memory-saccade amplitude is consistent with vector averaging or subtraction, but not with summation (see Section 2: “Readout algorithms”). Saccade direction change is defined as the angular difference between saccade direction and target direction. Fig. 6C shows the distribution of saccade direction changes. At the population level, one expects the mean for all sites to be close to zero as the direction change can be either positive or negative, and this was indeed the case. However, there were $n = 58$ (40%) sites with a statistically significant direction difference ($p < 0.05$; ANOVA). Memory-guided saccades tend to have an upward bias. If this bias were affected by

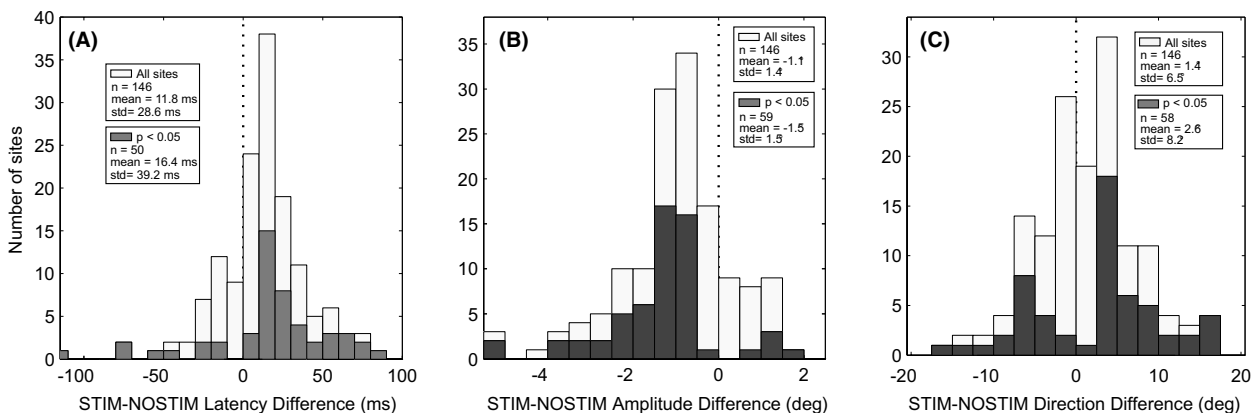


Fig. 6. Microstimulation effect on saccade latency, amplitude and direction. (A) Overlay histograms showing the distribution of saccade latency difference between STIM and NOSTIM trials. (B) Overlay histograms showing the distribution of saccade amplitude differences. (C) Histograms showing the distribution of saccade direction differences between STIM and NOSTIM trials. For all panels, the sites that meet the significance criterion ($p < 0.05$) are shown as the shaded histograms.

stimulation, it might confound the results. The effect of stimulation on upward bias was tested by analyzing the vertical component of memory-saccades for stimulated and non-stimulated trials. Specifically, for each site, we calculated the vertical component of each saccade (endpoint–startpoint), and then averaged the vertical components to determine the mean drift. We found that the upward drift, averaged across all sites, was 0.36 deg for no-stim trials and 0.32 deg for stim trials. The difference between stim and no-stim was not significant ($p = 0.22$, t -test paired by site).

3.3. Vectorial readout algorithms

The effect of subthreshold stimulation can be quantified using the regression analysis of Groh et al. (1997); see Section 2.5.2. The example site in Fig. 7A had a regression gain (Eq. (4)) $g = 0.29$ with significant shifts in the distribution of saccade endpoints (ANOVA, $p < 0.05$) away from the RF/MF of the stimulation site. This site had a high threshold for stimulation evoked saccades ($>100 \mu\text{A}$), although nearby sites (700 μm above and 600 μm below) were low threshold FEF (the electrical saccade vector for the nearer low threshold site was rightward, amplitude = 5 deg, direction = 30 deg). It is therefore possible that this site was within the physiologically-defined FEF, but in the superficial layers where thresholds for evoking saccades are higher.

To quantify the stimulation effects, we used a multivariate regression analysis (see Section 2). The distribution of gain terms g (Eq. (4)) indicates a weak but statistically significant effect of stimulation at the population level (Fig. 7B; p -values are the results of t -tests comparing the mean of each distribution against zero) for both low-threshold FEF and higher threshold PAC sites. The gains were larger for FEF than PAC sites, but the differences were not significant (t -test, $p > 0.3$).

