

Role of expected reward in frontal eye field during natural scene search

Joshua I. Glaser,^{1*} Daniel K. Wood,^{2*} Patrick N. Lawlor,¹ Pavan Ramkumar,¹
Konrad P. Kording,¹ and Mark A. Segraves²

¹Department of Physical Medicine and Rehabilitation, Northwestern University and Rehabilitation Institute of Chicago, Chicago, Illinois; and ²Department of Neurobiology, Northwestern University, Evanston, Illinois

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Glaser JI, Wood DK, Lawlor PN, Ramkumar P, Kording KP, Segraves MA. Role of expected reward in frontal eye field during natural scene search. *J Neurophysiol* 116: 645–657, 2016. First published May 11, 2016; doi:10.1152/jn.00119.2016.—When a saccade is expected to result in a reward, both neural activity in oculomotor areas and the saccade itself (e.g., its vigor and latency) are altered (compared with when no reward is expected). As such, it is unclear whether the correlations of neural activity with reward indicate a representation of reward beyond a movement representation; the modulated neural activity may simply represent the differences in motor output due to expected reward. Here, to distinguish between these possibilities, we trained monkeys to perform a natural scene search task while we recorded from the frontal eye field (FEF). Indeed, when reward was expected (i.e., saccades to the target), FEF neurons showed enhanced responses. Moreover, when monkeys accidentally made eye movements to the target, firing rates were lower than when they purposively moved to the target. Thus, neurons were modulated by expected reward rather than simply the presence of the target. We then fit a model that simultaneously included components related to expected reward and saccade parameters. While expected reward led to shorter latency and higher velocity saccades, these behavioral changes could not fully explain the increased FEF firing rates. Thus, FEF neurons appear to encode motivational factors such as reward expectation, above and beyond the kinematic and behavioral consequences of imminent reward.

electrophysiology; modeling; saccades

NEW & NOTEWORTHY

As expected, reward affects the latency and vigor (velocity) of eye movements (saccades); it is crucial to parse apart the effects of motor variables and expected reward on neural activity. We recorded from frontal eye field in monkeys while they searched for a target (associated with reward) in natural scenes. Although frontal eye field activity did represent latency and vigor, it represented expected reward above and beyond those motor parameters.

WHEN AN ANIMAL EXPECTS A MOVEMENT to result in a reward, activity in motor circuits of the brain is modulated (Ikeda and Hikosaka 2003; Kawagoe et al. 1998; Nakamura et al. 2008; Tachibana and Hikosaka 2012). This results in movements with greater vigor (higher velocity), lower latency, and greater accuracy (Chen et al. 2013; Choi et al. 2014; Reppert et al. 2015). In other words, the movement itself reflects the expect-

tation of reward. Hence, the muscles and motor units driving the movement reflect reward expectancy, but only to the extent that the movement itself is different when reward is expected. As the motor pathway is traced farther back from motor units to the more complex cortical and subcortical circuits that plan the movements, it becomes more likely that reward expectancy influences variables other than movement alone (Maunsell 2004). In any given brain area, to test whether reward is represented beyond its obvious influence on movement, it is essential to consider movement and reward parameters simultaneously.

The oculomotor system has been an important model for understanding the effects of reward on neural activity and movement (Bisley and Goldberg 2010; Gottlieb et al. 2014; Hikosaka 2007). However, much is still unknown about reward processing in the frontal eye field (FEF), a prefrontal cortical area involved in the control of saccades (Bruce and Goldberg 1985; Schiller et al. 1979) and spatial attention (Bichot et al. 2015; Moore and Fallah 2003; Schall 2004). In the past, when researchers have discovered expected reward modulation in FEF (Ding and Hikosaka 2006; Roesch and Olson 2003), the underlying cause has been unclear. Was activity only modulated because it led to a modulated saccadic output, or did expected reward affect neural activity above and beyond its effects on motor output, due to factors such as motivation and attention?

Here, we investigated reward expectancy in FEF while monkeys searched for a target embedded in natural scene images. This natural search behavior comprised a broad range of saccadic velocities and latencies, which allowed us to disentangle motor output and expected reward as drivers of neural modulation. We found that saccadic vigor and latency were correlated with FEF activity. After accounting for this, reward expectancy still contributed unique variance to the neural response, suggesting that reward modulation in FEF plays a role that is not limited to the programming of eye movements.

METHODS

Animals and Surgery

Northwestern University's Animal Care and Use Committee approved all procedures for training, surgery, and experiments. We used three adult female rhesus monkeys (*Macaca mulatta*), which we referred to as M14, M15, and M16. Each monkey received preoperative training followed by an aseptic surgery to implant a recording cylinder above the FEF, as well as a titanium receptacle to allow head fixation. Surgical anesthesia was induced with thiopental (5–7 mg/kg iv) or propofol (2–6 mg/kg iv) and maintained using isoflurane (1.0–2.5%) inhaled through an endotracheal tube. For single electrode

* J. I. Glaser and D. K. Wood contributed equally to this work.

Address for reprint requests and other correspondence: J. Glaser, Rehabilitation Institute of Chicago, 345 E Superior St., Rm. 1479, Chicago, IL 60611 (e-mail: j-glaser@u.northwestern.edu).

recordings performed in M14 and M15, an FEF cylinder was centered over the left hemisphere at stereotaxic coordinates anterior 25 mm and lateral 20 mm. A chronic array was used to record from multiple units in monkeys M15 (right hemisphere) and M16 (left hemisphere). The recording chambers for these arrays were centered and mounted over the arcuate and principal sulci at stereotaxic coordinates anterior 24 mm and lateral 20 mm.

Behavioral Paradigms

Setup. To control experimental stimuli and data collection, we used the personal computer (PC)-based REX system (Hays et al. 1982), running the QNX operating system (QNX Software Systems, Ottawa, Ontario, Canada). Visual stimuli were generated by a second independent graphics process (QNX-Photon) and rear projected on a tangent screen in front of the monkey by a CRT video projector (Sony VPH-D50, 75-Hz noninterlaced vertical scan rate, $1,024 \times 768$

resolution). The distance between the front of the monkey's eye and the screen was 109.22 cm (43 in). Each natural scene spanned $48^\circ \times 36^\circ$ of the monkey's visual field.

Search tasks. Monkeys M14 and M15 searched for a fly embedded in a natural scene (Fig. 1A). The monkey made saccades around the scene until a saccade landed near the fly target (within 5°), and she held fixation there for 200 ms, at which point she received a water reward. If she made 25 saccades without finding the target, the trial ended. Each trial was initiated by the monkey fixating on a red dot in the center of the blank screen.

Monkeys M15 and M16 performed a Gabor search task, which was identical to the fly search task with the exception that a Gabor target (rather than a fly) was embedded in a natural scene (Fig. 1B).

Typically, between 1,000 and 2,500 saccades were made each day. The first saccade from every trial was excluded from our main analyses due to the confounding visual onset effects.

