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CONTRIBUTION OF THE FRONTAL EYE FIELD TO GAZE SHIFTS IN THE HEAD-UNRESTRAINED RHESUS MONKEY: NEURONAL ACTIVITY

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Abstract

The frontal eye field (FEF) has a strong influence on saccadic eye movements with the head restrained. With the head unrestrained, eye saccades combine with head movements to produce large gaze shifts, and microstimulation of the FEF evokes both eye and head movements. To test whether the dorsomedial FEF provides commands for the entire gaze shift or its separate eye and head components, we recorded extracellular single-unit activity in monkeys trained to make large head-unrestrained gaze shifts. We recorded 80 units active during gaze shifts, and closely examined 26 of these that discharged a burst of action potentials that preceded horizontal gaze movements. These units were movement or visuomovement related and most exhibited open movement fields with respect to amplitude. To reveal the relations of burst parameters to gaze, eye, and/or head movement metrics, we used behavioral dissociations of gaze, eye, and head movements and linear regression analyses. The burst number of spikes (NOS) was strongly correlated with movement amplitude and burst temporal parameters were strongly correlated with movement temporal metrics for eight *gaze-related burst neurons* (GBNs) and five *saccade-related burst neurons* (SBNs). For the remaining 13 neurons, the NOS was strongly correlated with the head movement amplitude, but burst temporal parameters were most strongly correlated with eye movement temporal metrics (*head-eye-related burst neurons*, HEBNs). These results suggest that FEF units do not encode a command for the unified gaze shift only; instead, different units may carry signals related to the overall gaze shift or its eye and/or head components. Moreover, the HEBNs exhibit bursts whose magnitude and timing may encode a head displacement signal and a signal that influences the timing of the eye saccade, thereby serving as a mechanism for coordinating the eye and head movements of a gaze shift.

Keywords

Frontal eye field; gaze shift; unit activity; eye-head coordination; monkey

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1 INTRODUCTION

When exploring their visual environment, primates move their eyes and head to aim the line of sight (i.e., gaze) at a target of interest to allow it to be inspected by the fovea. To achieve accurate gaze shifts, head movements must be precisely coordinated with the eye saccade. These gaze shifts have been well studied in non-human primates (Tomlinson and Bahra, 1986, Phillips et al., 1995, Freedman and Sparks, 1997a, b), but the neural basis of how eye and head movements are coordinated remains unanswered. Recent studies in head-unrestrained monkeys (Tu and Keating, 2000, Martinez-Trujillo et al., 2003, Constantin et al., 2004, Chen, 2006, Elsley et al., 2007, Knight and Fuchs, 2007, Monteon et al., 2010), however, point to the probable involvement of the frontal eye field (FEF).

With the head restrained, FEF neurons are active during rapid shifts of gaze achieved with eye movements alone (Goldberg and Segraves, 1989, Schall, 1997, Tehovnik et al., 2000). Movement-related cells of the FEF discharge a burst of spikes that begins before saccades to simple step changes in target position (Bruce and Goldberg, 1985, Segraves and Goldberg, 1987, Segraves, 1992). These cells constitute the largest population of neurons that project to pre-motor brain stem areas, such as the superior colliculus (SC) and pons, that are involved with saccade generation (Bruce and Goldberg, 1985, Segraves and Goldberg, 1987, Leichnetz and Goldberg, 1988, Segraves, 1992, Sommer and Wurtz, 2000). FEF movement-related neurons are most active for particular directions of eye movements, and the discharge of most of these neurons increases with increases in saccade amplitude, that is, each has an *open movement field* (Bruce and Goldberg, 1985). Stimulation of the FEF in the alert monkey evokes short-latency eye movements whose metrics match those of saccades elicited by visual targets (Robinson and Fuchs, 1969) and the amplitude of saccades evoked by microstimulation varies topographically: large amplitude saccades can be evoked from dorsomedial areas and smaller saccades from ventrolateral regions (Robinson and Fuchs, 1969, Bruce et al., 1985). This topography is preserved in corticotectal projections from the FEF, and the dorsomedial FEF (large amplitude saccade region) projects to the caudal SC (Stanton et al., 1988, Sommer and Wurtz, 2000). These earlier studies implicate the FEF in the generation of eye saccades, but FEF unit activity is not related to eye saccade movement parameters other than direction and amplitude, at least during movements in head-restrained monkeys (Schiller et al., 1980, Bruce and Goldberg, 1985, Segraves and Park, 1993, Schall, 1997). Furthermore, while chronic lesions to the SC suggest that, after recovery, the FEF may be sufficient for saccade generation, chronic lesions to the FEF have shown it is not necessary to generate saccades (Schiller et al., 1980). Furthermore, recent results of reversible lesions of the SC conclude that without a recovery period, the FEF is not sufficient for saccade generation (Hanes and Wurtz, 2001).

The role of the FEF in the motor commands that generate eye saccades remains unclear from experiments that required the head to be restrained, but at least two sets of experimental evidence suggest that investigation of gaze shifts in more natural conditions might clarify the role of the FEF in movement generation. First, experiments in the head-restrained cat and monkey showed that neck muscle activity occurs synergistically during eye movements, suggesting that during tasks requiring eye movement behavior, motor commands were not limited to the eye saccade system (Vidal et al., 1982, Lestienne et al., 1984). Second, experiments in the head-unrestrained monkey suggest that most SC neurons encode a motor command for the generation of eye-head combined gaze shifts, while some encode a command for head movement only (Freedman and Sparks, 1997a, Walton et al., 2007).

Therefore, examination of the motor contribution of the FEF during head-unrestrained behavior may reveal whether the FEF contributes a necessary motor command for eye saccades or the overall gaze shift. The only study that has described FEF unit activity during

horizontally head-unrestrained, combined eye-head gaze shifts showed that some neurons' activity was related to head movement of the gaze shift (Bizzi and Schiller, 1970). Unfortunately, this study did not quantitatively test whether the discharge of FEF neurons was associated with the eye saccade, rapid head movement, or the combined eye-head gaze shifts, necessary for large amplitude (e.g., 35°) gaze shifts. With the head unrestrained, microstimulation of the FEF evokes eye-only, head-only, and combined eye-head gaze movements, depending on the starting positions of the eyes and head (Tu and Keating, 2000, Knight and Fuchs, 2007, Monteon et al., 2010); but see Chen 2006) and can evoke neck muscle activity without a head movement (Elsley et al., 2007, Corneil et al., 2010). Therefore, when the head is free to move, the FEF may be involved with the generation of the overall eye-head gaze shift, its eye and head components or their coordination. In support of this latter possibility, unilateral FEF lesions have little effect on gaze movement amplitude, but double head movement amplitude while decreasing eye saccade amplitude (van der Steen et al., 1986).

Thus, several pieces of evidence converge on the notion that the FEF is involved in the control of eye and head movements during rapid gaze shifts. In this study, we examined the movement-related discharge of FEF neurons during head-unrestrained gaze shifts to determine whether the discharge is related to the gaze movement and/or its component eye or head movements. We show that the burst timing of these units was related to eye/gaze movement timing; half of these units also had burst magnitude (number of spikes, NOS) related to the head movement amplitude, while fewer units exhibited NOS related to the eye saccade or overall gaze movement. Taken together, we conclude that different FEF neurons encode signals for the generation of the overall gaze shift, the eye saccade only, or for coordination of the eye and head components of eye-head combined gaze shifts. Some of these results have been presented in abstract form (Knight and Fuchs, 2001).

2 EXPERIMENTAL PROCEDURES

2.1 General procedures

These experiments were performed with two male rhesus monkeys, *Macaca mulatta* (4–9 Kg), as described in detail previously (Knight and Fuchs, 2007). Briefly, we implanted search coils to measure gaze and head position in space (Fuchs and Robinson, 1966), and implanted a magnetic resonance imaging (MRI)-compatible recording cylinder (Crist instruments) over each FEF in the first animal (right FEF cylinder centered at A24, L20 [stereotaxic coordinates]; left FEF at A18.5, L20) and over the right hemisphere in the second animal (A22, L16). To determine the location of electrode penetrations, postoperative magnetic resonance imaging (MRI) was used to identify the anatomic locations of the electrode paths in each FEF (Kim and Shadlen, 1999). For a recording session, the monkey was secured inside a primate chair that limited torso rotation and placed within a sound-deadened booth. The primate chair was centered in front of the visual display, a hemisphere-shaped, constant radius (61 cm from the eyes) array of light emitting diodes (LEDs). The LEDs were spaced every 1° of visual angle along eight arms/directions (0, 45, 90, 135, 180, 225, 270, 315°); i.e., $\pm 100^\circ$ horizontally, $\pm 30^\circ$ vertically, and $\pm 30^\circ$ at the obliques, which allowed target steps from 1 to 100° in amplitude from many possible positions and in several directions via two sequentially illuminated LEDs as controlled by a Macintosh PowerPC (Apple, Inc.) and custom software.

A single, visually guided target-step trial started with the presentation of a single LED as the fixation point at any position on the array. Following accurate fixation by the monkey (across a pseudorandomly varied interval of 500 – 1500 ms), this LED extinguished and a single, different LED target was lit (within 5 ms) at a distance of 1 to 100° from the fixation point in one of many possible directions. If the animal made a gaze shift to acquire the new

LED that landed within a window surrounding the target position ($\sim\pm 10\%$ of the target step amplitude), an applesauce reward was delivered (see below) via a tube that moved with the animal's head. This newly acquired target position then served as the fixation point for the subsequent trial. Target positions were selected pseudorandomly by the software (randomly from a predetermined list of >50 possible amplitude and direction combinations) resulting in a very large number of possible target positions. Trials did not necessarily begin at center and were not confined to horizontal directions or to a single axis of the array; a trial could begin with the fixation point at 60° to the right of center on the horizontal (0°) axis followed by a target step to 20° from center along the 135° axis. We did not only record large amplitude gaze shifts that crossed the center position along the horizontal meridian, and did not use series of repeated target steps (e.g., 0 to 80° to 0° , repeatedly), though repeat target steps were possible given the random selection of target positions from the pre-programmed list. The program also reduced the likelihood of anticipatory or "re-centering" centripetal gaze shifts following extinction of an eccentric fixation point by pseudorandom presentation of a "distractor" target at an increased eccentric or oblique position, and "catch" trials (where no target LED was lit following extinction of the fixation point) to confirm that elicited movements were visually guided. Finally, the program rewarded the animal at a variable rate ($\sim 33\%$ of successful trials) regardless of LED position, so that rewards were not associated with any particular fixation position, target position, hemifield, or gaze shift amplitude. This protocol was carefully designed to reduce the likelihood of predictability of ensuing target position since eye-head coordination in humans can be modified by expectation of future target positions (Oommen et al., 2004) and it was used for all recording sessions except for a small number of single trials where it was overridden if it appeared that more distractor trials, oblique target steps, etc. were needed to reduce predictability, or improve variability in direction and amplitude for mapping of a response field, respectively. We collected behavioral and neuronal data while the animals performed the above task with the head completely unrestrained and able to move in three dimensions.

The Animal Care and Use Committee at the University of Washington approved all the surgical, training, and experimental procedures. The veterinary staff of the Washington National Regional Primate Research Center cared for the animals, which were housed under conditions that comply with National Institutes of Health standards, as stated in the *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* (Compiled by the National Research Council. Washington, D.C., Natl. Acad. Press, 2003), and recommended by the Institution of Laboratory Resources and the American Association for Accreditation of Laboratory Care International.

2.2 Data acquisition

Gaze (G) and head in space (H) position signals were acquired using the magnetic search coil technique (Robinson, 1963, Fuchs and Robinson, 1966); signals were low-pass filtered and recorded to VCR tape (Vetter 4000A PCM recorder, A.R. Vetter) and digitized at 1 kHz with a Macintosh Power PC (National Instruments A/D conversion board, PCIMO6). Eye position in the orbit (eye, E) was calculated offline as $G - H$. We recorded the activity of single units in the FEF by tungsten microelectrodes (impedance $\sim 1.0\text{ M}\Omega$) introduced into the brain through a cannula and advanced with a hydraulic microdrive (Trent Wells). Action potentials were amplified, filtered (300 Hz – 10 kHz), displayed on an oscilloscope, and played on an audio monitor. Single units were isolated with a time/amplitude window discriminator (custom made) and each action potential was digitized as a time stamp event at $10\text{ }\mu\text{s}$ resolution. To confirm that we were recording from the FEF (as functionally defined by Bruce and colleagues (Bruce and Goldberg, 1985, Bruce et al., 1985)), and to examine the effects of stimulation on eye-head gaze shifts, we delivered low-intensity (threshold

current < 50 μ A) microstimulation at most recording sites immediately following unit recording (Bruce et al., 1985, Knight and Fuchs, 2007).