3.4. Relationship between microstimulation effects and neuronal activity

How is the preferred direction of the delay period activity related to the effects of subthreshold microstimulation? To show a quantitative relationship between delay period activity and the effect of sub-threshold stimulation, we computed the preferred direction of single neuron activity with the direction of the subthreshold stimulation vector (vector sum of the difference vectors, see Fig. 3 and Section 2, Eq. (5)). We did this for each site where we had recorded at least one neuron with the memory-guided saccade task and performed stimulation with the memory-saccade task ($n = 123$ neuron–stimulation site pairs). The distribution of angular differences between the subthreshold stimulation vector and the preferred neural activity direction are shown in Fig. 8A–C. In each subpanel, the data are split according to which part of the delay period was used for computing neuronal tuning: “Delay” indicates the interval starting 100 ms after cue offset and ending with go signal (900 ms, light bars); “Presacc” indicates just the 100 ms interval prior to saccade onset (dark bars). At the population level (Fig. 8A), there was an inverse relationship between preferred delay/presaccadic activity and the direction of the largest influence of subthreshold microstimulation on memory guided saccades ($p < 0.001$, Rayleigh test). This relationship was also observed for presaccadic activity when the data were split between FEF (Fig. 8B) and PAC (Fig. 8C), but not for delay period activity at high threshold PAC sites ($p = 0.388$, Rayleigh test). This inverse relationship is consistent with vector subtraction.

As a further test, we compared the direction of the subthreshold stimulation effect with the direction of the saccades evoked by suprathreshold stimulation (Fig. 8D). The distribution of angular differences was

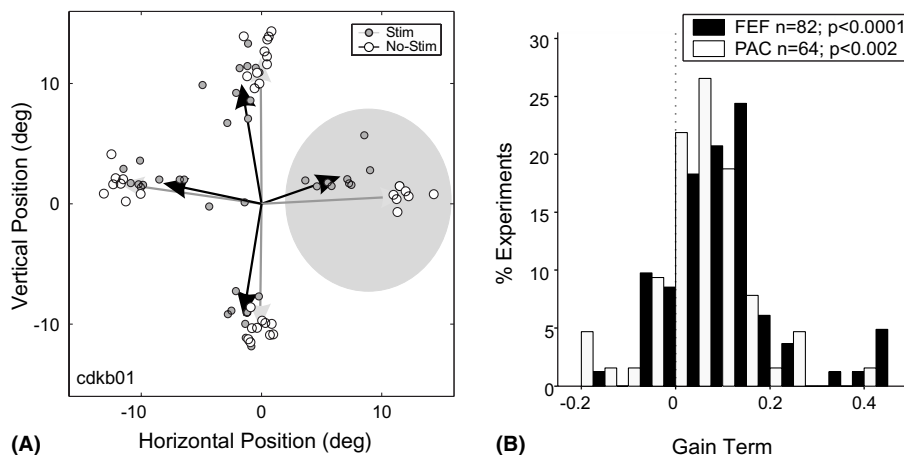


Fig. 7. (A) Example of effects of stimulation on saccade vectors. Grey vectors and open dots correspond to the NOSTIM condition, while black vectors and filled circles stand for STIM condition. Microstimulation current was 50 μA (threshold $> 100 \mu\text{A}$). The gray oval indicates the RF location for the neuron recorded at this site. (B) Distribution of gain terms for FEF and PAC stimulation sites.