Experimental Tasks

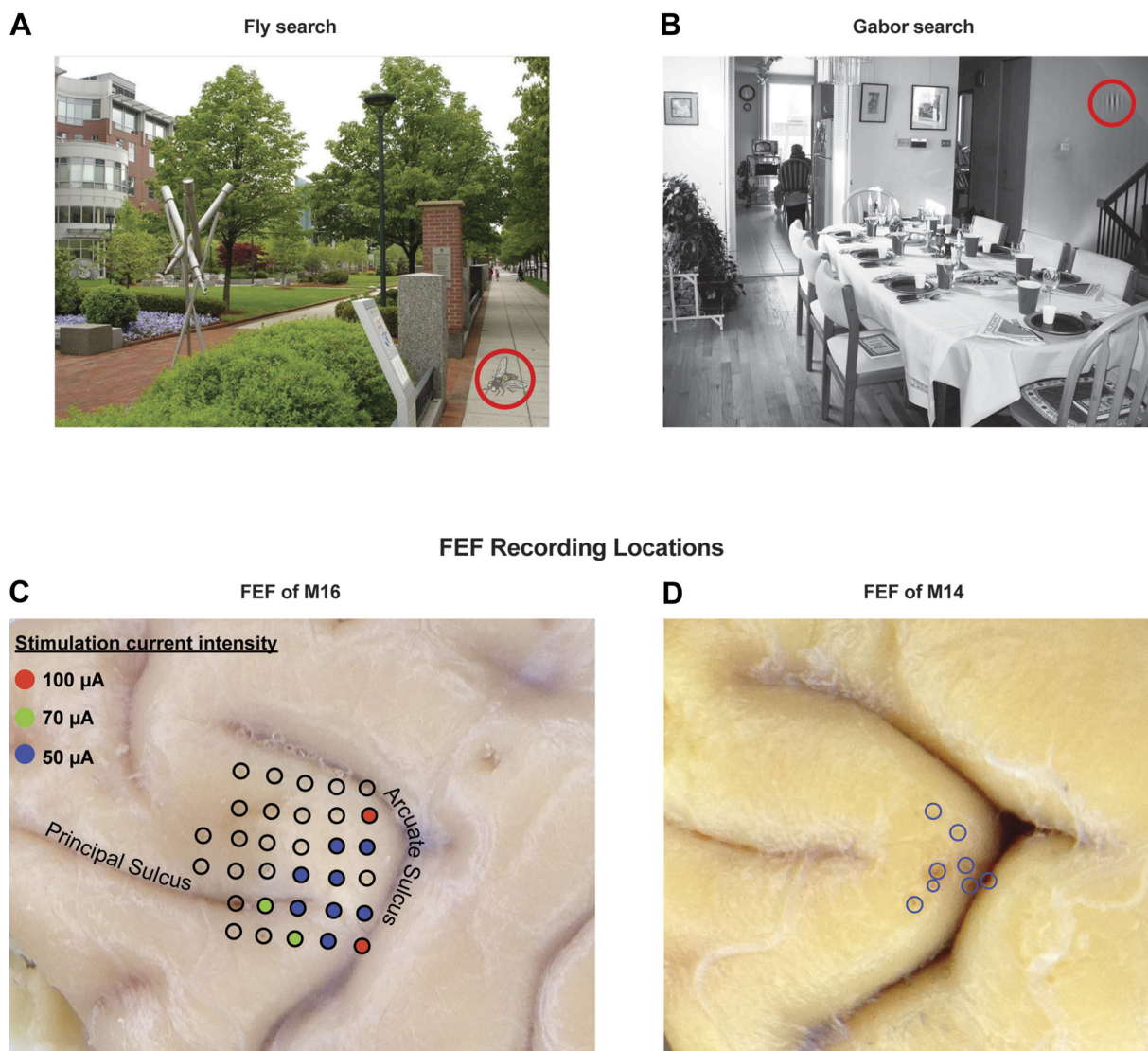


Fig. 1. Experimental setup. *A* and *B*: in our experiments, monkeys freely searched for targets in natural scenes. In the fly search task (*A*; done by M14 and M15), the target was an embedded fly. In the Gabor search task (*B*; done by M15 and M16), the target was an embedded Gabor wavelet. Monkeys were rewarded only after fixating the target for a specified duration. *C*: functional characterization of frontal eye field (FEF) in M16 based on stimulation results for the semichronic array. Colors indicate current intensities at (or below) which saccades were reliably elicited. Only neurons at locations where current intensity was $\leq 50 \mu$ A were used in our analyses. *D*: characterization of FEF in M14. A subset of locations for acute recordings are marked by blue circles. All recording locations were characterized as FEF by elicitation of saccades with $\leq 50 \mu$ A during stimulation.

Data Acquisition

Eye tracking. In the fly search task (M14 and M15), eye movements were tracked with a subconjunctival wire search coil, sampled at 1 kHz (Judge et al. 1980; Robinson 1963). In the Gabor search task (M15 and M16), eye movements were tracked with an infrared eye tracker (ISCAN, Woburn, MA, <http://www.iscaninc.com/>) at 60 Hz.

Single-unit recording. During the fly search task, single-unit activity was recorded using tungsten microelectrodes (A-M Systems, Carlsborg, WA). Electrode penetrations were made through stainless steel guide tubes that just pierced the dura. Guide tubes were positioned using a Crist grid system (Crist 88; Crist Instrument, Hagerstown, MD). Recordings were made using a single electrode advanced by a hydraulic microdrive (Narashige Scientific Instrument Lab, Tokyo, Japan). On-line spike discrimination and the generation of pulses marking action potentials were accomplished using a multi-channel spike acquisition system (Plexon, Dallas, TX).

Recordings were confirmed to be in the FEF by ability to evoke low-threshold saccades with current intensities of $\leq 50 \mu\text{A}$. To stimulate electrically, we generated 70-ms trains of biphasic pulses, negative first, 0.2 ms width/pulse phase, delivered at a frequency of 330 Hz.

Chronic recording. During the Gabor search task, recordings were performed using a 32-channel chronically implanted electrode array (Gray Matter Research, Bozeman, MT). The depth of each individual tungsten electrode (Alpha-Omega, Alpharetta, GA) was independently adjustable over a range of 20 mm.

All electrodes were initially lowered to pierce the dura. Individual electrodes were then gradually lowered until a well-isolated unit was located. In general, only a subset of electrodes was moved on any given day, and electrodes were left in place for at least 3 days before further lowering.

Spikes were recorded at 40 kHz with a multichannel acquisition system (Plexon) on a separate PC. Automatic spike sorting was performed offline using the Plexon Offline Sorter (Plexon).

Because any given electrode was often left in place for multiple days, we often recorded from the same neuron across sessions. To make use of this, we combined data from units that persisted across recording sessions on different days. To do this, we manually compared spike waveforms from units recorded at the same site on different days. Generally, we merged units sharing waveform shape (rise/fall characteristics, concavity/convexity, etc.) and time course. Ambiguous cases were not combined. Additionally, we included multiunit activity in our present analysis.

Because stimulation quickly degrades the recording fidelity of the tungsten electrodes in the array, we were unable to stimulate until the array was ready to be removed. Because of this, we were able to verify FEF location with stimulation (using the same parameters described for single-unit recording) in only one (M16) of the two chronically implanted monkeys (Fig. 1C). In M16, only units recorded on electrodes where saccades were reliably elicited at or below $50 \mu\text{A}$ at any depth were included in our analyses. The cluster of electrodes where stimulation evoked saccades in M16 roughly matched the location of maximum FEF-evoked saccade sites in M14 (Fig. 1D). However, many of the recordings were more superficial than the depths at which we observed consistent elicitation of saccades. This does not rule out these cells being part of FEF, but it does increase the probability that some of the cells that we recorded were not from FEF.

In M15, the chronic array was centered at the same stereotaxic location as M16 and a sample of three monkeys used in earlier studies. Furthermore, the spatial pattern of electrode grid locations where FEF-like responses were observed closely resembled the pattern of FEF locations in the grid of M16. We note here that, similar to M16, chronic recordings for M15 were at relatively shallow depths (e.g., $\sim 3\text{--}5$ mm below dura).

In M15 and M16, we limited our analyses to units that had presaccadic properties expected in the FEF (see below). This de-

creased the chance of analyzing units from nearby brain regions that were not part of the FEF. However, we cannot rule out the possibility that some of the units included in our analysis were from prefrontal regions other than FEF, especially in the case of M15.

Neuron Characterization and Selection

Cell selection. We analyzed units that had presaccadic activity. To determine whether there was presaccadic activity, we looked at perisaccadic time histograms (PSTHs) aligned to the start of the upcoming saccade, binned into eight angular directions (according to saccade direction), with each bin subtending 45° . In any bin, if there was a significant difference between a firing rate and baseline, and the rise started before the saccade onset, then there was presaccadic activity. Additionally, we only analyzed cells with average firing rates of at least 5 spikes/s during the task. These criteria gave us 142 units to analyze: 27 from M14, 79 from M15, and 36 from M16.

Most neurons recorded during the fly task were classified using a memory-guided saccade task as having visual, delay, and/or movement activity. The neurons recorded during the Gabor task were not classified.

Importantly, a neuron having presaccadic activity in our natural scene search does not mean that it is classically a “movement” neuron. It has previously been shown that purely “visual” cells (according to the classic nomenclature) have presaccadic activity during a natural scene search task (Burman and Segraves 1994). Moreover, from our 38 classified neurons, 4 were purely visual, 18 were visual/delay, 11 were visual/delay/movement, 2 were visual/movement, and 3 were purely movement. Within this small number of (mostly visual) neurons, we did not observe a noticeable difference in results based on classification. However, because the majority of our neurons were not classified in a traditional manner, we were unfortunately unable to do a thorough analysis of the effects of cell type on our results.