2.3 Data analysis

2.3.1 Movement and neuronal burst parameters—Offline data analysis was performed with laboratory-designed software on Macintosh G4 computers (Apple, Inc.). Digitized gaze, eye, and head position signals were digitally filtered (Marchand and Marmet, 1983, Pong and Fuchs, 2000) and differentiated to produce velocity signals. The data were analyzed with a custom program that displayed the movement positions and velocities and the action potential events (spikes) associated with individual gaze movement trials. The program automatically detected the occurrence of a gaze shift when gaze velocity exceeded 75°/s. It then marked the onset and offset of the gaze, eye, and head movements when their respective velocities first exceeded (onset) and subsequently dropped (offset) to 10°/s. The program also marked the peak movement velocities and determined the size and time of occurrence of the associated target step. We inspected the automatic markings and made corrections on a minority of trials. Based on these markings, the analysis software determined movement metrics such as amplitude, peak velocity and duration and the timing of movement onset, end and peak velocity.

Because the head continues to move after the gaze movement has ended, we considered two aspects of the head movement separately. The total head movement amplitude (H) was the change in vectorial head position from head movement start time to head movement end time. The head contribution to the gaze shift (H_c , head contribution) was the change in head position from gaze movement start time to gaze movement end time (Freedman and Sparks, 1997b).

The same interactive program also marked the onset and end of the burst of the FEF neuron, when its rate first exceeded, then fell below, 40 spikes/s in excess of the resting/tonic firing rate, respectively. We visually inspected the automatic markings and changed them in two situations: 1. If the resting rate, which was variable in these units, was particularly high (> 40 Hz) on a specific trial, we designated a sudden increase in frequency (as seen in the instantaneous frequency histogram) as the burst onset and the first sudden decrease from the elevated frequency as the burst offset; or 2. If a corrective eye saccade or reacceleration of the head occurred, we marked the burst offset at the nearest sudden decrease in frequency at least 50 ms prior to the reacceleration event (i.e., we only considered burst activity as it related to a single gaze shift). We applied this visual inspection method consistently without regard to effect on burst parameters, relation to movements, and only before subsequent statistical analyses, and this altered fewer than 10% of the trials (Fuchs et al., 1993). The program then determined the burst's duration, number of spikes (NOS), average firing rate (AFR), and peak firing rate (5spFR, the firing rate across the five spikes at highest frequency). NOS was least influenced by the determination of burst onset and offset compared to AFR and 5spFR, which also exhibited weaker associations to movement metrics (see RESULTS, 3.2. *Response fields*).

The measurements describing the burst and its associated movements were exported to Matlab (The Mathworks), Excel (Microsoft, Inc.), and Statview (SAS Institute, Inc.) for further analyses. We analyzed only those gaze shifts that started at least 100 ms after the target step (to avoid anticipatory or express saccades), traveled 80% of the distance to the target (i.e., were accurate, single, visually guided gaze shifts), were "primary movements" 100° in amplitude, without reaccelerations of the eye or head (i.e., no corrective eye saccades). Finally, we considered no trials with burst start times occurring earlier than 50 ms after target step time (indicative of anticipatory neural responses, because the minimum latency of FEF neurons to visual stimulus is 55 ms; Bruce and Goldberg 1985). Before

subsequent analyses, to protect against undue influence of a few extreme data points, we excluded all data beyond three standard deviations from the mean of the parameter considered. This constraint was necessary because data recording, digitization, and automated measurement occasionally gave rise to possibly erroneous values that could have had too much influence on regression analyses. This limitation was performed first, before subsequent analyses and additional limits based on preferred direction, etc., and eliminated only a small number of trials — e.g., for data sets of ~200 points, approximately five points (max. of 10) were removed by the 3 SD cutoff (~2.5% of points). This objective error/outlier elimination was chosen because it allowed regression statistics more consistent with previously published FEF studies, and across simple linear regression (SLR) and multiple linear regression (MLR) methods. We subjected all units described here to the same analyses except when specific requirements for an analysis were not met, as indicated below.

2.3.2. Response fields and directional and amplitude sensitivity—The overall response field for each unit was determined by plotting the NOS in the burst as a function of the amplitude of the horizontal and vertical components of gaze in a retinotopic framework, that is, as if each movement were initiated from the center, straight-ahead position. Because our analyses required head movements that contributed to the gaze shift — which most commonly occur during horizontal gaze shifts (Freedman and Sparks, 1997b) — we used the response fields to approximate each unit's directional sensitivity (i.e., 0, 45, 135, 180, 225, 315°) across all trials and confirm that its discharge exhibited a change in magnitude for gaze shifts within $\pm 20^\circ$ of one horizontal direction (0 or 180°); i.e., that it had a “preferred hemifield” (contraversive or ipsiversive). Corresponding response fields showing NOS as a function of eye (in head) movement and head movement amplitudes were also generated.

To determine a unit's amplitude sensitivity, we plotted the NOS as a function of gaze movement amplitude for trials with gaze shift directions within $\pm 20^\circ$ of the unit's preferred horizontal direction. We described the relation between the burst NOS and gaze movement amplitude with SLR unless a quadratic function statistically improved the goodness of fit (*extra sum of squares/partial F-test*; (Draper and Smith, 1981, Kleinbaum et al., 1988). We designated a unit as having an *open movement field* if it was best fit with a linear regression with a positive slope, and therefore had no optimal amplitude for gaze shifts 100° . We designated a unit as *closed* if it was best fit with a quadratic function and had an optimal amplitude less than the maximum we could test (i.e., 100°).

2.3.3 Characterization of units as visual, movement, or visuomovement related—Because we used a “saccade task” (modified for large gaze amplitudes) and did not use the “delayed saccade task” to separate possible visual and motor burst activity, we determined whether neuronal bursts were associated with the target step or the gaze movement by comparing SLR fits of burst start time vs. movement (gaze/eye and head) start time and target step time as previously shown for FEF movement-related cells (Hanes et al., 1995). We classified a unit as movement related if the regression to movement start time was statistically significant (i.e., its slope was statistically different from 0.0 at $p = 0.05$) and stronger than that to the target step time (*equal correlations test*; (Kleinbaum et al., 1988). We also tested whether the variance of burst start time relative to the movement start time was less than that to the target step time (*variance ratio F-test*; (Commenges and Seal, 1985, Hanes et al., 1995, Zar, 1999).

2.3.4 Associations between unit burst parameters and movement metrics

2.3.4.1 Dissociation analyses – behavioral limits on eye and gaze movement amplitude:

To determine whether a unit's burst activity was related to the gaze, eye, or head movement, we used two *dissociation analyses* similar to those developed by Freedman and Sparks (1997a). We used two analyses on specific subsets of behavioral data to reduce intercorrelations between gaze, eye, and head movement amplitudes, so that relations between the NOS in the burst and gaze, eye, and head movement amplitudes could be examined with SLR. Statistically significant SLR results (slopes and r^2 , $p < 0.05$) were then compared to the relations predicted if the unit were only related to gaze, eye, or head movement amplitude (Fig. 4B–D and Fig. 5B–D).

In the first dissociation situation (*Behavioral limits on eye movement amplitude*) we required the monkey to make large amplitude ($\sim 35^\circ$) head-unrestrained horizontal gaze shifts from a narrow range of horizontal initial eye positions (Freedman and Sparks, 1997a, b). Across trials with gaze movement amplitude greater than $\sim 35^\circ$, and for which initial eye position was near the center position, eye movement amplitudes saturated (with slight variation) near a maximum of $\sim 35^\circ$ (e.g., our Fig. 4A, black dotted line, E), whereas head movement amplitudes continued to increase monotonically (gray dashed line, H). This allowed the predictions that a unit whose burst was related to the eye movement only would show little/no variation (because there was little/no variation from one gaze shift's eye saccade to the next), while one related to gaze or head movement amplitude would have burst NOS that correlated with those movement amplitudes. We observed robust results when subsets of data met specific requirements: 1. The initial eye position (IEP) range was 10° (but was not necessarily around the central orbital position) so that the slope of eye movement amplitude vs. gaze movement amplitude showed little/no slope (i.e. little/no variation for these trials; see Fig. 4A); 2. The gaze movement amplitude threshold was the sum of the largest off-direction IEP and 35° (e.g., for IEP = -10 to 0 , then the threshold = 45°); 3. The range of gaze and head movement amplitudes was wider than that of eye movement amplitude. For nearly all units, we found more than two data subsets (e.g., one subset with IEP of -10 to 0° , and one subset with IEP of 0 to 10°), each with > 15 trials, that met these criteria. The regression results from every subset had to be consistent for us to report a relationship for a unit; i.e., although we report only one subset's results, with number of trials often ~ 20 , this result was consistent across all subsets. When results were not consistent across subsets (e.g., two subsets matched predictions for a relation to gaze or head, but one subset matched predictions for a relation to eye movement), we reported the result as “*inconclusive*”.

In the second situation (*Behavioral limits on gaze movement amplitude*), the monkey made horizontal gaze shifts of relatively constant amplitude (Fig. 5A, gray solid line, G) from a wide range of horizontal IEPs and eye and head movement amplitudes varied inversely. For example, when the eyes were initially in the opposite direction of the ensuing gaze shift (an “off-direction IEP”), the eye saccade (black dotted line, E) contributed proportionately more to the gaze shift than did the head movement (gray dashed line, H); the opposite was true when the IEP was in the same direction as the ensuing gaze shift (Freedman and Sparks, 1997a, b). This dissociation allowed the predictions that a unit whose burst was related to the gaze movement only would show little/no variation, while one related to eye or head movement amplitude would exhibit a correlation between its burst NOS and those movement amplitudes: significant negative and positive regression fits for eye and head, respectively, would match the prediction for a relation to head movement only, while the opposite result would match the prediction for a unit related to eye movement only. Our subsets of data were constrained by specific requirements: 1. Gaze movement amplitude range spanned 15° between 40 and 80° (e.g., 50 to 59°); 2. The horizontal IEP range was 20° and horizontal initial head position (IHP) was $\pm 20^\circ$; 3. Eye movement amplitude

showed a negative correlation with IEP and head movement amplitude showed a positive correlation with IEP; 4. The range of eye and head movement amplitudes was greater than that of gaze movement amplitude. As with the dissociation described previously, we typically found more than two data subsets for each unit, and the regression results from every subset were consistent or we reported the result as “*inconclusive*”.

2.3.5 Regression analyses of unit burst parameters and movement metrics—

The dissociation analyses examined only relations between the NOS and movement amplitudes and were limited to small data sets. We therefore also used simple and multiple linear regression (SLR and MLR) to test for relations between additional parameters of the burst (e.g., temporal) and movement metrics from larger data sets. Movement metrics tested included gaze, eye, and head movement (and head contribution) amplitudes, onsets, durations, and offsets, and initial and final eye and head positions. Burst parameters were poorly correlated, if at all, with velocity parameters, which were not considered further. Because several metrics are equivalent (e.g., eye and gaze movement start times) or highly correlated (e.g., eye movement and gaze movement amplitude (Phillips et al., 1995, Freedman and Sparks, 1997b), MLR was necessary (in the absence of a dissociation condition) to protect against possible misinterpretations when determining the strength of the primary correlation.