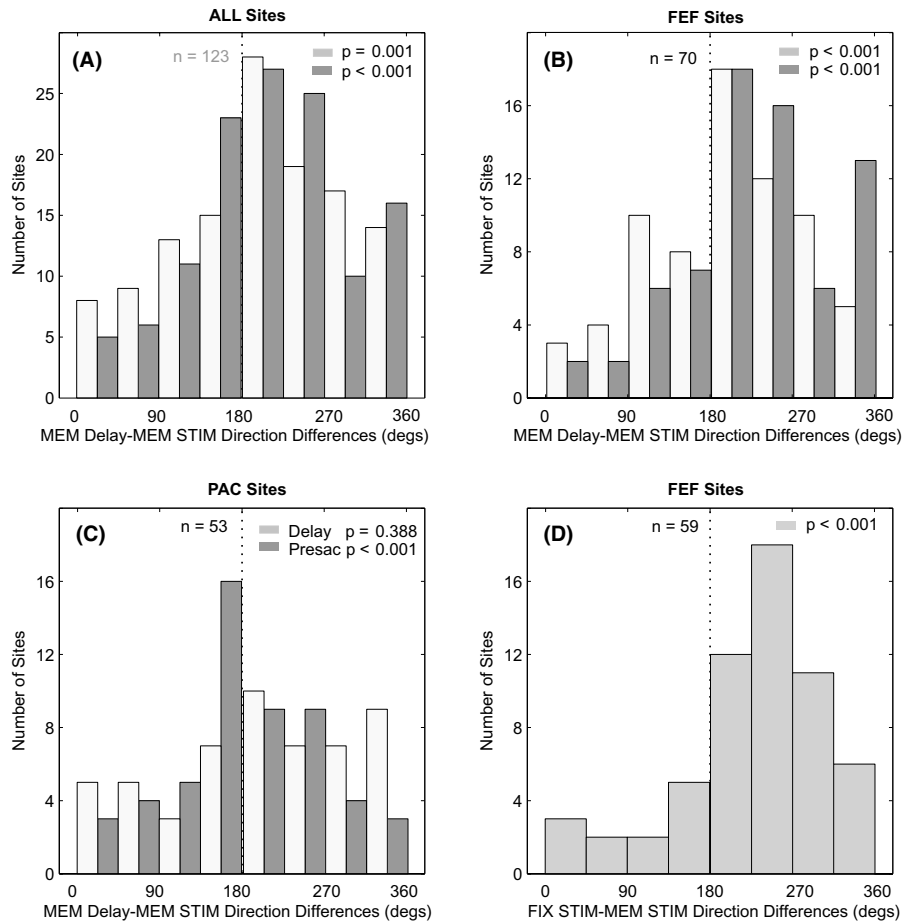


Fig. 8. Population histograms showing the difference of the sub-threshold stimulation vector relative to the preferred neural activity direction (panels A–C). (A) All sites in the population. Light gray bars correspond to the delay epoch and dark grey bars correspond to the presaccadic neural activity. (B) Low threshold FEF sites. (C) High threshold PAC sites. (D) Subthreshold memory stimulation vs. suprathreshold electrically elicited saccade vectors.

significantly non-uniform ($p < 0.001$, Rayleigh test). This comparison was also suggestive of an inverse relationship, although there were many sites where the difference angle was closer to perpendicular, which is consistent with vector averaging.

To look at the relationship between neuronal tuning and subthreshold stimulation effects in more detail, we pooled all the subthreshold stimulation data ($n = 123$ neurons/stimulation sites). To combine data from different sites, we rotated the difference vectors (Section 2, Eq. (5)) by an amount equal and opposite to the direction of the neuronal tuning vector for each site. (Imagine taking Fig. 3A and rotating it until the \mathbf{E} vector points directly to the right, except instead of the \mathbf{E} vector, the direction of the neuronal tuning vector was used as the rotation angle). The results of this transformation and pooling are shown in Fig. 9. Fig. 9A and C shows the result when the rotation was based on the neuronal tuning vector for delay activity, while Fig. 9B and D shows the result when the rotation was based on the tuning vector for presaccadic activity. The thin lines represent

the difference vectors for individual experiments. The vectors were sorted by cue direction (relative to the preferred direction of the neuronal response), and the tails of the vectors were offset accordingly. The distribution of vector directions was significantly non-uniform (Rayleigh test, $p < 0.01$) for all 8 conditions in FEF (Fig. 9A and B), but only for 4 of 8 conditions in PAC (Fig. 9C and D).

The open arrows indicate the population average of the difference vectors for each cue direction (note: the length of the individual difference vectors has been reduced by a factor of 2 so that they can be plotted on the same scale as the average vectors). The sum of the population average vectors is shown by the large filled arrow in the center of each plot. This summed vector should approximate the direction of the scaled electrical vector, $w_e \mathbf{E}$, (see Section 2.5.2), and will be referred to as $\hat{\mathbf{E}}$. The direction of the $\hat{\mathbf{E}}$ vector was significant (Rayleigh $p < 10^{-4}$) for all but Fig. 9C ($p = 0.4$), and the amplitude was significant (t -test, one-tailed, $p < 10^{-4}$) in all 4 conditions. For vector averaging or

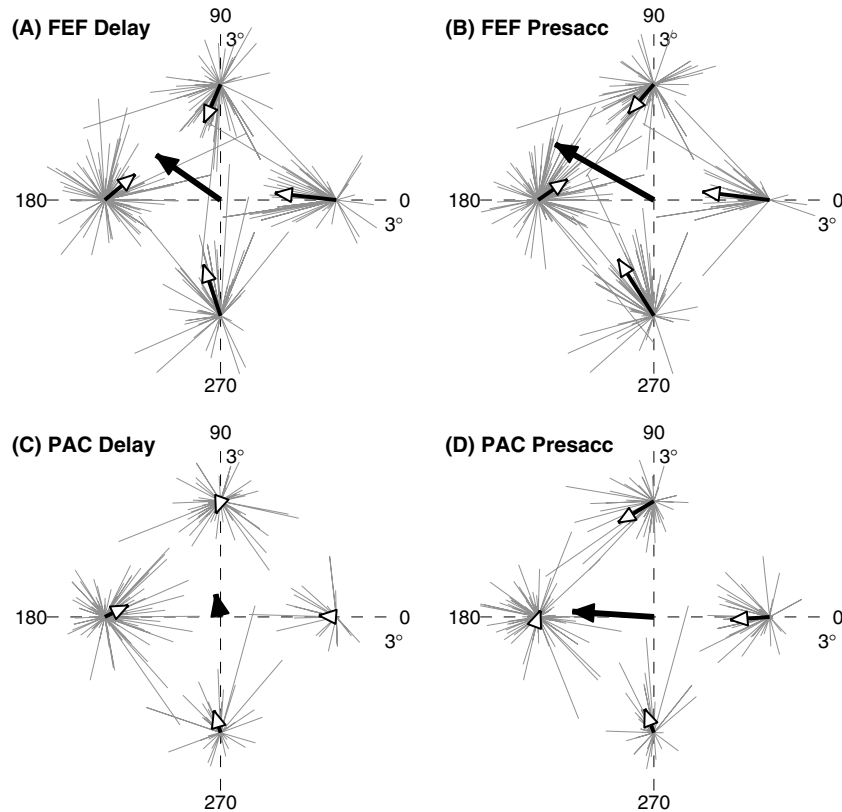


Fig. 9. Population vector plots. (A) Delay period and (B) presaccadic epoch. Thin lines represent the difference vectors for individual experiment and the open arrow indicate the population average of the difference vectors for each cue direction (length of individual difference vectors has been reduced by a factor of 2). Heavy filled arrows represent the sum of the average difference vectors (open arrows).