Receptive field characterization. To map receptive fields, we first looked at the binned (by saccade angle) PSTHs. We initially assigned the receptive field (RF) as the bin that had the largest difference between baseline and the peak. We then found the time point corresponding to the peak firing rate in this bin.

We then calculated a better estimate of the RF at this time point. To do this, we calculated a smoothed version of the average firing rate across space. More specifically, we tiled space with square “pixels” that were $\sim 3/4$ of a degree. Each pixel was given the average firing rate (at the given time) of the 200 nontarget saccades that landed nearest to that pixel. After creating this smoothed firing rate map, we said that the RF was all of the pixels with a smoothed firing rate $> 50\%$ of the way from the minimum to the maximum smoothed firing rate.

Note that, when we previously ran all our analyses using a simpler (but less accurate) RF characterization that only consisted of angle bins, we obtained the same general results.

Behavioral Data Analysis

Saccades were classified into three types. First, “target, expected reward” ($T+/ER+$) saccades were those that landed near the target followed by a fixation and reward, indicating knowledge of the target. Second, “target, no expected reward” ($T+/ER-$) saccades were those that landed near the target but were not followed by a fixation long enough (200 ms) to receive a reward. We assumed that this indicated lack of knowledge regarding the target, and thus a lack of expected reward. Third, we defined “nontarget, no expected reward” ($T-/ER-$) saccades as those not landing near the target.

To statistically compare the latencies between $T+/ER+$ and $T-/ER-$ saccades, we used a two-tailed Wilcoxon rank-sum test. Note that latencies < 90 ms were excluded in this analysis under the assumption that anything below this cutoff would be an express

saccade. Additionally, we exclude latencies $>1,000$ ms, since it is likely the next saccade was not detected. For M15, this statistical test was done separately for the fly and Gabor task. A single result was reported, since it was the same for both tasks. When plotting the distribution of latencies (Fig. 2C), we put latencies in 40-ms bins between 90 and 490 ms. The small number of saccades with latencies >490 ms were not plotted.

Because saccade velocities are strongly dependent on saccade magnitude, we plotted the peak saccade velocity as a function of saccade magnitude for both T+/ER+ and T-/ER- saccades. We put saccades with magnitudes between 5 and 25° in bins with a size of 1°. Note that, for the fly task, M14 and M15 had eye movements tracked with an eye coil, whereas, for the Gabor task, M15 and M16 had eye movements tracked with an IR camera (see METHODS). The recorded peak velocities were consistently smaller when using the IR camera, due to its limited 60-Hz resolution (Fig. 2E). Because we are comparing velocities of saccade types, rather than being concerned with absolute velocities, we do not view these differences as problematic. Note that, for M15, we averaged the plots created using the fly and Gabor task.

To statistically compare the peak velocities between T+/ER+ and T-/ER- saccades, for each saccade magnitude bin, we computed the relative change in peak velocity $[(v_T - v_{NT})/v_T]$, where v_T and v_{NT} are the peak velocities for T+/ER+ and T-/ER- saccades, respectively. This created a vector of 21 proportions of change. We did a two-tailed Wilcoxon signed-rank test to determine whether this proportion was significantly greater than zero.

We defined vigor as the velocity of a saccade divided by the expected velocity of that saccade, given its amplitude (Fig. 2F). The expected velocity of a saccade was calculated by averaging the velocities of the 25 saccades with the closest amplitudes to that of the given saccade for that monkey (regardless of whether they were T+/ER+ or T-/ER-). When plotting the distribution of vigor (Fig. 2G), we put vigor in bins of 0.1. Vigor <0.5 or >1.5 was not plotted. When plotting vigor vs. saccade latency (Fig. 2H), latencies were put in 40-ms bins and scaled velocities in bins of 0.02 (M14) or 0.01 (M15, M16).

To examine whether latency and vigor were correlated, we tested whether the correlation coefficient was significantly different from zero using a two-tailed *t*-test. For M15, this statistical test was done separately for the fly and Gabor task. A single result was reported, since it was the same for both tasks.

To look at the effect of expected reward as a function of latency and vigor simultaneously (Fig. 4A), we put latencies in 40-ms bins and scaled velocities in bins of size 0.1. We plotted the logarithm of the ratio of the probability distribution of T+/ER+ saccades vs. the probability distribution of T-/ER- saccades (over all shown behavioral conditions). Each probability distribution was smoothed (in a 3 row \times 3 column window with a Gaussian filter of $\sigma = 0.5$) before taking the ratio. We did not show bins with $<0.1\%$ of saccades for either condition. When averaging across monkeys, the plot for M15 was first averaged across the fly and Gabor tasks.

Neural Data Analysis

For all subsequent analyses, we put spikes in 10-ms bins. We excluded the first saccade in each trial from the analysis due to the confounding effects of the image onset. We only included saccades that started and ended on the screen. In general, we focus on analyzing activity around the time neurons are most active. This is because 1) our heterogeneous population of neurons is active at different times in our natural scene search task (e.g., see Fig. 3C); and 2) averaging activity over a large static time window can nullify effects (e.g., if a condition increases the firing rate at one time and decreases it at another; as in Fig. 3C, M14: cell 22).

Comparing Peak Firing Rates Between Conditions

To compare firing rates between conditions, we computed PSTHs of spiking activity. When showing PSTHs of individual neurons (Fig. 3C), we show the mean firing rate across saccades. The error bars on shown PSTHs are the SE across saccades. When showing the PSTHs averaged across neurons, we first normalize the mean firing rate for each neuron by dividing by the peak firing rate when saccades are made in the RF, but not to the target (Fig. 3C). We then show the average of these normalized firing rates across neurons. Error bars are the SE across neurons. All traces are smoothed using a 50-ms sliding window.

To determine whether there was a significant difference in the peak firing rate of the PSTHs between two conditions for a monkey (averaged across neurons), we 1) for a given condition found the time bin that had the highest firing rate in the smoothed PSTH; 2) for that condition, for every neuron, computed the normalized average firing rate in a 50-ms interval around that bin (i.e., the previous two 10-ms bins, that 10-ms bin, and the next two 10-ms bins). This creates a vector of firing rates for each neuron in a given condition (e.g., firing rates around each T+/ER+ saccade); and 3) used a two-tailed Wilcoxon signed-rank test to compare peak firing rates between the two conditions.

Tuning Curves

For our tuning curve analysis (Fig. 3, F and G), we calculated firing rates in the 50-ms window that contained the highest firing rate in the PSTH of all saccades in the RF. The time window was independently determined for each neuron.

To fit tuning curves, we created a scatterplot showing the firing rate (*y*-axis) vs. direction (*x*-axis) of each saccade. We then fit a Von-Mises function to these data points to model how firing rate varies as a function of direction (Fig. 3F). We fit a standard four-parameter model (Amirikian and Georgopoulos 2000)

$$\lambda = \alpha + \beta \exp[\kappa \cos(\theta - \theta^*)],$$

where λ is the firing rate for each saccade, θ is the saccade direction for the trial, and $[\alpha, \beta, \kappa, \theta^*]$ are the parameters. We estimated these parameters using nonlinear least-squares fitting, constraining the minimum of the tuning function to be nonnegative, $\kappa \leq 10$, $\alpha > 0$, and $-\pi \leq \theta^* \leq \pi$. We then computed the following quantities from the estimated parameters: baseline, the minimum of the tuning curve, i.e., $\alpha + \beta e^{-\kappa}$; gain, the difference between the maximum and minimum, i.e., $\beta e^{\kappa} - \beta e^{-\kappa}$; width, the empirical full-width half-maximum of the tuning curve; and preferred direction, θ^* .

To determine whether a parameter was significantly different across neurons between T+/ER+ and T-/ER- saccades, we used a two-tailed Wilcoxon signed-rank test. For each monkey, we plotted (Fig. 3G) the median of the ratio between the parameters for T+/ER+ and T-/ER- saccades. For error bars, we plotted the SE of the median, computed by bootstrapping. The median and SE of the median (as opposed to the mean) were used due to skewed distributions with outliers.