For every unit, we ran a SLR test for the unit discharge parameter of interest (dependent variable) vs. each movement parameter (e.g., burst start time vs. eye movement start time) to determine whether any SLR relations were “physiologically relevant” (our threshold of $r^2 \geq 0.15$, and $p \leq 0.05$). If more than one SLR relation was found, we tested whether any one was statistically better than the other(s) (e.g., burst start time and head movement start time) with the equal correlations test (Kleinbaum et al., 1988). If one relation was statistically stronger, we used that movement parameter (e.g., as X_1) in MLR tests along with other physiologically relevant movement parameters (e.g., X_2 , X_3 , etc.) that were *not intercorrelated with X_1* (i.e., the R^2 of one movement metric predicted by the other movement metrics included in testing had to be < 0.90 ; *variance inflation factor test*, Kleinbaum et al. 1988) to obtain the best-fitting MLR model (*extra sum of squares/partial F-test*).

In some cases — when a movement metric was the sum of two others (e.g., $G = E + Hc$), — SLR fits using different movement metrics were not statistically different (e.g., G and Hc amplitudes). In these cases, we eliminated the need for alternative models by determining which metric to consider “primary”. If the two component metrics of the gaze movement could be included (e.g., E and Hc coefficients were statistically significant) in the MLR model:

$$Y = b_0 + b_1(\text{eye movement amplitude}) + b_2(\text{head contribution amplitude}) \quad (1)$$

then this two-parameter model was an improvement over a SLR model relating Y to either E or Hc . If b_1 and b_2 were *not* statistically different from each other (*partial coefficient test*, (Zar, 1999)), then G amplitude was considered to be the primary metric and no alternative models with E or Hc were considered (modified from Cullen and Guitton, 1997). If this model was not better than a SLR model relating Y to either E or Hc and the partial regression coefficients were statistically different, then the movement component amplitude with the statistically better SLR fit was considered primary (e.g., Hc) and G was excluded as a possible predictor of Y .

To corroborate the results of our MLR testing, and in cases when two or more SLR relations were statistically equivalent, we applied automatic forward and backward stepwise MLR

testing (Statview). This series of steps accounted for correlation among the independent variables (movement metrics) and objectively included only those with statistically significant effects on the dependent variable (burst parameter) in a MLR model. In all cases, our results were consistent across both methods, and only those models that were statistically significant and resulted in $R^2 \geq 0.15$ were used to characterize a unit. From these models, we used the standardized regression coefficient for each included X variable (SRC; reported with MLR results) to compare the relative strength of variables within a MLR model. Initial position parameters, which were often found to be statistically significant secondary variables in our MLR models, could not often be distinguished as initial eye, initial head, or initial gaze due to intercorrelations; in these cases, a generic POS (position) parameter was reported. For all analyses, the threshold for statistical significance was $\alpha = 0.05$; means are reported with $\pm$ standard deviation (SD); medians are reported $\pm$ 95% CI.

2.4 Histological confirmation of recording sites

In addition to the MRI data for each animal, following the final recording session with the first animal (T), we made electrolytic lesions in the right and left FEFs by passing 30 μ A of positive DC current (constant-current stimulator, Nuclear Chicago) for 30 sec at two depths along medial and lateral recording tracks. After 10 days the monkey was anesthetized and sacrificed, and the brain was removed and processed (Robinson et al., 1994).

3 RESULTS

3.1 General description of neuronal burst behavior with the head unrestrained

Across the area and depth of the low-threshold-defined FEF (Bruce and Goldberg, 1985), we recorded from 80 well-isolated units during head-unrestrained gaze shifts in two monkeys. Because we were interested in characterizing units involved in commanding elements of eye-head combined gaze shifts, we concentrated on 65 units that exhibited clear burst or burst-tonic activity, were movement-related, and burst before the gaze movements began, as qualitatively determined during recording via burst frequency histograms and movement traces on a storage oscilloscope (excluded units burst well after the start of the gaze movement (9) or were tonically active (4)). From these 65, we selected 26 units for (and before) close, quantitative examination because: 1. Each discharged a burst of spikes that began before the onset of large, primarily horizontal gaze shifts and showed variability in burst magnitude across a range of amplitude for these mostly horizontal gaze shifts — units with primarily vertical preferred directions were excluded (17 were excluded, 14 of which were primarily vertical); 2. Each exhibited consistent burst activity for these amplitudes and directions (the bursts of 10 excluded units were much less consistent across similar trials); 3. For each we had at least 18 min of behavioral data (i.e., > 200 trials) to ensure adequate variety of amplitudes, directions, initial positions, and numbers of trials, e.g., for dissociation analyses (see EXPERIMENTAL PROCEDURES; five units were excluded); and 4. We evoked gaze shifts with low-threshold microstimulation from the same locations (immediately following recording for 23 of the 26); seven units were excluded). All 26 neurons were located in the dorsomedial region of the FEF according to anatomical information obtained with MRI and histological examination (see below).

The general behavior of these neurons is illustrated by the neural activity of the representative unit shown in Fig. 1 (P20-1). With the head restrained, this neuron, like six others recorded with the head restrained, discharged a burst of spikes associated with eye saccades in one direction (here rightward; Fig. 1A and B), and exhibited a decrease of activity for saccades in the opposite direction (Fig. 1C). With the head free to move, this unit had qualitatively similar discharge patterns for gaze shifts of amplitude-matched trials (Fig. 1D–F). Bursts associated with larger rightward gaze shifts beyond those possible with the

head restrained exhibited a much greater number of spikes (NOS), longer durations and higher firing rates (Fig. 1*G,H*).

3.2 Response fields

The burst behavior of all 26 units depended on the amplitude and direction of a gaze shift. Figure 2 plots the NOS associated with the vectorial gaze, eye, and head movements (i.e., response fields) for three representative neurons. For each neuron, the NOS was greatest for horizontal movements in one direction (rightward in top and middle rows, leftward in bottom row), and essentially unresponsive for movements in the opposite direction. Indeed, movements in the opposite direction were often accompanied by a pause in firing (see also Fig. 1*C, F, and J*). For each neuron, the response fields for gaze, eye, and head movements were qualitatively similar — the NOS increased with gaze movement amplitude near a “preferred”, mostly horizontal direction. Fourteen units were most responsive for movements contraversive to the recording site, and 12 were most active for ipsiversive movements (Table 1, *Response sensitivity: Preferred hemifield* column).

We determined quantitative movement fields with respect to amplitude for all 26 units. For the unit illustrated in Fig. 2*A–C*, the NOS increased monotonically with gaze amplitude and the relation between the NOS and gaze movement amplitude (for gaze shifts directed within $\pm 20^\circ$ of the horizontal in the preferred hemifield) was described with a linear fit ($r^2 = 0.64$, $p < 0.05$, $n = 214$; Fig. 3*A*). The relation of AFR and peak firing rate to gaze movement amplitude was much weaker ($r^2 = 0.20$ and 0.38 , respectively, both $p < 0.05$). Sixteen other units exhibited similar linear relations, and NOS vs. gaze movement amplitude consistently exhibited the strongest relationship. The nine remaining neurons had response fields similar to the unit in Fig. 2*D–F*, where the NOS increased to a maximum for gaze amplitudes near $50 - 70^\circ$ and then decreased for larger gaze movement amplitudes of $80 - 100^\circ$. For this unit, the NOS vs. amplitude relation was fit better by a quadratic function for gaze shifts directed within $\pm 20^\circ$ of the preferred horizontal ($r^2 = 0.47$ vs. 0.34 , *extra sum of squares/partial F-test*, $p < 0.05$, $n = 230$; Fig. 3*B*). The relation of AFR and peak firing rate to gaze movement amplitude was also much weaker than was NOS for this quadratic fit ($r^2 = 0.20$ and 0.25 , respectively, both $p < 0.05$). The eight other units also were best fit with quadratic functions using NOS.

The relation between NOS and gaze amplitude for all 26 units is summarized in Figs. 3*C* and *D* (for gaze shifts directed within $\pm 20^\circ$ of the horizontal in the preferred hemifield). For each linear-fit unit (Fig. 3*C*), the relation was best fit by simple linear regression (mean $r^2 = 0.45 \pm 0.19$, all $p < 0.05$), resulting in lines with positive slope, ranging from 0.08 to 0.57 spikes/ $^\circ$ (mean = 0.28 ± 0.17). Nonlinear regression with quadratic functions did not improve the fit for these 17 neurons. Therefore, within the amplitude range of gaze shifts we tested (up to $\sim 100^\circ$), we classified these units as having *open movement fields*. In contrast, the remaining nine units were fit best with quadratic functions, and we classified them as having *closed movement fields* (mean $r^2 = 0.46 \pm 0.13$, all $p < 0.05$; Fig. 3*D*). In Table 1, we report the movement field for each neuron as open or closed. Except for one unit (TL23-2) whose maximum gaze movement amplitude was 60° (see fit with negative slope in Fig. 3*D*), we reported a closed movement field unit's peak gaze amplitude in parentheses (*Response sensitivity: Movement field* column).

We used these amplitude and direction sensitivities to limit our subsequent analyses. Because all 26 neurons exhibited robust increases in firing along one horizontal direction and could be expected to contribute to horizontal gaze shifts (and gaze-related head movements are predominantly horizontal (Freedman and Sparks, 1997b)), we limited our subsequent analyses to gaze shifts directed within $\pm 20^\circ$ of the preferred horizontal direction. In addition, we considered only those trials with gaze amplitudes that were less than or equal

to either 100° or to the peak of the quadratic fit. Also, to ensure the presence of a head movement we considered only trials where the head contribution amplitude was $\geq 2^\circ$.

3.3 Classification of units as visual, movement, or visuomovement

We examined trials within these preferred ranges of movement direction and amplitude to determine whether each unit's burst was more closely associated with movement start than with target step time (i.e., the units were movement related). Because eye and gaze movement start times, end times, and durations were equivalent in our observations (see Figs. 6A and 7A below; see also (Tomlinson and Bahra, 1986, Freedman and Sparks, 1997b), we treated eye and gaze movement temporal parameters (start time, end time, and duration) as equivalent. For 21 units, burst start time was better correlated with eye/gaze or head movement onset than with target start time (mean $r^2 = 0.51 \pm 0.14$ vs. $r^2 = 0.05 \pm 0.06$; $n = 129 \pm 56$; *equal correlations tests*, $p < 0.05$). Moreover, the variance of the burst start time relative to eye movement onset was less than that relative to target onset in all but three of these units (*variance ratio F-test*, $p < 0.05$). These 21 were therefore classified as *movement related* units. The remaining five units exhibited bursts with equally strong regression fits to the target and eye/gaze movement onsets and no difference in variances, and were classified as *visuomovement related* (Table 1, *Response sensitivity: VM test* column). The bursts of all 26 units started before the eye and head movement onset (see *Burst start time* regression analysis below and Table 2, *Burst start time* columns).

3.4 Relation of burst number of spikes to movement amplitude

3.4.1 Dissociation analysis -- behavioral limits on eye movement amplitude—

Because the above analyses did not allow a determination of whether a unit's burst activity was best related to the overall gaze movement or its separate eye or head components, we analyzed data where the eye movement was behaviorally dissociated from the gaze movement and head component. For each of 22 units, we identified at least one subset of data with 19 to 55 (mean = 29 ± 10) trials with a relatively narrow range of eye saccade amplitude (mean $14 \pm 3^\circ$, minimum of 8 to maximum of 19°), but with much greater ranges of gaze and head movement amplitudes (e.g., 45°). The remaining four units had insufficient numbers of trials to allow this analysis (Table 1, *Eye limit* columns "na", $n < 15$). For the hypothetical eye-amplitude-limited behavioral data in Fig. 4A, as gaze movement amplitudes increase above $\sim 40^\circ$, eye saccade amplitude saturates (black dotted line), but a linear, almost equal increase of head amplitude with gaze amplitude (gray dashed line) can be observed. Fig. 4B–D show the ideal predicted regressions if the burst NOS were related to head or gaze (gray dashed and solid lines with positive slopes, respectively), or to eye movement amplitude (dotted black lines and squares). Figure 4E–L shows the data and the lines of best fit for two of these 22 units. For the unit illustrated in Fig. 4E–H (P20-1), the NOS vs. gaze and vs. head amplitude SLR fits had positive slopes (*modified t test*, $p < 0.05$; Table 1, *Eye limit*, *GEH slope* column, slopes with "*"), consistent with the predictions for a relation to gaze or head movement amplitude and not (there was no relation) to eye movement amplitude (slope of SLR line not statistically different from 0.0; $p > 0.05$). This result underscored a point of Fig. 1, namely, that without the appropriate dissociation, a unit's best relation would remain ambiguous. The present dissociation was useful for determining only whether or not there was a relation to the eye movement (making the subsequent dissociation analysis necessary to determine a relation to gaze or head). In contrast, the regressions for the unit illustrated in Fig. 4I–L (T97-3) matched the predictions for a relation to eye movement amplitude — there was no relation between the NOS and gaze or head amplitude. Of the 22 units, 18 fit the predictions for a relation of NOS to gaze or head movement amplitude (with positive slopes and mean $r^2 = 0.29 \pm 0.11$, and 0.33 ± 0.11 , respectively), and no relation with eye movement amplitude (mean $r^2 = 0.03 \pm 0.04$ slope not different from 0.0, $p > 0.05$). In the *Eye limit*, *GEH sum* column of Table 1, these

units are identified by “+” under G and H and a “-” under E (“+” or “-” do not indicate the slope of the particular regression test). For four other units, the activity fit the prediction for a relation to eye movement and not gaze or head (Table 1, “- + -” for G, E, and H columns, respectively; units T48-2, T97-3, T102-1, TL30-1).