summation, one would expect that the $\hat{\mathbf{E}}$ vector would point to the right ($w_e > 0$). The $\hat{\mathbf{E}}$ vector actually points to the left ($w_e < 0$), which is consistent with a combination of vector averaging and vector subtraction (compare with Fig. 3D).

4. Discussion

These experiments address the relationship of prefrontal cortex and the mechanism used in saccade planning and initiation (Balan & Ferrera, 2003; Funahashi, 2001; Goldman-Rakic, 1996; Hanes & Schall, 1996; Miller & Cohen, 2001; Schall, 2004; Schlag Rey, Schlag, & Dassonville, 1992; White & Snyder, 2004). The results suggest that a linkage between neuronal activity and saccade planning exists. This linkage is illustrated by the effects of microstimulation on saccade parameters. We found that sub-threshold currents injected during the memory delay period can cause small but statistically reliable changes in saccade amplitude, direction, and latency at about 40% of the stimulation sites. Here we discuss: (a) the behavioral effects of microstimulation, (b) the relationship between neuronal activity and microstimulation effects, and (c) the readout algorithms.

4.1. Microstimulation effects

The main findings are that the saccade planning mechanism becomes altered by electrical stimulation, causing behavioral changes in the saccadic eye movement vector and shifts in saccade latency. The distributions of saccade latency, mean saccade amplitude, and mean direction (Fig. 5) showed significant differences between the stimulation and no-stimulation conditions. These effects illustrate a causal relationship between delay period stimulation in peri-arcuate cortex and saccade planning. The increase in saccade latency may happen because the stimulating current disrupts cognitive signals involved in the planning and control of saccades (Constantinidis, Williams, & Goldman-Rakic, 2002; Goldberg & Bushnell, 1981; Tanji & Hoshi, 2001). Or it may result from the activation of neurons that inhibit saccade production (Burman & Bruce, 1997). Electrical stimulation modified memory-saccade vectors by reducing their amplitude and altering their direction. The reduction in amplitude was consistent with an averaging mechanism, as the electrical saccade vector was generally shorter than the desired voluntary saccade. The changes in both saccade direction and amplitude were consistent with vector subtraction in that (1) the change

in amplitude at the preferred location was greater than that opposite the preferred location, and (2) the shift in direction of the saccade vectors for locations orthogonal to the preferred-null axis was away from the preferred location (Fig. 9).

Stimulation sites were categorized as high or low threshold based on the stimulation threshold measured during a gap-fixation task. At the population level, stimulation effects were strongest and most reliable for low threshold sites (Fig. 9A and B). For both high and low threshold sites, presaccadic activity (Fig. 9B and D) was a better predictor of the stimulation effect than was delay activity (Fig. 9A and C). The strongest and most reliable effect was obtained when the effect of stimulation on saccade vectors was compared with presaccadic activity at low threshold sites (Fig. 9B). These results favor the idea that stimulation in FEF and periarculate cortex mainly affects saccade planning rather than the memory of cue location.

The outcome of any stimulation experiment may depend on the strength or frequency of the stimulating current. For extremely low currents, the visually-evoked saccade should win; for extremely high currents, the electrically-evoked saccade may win, and for intermediate currents one may observe vector averaging. This might present difficulties in discerning the read-out algorithm for experiments in which the full range of outcomes is obtained. However, in the present experiments, there was always a strong tendency for the visual cue memory to win out and the effects of stimulation could best be described as a perturbation away from this visually dominant mode. The perturbation resulted in a tendency toward vector averaging and subtraction, but “pure” averaging and subtraction were never observed, much less electrical WTA. This makes the interpretation more straightforward because it is clear that increasing the subthreshold current might enhance the magnitude of the effect, but would not affect the results qualitatively (e.g. by changing a vector averaging outcome into electrical WTA, or by changing summation to subtraction).

Stimulation frequency, which was set at 350 Hz, may also play a role. There is evidence that inhibitory interneurons fire at higher frequencies than excitatory neurons (see Constantinidis & Goldman-Rakic, 2002). Thus, high frequency stimulation may selectively activate inhibitory mechanisms. On the other hand, Murasugi, Salzman, and Newsome (1993) have looked at the effects of varying stimulus frequency (up to 500 Hz) in area MT. They found that increasing stimulation frequency increased the strength of the effect they observed, but did not change its direction. They concluded that “increasing current frequency appears to amplify the directional signal within the cortex without degrading the specificity of the signal.”