Generalized Linear Models

We used a Poisson generalized linear model (GLM) to determine whether neurons uniquely encoded saccade latency, saccade vigor, and expected reward (whether the saccade was to the target). In this analysis, we only considered saccades in the receptive field and those with latencies $<1,000$ ms.

For each neuron, we aimed to predict the number of spikes during each saccade (in the RF) during the 50 ms of peak activity for that neuron. In other words, we found the 50-ms window with the highest firing rate (averaged across saccades in the RF; as described in *Comparing Peak Firing Rates Between Conditions*) and then found

the number of spikes in this window for each saccade. This yielded a vector of spike counts, Y . Note that we also ran a GLM where we always used a 100-ms time window before saccade onset and found the same general results.

To explain the spike counts, we used four covariates: 1) saccade latency, θ_L (a vector of the latencies for each saccade); 2) saccade vigor, θ_V ; 3) expected reward (a binary variable for whether the saccade was to the target), θ_T ; and 4) the expected firing rate given the saccade vector, θ_{RF} (the smoothed average firing rate at the location of the saccade vector, see *Receptive field characterization*). This last covariate was included because the proximity of the saccade vector to the preferred vector of the cell could help explain the firing rate.

Overall, the model that generates the firing rate (λ) can be written as:

$$\lambda = \exp(\beta_0 + \beta_L \theta_L + \beta_V \theta_V + \beta_T \theta_T + \beta_{RF} \theta_{RF})$$

where the β s are the weights for each covariate (β_0 is a baseline term) that we fit. Note that the covariates are passed through an exponential nonlinearity, ensuring that firing rates are positive. The model assumes that spikes are generated from the firing rate, λ , according to a Poisson distribution. We fit the weights to the data using maximum likelihood estimation, that is, we found the β s that were most likely to produce the true spike output (assuming spikes were generated from the firing rate in a Poisson nature).

For each neuron, we tested whether β_L , β_V , and β_T were significantly different from zero using a two-tailed t -test.

Multiple-Comparisons Testing

When listing the number of significant neurons in our GLM analysis, we listed uncorrected (for multiple comparisons) statistics. This was because we were not concerned with whether specific individual neurons were significant; rather, we wanted to show an uncorrected comparison of the numbers of neurons that had significant positive and negative effects. Nonetheless, there were many individual neurons that do survive Bonferroni corrections.

RESULTS

In two separate search tasks, three head-fixed monkeys (M14, M15, and M16) freely searched for a target embedded in a natural scene (Fig. 1). Monkeys were rewarded for locating and holding fixation on the target. Targets were blended in the background, making the task difficult enough that the monkeys typically had to make several saccades (on average, 5–7) to locate the target.

We defined T+/ER+ saccades as those that landed near the target followed by a fixation and reward, indicating knowledge of the target (Fig. 2A). The trial ended following these saccades. Similarly, we defined T-/ER- saccades as those not landing near the target (although this could also include a small number of saccades where reward was expected; Fig. 2A). The trial continued after these saccades unless the maximum number of saccades allotted per trial was reached. Our main comparison was between these two saccade types.

Expected Reward Alters Saccade Latencies and Velocities

Before testing for neural differences resulting from expected reward, we investigated whether there were behavioral differences between T+/ER+ and T-/ER- saccades. Specifically, we tested for differences in latency and velocity of saccades, since previous studies have shown that expected reward can decrease the latency and increase the velocity of saccades

(Kawagoe et al. 1998; Haith et al. 2012; Beierholm et al. 2013; Choi et al. 2014).

Indeed, while there was a large range of latencies (Fig. 2C), T+/ER+ saccades had significantly shorter latencies than T-/ER- saccades ($P < 0.001$ for all monkeys; Fig. 2B). Interestingly, for T-/ER- saccades, the latencies systematically depended on the saccade amplitude, and this pattern was different for each monkey, likely reflecting individual search strategies (Fig. 2D). However, for T+/ER+ saccades, latencies were consistent across saccade amplitudes (Fig. 2D). Monkeys appear to have idiosyncratic exploration strategies but share a common fast strategy for making saccades to the target (for which they expect reward).

One might also predict that reward expectation leads to higher saccade velocities. We observed that T+/ER+ saccades had a significantly higher peak velocity than T-/ER- saccades ($p < 0.001$ for all monkeys; Fig. 2E), especially for larger-amplitude saccades. For both types of saccades, however, velocity increased with amplitude, consistent with the main sequence for saccades (Bahill et al. 1975). Therefore, to ask whether saccade velocity varies with reward expectancy, we needed a velocity measure that accounts for the fact that velocity varies as a function of amplitude. We use “vigor” (Choi et al. 2014), which describes how much the velocity of a saccade is above or below the expected velocity (for all saccades) given the saccade amplitude (see METHODS for calculation of vigor; Fig. 2, F and G). Furthermore, vigor and latency are unlikely to be independent; for example, a high degree of motivation may lead to both increased velocity and decreased latency. Indeed, vigor and latency are significantly negatively correlated ($p < 0.001$ for all monkeys; Fig. 2H), suggesting a related neural mechanism.

Increased Firing Rates for Saccades in the Receptive Field, When Reward is Expected

We aimed to understand whether FEF activity is modulated by the expected reward of saccades. To do this, we first computed PSTHs (aligned to saccade onset) for T+/ER+ and T-/ER- saccades made in the RF for each neuron (see METHODS for RF characterization). To examine the average effect, we then normalized and averaged these PSTHs across neurons. Average peak firing rates were significantly higher for T+/ER+ saccades vs. T-/ER- saccades (Fig. 3, A–D) for all monkeys (M14, $p < 0.001$; M15, $p < 0.001$; M16, $p = 0.0218$). This effect was not due to the increased fixation times that followed saccades to the target (fixation was required for reward), since long fixation times did not increase firing rates for T-/ER- saccades (M14, $p = 0.029$ for short fixation times increasing firing rates; M15, $p > 0.05$; M16, $p > 0.05$; Fig. 3E). Therefore, it appears that expected reward does modulate FEF neurons' activities during saccades in the RF.

To more generally understand how expected reward modulates FEF activity during saccades across visual space (rather than just in the RF), we fit directional tuning curves to both T+/ER+ and T-/ER- saccades (Fig. 3, F and G). We found that T+/ER+ saccades led to significantly larger tuning curve gains (maximum – minimum of the tuning curve) in all monkeys (M14, $p < 0.001$; M15, $p < 0.001$; M16, $p = 0.031$), but neither the width nor the baseline of the tuning curves changed systematically across all monkeys