3.4.2 Dissociation analysis -- behavioral limits on gaze movement amplitude—

To determine whether units were better related to gaze or head movement amplitude (i.e., the predictions in Fig. 4B and D are equivalent and were met by 18 units), we next limited the range of gaze shift amplitudes initiated from a wide range of initial eye positions. For this analysis, 20 neurons had at least one subset with sufficient numbers of trials (mean $n = 26 \pm 6$) within $\sim 10^\circ$ ranges of gaze movement amplitudes (e.g., 55 to 64°) concurrent with $\sim 25^\circ$ ranges of eye and head movement amplitudes (see Fig. 5A for hypothetical behavioral data); six units had insufficient data and could not be tested under these gaze limit constraints (Table 1, *Gaze limit* columns, “na”, $n < 15$). Figure 5B–D shows the fits predicted given relations of NOS with gaze (triangle or solid gray lines), eye (black dotted lines), and head movement amplitude (gray dashed lines), respectively. For the unit illustrated in Fig. 5E–I (P20-1, the same unit observed to be gaze or head related above, Fig. 4E–H), the data were consistent with the prediction for a relation with head movement and not consistent with that for gaze or eye: *F* shows a large variation in NOS despite a small range of gaze movement (slope = 0.16 , $r^2 = 0.00$, $p > 0.05$, $n = 33$), *G* shows a significant negative correlation with eye amplitude (slope = -1.21 , $r^2 = 0.42$, $p < 0.0001$), and *H* shows a nearly significant positive correlation between NOS and head movement amplitude (slope = 0.61 , $r^2 = 0.10$, $p = 0.076$). Additionally, Fig. 5I shows a stronger positive correlation between the NOS and *head contribution* (slope = 0.54 , $r^2 = 0.40$, $p < 0.0001$). Taken together, these results matched the prediction for a relation to the head movement and in no way resembled a prediction for a relation to gaze (or eye). The bursts of 10 additional neurons also matched the predictions for a head movement-only relation (Table 1, *Gaze limit*, *GEH sum* column, “- - +”, “+” under H). These 11 neurons exhibited no clustered relation between NOS and gaze movement amplitude, and each showed a significant negative correlation with eye movement amplitude (negative slopes; mean $r^2 = 0.28 \pm 0.08$, $p < 0.05$), sufficient to rule against a gaze or eye relation, the latter of which would have required a positive correlation as shown in Fig. 5C and a negative correlation as shown in Fig. 5D (black dotted line), respectively. Nine of these units also showed a positive correlation with head movement; positive slopes; mean $r^2 = 0.29 \pm 0.08$, $p < 0.05$; Table 1, *Gaze limit*, *GEH slope* column). Two of these units had nearly significant correlations of NOS and head movement amplitude (P20-1 in Fig. 5H and P12-2, $p < 0.10$), and significant negative correlations between NOS and eye movement amplitude (e.g., Fig. 5H), sufficient to rule against a gaze or eye relation, even though the correlation with head movement amplitude was not statistically significant (though not necessary for this result, significant correlations for NOS and head contribution were also observed (e.g., Fig. 5I, $p < 0.001$). In sum, these 11 units exhibited a relation to head movement amplitude and no relation to eye or gaze movement amplitude.

In contrast, Fig. 5J–N shows a unit (T88-3) whose data were consistent with the predictions for a relation with gaze movement amplitude only: data points were clustered in *K*, showing that with little change in gaze movement amplitude, there was little change in the NOS. Moreover, there was no relationship between the NOS and eye, head, or head contribution amplitude in Fig. 5L–N (slopes not different from 0.0, all $r^2 < 0.10$, $p > 0.05$). Four additional units were similarly related to gaze movement amplitude only. Only two of these 20 units matched the predictions for a relation to eye movement amplitude, consistent with the previous test. Results from the remaining two of 20 units did not consistently fit the predictions, and were classified as *inconclusive* (Table 1, *Gaze limit*, *GEH sum* column).

The combined results of these two dissociation analyses are shown in Table 1, *Dissociation summary* column: 11 units had burst activity related only to head movement amplitude (matching that shown for P20-1 in Fig. 5E–I), five to gaze movement amplitude (matching that shown for T88-3 in Fig. 5J–N), and four to eye movement amplitude (matching that shown for T97-3 in Fig. 4I–L). Four additional units were not related to eye movement amplitude, but could only be designated as G or H with these results (Table 1, *Dissociation summary* column “G or H”). Finally, two of the 26 could not be tested with either dissociation analysis and could not be classified.

3.4.3 Regression analysis of number of spikes vs. movement amplitude—To assess associations between the burst NOS and movement metrics further — across a larger number of trials and movement amplitude ranges — we tested all 26 units with simple linear regression (SLR) where intercorrelation among the movement parameters was low, and multiple linear regression (MLR) where it was not. SLR revealed significant correlations between NOS and at least one movement parameter for 25 units. Correlations were strong with gaze, head movement, and head contribution amplitude (mean $r^2 = 0.38 \pm 0.15$, 0.33 ± 0.15 , and 0.38 ± 0.15 , respectively) and much weaker with eye movement amplitude (mean $r^2 = 0.25 \pm 0.13$; mean number of trials = 120 ± 55). Because the correlations with many movement amplitudes were similar, we next tested whether MLR with models including two or more movement parameters accounted for more of the variance in NOS. Table 2, *Number of spikes, Best model* column, shows that each of 12 units remained best described by a single-parameter SLR model parameter. Thirteen of the remaining 14 units were each described with a single two-parameter MLR model, which significantly improved upon the mean SLR r^2 of 0.38 ± 0.13 to mean MLR R^2 of 0.46 ± 0.13 (*paired t-test*, $p < 0.0001$). One unit was described as having no relation (was fit with r^2 and $R^2 < 0.15$ (Table 2, *Number of spikes, Best model* column, “no relation” (unit T102-1)). In these 13 two-parameter models, the primary variable — that with the greatest standardized regression coefficient (SRC), i.e., the variable most influential in predicting the NOS for a unit — was always a movement amplitude variable, and eye or head position (POS) was the secondary parameter, with median SRCs (0.36 ± 0.08) less than those for the primary variable (0.65 ± 0.13 ; *paired signed rank test*, $p < 0.001$). That is, in 50% of our units, position had a secondary, modulatory effect on NOS, which explained an additional 8% of the variance in NOS (on average). The effect of POS was aligned with the preferred hemifield for seven of 13 units, such that movements that began in the on-direction hemifield increased the NOS relative to movements starting from a central initial position; position effects were opposite to the preferred hemifield for the remaining six units (Table 2, *Number of spikes, Best model* column; the sign of the coefficient (value not shown) of the POS variable indicates aligned (+) or opposed (–)). Although we could not determine if the POS parameter was IEP or IHP due to high intercorrelation, for either parameter the sign of the coefficient was the same, so that the position effect was in the same direction regardless of whether IEP or IHP were involved.

In sum, 25 of the 26 units were described by single regression models, and head movement amplitude was the only or primary variable in 13 (Table 2, *Number of spikes, Best model* column). Six of these 13 were each described with a one-parameter model and six with a two-parameter model; the only or primary variable, respectively, was the overall head movement amplitude (we considered only the total head movement amplitude effect in these results, though similar models including head contribution were equivalent for eight, and greater for five units). For eight other units, gaze movement amplitude was the only (3), or primary (5) variable. For four units, eye movement amplitude was the only (2) or primary (2) variable.

3.5 Relation of burst and movement temporal parameters

3.5.1 Correlations with burst start time—For all 26 units, the burst started, on average, before the start of the eye/gaze movement (45 ± 23 ms) and the head movement (41 ± 24 ms; number of trials = 35 to 233; Table 2: *Burst start time*, *Best model* columns). Figure 6 indicates this temporal relation for a representative unit, and Fig. 6C, D shows that the association between burst start and the start of the eye/gaze movement was much stronger than that with head movement start time. We used SLR and MLR analyses to determine whether burst onset was best timed with eye/gaze, or head movement onset, and if initial eye or head position parameters also influenced burst start time. We found that the burst onset was strongly related to eye/gaze movement onset in 22 units (mean best r^2 or $R^2 = 0.49 \pm 0.15$), and strongly related to head movement start time in two units; two of the 26 neurons showed *no relation* (r^2 and $R^2 < 0.15$; Table 2, *Burst start time*, *Best model* column). Of the 13 neurons that had shown a strong relation between burst NOS and head movement amplitude (above), 11 exhibited burst onsets best associated with the eye/gaze movement onset. Although 12 of the 24 units remained best described by single one-parameter models, for 12 neurons, MLR revealed a single two-parameter model for each unit that improved the fit relating burst start time to movement start time (mean SLR r^2 of 0.45 ± 0.15 SD improved to mean MLR R^2 of 0.51 ± 0.15 ; *paired signed rank test*, $p < 0.001$). These 12 models included initial eye or head position (POS) as the secondary variable — the only other parameter consistently included in MLR models — and this always had a secondary/smaller influence on burst start time (median POS SRC = 0.24 ± 0.04 vs. primary SRC = 0.65 ± 0.09 ; *paired signed rank test*, $p = 0.005$). The parameters included in the best regression models are given for individual neurons in Table 2, *Burst start time*, *Best model* column (E/G = eye/gaze movement start time, H = head movement start time).

3.5.2 Correlations with burst end time—For all 26 units, the burst ended, on average, after the end of the eye/gaze movement (14 ± 57 ms) and before the end of the head movement (231 ± 50 ms; number of trials = 35 to 237). Figure 7 shows that, for the same unit shown in Fig. 6, the burst ended nearer the end of the eye/gaze movement (Fig. 7A) than the head movement end time (Fig. 7B), and the association between burst end time and the end of the eye/gaze movement was much stronger than that with the end of the head movement (Fig. 7C, D). We observed the same result for all 26 units — the burst end time was more strongly related to eye/gaze movement end time (mean best r^2 or $R^2 = 0.55 \pm 0.16$) than any other variable. The burst end time of 15 units was best predicted by eye/gaze movement end time alone. Each of the remaining 11 neurons was best described by a single two-parameter model that improved the fit to burst end time (mean SLR r^2 of 0.47 ± 0.10 to mean MLR R^2 of 0.67 ± 0.10 ; *paired signed rank test*, $p = 0.002$). Eye/gaze movement end time was the primary variable and eye or head position (POS) had a small secondary influence on burst end time (mean SRC = 0.23 ± 0.07 vs. primary SRC = 0.61 ± 0.17 ; *paired signed rank test*, $p = 0.005$). Any relation of burst end time to head movement end time or time to head peak velocity was statistically weaker in SLR testing (*equal correlations test*, $p > 0.05$) and neither could enter (with a statistically significant coefficient) into any MLR models. The parameters included in the best regression models are given for individual neurons in Table 2, *Burst end time*, *Best model* column (E/G = eye/gaze movement end time).