4.2. Presaccadic remapping of visual spatial signals

Our results show an inverse relationship between the preferred direction of delay/presaccadic activity and the direction shift caused by subthreshold microstimulation on memory guided saccades (Figs. 8 and 9). This relationship is consistent with vector subtraction (Fig. 3D). We speculate that microstimulation might mimic a motor command for a saccade toward the movement field of the stimulation site. This motor command might then induce a remapping of visual space that results in a correspond to a modification of the memory-saccade plan. This idea is consistent with the emerging view that the FEF region is involved in maintaining a spatially accurate representation of target location that compensates for eye movements that intervene between target disappearance and movement onset (Balan & Ferrera, 2003; Goldberg & Bruce, 1990). It should be noted that the present results do not show pure vector subtraction, but rather a combination of vector averaging and subtraction. This is reasonable as cortical circuits that control movement may perform both computations; averaging to ensure that movement amplitude is appropriately scaled (Lisberger & Ferrera, 1997), and subtraction-based remapping to adjust both the proper amplitude and direction of movement (Quaia et al., 1998; Umeno & Goldberg, 1997). These functions, averaging and subtraction, may be carried out by the same neurons or by different groups of neurons. If they are carried out by separate subpopulations of neurons, extracellular stimulation may not have fine enough spatial resolution to selectively activate one group or the other.

4.3. Comparisons with other stimulation studies

Microstimulation of direction columns in area MT during perceptual tasks (Nichols & Newsome, 2002; Salzman, Murasugi, Britten, & Newsome, 1992) and pursuit initiation (Groh et al., 1997) have revealed a range of computations supported by this area, including weighted vector averaging and winner-takes-all outcomes. For example, in the context of perceptual tasks, neurons with disparate preferred directions (up to 140 deg) cooperate in influencing monkey’s directional estimates; for neurons with more disparate directions the computation mechanism becomes more competitive (Nichols & Newsome, 2002). For motor tasks (smooth pursuit and saccade velocity compensation; Groh et al., 1997), the resulting movement can be described as a weighted average of the electrically-induced velocity vector and the visually-guided movement. The present results are consistent with vector averaging that is strongly weighted toward the direction of the remembered cue, and further suggest that averaging is combined with another possible outcome, i.e. vector subtraction.

Judging by the distribution of electrical gains (Fig. 7), the subthreshold stimulation effects reported here are not as strong as those found with stimulation of cortical areas that are earlier in the sensorimotor pathway (Groh et al., 1997). There are several possible reasons for this. First, it is possible that, for technical reasons, subthreshold stimulation failed to work at all. The fact that there were reliable effects on saccade latency, and that these effects were consistent with other studies (Burman & Bruce, 1997) suggests that the microstimulation parameters and method of delivery were effective. One technical factor that is likely to play a role is that in the current study, the offset of electrical stimulation was separated from movement onset by at least 80 ms, and generally by about 200 ms. In previous studies, stimulation was coincident with the movement (Groh et al., 1997). In the colliculus, subthreshold stimulation can also bias the direction of voluntary saccades (Glimcher & Sparks, 1993). These effects are critically dependent on the temporal overlap between the electrical stimulus and eye movement. Terminating the stimulus as late as 40–60 ms before the initiation of movement can eliminate the stimulation effect entirely. The temporal separation of stimulation and movement was a critical feature of this study as we were interested in the effects of stimulation on memory and planning, not on movement initiation. A final and perhaps most important factor is that FEF is embedded in a network of areas for saccade control, and there is evidence of functional redundancy in this network (Schiller, True, & Conway, 1979). This redundancy is consistent with memory-attractor theory (Wang, 2001); a small perturbation induced through microstimulation is handled by the prefrontal recurrent neural network without damaging the content of the memory. Subthreshold currents may have limited ability to disrupt a memory-attractor.

Burman and Bruce's (1997) experiments show a role for FEF in suppressing pro- or antisaccades by the application of intracortical microstimulation after delay offset. Their findings indicate that the primate FEF can suppress inappropriate saccade vectors. The main difference between their experiment and ours is that they stimulated after the delay epoch, when the monkey is preparing to initiate an eye movement, while in our experiments the stimulation was applied during the delay epoch, which may affect saccade planning more than initiation.

Other studies show that microstimulation of cortical area MT during cue presentation or delay epoch affects the performance on a visual working memory task (Bisley, Zaksas, & Pasternak, 2001), or performs the temporal gating of perceptual information (Seidemann, Zohary, & Newsome, 1998). These effects are also dependent on the timing of stimulation during the task. In a delayed motion match-to-sample task, responses were affected as if the stimulation altered the perceived

direction of the motion cue if the stimulation was applied during the presentation of the cue, but not if applied during the subsequent delay interval (Bisley et al., 2001). Based on recent work, FEF appears to gate both visual signals involved in attention as well as movement signals used for saccade preparation (Moore & Fallah, 2001; Moore & Armstrong, 2003). The stimulation in supplementary eye fields (Russo & Bruce, 2000), posterior parietal cortex (Thier & Andersen, 1998) and superior colliculus (Stanford, Freedman, & Sparks, 1996) contribute to the growing evidence of distributed networks for saccade planning, initiation and execution (Hanes & Schall, 1996). It should be kept in mind that microstimulation effects may spread quite some distance from the stimulation site (Butovas & Schwarz, 2003; Seidemann, Arieli, Grinvald, & Slovlin, 2002). Hence, it is possible that stimulation applied to FEF actually activates much of the network of areas that send and receive inputs to and from the FEF.