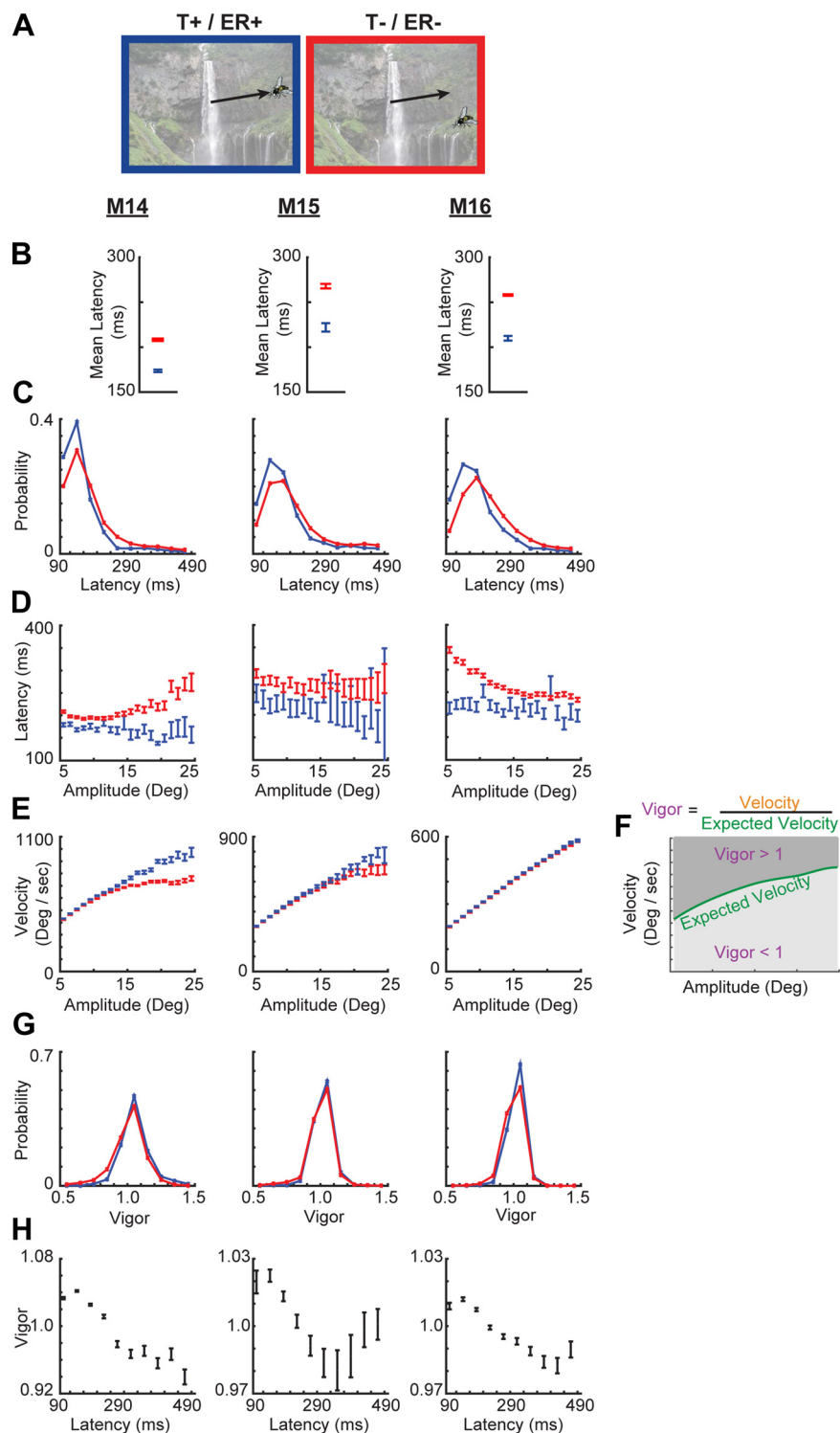
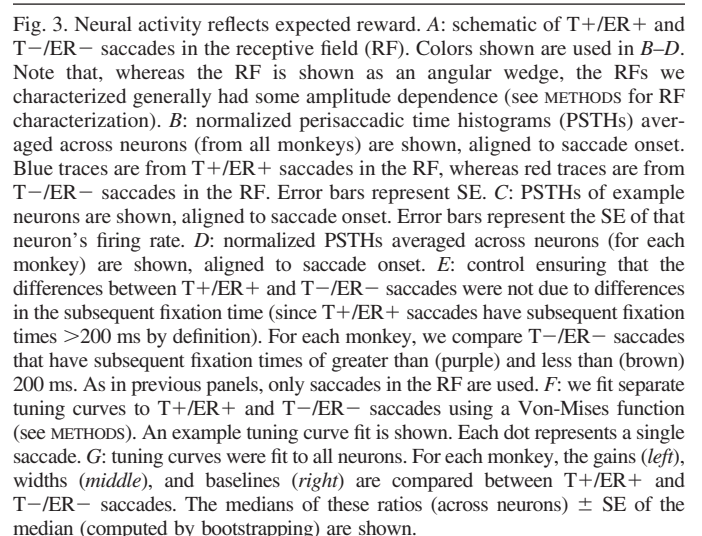


Fig. 2. Behavioral differences of saccades due to expected reward. **A**: saccades that land near the target followed by fixation are defined as “target, expected reward” (T+/ER+) and are shown in blue in subsequent panels. Saccades that do not land near the target are defined as “nontarget, not expected reward” (T-/ER-) and are shown in red in subsequent panels. **B**: latencies are compared between T+/ER+ (blue) and T-/ER- (red) saccades. Means \pm SE are shown. For this, and subsequent, panels, each column is behavior from a different monkey. **C**: latency distributions. **D**: mean latencies (\pm SE) of T+/ER+ and T-/ER- saccades are shown as a function of saccade amplitude. **E**: velocities are compared between T+/ER+ (blue) and T-/ER- (red) saccades. Mean velocities (\pm SE) are shown as a function of amplitude. Note that differences in the magnitude of velocities are due to differences in eye tracking technology across monkeys (IR camera vs. eye coil; see METHODS). **F**: because velocity is dependent on amplitude, we define vigor as the velocity divided by the expected velocity for that amplitude (for all saccades). Shading is based on whether vigor is greater or less than 1. **G**: vigor distributions. **H**: vigor is shown as a function of saccade latency for all monkeys. All saccades, regardless of expected reward, were combined, since they had the same trends. Note the different y-axis limits for monkey M14.

($p > 0.05$ for all except $p = 0.047$ for M15 width). These results support an increase in neural activity that is specific for the upcoming saccade direction rather than a general enhancement (e.g., due to arousal). This gain increase could be beneficial because it increases information (Butts and Goldman 2006) about the rewarded target location for downstream brain areas (Monosov et al. 2010; Noudoost et al. 2014; Segraves 1992; Segraves and Goldberg 1987; Sommer and Wurtz 2000).

Velocity and Latency Differences Explain Some, But Not All, of the Neural Differences Due To Expected Reward

Because expected reward affects motor output (e.g., the latency and velocity of saccades), any brain structure that leads to motor output can be modulated by expected reward. For example, neurons in the brain stem that affect the velocity of saccades will be modulated by expected reward.



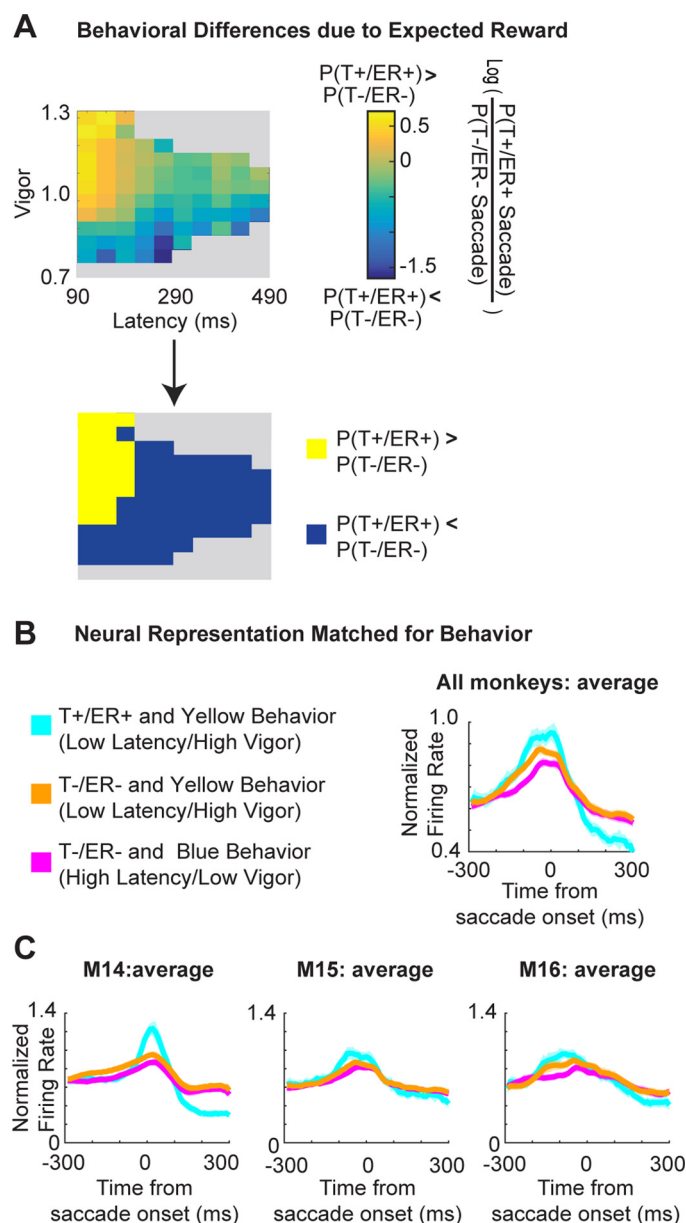


Fig. 4. Increased firing rates due to expected reward, short latency, and high-velocity saccades: PSTHs. *A*: because latency and vigor are correlated, we look at the effect of expected reward across the behavioral space of latency and velocity. *Top*, the relative likelihood of a saccade having a certain latency and vigor for T+/ER+ compared with T-/ER- saccades, averaged across monkeys. More yellow areas mean that a particular latency and vigor are more likely for T+/ER+ saccades. *Bottom*, a threshold is put on panel on *top* to determine behavioral regions that are more likely to contain saccades accompanied by expected reward (yellow) or no expected reward (blue). *B*: normalized PSTHs averaged across neurons (from all monkeys) constructed from 3 conditions: 1) T+/ER+ saccades in the yellow behavioral region of the panel on *top* (cyan); 2) T-/ER- saccades in the yellow behavioral region (orange); 3) T-/ER- saccades in the blue behavioral region (pink). *C*: same as *B* for individual monkeys.