3.5.3 Correlations with burst duration—Because the timing of burst onset was strongly related to the onset of the eye/gaze movement, burst start time did not vary with movement amplitude, and the burst end time was correlated with the end of the eye/gaze movement, burst duration was also strongly correlated to the duration of the eye/gaze movement. Across all units, the mean burst duration was longer than that of the eye/gaze

movement (mean = 60 ± 51 ms longer; range: -27 to 141); for each of 23 units, the mean burst duration was longer than the eye/gaze movement duration; the three other units exhibited mean durations shorter than the eye/gaze movement (mean number of trials per unit = 36 to 238). For all 26 units, the burst duration was always shorter than head movement duration (mean = 190 ± 50 ms shorter, range 118 to 303). For 25 units, the burst duration was more strongly related to eye/gaze movement duration than any other variable (equal correlations test, $p < 0.05$; mean best r^2 or $R^2 = 0.47 \pm 0.14$); one neuron showed no relation (r^2 and $R^2 < 0.15$; Table 2, *Burst duration*, *Best model* column, “no relation”) and was not examined further. The burst duration of 16 of these 25 units was best predicted by eye/gaze movement duration alone. Each of the nine remaining neurons was best described by a single two-parameter MLR model that improved the fit to burst duration (mean SLR r^2 of 0.38 ± 0.15 to mean MLR R^2 of 0.45 ± 0.14 ; *paired signed rank test*, $p = 0.004$). Eye/gaze movement duration was the primary variable and eye or head position (POS) was again the only secondary variable in MLR models (with a small influence on burst duration: mean SRC = 0.27 ± 0.10 vs. primary SRC = 0.59 ± 0.11 ; *paired signed rank test*, $p = 0.004$). Head movement duration was not included in the model for any unit. The parameters included in the best regression model are reported for individual neurons in Table 2, *Burst duration*, *Best model* column (E/G = eye/gaze movement duration).

3.6 Overall designation of FEF neuron behavior

We combined the results of the dissociation and regression analyses to classify the burst activity of the 26 units as related to aspects of the gaze, eye, or head movement (Table 2, *Final unit class* column). For all 26 units, the result of the number of spikes regression analysis was not inconsistent with that of the dissociation analyses (24 units were in complete agreement; one had no dissociation sum (T32-1), one had “no relation” for number of spikes (T102-1); cf. Table 1, *Dissociation summary* and Table 2, *Number of spikes* columns). For nine units the regression analyses examining burst temporal parameters for those neurons related to gaze (5) and eye (4) movement amplitude were also consistent with the dissociation analyses results. We therefore classified these as five *gaze-related burst neurons* (GBNs) and four *saccade-related burst neurons* (SBNs). For 11 units the dissociation analyses revealed a head movement amplitude relation (and no relation to eye or gaze movement amplitude) and the number of spikes regression analysis revealed the strongest, primary relation to head movement amplitude only. The regression analyses results showed that the temporal parameters of the bursts of these neurons were most strongly related to gaze/eye movement timing, except for two that exhibited a relation between burst start time and head movement start time. Because it is the movement of the eye that moves gaze, we designated these neurons as *head-eye-related burst neurons* (HEBNs). Six of the remaining units exhibited burst characteristics that were qualitatively similar to the others but were less readily classified — the dissociation results were ambiguous (G or H) for four units (T97-2, TL21-2, TL23-2, P30-1), and were unavailable for two (T34-2, T44-3; Table 1, *Dissociation summary* column). The results of the number of spikes regression analysis (with fewer constraints and higher numbers of trials than the dissociation analyses), however, unambiguously identified gaze, eye or head movement amplitude correlations, which allowed us to cautiously classify three of these six units as GBNs, two as HEBNs, and one as a SBN (Table 2, *Final unit class* column, “b”).

3.7 Sites of single neuron recordings

We restricted our sampling to the dorsomedial FEF, so nearly all units were recorded from a relatively narrow region of the anterior bank of the arcuate sulcus dorsomedial to the principal sulcus (i.e., the large-amplitude FEF). The reconstructed locations of our 26 neurons are shown in Fig. 8A–C, which represent views normal to the cortical surface reconstructed from MR images of each FEF and its recording cylinder (as shown for animal

T in Fig. 8E). There was no apparent relation between a neuron's classification and its recording site.

At the site of each neuron reported here, we also evoked saccades and/or gaze shifts with low-intensity microstimulation to verify the electrode's location within the classically defined low-threshold FEF (Bruce et al., 1985, Knight and Fuchs, 2007). The locations of the recording electrodes were further verified by histological examination of electrolytic lesions in the left FEF of animal T (Animal P was participating in on-going experiments that precluded histological examination). The lesion in Fig. 8D was made at a site from which we had recorded movement-related activity and evoked gaze shifts with low-intensity microstimulation. It was located near the reconstructed location of the HEBN sites (Fig. 8A, O).

4 DISCUSSION

Conclusions about the role of the frontal eye field (FEF) in gaze movement control have been based on the discharge of its units relative to gaze shifts made with the head restrained — movements that employ saccadic eye movements only. We asked whether, with the head completely unrestrained, movement-related neurons in the dorsomedial FEF carry signals related only to the overall gaze shift. Our results did not support the gaze movement-only hypothesis, since we described three categories of burst or burst-tonic, movement-related neurons whose burst activity was related to head movement amplitude and the eye saccade timing (HEBNs), the overall gaze movement (GBNs), or the eye saccade alone (SBNs). We closely examined only movement-related neurons and found that: when tested within their movement field along their preferred horizontal directions, all 26 neurons discharged bursts that preceded (and were correlated with) the onset of horizontal gaze shifts alone (21 movement neurons) or with the gaze shift and the target step (five visuomovement neurons). These neurons also exhibited amplitude sensitivities — most with *open movement* fields — and directional sensitivities were similar to those described previously (not shown); unexpectedly, only 14 of 26 discharged best for contraversive gaze shifts, a much lower percentage than with the head restrained (Bruce and Goldberg, 1985).

4.1 Unit identification

Because the metrics of eye, head and gaze movements can be strongly intercorrelated (Freedman and Sparks, 1997a), we collected subsets of data by behavioral dissociation that limited the range of gaze or eye movement amplitudes to reduce intercorrelation, and we also tested all data with single and multiple linear regression (SLR and MLR, respectively). For every one of our 26 neurons, the results of a minimum of three and most often all six of these analyses (two dissociation, four regression) converged on a single diagnosis for the relation of burst properties to movement metrics. In nearly all cases, the timing of burst was best related to the start, end, and duration of the eye movement (which we found to be equivalent to the start, end, and duration of the overall gaze shift (Tomlinson and Bahra, 1986, Freedman and Sparks, 1997a, b)). Thirteen neurons coupled these burst temporal relations *and* the amplitude of head displacement (*head-eye-related burst neurons*, HEBNs), eight did so for gaze movement amplitude (*gaze-related burst neurons*, GBNs), and five were best related to the eye saccade amplitude and timing or *saccade-related burst neurons* (SBNs; see Table 2, *Final unit class* column).

We found no association between unit designation and the site of recording, type of movement field (open or closed with respect to amplitude), or preferred gaze direction (contra- or ipsiversive). We have no clear explanation for the unexpected number of ipsiversive-sensitive units, but head-restrained results have shown that ipsiversive-sensitive FEF neurons are not uncommon and that these predominantly receive information from the

contralateral SC (Crapse and Sommer, 2009). We found a strong correspondence between the unit's preferred direction and the stimulation-evoked characteristic vector (CV) for five contraversive-sensitive units (Knight and Fuchs, 2007), but found no clear result for the ipsiversive-sensitive units — two roughly corresponded with ipsiversive CVs, the third not at all (contraversive CV). We suggest that the unit designations and their putative roles in gaze shifts (below) are equally feasible for ipsiversive and contraversive units.

For the 13 HEBNs, the number of spikes (NOS) was most strongly correlated with head movement amplitude. In contrast, burst start time, end time, and duration were nearly always strongly correlated with eye movement start time (except for two units with a stronger relation to head movement start time), end time, and duration. The burst NOS was used to describe the units' response fields because it was consistently better associated with movement amplitudes than was AFR or peak firing rate. Because the movement field was the basis for subsequent analyses of subsets of the data, analysis with NOS was more likely to reveal physiologically relevant associations. Indeed, for most units, regressing AFR or peak firing rate on movement amplitudes resulted in no statistically significant relation and no fit to any predictions of the dissociation analyses; it was never the case that using NOS resulted in a fit matching a dissociation prediction for one relation (e.g., head movement) while using AFR resulted in a fit matching a prediction for a different relation (e.g., eye movement). Peak firing rate was not related to peak head velocity for any of these neurons (not shown). Although the peak head velocity occurred near the eye/gaze movement end, we found no correlation between burst end time and peak head velocity time.

Finally, MLR also identified initial eye or head position as secondary movement-related parameters with small but significant effects in at least one regression model for 22 units (POS in Table 2). Early studies found no effect of eye position on saccade-related discharge in head-restrained FEF units (Goldberg and Bruce, 1990, Russo and Bruce, 1996). Our results are in partial agreement with those of a more recent study that did find an effect of eye position on FEF unit activity (Cassanello and Ferrera, 2007), except that we did not find all eye position effects in opposition to the unit's preferred vector as they describe. This may have been due to the difference in head restraint, or that most of our cells were movement-related (since they suggest that any eye position effect was weakest in movement related cells). This difference in position effects alignment was not due to our consideration of head position relative to the body (initial head position, IHP) as the POS variable because the alignment was identical whether we considered IHP or initial eye position (IEP). Our result of equal proportions of aligned and opposite position effects is consistent with that described for movement-related cells in the SC recorded with the head-unrestrained, suggesting that position effects may be less uniformly used in movement commands compared to sensory signaling. It also suggests that our results were inconsistent with a re-centering bias and that these signals are likely routed from the FEF to the SC (Nagy and Corneil, 2010). Additionally, position effects based on IHP would be similar to those reported for pursuit neurons of the caudal FEF, which are influenced by a head-re-trunk signal (from neck proprioception), and which add linearly to most FEF gaze and eye pursuit neurons' activity (Fukushima et al., 2010).

Though microstimulation tests population output effects that may be different from single unit sensitivities based on uniformity of topographical function, microstimulation of the FEF with the head restrained does evoke saccades with small, but statistically significant, eye position-dependent effects (Russo and Bruce, 1993). Moreover, with the head unrestrained, FEF microstimulation evokes eye and gaze movements that are strongly influenced by initial eye position (Tu and Keating, 2000, Chen, 2006, Knight and Fuchs, 2007, Monteon et al., 2010). The alignment of these position effects was not consistent for microstimulation and unit recording, however. Twenty of our 24 linearly described stimulation sites showed

effects of IEP (and six showed effects of IHP) on gaze (and eye) movement amplitude, and in all 20 cases, the position effect (both IEP and IHP) was in opposition to the characteristic vector (CV) for the site (Knight and Fuchs, 2007). In contrast, eight of our 26 units were recorded before microstimulation at the exact site and while six of these exhibited position effects on NOS, the position effect aligned with the preferred hemifield in five. Finally, we found no pattern in location of units with position effects in the dorsomedial FEF, no relation to movement field type (position effects were found for open MF (8) and closed MF (5) units), and there was no correlation between unit classification and presence of position effect.

4.2 The function of the FEF in head-unrestrained gaze shifts

We propose that the FEF could influence gaze shifts by two mechanisms consistent with our results and those of previous reports: 1. Different FEF neurons could provide timing and displacement commands for eye or gaze movements; and 2. The FEF could coordinate the proportions of eye and head components of gaze shifts by combining a head displacement command with temporal control of the eye saccade, as exhibited by HEBNs.