To summarize, memory-saccades following electrical stimulation during the delay period were strongly weighted toward the visual cue direction, yet there was often a consistent bias introduced by the electrical stimulus that caused significant changes in saccade vector and latency. We found a consistent difference in the direction of the sub-threshold stimulation vector relative to the preferred direction of neural activity for both delay and presaccadic epochs, suggesting that subthreshold microstimulation might cause a remapping of presaccadic spatial signals. The pattern of saccade endpoints following microstimulation is consistent with a combination of vector averaging and subtraction, the latter of which may be involved in updating of motor plans to remembered targets when other saccades intervene between the presentation of the target and the saccade that finally acquires the target.

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References

- Baddeley, A. (1986). *Working memory*. London: Oxford University Press.
- Balan, P., & Ferrera, V. P. (2003). Effects of gaze shifts on maintenance of spatial memory in macaque frontal eye field. *Journal of Neuroscience*, 23, 5446–5454.

- Barborica, A., & Ferrera, V. P. (2003). Estimating invisible target speed from neuronal activity in monkey frontal eye field. *Nature Neuroscience*, 6, 66–74.
- Bisley, J. W., Zaksas, D., & Pasternak, T. (2001). Microstimulation of cortical area MT affects performance on a visual working memory task. *Journal of Neurophysiology*, 85, 187–196.
- Boch, R. A., & Goldberg, M. E. (1989). Participation of prefrontal neurons in the preparation of visually guided eye movements in the rhesus monkeys. *Journal of Neurophysiology*, 61, 1064–1084.
- Bruce, C. J., & Goldberg, M. E. (1985). Primate frontal eye fields. I. Single neurons discharging before saccades. *Journal of Neurophysiology*, 53, 603–635.
- Bruce, C. J., Goldberg, M. E., Bushnell, M. C., & Stanton, G. B. (1985). Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *Journal of Neurophysiology*, 53, 714–734.
- Burman, D. D., & Bruce, C. J. (1997). Suppression of task-related saccades by electrical stimulation in the primate's frontal eye field. *Journal of Neurophysiology*, 77, 2252–2267.
- Butovas, S., & Schwarz, C. (2003). Spatiotemporal effects of microstimulation in rat neocortex: A parametric study using multielectrode recordings. *Journal of Neurophysiology*, 90(5), 3024–3039.
- Chafee, M. V., & Goldman-Rakic, P. S. (1998). Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *Journal of Neurophysiology*, 79, 2219–2240.
- Constantinidis, C., Franowitz, M. N., & Goldman-Rakic, P. S. (2001). The sensory nature of mnemonic representation in the primate prefrontal cortex. *Nature Neuroscience*, 4, 311–316.
- Constantinidis, C., & Goldman-Rakic, P. S. (2002). Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. *Journal of Neurophysiology*, 88(6), 3487–3497.
- Constantinidis, C., Williams, G. V., & Goldman-Rakic, P. S. (2002). A role for inhibition in shaping the temporal flow of information in prefrontal cortex. *Nature Neuroscience*, 5, 175–180.
- Courtney, S. M., Ungerleider, L. G., Kell, K., & Haxby, J. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature*, 386, 608–611.
- Duhamel, J.-R., Colby, C. L., & Goldberg, M. E. (1992). The updating of the representation of visual space in parietal cortex by intended eye movements. *Science Wash DC*, 255, 90–92.
- Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1991). Neuronal activity related to saccadic eye movements in the monkey's dorso-lateral prefrontal cortex. *Journal of Neurophysiology*, 65, 1464–1483.
- Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology*, 61, 331–349.
- Funahashi, S. (2001). Neuronal mechanisms of executive control by the prefrontal cortex. *Neuroscience Research*, 39, 147–165.
- Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science*, 173, 652–654.
- Fuster, J. M., Bauer, R. H., & Jervey, J. P. (1982). Cellular discharge in dorsolateral prefrontal cortex of the monkey in cognitive tasks. *Experimental Neurology*, 77, 679–694.