Last, we asked whether expected reward, latency, and vigor were represented by separate populations of neurons (i.e., each neuron represents a single feature) or overlapping populations of neurons (i.e., neurons represent multiple features). To answer this, we determined the percentage of neurons that was significant for representing features (in the above GLM analysis), conditional on the neuron representing other features

(Fig. 5C). If neurons represented only individual features, then the probability of a neuron representing one feature (e.g., expected reward), conditioned on that neuron already representing another feature (e.g., latency; Fig. 5C), should be lower than the general probability of representing the original feature (expected reward; Fig. 5C). However, that was not the case. Neurons were more likely to represent a given feature if they already represented an additional feature (Fig. 5C). Thus, overlapping populations of neurons represent expected reward, latency, and vigor.

Enhanced FEF Responses Are Due To Expected Reward, Not Simply Due To Moving To The Target

In our previous analyses, all target saccades (T+) were associated with expected reward. It is possible that the neural differences based on expected reward were actually due to the visual presence of the target in the receptive field. The natural search task offered us a simple way of controlling for this possibility. Because the target is difficult to find in the complex background, it is likely that the monkey will occasionally saccade toward a target without awareness of the target. We thus looked at a third type of saccade: that which lands near the target, but is not followed by a fixation long enough (200 ms) to receive a reward. We assume that this indicates lack of awareness of the target, and thus a lack of expected reward. We defined these types of saccades as T+/ER- saccades (Fig. 6A).

These T+/ER- saccades give us an opportunity to ask if target presence was represented, independent of expected reward. We observed lower firing rates for T+/ER- saccades compared with T+/ER+ saccades (Fig. 6B). Furthermore, these differences were significant for each monkey (M14, $p < 0.001$; M15, $p = 0.0044$; M16, $p < 0.001$; Fig. 6C). In fact, the firing rate of T+/ER- saccades was generally the same as the firing rate of T-/ER- saccades (M14, $p < 0.021$; M15, $p > 0.05$; M16, $p > 0.05$; Fig. 6, B and C). Note that, for M14, the firing rate for T+/ER- saccades was slightly, but significantly, higher than the firing rate of T-/ER- saccades. We believe this is due to a small number of classification errors, that is, some of the T+/ER- saccades may have been reward expecting, but the monkey did not fixate long enough, or some of the T+/ER+ saccades may not have been reward expecting, but the monkey fixated long enough by chance. These results demonstrate that FEF indeed is modulated by the expected reward of saccades rather than the presence of the target in the RF or merely saccades to locations near the target.

A potential confound is that T+/ER+ saccades landed closer to the target than T+/ER- saccades (Fig. 6D). Thus, it could be possible that the landing distance from the target, rather than reward expectation, was responsible for the neural differences between T+/ER+ and T+/ER- saccades. This does not appear to be the case, since T+/ER+ saccades landing far from the target (defined as greater than the median distance from the target) have higher firing rates than T+/ER- saccades landing far from the target (M14, $p = 0.0022$; M15, $p = 0.042$; M16, $p = 0.031$; Fig. 6E). This is also true for saccades landing near the target (M14, $p = 0.0025$; M15, $p = 0.032$; M16, $p = 0.0055$; Fig. 6E). In fact, T+/ER+ saccades landing far from the target even have higher firing rates than T+/ER- saccades landing near the target (M14, $p < 0.001$; M15, $p = 0.098$; M16, $p = 0.048$; Fig. 6E). Nonetheless, it is

important to note that, for T+/ER- saccades, landing closer to the target does increase firing rates. This is likely due to classification errors, that is, some of the T+/ER- saccades landing near the target were probably associated with expected reward. These results confirm that, when controlling for the landing distance from the target, FEF firing rates are enhanced by expected reward rather than target presence.

Differences Between Monkeys

It is worth noting that there were differences in results between monkeys. One main difference is the proportion of neurons that significantly represent features (expected reward,

latency, or vigor) in the GLM analysis (or similarly, the effect size of the results in the PSTH analyses). M14 had the greatest proportion of neurons that represented features, whereas M16 had the fewest. Indeed, the GLM analysis yielded no cells for M16 where expected reward was significantly represented after accounting for latency and vigor. Another notable difference between monkeys is that the peak of the PSTHs happened near saccade onset in monkey M14, but ~50 ms before onset in monkeys M15 and M16.

One reason for these differences is the way cells were selected. All units from M14, and some units from M15, were recorded using acute recordings (see METHODS). In these cases, cells with strong visual or visuomovement responses were almost always selected. However, all cells from M16 and most cells from M15 were recorded with chronic arrays. In those cases, cells were not carefully selected. Thus, these differences in selection could have led to differing results between monkeys.

Another reason for differences in results across monkeys is due to potential differences in anatomical location. Cells that were acutely recorded in M14 and M15 were confirmed to be in FEF. However, some of the cells that were chronically recorded in M15 and M16 may have been in nearby regions. Moreover, differences in recording location within FEF could have led to differences between monkeys, or between neurons in an individual monkey (see METHODS).

Last, these differences in results could also be caused by different cell types being recorded across monkeys, since the majority of our neurons were not classically categorized into cell types (see METHODS). Overall, we find it especially interesting that, even though there may be differences in the relative distributions of cell types recorded from each monkey, most of the general trends are consistent.

DISCUSSION

We recorded single-cell FEF activity while monkeys freely searched for targets in natural scenes. We found that