4.2.1 Saccade-related burst neurons—Our saccade-related burst neurons (SBNs) discharged bursts whose start, end, duration, and NOS were correlated with the eye saccade component's start, end, duration and amplitude, respectively, implying that they may trigger and control the amplitude of saccadic eye-only movements. Because reversible inactivation of the SC interferes with FEF-stimulation evoked eye saccades, our SBNs most likely participate in the generation of gaze shifts via projections to the SC (Hanes and Wurtz, 2001). This is also consistent with known anatomy, so it seems reasonable to suggest that our FEF SBNs project to large-amplitude, caudal sites in the intermediate and deep SC gray (Stanton et al., 1988). That is, because our FEF SBNs were characterized with large-amplitude response fields, they likely project to more caudal SC sites. This is consistent with results from the head-restrained monkey that show the movement fields of our FEF SBNs and SC units aligned/in register, as demonstrated with unit recording and antidromic stimulation thresholds (lower for those in register) (Segraves and Goldberg, 1987). Because caudal SC units are known to fire bursts related to eye-head combined gaze movement generation (Freedman and Sparks 1997b), we suggest that the signal carried by the FEF SBNs contributes to the motor command that generates the eye saccade component of the resulting eye-head combined gaze shift. This is consistent with our results since it is important to remember that our FEF SBNs discharged a burst of action potentials just before and during large, eye-head combined gaze shifts, but the burst was not related to the gaze or head movement amplitude, only that of the eye saccade. In this, our results were not inconsistent with those of the only other study recording FEF neurons in head-unrestrained (horizontally) monkeys, which described neurons that burst in association with contralateral eye movements (Bizzi and Schiller, 1970).

This is only one possibility for future testing, and is not meant to exclude the possibility of a convergence of FEF and SC signals downstream of the SC, nor does it rule out the possible effects these SBNs might have via a caudate/striatum route or via omnipause neurons (OPNs, see below). In fact, if these neurons are part of a direct path from the FEF to brainstem premotor circuits (in total or via bifurcation) then their effect on OPNs may be likely since a direct path to the PPRF (while present, Segraves 1992) appears to have limited abilities to drive an eye saccade. Future investigations that examined more of the ventrolateral, small-amplitude FEF in head-unrestrained animals would also likely reveal a larger proportion of SBNs.

4.2.2 Gaze-related burst neurons—Our gaze-related burst neurons (GBNs) discharged bursts whose start, end, duration, and NOS were correlated with gaze start, end, duration and amplitude, respectively, implying that they trigger and control the amplitude of the overall gaze shift. These burst characteristics were similar to those reported for the gaze displacement-related neurons of the SC described via similar *dissociation analyses* (Freedman and Sparks, 1997a), and we suggest that these GBNs contribute to the control of the gaze shift by sending a gaze command to the SC. Because the information represented in the burst of a GBN does not itself relate to the amplitude of separate eye or head displacements, it must be subsequently modified into separate eye and head movement signals. The most parsimonious suggestion is that GBNs send their gaze movement amplitude-related signal to the SC and contribute to the SC gaze displacement signal, which is subsequently decomposed into separate eye and head movement commands (Freedman and Sparks, 1997a).

4.2.3 Head-eye-related burst neurons—We classified half of our 26 neurons as head-eye-related burst neurons (HEBNs) because their burst activity was correlated with the amplitude of the head movement *and* the temporal metrics of the associated eye saccade. While it may seem improbable for a neuron's burst activity to relate to both head displacement and eye movement timing, our results were not inconsistent with this suggestion. First, in terms of movement amplitude, we found no inconsistencies between the results of the dissociation analyses and the less constrained number of spikes regression analysis for all 26 units (Table 1, *Dissociation summary* and Table 2 *Number of spikes* columns). Thirteen units exhibited a relation to head movement amplitude, eight were consistently described as related to the overall gaze movement, and five were consistently described as related to eye movement. Thus, there was no inconsistency between the results of the dissociation and the number of spikes regression analyses, and this agreement indicates the value of applying both types of analyses to this question. Second, the results of the temporal regression analyses (burst start time, end time, and duration) was not in obvious conflict with the result that the NOS was related to the movement amplitude for the five SBNs and eight GBNs. While there was no need to re-examine our methods and results based on the SBN and GBN results, our description of HEBNs appears problematic in that they do not fit an intuitive description as easily. We forward this description because the methods worked for half of our neurons (the SBNs and GBNs), and it was the most parsimonious explanation consistent with our data for the remaining half (HEBNs).

We suggest there is no *a priori* reason that a HEBN's burst could *not* relate strongly to head displacement via burst magnitude (i.e., NOS) and simultaneously relate strongly to eye movement timing via burst timing (i.e., *burst start*, *burst duration*, *burst end time*). Why would it be impossible for a neuron's discharge to be related to two different movements? First, it is clear from the consistent results of the dissociation and regression analyses (Tables 1 and 2) that designating a role for these HEBNs in head movement was not due to small sample size or inappropriate analyses — these analyses showed that the HEBNs had little (not primary or secondary), and often no relation between NOS and eye or gaze movement amplitude despite strong temporal relations between their bursts and eye/gaze movements. This was very different from what we described for the SBNs and GBNs — that the NOS and movement amplitude associations and temporal relations all pointed to an important, primary association with the eye or gaze movement amplitude, respectively. Second, results of previous studies are not inconsistent with the idea that burst discharge may relate to both eye and head movements. Studies examining both eye and neck muscle activation or head movement in cats have described single neurons that exhibit burst discharge *and* temporal parameters correlated with *both* neck EMG activation *and* eye saccades (Vidal et al., 1983, Grantyn and Berthoz, 1987). Furthermore, Grantyn and Berthoz (1987) describe single reticulospinal neurons whose phasic (burst) discharge was closely

related to both the eye movement and neck EMG (head movements not measured) *and* whose microanatomy shows bifurcation of single neurons to the abducens nucleus and neck premotor centers. Recently, neurons in the monkey SC shown to relate to the saccade (perisaccadic burst) were shown to also exhibit low-frequency firing rates strongly correlated with agonist neck muscle EMG activity (Rezvani and Corneil, 2008). While the above were not FEF neurons, it has been shown that corticofugal neurons from the rat-equivalent of the FEF have axon collaterals that terminate in more than one brainstem premotor region, e.g., the SC and pontine reticular formation (Leichnetz and Gonzalo-Ruiz, 1987). To our knowledge, there is no evidence to suggest that primate FEF neurons could not bifurcate the same way and no *a priori* reason to suggest that these FEF neurons could not have phasic discharge correlated in timing and magnitude with eye and head movements, respectfully.

That HEBNs encode motor information for both the eye and head components of eye-head gaze shifts suggests that they are different from recently described SC cells related to head-only movements (Walton et al., 2007). Some aspects are comparable because some of their cells were also active before and during eye-head gaze shifts, but important differences may exist: temporal aspects of their head-only cells' bursts were best related to the head movement in isolation or as a component of gaze; the burst activity for all 13 HEBNs was much more strongly associated with head movement amplitude than was that of the SC units; and seven of our 13 HEBNs exhibited ipsiversive direction sensitivity while head-only appear to prefer contraversive movement. Because we did not record during head-only movement trials as they did, it is interesting to consider whether our HEBNs would show similar modulation during head-only movements; certainly microstimulation of the FEF can evoke head-only movements (Tu and Keating, 2000, Elsley et al., 2007, Knight and Fuchs, 2007). Indeed, our HEBNs were similar to the SC head-only cells in that most had monotonically increasing discharge with respect to amplitude, and that the burst onset led the head movement start for all cells.

Given the properties of the HEBNs and differences with SC gaze-only units and head-only units, we suggest that our HEBNs project to regions of the brainstem reticular formation that generate head movement and the timing of eye saccades (Robinson et al., 1994, Walton et al., 2008). We further suggest that these HEBNs' relations to eye movement timing means that they may also provide a way to coordinate the appropriate amount of eye and head displacement for accurate gaze shifts. Here we describe a novel mechanism for how these unusual neurons might contribute to a gaze shift.

First, we suggest that HEBNs directly *influence* the head displacement during eye-head gaze shifts. A corticopontine HEBN could send the head displacement command directly to head premotor elements in the brainstem, bypassing the SC. A projection from the cortex to the neck premotor regions that is independent of the SC is implicated, since reversible inactivation of the SC does not alter head movement amplitude during eye-head gaze shifts (Walton et al., 2008). Additionally, head-unrestrained monkeys conditioned to view targets through pinhole goggles were not adapted as predicted if there were only a corticotectal channel that controlled gaze movements, implying that a direct cortical projection to head premotor regions exists (Constantin et al., 2004). These same authors have shown that the supplementary eye field (SEF) provides only a gaze command to downstream oculomotor elements (Martinez-Trujillo et al., 2003), leaving the FEF as a possible source of the cortical head movement command.

Finally, neuroanatomical investigations have demonstrated that neurons of the primate FEF project to brainstem reticular regions involved in head movement (Stanton et al., 1988, Segraves, 1992). An active population of neurons with head movement amplitude-related

bursts could then directly influence the appropriate head displacement of gaze shifts. These HEBN burst relations could not have been discovered with the head restrained; indeed, the FEF neurons described in the only other unit recording study in the head-unrestrained monkey are similar to ours in that they were qualitatively related to head movement (Bizzi and Schiller, 1970). Our HEBNs, under closer examination, behaved differently from those of this previous study — HEBN temporal burst parameters were correlated with the temporal metrics of the eye saccade during head-unrestrained gaze shifts.

Thus, the second way these same HEBNs may influence gaze shifts is by influencing the timing of the eye saccade, perhaps by sending collaterals to inhibit the omnipause neurons (OPNs) of the raphe interpositus nucleus. The OPN pause is strongly correlated with the onset, duration, and offset of the eye saccade in the head-unrestrained monkey, but does not affect the head movement (Phillips et al., 1999, Gandhi and Sparks, 2007). The eye-movement-related temporal activity of HEBNs could indirectly provide an inhibitory command to turn off the OPNs allowing a gaze shift to occur. Because movement-related neurons of the FEF have been shown to project to (Stanton et al., 1988) and inhibit the OPNs of monkeys (Segraves, 1992), we suggest that our HEBNs — whose bursts also code head displacement — could, via the same bursts, influence the eye displacement of the gaze shift. The HEBNs would not *directly* command the eye movement amplitude, since there was no correlation of saccade amplitude with the burst NOS, but would instead *gate* the start, end, and duration of an eye saccade via corticopontine control of OPNs. Twelve of our 13 HEBNs exhibited a strong relation between burst duration and eye movement duration. Because other neural circuits concurrently command eye saccade displacement (e.g., our FEF SBNs and the SC), the HEBNs would not directly drive the saccade, *but provide a window within which it could occur*, thereby influencing eye movement amplitude. This model is consistent with earlier results suggesting a role for the FEF as one possible trigger input to the brainstem burst generator (Robinson and Fuchs, 1969, Segraves, 1992, Scudder et al., 2002).

Because the novel designation of our HEBNs relies heavily on accurate identification of movement start and end times, it is worth considering whether the temporal relations of these cells was an artifact of imperfect methods. This problem centers on whether the measurement of head movement temporal metrics was done as accurately as that for eye and gaze — identification of the end of a head movement was sometimes challenging (e.g., because it could be complicated by a secondary reacceleration), but identifying the onset of head movement was no more complicated than doing so for the eye saccade or gaze shift. That is, our results of the burst start regression analysis should not have been biased toward eye/gaze start relations. Indeed, for two HEBNs, the burst start was most strongly related to the head movement start, which suggests that because we were consistent in how we identified movement metrics, our methods would have likely detected stronger associations with head movement timing if present (note that many units *did* exhibit associations between burst and head movement timing, but these were, except as noted above, statistically weaker than that for eye/gaze movement timing). It is worth emphasizing that even if our methods had obscured a relation of burst timing to the head movement, these HEBNs *were still related* to the head movement amplitude, and *not* the overall gaze movement or eye saccade amplitude — that is, these movement-related FEF cells did not exclusively encode a motor command for the gaze movement.

We are also cautious in presenting this hypothesis because our HEBNs had bursts that ended (on average) slightly after the end of the eye movement (mean 18 ± 56 ms; range: -43 to 103 ms re eye/gaze movement end time). At first glance, this seems incompatible with influencing the end and duration of the eye saccade. However, during head-unrestrained gaze shifts, OPNs themselves stop pausing on average 6 ± 16 ms after the end of the eye

movement, with some ceasing to pause at ~60 ms after eye movement end (Phillips et al., 1999). Influence over the OPN pause would allow FEF control of the termination of eye saccades since, in cats, it is the resumption of OPN discharge that halts the eye movement rather than the offset of excitatory drive to reticular excitatory burst neurons (Iwamoto et al., 2009).