- Glimcher, P. W., & Sparks, D. L. (1993). Effects of low-frequency stimulation of the superior colliculus on spontaneous and visually guided saccades. *Journal of Neurophysiology*, 69(3), 953–964.
- Gnadt, J. W., & Anderson, R. A. (1988). Memory related motor planning activity in posterior parietal cortex of macaques. *Experimental Brain Research*, 70, 216–220.
- Goldberg, M. E., & Bruce, C. J. (1990). Primate frontal eye fields. III. Maintenance of a spatially accurate saccade signal. *Journal of Neurophysiology*, 64, 489–508.
- Goldberg, M. E., & Bushnell, M. C. (1981). Behavioral enhancement of visual responses in monkey cerebral cortex. II. Modulation in frontal eye fields specifically related to saccades. *Journal of Neurophysiology*, 46, 773–787.
- Goldberg, M. E., Bushnell, M. C., & Bruce, C. J. (1986). The effects of attentive fixation on eye movements evoked by electrical stimulation of the frontal eye fields. *Experimental Brain Research*, 61, 579–584.
- Goldman-Rakic, P. S. (1995a). Architecture of the prefrontal cortex and central executive. *Annals of the New York Academy of Sciences*, 769, 71–83.
- Goldman-Rakic, P. S. (1995b). Cellular basis of working memory. *Neuron*, 14, 477–485.
- Goldman-Rakic, P. S. (1996). The prefrontal landscape: Implications of functional architecture for understanding human mentation and the central executive. *Philosophical Transactions of the Royal Society of London B*, 351, 1445–1453.
- Groh, J. M., Born, R. T., & Newsome, W. T. (1997). How is a sensory map read out? Effects of microstimulation in visual area MT on saccades and smooth pursuit eye movements. *Journal of Neuroscience*, 17, 4312–4330.
- Hanes, D. P., & Schall, J. D. (1996). Neural control of voluntary movement initiation. *Science*, 274, 427–430.
- Helminski, J. O., & Segraves, M. A. (2003). Macaque frontal eye field input to saccade-related neurons in the superior colliculus. *Journal of Neurophysiology*, 90, 1046–1062.
- Henriques, D. Y. P., Klier, E. M., Smith, M. A., Lowy, D., & Crawford, J. D. (1998). Gaze-centered remapping of remembered visual space in an open-loop pointing task. *Journal of Neuroscience*, 15, 1583–1594.
- Judge, S. J., Richmond, B. J., & Chu, F. C. (1980). Implantation of magnetic search coils for measurement of eye position: An improved method. *Vision Research*, 20, 535–538.
- Kubota, K., & Niki, H. (1971). Prefrontal cortical activity and delayed performance in monkeys. *Journal of Neurophysiology*, 34, 337–347.
- Lisberger, S. G., & Ferrera, V. F. (1997). Vector averaging for smooth-pursuit eye movements initiated by two moving targets in monkeys. *Journal of Neuroscience*, 17, 7490–7502.
- Mays, L. E., & Sparks, D. L. (1980). Dissociation of visual and saccade-related response in superior colliculus. *Journal of Neurophysiology*, 43, 207–232.
- Miller, E. K., & Asaad, W. F. (2002). The prefrontal cortex: Conjunction and cognition. In J. Grafman (Ed.). *Handbook of neuropsychology* (Vol. 7, pp. 29–54). Elsevier Science.
- Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, 24, 167–202.
- Miller, E. K., Erickson, C. A., & Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of macaque. *Journal of Neuroscience*, 16, 5154–5167.
- Moore, T., & Armstrong, K. M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. *Nature*, 421, 370–373.
- Moore, T., & Fallah, M. (2001). Control of eye movements and spatial attention. *Proceedings of the National Academy of Sciences*, 98, 1273–1276.
- Murasugi, C. M., Salzman, C. D., & Newsome, W. T. (1993). Microstimulation in visual area MT: effects of varying pulse amplitude and frequency. *Journal of Neuroscience*, 13(4), 1719–1729.
- Nichols, M. J., & Newsome, W. T. (2002). Middle temporal visual area microstimulation influences veridical judgments of motion direction. *Journal of Neuroscience*, 22, 9530–9540.
- Opris, I., & Barborica, A. (2001). Microstimulation in monkey prefrontal cortex during a memory-guided-saccade task. *Society for Neuroscience Abstracts*, 27, 852.18.
- Opris, I., Barborica, A., & Ferrera, V. P. (2001). On the gap effect for saccades evoked by electrical microstimulation of frontal eye fields in monkeys. *Experimental Brain Research*, 138, 1–7.