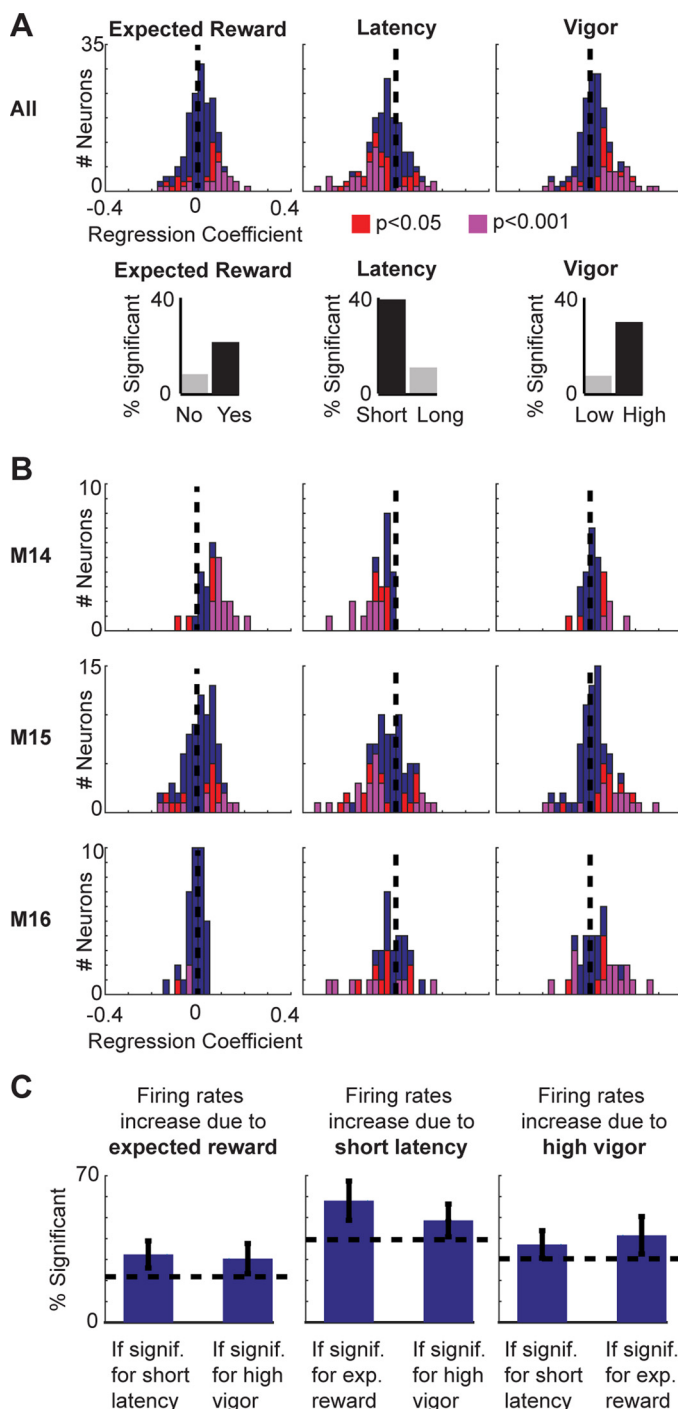


Fig. 5. Increased firing rates due to expected reward, short latency, and high-velocity saccades: generalized linear models (GLMs). **A**: using a GLM, we used the latency, vigor, and expected reward of the saccade (whether it was to the target) to explain the peak firing rate of each neuron. Histograms of the regression coefficients for each covariate are shown across all monkeys, colored based on their significance (dark blue is not significant). *Insets* (on bottom) show the percentage of neurons that is significant. For “target” (left), having positive regression coefficients signifies that going to the target (T+/ER+ saccade) increased the firing rate. For “latency” (middle), having positive coefficients signifies that longer latency saccades increased the firing rate. For “vigor” (right) having positive coefficients signifies that higher vigor increased the firing rate. **B**: same as **A**, with individual monkeys shown in each row. **C**: bars show conditional probabilities (the probability of a neuron representing one feature, e.g., expected reward, conditional on the neuron representing another feature, e.g., latency) from the GLM results across all monkeys. Broken lines show the general probabilities of a feature being significant in the GLM (not conditioned on the neuron representing any other features). Error bars are SEs from bootstrapping. *Left*, probability that neuron firing rates significantly increase due to expected reward (broken line) conditioned on the neurons having significantly higher firing rates due to shorter latencies (bar on left) and higher vigor (bar on right). *Center*, probability that neuron firing rates significantly increase due to short latency conditioned on the neurons having significantly higher firing rates due to expected reward and higher vigor. *Right*, probability that neuron firing rates significantly increase due to higher vigor conditioned on the neurons having significantly higher firing rates due to shorter latencies and expected reward.

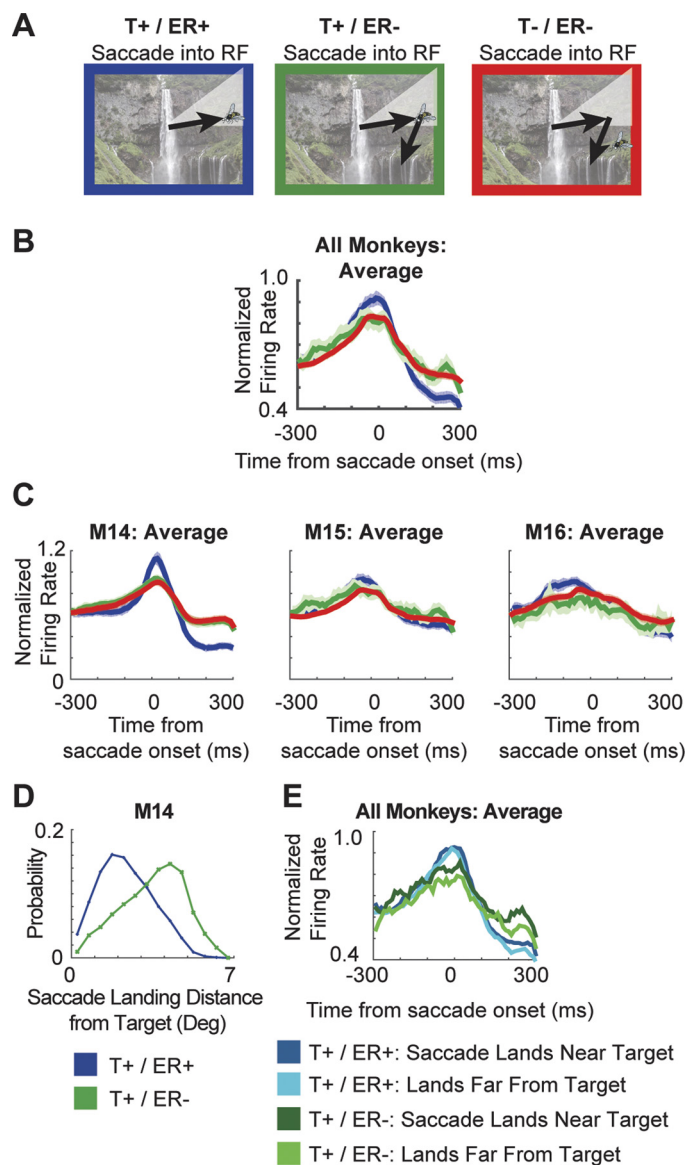


Fig. 6. Modulation in FEF due to expected reward rather than target presence. *A*: we compared T+/ER+ (blue), “target, no expected reward” (T+/ER-, green), and T-/ER- (red) saccades in the RF. *B*: PSTHs show the average normalized firing rate \pm SE of saccades across all neurons (from all monkeys). *C*: same as *B*, but for individual monkeys. *D*: for an example monkey, M14, we show the difference in the distributions of landing distances from the target for T+/ER+ and T+/ER- saccades. *E*: we control for the possibility that T+/ER+ saccades only have a higher peak firing rate than T+/ER- saccades because T+/ER+ saccades land closer to the target on average (*D*). We plot PSTHs for T+/ER+ and T+/ER- saccades that land close to and far from the target. “Close” and “far” are defined as less and more, respectively, than the median distance from the target for all T+ saccades. Error bars are not shown to ensure that the means are visible.

expected reward modulated the activity of FEF neurons during saccades in their receptive fields. This modulation was due to the expected reward, and not simply the presence of the target, since there was no modulation when monkeys accidentally made a saccade near the target. Importantly, expected reward altered saccadic parameters; velocity was increased and latency was decreased. Although FEF activity was modulated by these saccadic parameters, it additionally reflected the expected reward above and beyond those parameters.

Expected Reward

The modulation of FEF activity due to expected reward was a central finding in our study. We classified all nontarget saccades, along with target saccades when the monkeys did not fixate long enough to receive a reward, as not expecting reward. This classification was not arbitrary but was based on our assumption that the monkeys learned the required fixation time to gain the reward. Undoubtedly, some of the saccades were misclassified. For instance, if the monkey intended to fixate the target but ended up at a nontarget location, the monkey expected a reward at the end of the saccade, but we misclassified the saccade as not expecting reward. Alternatively, if the monkey fixated near the target by chance and got rewarded, the saccade was misclassified as expecting reward. Importantly, errors of either kind in our data analysis would only lead us to underestimate the true effect size of the neural differences.

The effects of expected reward in the oculomotor circuits of the brain have been studied extensively. Aside from FEF, for example, many cortical areas have been investigated: lateral intraparietal sulcus (Bendiksy and Platt 2006; Peck et al. 2009), supplementary eye fields (Roesch and Olson 2003; So and Stuphorn 2010), dorsolateral prefrontal cortex (Leon and Shadlen 1999), ventrolateral prefrontal cortex (Kennerley and Wallis 2009), orbitofrontal cortex (Roesch and Olson 2004; Schultz et al. 2000), and premotor cortex (Roesch and Olson 2004), among others. The effects of expected reward also appear in subcortical areas, for example, superior colliculus (Ikeda and Hikosaka 2003, 2007), the basal ganglia (Hikosaka et al. 2014; Kawagoe et al. 1998), and ventral tegmental area (Matsumoto and Hikosaka 2009). Past studies that tested for reward size effects in FEF have yielded mixed results: no reward modulation (Leon and Shadlen 1999), a general reward effect but no effect of reward size (Ding and Hikosaka 2006), and an effect of reward size (Roesch and Olson 2003). In our study, although we did not manipulate reward size, we did observe a clear effect of expected reward on FEF activity while a monkey searched natural images to find a target.