If this is also the case in primates, then HEBNs may serve a critical role in the coordination of the contributions of eye saccades and head movements to the eye-head gaze shift. Indeed, the results of unilateral FEF lesions in the head-unrestrained monkey are consistent with this suggestion – gaze shifts are accurate following recovery — suggesting that the FEF is not necessary for the gross head movement itself — but the proportion of head displacement is twice normal and eccentric post-VOR eye position is not possible (van der Steen et al., 1986). Because the FEF (and its HEBNs) are not the only source of head displacement commands — the SC may also issue a head displacement signal (Corneil et al., 2002, Walton et al., 2007) — head movements of gaze shifts are not lost — instead they are dramatically increased in amplitude so that they comprise an abnormally large proportion of gaze shift amplitude. This implies that the FEF (and perhaps HEBNs) is *not necessary for driving the head movement*, but that it (and its HEBNs) may be necessary for achieving the proper proportion of head and eye movement amplitudes for a given gaze movement. Indeed, we have shown that in the unlesioned monkey, microstimulation at many of these same FEF sites results in site-specific commands that move the head only or in combination with an eye saccade to return the eyes to central position or achieve a goal-directed final eye position (Knight and Fuchs, 2007). That is, our microstimulation and recording evidence suggest that the FEF does not issue *only* a gaze movement command. It may also encode signals to coordinate eye and head movements to provide context-appropriate post-VOR eye position before or after an overall eye-head gaze movement.

4.3 Conclusion

We conclude that when examined with the head-unrestrained, the motor function of the FEF is made more clear; its movement-related neurons are active during, and related to the components of, rapid combined eye-head gaze shifts. The dorsomedial FEF does not exclusively encode a gaze command, but individual neurons within it appear to encode gaze, eye, or head displacements. Moreover, for the FEF neurons whose burst was correlated with head movement amplitude, the burst temporal profile also matched that of the associated eye saccade. Because of the relatively high proportion of these head-eye-related burst neurons (HEBNs) in the dorsomedial FEF, we suggest that they may provide a mechanism for cortical control of the coordination of eye and head components of gaze shifts.

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ABBREVIATIONS

FEF Frontal eye field

SEF	Supplementary eye field
SC	Superior Colliculus
PPRF	Paramedian pontine reticular formation
OPN	Omnipause neuron
VOR	Vestibuloocular reflex
G	Gaze position in space, or, for example, Gs, Gaze movement start time
E	Eye position in head/orbit, or, for example, Es, Eye movement start time
H	Head position in space, or, for example, Hs, Head movement start time
B	Unit burst parameter, for example, Bs, Burst start time
Hc	Head contribution to the gaze shift
IEP	Initial eye position (in head)
IHP	Initial head position (in space)
POS	Position (IEP, IHP, or initial gaze position, IGP)
SLR	simple linear regression
MLR	Multiple linear regression
SRC	Standardized regression coefficients
NOS	number of spikes in unit burst
GBN	Gaze-related burst neuron
SBN	Saccade-related burst neuron
HEBN	Head-eye related burst neuron

GLOSSARY

Frontal eye field (FEF)	a region of the frontal cortex of mammals, best defined by Bruce and colleagues in 1985 via unit recording and microstimulation. Anatomically equivalent to Brodmann's area 8 and occupying the rostral bank of the arcuate sulcus in rhesus monkeys
Unit	a single, isolated, action potential discharging neural component, most likely a neuron
Supplementary eye field (SEF)	a region of the dorsomedial frontal cortex of mammals, considered to be important in issuing a gaze command, likely via extensive efferents to the FEF
Superior Colliculus (SC)	a region of the dorsal midbrain that receives extensive projections from the FEF, with sensory and movement related neurons that is critical for orienting behavior such as eye-head gaze shifts
Paramedian pontine reticular formation (PPRF)	a region of the brainstem that receives projections from the FEF, SEF, and SC and houses assemblies of premotor neurons for eye and head movements
Gaze	one's line of sight in space

Saccade	one of five major types of mammalian eye movement, used to rapidly change gaze. Saccades have high velocity, short duration, and are thought to be too rapid for control via visual feedback
Gaze shift	the change in position of one's line of sight. Rapid gaze shifts are most commonly achieved by eye saccades alone (for small amplitude) and by an eye saccade and simultaneous rapid head movement. One can achieve a gaze shift via smooth pursuit using eye or eye and head movements
Head contribution (to gaze)	the head displacement that occurs between eye saccade start and end (the duration of the gaze shift); this is different from the overall or <i>total head movement amplitude</i> associated with eye-head gaze shifts, which can be much larger if the head continues to move after the gaze shift has ended

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FIG. 1. Variation of a FEF neuron's burst activity during head-restrained and head-unrestrained gaze shifts

All panels illustrate activity from the same, representative unit, P20-1 (later designated HEBN). *A–C*: Head-restrained, horizontal (within $\pm 20^\circ$) gaze shifts and their associated neuronal discharge. *A*: Rightward gaze shifts $\sim 20^\circ$ ($\pm 5^\circ$) in amplitude. The horizontal gaze position trace is shown at top (equivalent to eye position, $G = E$, since the head is restrained). Raster plots, with each horizontal raster (row) representing one trial, illustrate the neural activity (action potentials) and are shown beneath the position traces. The histogram summarizes the neural activity across all trials shown. The position trace, rasters, and histogram are aligned on eye/gaze movement start time (vertical line). *B*: Rightward gaze shifts $\sim 40^\circ$ ($\pm 5^\circ$) amplitude. *C*: Leftward $\sim 40^\circ$ ($\pm 5^\circ$) gaze shifts; note the corresponding pause in cell activity. *D–F*: Head-unrestrained gaze shifts matching the amplitude and direction of those in *A*, *B*, and *C* (and initial head position within $\pm 15^\circ$ of center). With the head free to move, three position traces, gaze (*G*), head (*H*), and eye (*E*), are shown in order from top to bottom. *G–I*: Large amplitude head-unrestrained gaze shifts. *G* and *H*: Rightward gaze shifts $\sim 60^\circ$ ($\pm 5^\circ$) and $\sim 80^\circ$ ($\pm 5^\circ$), respectively in amplitude. *I*: Leftward gaze shifts $\sim 80^\circ$ in amplitude. Each plot illustrates 20 randomly selected trials except in *A*, *C*, *E*, and *I* ($n = 9, 10, 18$, and 14 , respectively). All plots to same scale, scale bars in *A*, *D*, and *G*; histogram bin width = 20 ms.

FIG. 2. Response fields of three FEF neurons

The number of spikes (NOS) of three neurons' movement-related bursts are plotted as a function of vertical and horizontal gaze (left), eye (*middle*), and head (*right*) movement amplitude. Each trial is plotted as a single point as if the movement started from straight ahead (origin; 0,0); i.e., the plot does not account for initial eye or head positions. Color bars at far right provide the NOS scale for each unit. *A–C*: Response fields for a unit from right FEF of animal P. This unit was later designated as a head-eye-related burst neuron (*HEBN*). *D–F*: Response fields for a unit from left FEF of animal T; later designated as a saccade-related burst neuron (*SBN*); note reduction in NOS for largest rightward amplitudes. *G–I*: Response field of neuron from left FEF of animal T; later designated as a *HEBN*.

FIG. 3. Amplitude sensitivity of neurons

Top: Amplitude sensitivity (with all trials within $\pm 20^\circ$ of preferred horizontal direction): *A:* NOS vs. gaze amplitude ($\square$) for the unit in Fig. 2A–C. These data were best fit with the linear function shown (black line), which indicates that the NOS continued to increase with increasing amplitude; this monotonic relation characterized this unit as having an “*open movement field (MF)*” with respect to amplitude. *B:* NOS vs. gaze amplitude ($\square$) for the unit in Fig. 2D–F. These data were best fit with a quadratic function (black curve), and a maximum NOS was obtained at gaze amplitudes near 70° ; since this maximum amplitude was less than the maximum gaze amplitude of several trials, this unit was characterized as having a “*closed MF*” with respect to amplitude. *Bottom:* Amplitude sensitivities of all 26 units: *C:* Seventeen open/linear MF units. *D:* Nine closed/nonlinear MF units.

FIG. 4. Results of behavioral limits on eye movement amplitude

A: Hypothetical behavioral data for situation where eye movement amplitude was limited. **B–D:** Predictions for the relations of burst NOS to movement amplitudes (see METHODS). **E:** Behavioral data recorded for the unit tested in **F–H**. Eye (□) and head (○) movement amplitude as linear functions of gaze movement amplitudes 40° showing requisite limitation (and dissociation) of eye movement amplitude (equation of line fit to eye data, labeled Y_e in plot with slope = 0.24, $r^2 = 0.29$, $p < 0.05$). **F–H:** Simple linear regression fits of NOS vs. gaze (Δ), eye, and head movement amplitudes, respectively, were consistent with the gaze- or head-related predictions seen in **B–D** (gray solid and dashed lines). **I–L:** Data from a unit whose fits were consistent with the eye-related prediction seen in **B–D** (□ and black dotted lines). Equations for linear regression fits are shown as statistically significant (*) or not significant (ns).

FIG. 5. Results of behavioral limits on gaze movement amplitude

A: Hypothetical behavioral data for condition where gaze movement amplitude is limited. **B–D:** Predictions for the relations of burst NOS to movement amplitudes (see METHODS). **E:** Behavioral data for the unit tested in **F–I** (the same unit in Fig. 4E–H). **E:** Gaze (Δ), eye (□), and head (○) movement amplitude as functions of initial horizontal eye position (IEP; negative values indicate off-direction IEPs) illustrating the requisite limitation (dissociation) of the gaze movement amplitude (independent of IEP, though eye and head amplitudes vary inversely with IEP). **F–I:** Least squares regression fits of NOS vs. movement amplitudes were consistent with the head-related prediction seen in **B–D** (gray dashed lines). Although the fit in **H** was not significant, the fit in **G** was and therefore was consistent with the H-related prediction. Note that the fit in **I** (NOS vs. head contribution) was also consistent with the head-related prediction. **J–M:** data consistent with the gaze-related prediction seen in **B–D** (Δ and gray solid lines); data were clustered in **K**, showing that with little change in gaze movement amplitude, there was little change in the NOS, and there was no association of NOS with eye or head movement amplitude. Equations for linear regression fits are shown as either statistically significant (*) or not significant (ns).

FIG. 6. Unit burst start time was most strongly correlated with eye/gaze movement start time
A: Unit activity and gaze (G), head (H), eye (E) horizontal position traces of 25 randomly selected trials aligned on eye/gaze movement start time. **B:** The same trials as in **A**, aligned on head movement start time. **C:** Burst start time vs. eye/gaze movement start time showing that the burst onset preceded, and was strongly correlated with movement start time. **D:** Burst start time vs. head movement start time, showing that burst start time preceded the movement, but was less correlated with movement start time. All plots to same scale; histogram bin width = 20 ms; regression plots with line of unity, dashed.

FIG. 7. Unit burst end time was most strongly correlated with eye/gaze movement end time
A: Unit activity and horizontal position traces of 25 randomly selected trials aligned on eye/gaze movement end time. **B:** The same trials, aligned on head movement end time. **C:** Burst end time vs. eye/gaze movement end time showing that the burst end time was strongly correlated with eye/gaze movement end time. **D:** Burst end time vs. head movement end time, showing that burst end time preceded, but was correlated less strongly with head movement end time. All plots to same scale; histogram bin width = 20 ms.