- Quaia, C., Optican, L. M., & Goldberg, M. E. (1998). The maintenance of spatial accuracy by the perisaccadic remapping of visual receptive fields. *Neural Networks*, *11*, 1229–1240.
- Robins, T. W. (1996). Dissociating executive functions in prefrontal cortex. *Philosophical Transactions of Royal Society of London B*, *351*, 1463–1471.
- Robinson, D. A., & Fuchs, A. F. (1969). Eye movements evoked by stimulation of frontal eye fields. *Journal of Neurophysiology*, *32*, 637–648.
- Russo, G. S., & Bruce, C. J. (2000). Supplementary eye field: Representation of saccades and relationship between neural response fields and elicited eye movements. *Journal of Neurophysiology*, *84*, 2605–2621.
- Salinas, E. (2004). Fast remapping of sensory stimuli onto motor actions on the basis of contextual modulation. *Journal of Neuroscience*, *24*, 1113–1118.
- Salzman, C. D., Murasugi, C. M., Britten, K. H., & Newsome, W. T. (1992). Microstimulation in visual area MT: effects on direction discrimination performance. *Journal of Neuroscience*, *12*, 2331–2355.
- Salzman, C. D., & Newsome, W. T. (1994). Neural mechanisms for forming a perceptual decision. *Science*, *264*, 231–237.
- Schall, J. D. (2004). On building a bridge between brain and behavior. *Annual Review of Psychology*.
- Schiller, P. H., True, S. D., & Conway, J. L. (1979). Paired stimulation of the frontal eye fields and the superior colliculus of the rhesus monkey. *Brain Research*, *179*, 162–164.
- Schlag Rey, M., Schlag, J., & Dassonville, P. (1992). How the frontal eye field can impose a saccade goal on superior colliculus neurons. *Journal of Neurophysiology*, *67*, 1003–1005.
- Seidemann, E., Arieli, A., Grinvald, A., & Slovin, H. (2002). Dynamics of depolarization and zation and hyperpolarization in the frontal cortex and saccade goal. *Science*, *295*(5556), 862–865.
- Seidemann, E., Zohary, E., & Newsome, W. T. (1998). Temporal gating of neural signals during performance on a visual discrimination task. *Nature*, *394*, 72–75.
- Segraves, M. A. (1992). Activity of monkey frontal eye field neurons projecting to oculomotor regions of the pons. *Journal of Neurophysiology*, *68*, 1967–1985.
- Segraves, M. A., & Goldberg, M. E. (1987). Functional properties of corticotectal neurons in the monkey's frontal eye field. *Journal of Neurophysiology*, *58*, 1387–1419.
- Smith, M. A., & Crawford, J. D. (2001). Implications of ocular kinematics for the internal updating of visual space. *Journal of Neurophysiology*, *86*, 2112–2117.
- Sommer, M. A., & Wurtz, R. H. (1998). Frontal eye field neurons orthodromically activated from the superior colliculus. *Journal of Neurophysiology*, *80*(6), 3331–3335.
- Sommer, M. A., & Wurtz, R. H. (2000). Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. *Journal of Neurophysiology*, *83*(4), 1979–2001.
- Sommer, M. A., & Wurtz, R. H. (2001). Frontal eye field sends delay activity related to movement, memory, and vision to the superior colliculus. *Journal of Neurophysiology*, *85*, 1673–1685.
- Stanford, T. R., Freedman, E. G., & Sparks, D. L. (1996). Site and parameters of microstimulation: evidence for independent effects on the properties of saccades evoked from the primate superior colliculus. *Journal of Neurophysiology*, *76*, 3360–3381.
- Stanton, G. B., Goldberg, M. E., & Bruce, C. J. (1988). Frontal eye field efferents in the macaque monkey: II. Topography of terminal fields in midbrain and pons. *Journal of Comparative Neurology*, *271*, 493–506.
- Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R., et al. (1996). Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *Journal of Neurophysiology*, *75*, 454–468.
- Szabo, J., & Cowan, W. M. (1984). A stereotaxic atlas of the brain of cynomolgus monkey (*Macaca Fascicularis*). *Journal of Comparative Neurology*, *222*, 265–300.
- Tanji, J., & Hoshi, E. (2001). Behavioral planning in the prefrontal cortex. *Current Opinion in Neurobiology*, *11*, 164–170.
- Thier, P., & Andersen, R. A. (1998). Electrical microstimulation distinguishes distinct saccade-related areas in the posterior parietal cortex. *Journal of Neurophysiology*, *80*, 1713–1735.
- Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., & Miyashita, Y. (1999). Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature*, *401*, 699–703.
- Umeno, M. M., & Goldberg, M. E. (1997). Spatial processing in the monkey frontal eye field. I. Predictive visual responses. *Journal of Neurophysiology*, *78*, 1373–1383.
- Wallis, J. D., & Miller, E. K. (2003). From rule to response: neural processes in the premotor and the prefrontal cortex. *Journal of Neurophysiology*, *90*, 1790–1806.
- Wang, X.-J. (2001). Synaptic reverberation underlying mnemonic persistent activity. *Trends in Neuroscience*, *24*, 455–463.
- White, R. L., & Snyder, L. H. (2004). Delay period microstimulation in the frontal eye fields updates spatial memories. *Society for Neuroscience Abstracts*.
- Wyder, M. T., Massoglia, D. P., & Stanford, T. R. (2003). Quantitative assessment of the timing and tuning of visual-related, saccade related and delay period activity in primate central thalamus. *Journal of Neurophysiology*, *90*, 2029–2052.
- Wurtz, R. H., & Mohler, C. W. (1976). Enhancement of visual responses in monkey striate cortex and frontal eye fields. *Journal of Neurophysiology*, *39*, 766–772.
- Zar, Z. H. (1999). *Biostatistical analysis* (4th ed.). Upper Saddle River, NJ: Prentice-Hall Inc.