Saccadic Velocity and Latency

Unlike in previous work (Segraves and Park 1993), we observed that vigor (velocity relative to the main sequence, Bahill et al. 1975) is reflected in FEF responses. Previous work may have not found this effect because classical tasks may elicit a more stereotyped relationship between saccade amplitude and velocity. Additionally, we observed that the greatest variability in velocity occurred in the 15–25° range of amplitudes (see Fig. 2*E*), whereas past work often looked at the lower end of this range. This demonstrates the importance of examining the full range of saccades to understand the neural encoding of saccade variables.

We have found a dependence of firing rate on latency. This is consistent with decision-making models that propose that there is a growing urgency signal (Cisek et al. 2009; Thura and Cisek 2014) or a decreasing threshold (Churchland et al. 2008; Rao 2010) over time. These models suggest that a higher firing rate is necessary early on to make a decision, but lower firing rates are sufficient with increasing latencies. Thus, urgency models may help explain the neural mechanisms of sensori-

motor decision-making not only during traditional multialternative choice tasks but also during naturalistic behavior.

Simultaneously Analyzing Expected Reward and Motor Variables

Given the effects of expected reward on saccadic parameters, it is important to understand the degree to which reward modulation in a particular area is a reflection of motor programming. While a small number of studies have used multiple regression to separate the variance accounted for by reward and movement (Ikeda and Hikosaka 2007; Itoh et al. 2003; Leon and Shadlen 1999), the vast majority of studies that examine reward in motor regions of the brain overlook this. Critically, in the cases where reward modulation has been observed in FEF (Ding and Hikosaka 2006; Roesch and Olson 2003), no effort was made to test whether the effect of reward could be explained by movement variables like vigor or latency. The present study demonstrates that, while much of the influence of reward on FEF activity can be accounted for by changes in saccadic vigor and latency, there are still unique effects of reward on FEF above and beyond this.

We used two separate methods to demonstrate that the FEF reflects expected reward above and beyond saccadic parameters. Specifically, we 1) matched saccadic parameters for different saccade types and 2) jointly modeled the effects of movement and reward on FEF activity using a GLM. Here we discuss potential weaknesses of these methods. In both methods, other saccade parameters, such as further derivatives of velocity (e.g., acceleration, jerk), could be uniquely driving neural activity. We used latency and velocity, since these have been previously shown to be affected by expected reward. In our GLM analysis, it could be the case that our model was unable to capture the true relationship between FEF firing and movement covariates. For example, some nonlinear combination of vigor and latency may better explain the neural activity. Additionally, there could be nonlinear effects (e.g., saturation) linking the movement covariates to the firing rate. It is possible that the neural activity that we are attributing to expected reward could be explained by movement in a more accurate model. Nonetheless, these potential sources of error in the GLM analysis are addressed by the matching analysis, which does not make assumptions about the relationship between the movement variables and neural activity. Both methods yield the same results.

Interpretation Limitations

While we distinguished between the neural representation of expected reward and motor variables, there are still many unanswered questions involving the neural mechanisms related to expected reward. First, we cannot be sure about causality. While it is possible that FEF activity is causally altering movement parameters, it is also possible that FEF activity is simply correlated with these motor outputs. In this scenario, expected reward would affect both the FEF and other oculomotor structures, but only a subset of the other oculomotor structures, exclusive of FEF, would be causally linked to the motor output. Observational studies like ours cannot ultimately answer such causal questions without further interventions.

Additionally, it is particularly difficult to determine the processes that are being modulated by expected reward in

cortical oculomotor circuitry where there is a unique confluence of cognitive, sensory, and motor processing (Wallis and Rich 2011). For example, expected reward modulates visuospatial working memory (Kennerley and Wallis 2009) and spatial attention (Louie et al. 2011; Maunsell 2004; Peck et al. 2009). In our study, the effect of expected reward that was observed above and beyond saccade parameters may thus have been due to an increase in attentional gain. While this is a likely explanation of our findings, in a naturalistic task, attention and expected reward are tied together, preventing mechanistic identification.

Last, neural activity may be related to the value of the reward itself, or the reward's behavioral relevance. Indeed, human and nonhuman primate studies suggest that more anterior regions of the cortex (e.g., orbitofrontal, dorsolateral prefrontal) tend to be modulated by the value of the reward, whereas more posterior regions of frontal cortex (e.g., FEF, premotor) tend to be equally modulated by rewarding and aversive stimuli. This suggests that the latter are sensitive to the behavioral relevance, rather than the value, of the stimulus (Litt et al. 2011; Roesch and Olson 2004, 2007). Thus, the effects of reward expectation in our study might more appropriately be attributed to the behavioral relevance of the target stimulus rather than its reward value.

Last, we want to reiterate that, while we aimed to record only from FEF, it is possible that some recorded neurons may have been in nearby areas (see METHODS and *Differences Between Monkeys* for details). Given the past observation of differences in reward modulation between FEF and other prefrontal areas (Leon and Shadlen 1999), it is important to consider the possibility that the individual differences in the reward-related effects we observed could be explained by differential contamination of the FEF recordings from other regions with different functional properties. Nonetheless, our main claim, that there are neurons in FEF that represent expected reward after controlling for saccadic variables, is strongest in monkey M14, whose recordings were confirmed to be in FEF.

Natural Scene Search

The interplay between the concepts of exploration and exploitation may provide meaningful insights into our natural scenes findings about expected reward. When searching for an object, we initially make exploratory saccades that aim to gather information about the scene (Najemnik and Geisler 2005). When we then find the object in the visual periphery, we make an exploitative saccade that aims to foveate the object to gain reward. The enhancement of neural activity associated with exploitative (expected reward) saccades could have several purposes. Along with allowing the subject to reach the object faster (due to increased vigor and decreased latency), the higher firing rates could lead to more precise saccades (due to the increased gains of tuning curves; Butts and Goldman 2006; Fig. 3G), which are likely more important for exploitative saccades. Tuning curves with higher gains could also more precisely allocate attention, which is useful to avoid distraction and ensure that this is the correct object (e.g., to make sure this is the berry you are looking for, not a poisonous one). Thus, the effects of expected reward during visual search can be under-

stood in the context of exploration and exploitation in the real world.

Our results also highlight the value of using natural scenes in vision experiments with nonhuman primates (Burman and Segraves 1994; Gallant et al. 1998; MacEvoy et al. 2008; Phillips and Segraves 2010; Rolls and Tovee 1995; Sheinberg and Logothetis 2001; Vinje and Gallant 2000). For instance, we were able to analyze saccades that landed near the target accidentally (without reward expectation), which would not occur in an experiment with simple stimuli. The finding that these accidental target saccades did not increase firing rates can help explain previous discrepancies between experiments using artificial stimuli and natural scenes. Although there have been studies using artificial stimuli that have found evidence that FEF encodes task-relevance or feature-based attention (i.e., visual similarity to a target) (Bichot et al. 1996; Zhou and Desimone 2011), studies using natural scenes have not yielded this result (Ramkumar et al. 2016). Similarly, in our study, T+/ER− were not accompanied by an enhanced response, even when the target was contained within the RF. It may be the case that the ease of localizing stimuli in the artificial stimulus paradigms more consistently leads to an awareness, and subsequent neural representation, of the target and objects similar to the target (Sheinberg and Logothetis 2001), as it did with the T+/ER+ saccades. These differences highlight the importance of using natural stimuli to test ecologically relevant behaviors.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.I.G., D.K.W., P.N.L., P.R., K.P.K., and M.A.S. conception and design of research; J.I.G., D.K.W., P.N.L., and P.R. performed experiments; J.I.G., D.K.W., P.N.L., and P.R. analyzed data; J.I.G., D.K.W., P.N.L., P.R., K.P.K., and M.A.S. interpreted results of experiments; J.I.G. and D.K.W. prepared figures; J.I.G. and D.K.W. drafted manuscript; J.I.G., D.K.W., P.N.L., P.R., K.P.K., and M.A.S. edited and revised manuscript; J.I.G., D.K.W., P.N.L., P.R., K.P.K., and M.A.S. approved final version of manuscript.

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