FIG. 8. Location of unit recording sites

A, B, C: scale schematics of recording cylinders (circles), cortical surface with sulci (thick black curves), and recording sites. *A:* Monkey T, left FEF, 4 recording sites. *B:* Monkey T, right FEF, 16 recording sites. *C:* Monkey P, right FEF, 6 recording sites. Scale is shown at 1 mm; rostral to top of page, lateral to left for *A*, and right for *B, C*. Classification of neurons found at each recording site indicated as: ○, HEBN; △, GBN; □, SBN (see text). *D:* histological confirmation of recording sites in Monkey T, left FEF. Arrow indicates electrolytic lesion corresponding to site near HEBNs in *A*. *E:* Magnetic resonance images showing location of recording cylinder of Monkey T on right hemisphere. *E1:* Coronal section at dashed vertical line shown in *E2*, lateral to right. *E2:* Right parasagittal section,

rostral to right. For all, *das*: dorsal arcuate spine; *vas*: ventral arcuate spine; *ps*: principal sulcus.

TABLE 1

Summary of general and dissociation analyses results

Response sensitivity columns report general characteristics for all 26 units. Each unit showed involvement with gaze shifts within 20° of the horizontal; the *Preferred hemifield* column reports this preferred horizontal direction relative to the recording site (left FEF indicated by units labeled “TL”). Units were classified as having *open* or *closed* movement fields with respect to amplitude, as shown in *Movement field column*; the peak gaze amplitude of closed units is reported in parentheses (except for TL23-2, where maximum gaze amplitude is indicated). Units were movement (M) or visuomovement (VM) neurons as indicated in *VM test* column. For the two dissociation analyses (*Eye limit* and *Gaze limit*), regression fit slopes for NOS vs. gaze, eye, and head movement amplitude are reported under G, E, and H, respectively, in the *GEH slope* column (“*” indicates statistically significant slope, “ns” indicates nearly statistically significant at $p < 0.10$). The *GEH sum* column indicates how these regression results matched the predictions of the dissociation analysis; “+” indicates consistency with the “related to G or H, but not E” prediction (i.e., “+” or “-” do not indicate positive or negative slopes of the regressions; see EXPERIMENTAL PROCEDURES and Fig. 4). The *Dissociation summary* column combines the results of the two analyses to report the movement (G, E, or H) to which the neuronal burst was best related. The number of trials for the particular dissociation subset is reported as “n”; for most neurons, there were more than two dissociation subsets obtained and slopes and summary reported were consistent across all subsets, except for those labeled as “inconclusive”, when results did not match a dissociation prediction or were inconsistent across different subsets of dissociation data; “na” indicates insufficient data to test ($n < 15$ and required criteria not met).

Response sensitivity				Dissociation analyses — Eye limit					Dissociation analyses — Gaze limit				
Unit ID	Preferred hemifield	Movement field	VM test	n	G	E	slope	sum	n	G	E	slope	sum
T32-1	contra	open	VM	25	0.26*	-0.18	0.36*	+	20	0.03	-0.54*	0.66*	-
T34-2	contra	closed (69)	M	<15	na	na	na	na	<15	na	na	na	na
T38-2	contra	open	M	20	0.43*	-0.77	0.47*	+	20	-0.24	-0.72*	0.88*	-
T41-2	contra	open	M	19	0.26*	0.24	0.37*	+	18	0.01	-0.76*	0.82*	-
T44-3	contra	open	VM	<15	na	na	na	na	<15	na	na	na	na
T46-2	ipsi	open	M	21	0.30*	0.10	0.31*	+	24	0.60	-0.70*	0.73*	-
T48-2	contra	closed (100)	M	24	0.09	-0.09	0.05	-	17	-0.36	0.68*	-0.49*	+
T57-1	contra	open	VM	34	0.15*	0.08	0.16*	+	19	-0.19	-0.31	-0.01	+
T61-1	ipsi	open	VM	19	0.93*	0.35	0.99*	+	25	0.89	-1.45*	1.16*	-
T64-1	ipsi	open	M	46	0.29*	0.21	0.22*	+	34	0.33	-0.50*	0.52*	-
T88-2	ipsi	open	M	39	0.20*	0.46	0.23*	+	27	-0.06	0.08	0.01	+
T88-3	contra	open	M	31	0.29*	0.04	0.29*	+	24	0.01	-0.14	0.04	+
T90-1	contra	open	M	28	0.23*	0.31	0.30*	+	29	0.06	-0.90*	0.69*	-

Response sensitivity			Dissociation analyses — Eye limit					Dissociation analyses — Gaze limit				
Unit ID	Preferred hemifield	Movement field	VM test	n	G	slope	E	H	G	E	H	sum
T97-2	ipsi	open	M	28	0.29*	0.27	0.34*	+	+	+	+	na
T97-3	ipsi	closed (92)	M	33	0.10	0.40	-0.02	-	+	-	-	+
T102-1	contra	open	M	24	0.06	-0.15	-0.02	-	+	-	-	na
TL21-2	contra	closed (100)	M	31	0.36*	-0.05	0.40*	+	+	+	+	inconclusive
TL23-2	ipsi	closed (60)	M	19	-0.20*	-0.01	-0.30*	+	+	+	+	na
TL30-1	contra	closed (70)	M	28	-0.03	0.26	-0.06	-	+	-	-	inconclusive
TL34-3	ipsi	open	M	32	0.29*	-0.03	0.40*	+	+	+	+	+
P12-2	ipsi	open	VM	19	0.82*	-0.23	1.06*	+	+	+	+	+
P20-1	ipsi	open	M	55	0.89*	0.13	1.02*	+	+	+	+	+
P25-1	ipsi	closed (74)	M	<15		na		na	na	na	na	na
P26-1	ipsi	closed (82)	M	<15		na		na	na	na	na	na
P30-1	contra	closed (100)	M	21	0.24*	0.22	0.32*	+	+	+	+	na
P36-1	contra	open	M	40	0.50*	0.08	0.91*	+	+	+	+	+

* slope of simple linear regression line was statistically different from zero at $p = 0.05$; if no “**”, then slope not different from zero (and no association).

^a nearly statistically significant at $p < 0.10$.

na = insufficient data ($n < 15$) to allow this particular analysis.

inconclusive = results of different data subsets matched different or no dissociation analysis predictions.

TABLE 2
Summary of regression results and classification of neuronal behavior

In the *Number of spikes* column, G, E, or H indicate which movement *amplitude* was primary. In the *Burst start time*, *Burst end time*, and *Burst duration* columns, the primary parameter was eye/gaze *start time*, *end time*, *duration*, respectively, as represented by E/G (since these times were equivalent), except in two cases (T32-1 and T41-2) where *head start time* (H) was primary. POS indicates the inclusion of initial eye or head position as a second parameter in the best model; negative or positive sign preceding POS indicates POS effect (coefficient) was opposite or aligned with preferred response field, respectively. All reported primary and secondary variables had statistically significant slopes/coefficients, and the model's SLR r^2 or MLR R^2 is reported in parentheses; “no relation” indicates that no model was obtained with r^2 or $R^2 < 0.15$. The mean burst start time relative to the eye or head movement start time — with negative indicating that the burst preceded the movement start time — is reported in *Bs re Es mean* and *Bs re Hs mean* columns, respectively. Similarly, the mean burst end time relative to the eye or head movement end time is reported for the *Burst end time* analysis. For each analysis, the number of trials is reported in the *n* column. “a” in the *Final unit designation* column indicates a cautiously assigned classification due to limited data and/or analyses.

Unit ID	Number of spikes			Burst start time			Burst end time			Burst duration		
	n	Best model (and r^2 or R^2)	Bs re Es mean	Bs re Hs mean	Best model (and r^2 or R^2)	n	Be re Ee mean	Be re He mean	Best model (and r^2 or R^2)	n	Best model (and r^2 or R^2)	Final unit class
T32-1	84	H + POS (0.48)	-63	-43	H - POS (0.21)	84	-30	-242	E/G + POS (0.35)	84	E/G + POS (0.30)	HEBN
T34-2	38	E (0.28)	-66	-69	E/G (0.33)	39	-39	-263	E/G - POS (0.65)	39	E/G (0.28)	SBN ^a
T38-2	78	H - POS (0.71)	-44	-48	E/G (0.38)	78	83	-187	E/G (0.61)	78	E/G (0.52)	HEBN
T41-2	60	H (0.26)	-47	-43	H + POS (0.47)	61	47	-171	E/G (0.48)	61	E/G (0.45)	HEBN
T44-3	39	G (0.52)	-21	-32	no relation	39	-49	-306	E/G (0.45)	39	E/G (0.25)	GBN ^a
T46-2	130	H (0.45)	-68	-80	E/G (0.42)	130	-33	-220	E/G (0.71)	130	E/G + POS (0.59)	HEBN
T48-2	161	E (0.40)	-55	-62	E/G (0.52)	161	3	-209	E/G (0.60)	161	E/G (0.47)	SBN
T57-1	77	G - POS (0.34)	-57	-71	no relation	78	-31	-294	E/G - POS (0.49)	79	E/G (0.23)	GBN
T61-1	168	H (0.26)	-20	-30	E/G - POS (0.18)	167	103	-185	E/G (0.44)	168	E/G + POS (0.44)	HEBN
T64-1	237	H - POS (0.34)	-20	-24	E/G (0.19)	237	71	-181	E/G (0.59)	238	E/G (0.30)	HEBN
T88-2	159	G (0.29)	-45	-33	E/G (0.24)	160	13	-261	E/G - POS (0.46)	158	E/G - POS (0.28)	GBN
T88-3	57	G - POS (0.53)	-40	-20	E/G + POS (0.34)	56	-69	-325	E/G (0.36)	57	E/G (0.27)	GBN
T90-1	158	H + POS (0.20)	-16	-18	E/G - POS (0.42)	158	55	-175	E/G + POS (0.51)	158	E/G + POS (0.34)	HEBN
T97-2	67	G + POS (0.66)	-15	-5	E/G - POS (0.69)	67	126	-207	E/G + POS (0.82)	67	E/G + POS (0.68)	GBN ^a
T97-3	149	E + POS (0.39)	-9	-8	E/G - POS (0.69)	149	135	-123	E/G + POS (0.68)	148	E/G + POS (0.48)	SBN
T102-1	72	no relation	-23	-9	E/G - POS (0.33)	71	-18	-234	E/G (0.26)	71	E/G (0.18)	SBN
TL21-2	166	H + POS (0.42)	-55	-51	E/G (0.47)	166	52	-176	E/G + POS (0.68)	167	E/G + POS (0.51)	HEBN ^a

Unit ID	Number of spikes			Burst start time			Burst end time			Burst duration			Final unit class
	n	Best model (and r^2 or R^2)	n	Bs re Es mean	Bs re Hs mean	Best model (and r^2 or R^2)	n	Be re Ee mean	Be re He mean	Best model (and r^2 or R^2)	n	Best model (and r^2 or R^2)	
TL23-2	35	H (0.49)	35	-20	-10	E/G (0.48)	35	-43	-305	E/G (0.14)	36	<i>no relation</i>	HEBN ^a
TL30-1	147	E + POS (0.34)	143	-37	-36	E/G (0.53)	148	61	-223	E/G + POS (0.33)	149	E/G + POS (0.35)	SBN
TL34-3	146	H (0.52)	143	-51	-29	E/G (0.30)	146	36	-193	E/G (0.54)	147	E/G (0.38)	HEBN
P12-2	150	H - POS (0.50)	145	-99	-82	E/G + POS (0.36)	149	20	-239	E/G (0.41)	149	E/G (0.42)	HEBN
P20-1	190	H (0.51)	186	-81	-69	E/G - POS (0.56)	189	-30	-260	E/G - POS (0.68)	188	E/G (0.65)	HEBN
P25-1	99	G (0.15)	98	-41	-30	E/G + POS (0.62)	98	-30	-262	E/G (0.55)	98	E/G (0.47)	GBN
P26-1	135	G + POS (0.31)	134	-59	-35	E/G + POS (0.73)	133	2	-219	E/G (0.77)	134	E/G (0.68)	GBN
P30-1	142	G - POS (0.56)	136	-69	-82	E/G (0.28)	141	-24	-258	E/G (0.68)	141	E/G (0.65)	GBN ^a
P36-1	173	H (0.61)	168	-52	-54	E/G (0.38)	173	-38	-279	E/G - POS (0.80)	172	E/G (0.70)	HEBN

^a indicates a tentative final unit designation based on limited data and analyses.

no relation = ρ^2 and $R^2 < 0.15$ and/or not statistically significant.