Persistent Spatial Information in the FEF during Object-based Short-term Memory Does Not Contribute to Task Performance

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Abstract

■ We previously reported the existence of a persistent spatial signal in the FEF during object-based STM. This persistent activity reflected the location at which the sample appeared, irrespective of the location of upcoming targets. We hypothesized that such a spatial signal could be used to maintain or enhance object-selective memory activity elsewhere in cortex, analogous to the role of a spatial signal during attention. Here, we inactivated a portion of the FEF with GABA-a agonist muscimol to test whether the observed activity contributes to object memory performance. We found that, while RTs were slowed for saccades into the inactivated portion of retinotopic space, performance for samples appearing in that region was unimpaired. This contrasts with the devastating effects of the same FEF inactivation on purely spatial working memory, as assessed with the memory-guided saccade task. Thus, in a task in which a significant fraction of FEF neurons displayed persistent, sample location-based activity, disrupting this activity had no impact on task performance. ■

INTRODUCTION

The unique role of pFC in the acquisition and retention of sensory information has long been appreciated (Gross & Weiskrantz, 1964). During spatial attention, in which the acquisition of sensory information is focused on an isolated region of space, a spatial signal enhances the representation of behaviorally relevant sensory information (McAlonan, Cavanaugh, & Wurtz, 2008; McAdams & Reid, 2005; McAdams & Maunsell, 2000; Reynolds, Pasternak, & Desimone, 2000; Yeshurun & Carrasco, 1998; Treue & Maunsell, 1996; Moran & Desimone, 1985). A variety of evidence points to the FEF, an area within pFC involved in gaze control, as one source of such modulatory feedback during spatial attention (Noudoost & Moore, 2011a; Schafer & Moore, 2007, 2011; Armstrong, Chang, & Moore, 2009; Buschman & Miller, 2009; Ekstrom, Roelfsema, Arsenault, Kolster, & Vanduffel, 2009; Gregoriou, Gotts, Zhou, & Desimone, 2009; Monosov & Thompson, 2009; Monosov, Trageser, & Thompson, 2008; Armstrong & Moore, 2007; Moore & Armstrong, 2003; Moore & Fallah, 2001; Kodaka, Mikami, & Kubota, 1997). We hypothesized that spatial feedback might play an analogous role during object working memory, enhancing mnemonic activity during memory similar to its effect on sensory responses during attention. We first determined whether such a persistent spatial signal was present in the FEF during a purely object-based STM task (Clark, Noudoost, & Moore, 2012). We recorded FEF activity during an object DMS task, in which the monkey had to report object identity independent of the location at which sample and potential target images appeared. We found that, despite the ostensible irrelevance of sample position for task performance, the FEF robustly signaled sample location through the delay period (Figure 1). This activity was unaffected by predictable changes in upcoming target location, instead reflecting memory for sample position.

Here, we test whether sample position-dependent FEF activity contributes to object memory performance. We inactivated a portion of the FEF with the GABA-a antagonist muscimol, measuring object STM performance before and after inactivation. We found that there was no specific impairment of memory for sample images appearing in the inactivated region. This is in contrast to the spatially specific deficits, which muscimol infusion produced on a memory-guided saccade (MGS) task. Although it is tempting to speculate about task modifications that might "reveal" a contribution of this activity to task performance, the fact remains that, under the task conditions in which this activity was recorded, it makes no apparent contribution to object memory.

METHODS

General and Surgical Procedures

Two male rhesus monkeys (*Macaca mulatta*, 11 and 12 kg) were used in these experiments. All experimental procedures were in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*,

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doi:10.1162/jocn_a_00599

the Society for Neuroscience Guidelines and Policies, and Stanford University Animal Care and Use Committee. General surgical procedures have been described previously (Armstrong, Fitzgerald, & Moore, 2006). Each animal was surgically implanted with a titanium head post and a scleral search coil. Surgery was conducted using aseptic techniques under general anesthesia (isoflurane), and analgesics were provided during postsurgical recovery. Structural magnetic resonance imaging was performed to locate the arcuate sulcus in each monkey for the placement of a recording chamber in a subsequent surgery. A craniotomy was performed on each animal, allowing access to the FEF on the anterior bank of the arcuate sulcus.

Recording, Microstimulation, and Inactivation of the FEF

Electrophysiological recordings, electrical microstimulation, and pharmacological inactivation of the FEF were each carried out using a custom-made, microinjectrode (Noudoost & Moore, 2011b). Our system consisted of a 32-gauge (236 μm outer diameter) stainless steel cannula containing a 75-μm, commercially available epoxy-coated, tungsten microelectrode (FHC, Inc., Bowdoinham, ME). The microelectrode was held in place inside the cannula via a cilux T-junction. The electrode was passed through the center of the T-junction and through a plastic ferrule where it was soldered to a connector for recording. The cannula was attached to a different opening of the T-junction via another ferrule. The drug line, composed of 363-μm (outer diameter) polyimide-coated glass tubing (Polymicro Technologies, Phoenix, AZ), was attached through a ferrule to the final T-junction opening. The polyimide tubing was then connected to a manual injection drive (Stoelting, Wood Dale, IL) and a gas-tight microsyringe (Hamilton, Reno, NV) via a series of high precision fluidic valves attached to a fluidic "circuit" board. The T-junctions, ferrules, fluid valves, and fluidic circuit board were all obtained from LabSmith (Livermore, CA). Because the inner diameters of the tubing and the cannula were equal (150 μm), drug flow was steady with a minimum of clogging or hysteresis. To measure fluid flow into the brain, we drew up into the fluid path an oil–dye–oil marker, whose movement inside the polyimide tubing could be observed with the naked eye. The oil in the marker was of low viscosity (~1 centistokes), and nontoxic food coloring was used for the dye. Within the 150-μm tubing, a 1-cm movement of the marker indicated a ~170-nl movement of the drug out of the cannula. Because we could measure movements of the dye marker by as little as 1 mm, the volume resolution of the microinfusion system was <17 nl.

To inactivate FEF neuronal activity, we used muscimol, a potent and selective $GABA_a$ agonist that has been widely used in studies involving in vivo inactivation of local neuronal activity, particularly in behaving monkey studies (Wardak et al., 2002; Dias & Segraves, 1999; Sommer & Tehovnik, 1997). Similar to previous studies, muscimol was dissolved in physiological saline at a concentration of 5 mg/ml (pH = 6.5–7.0). Before delivery of the drug, the entire fluid delivery system was soaked and thoroughly flushed with cold sterilant (chlorhexidine diacetate, Nolvasan), flushed with sterile water and then allowed to dry. We infused 0.5–1.0 μl of muscimol at sites within the FEF over a period of 10–15 min. On the basis of pilot experiments on the time course of the inactivation effects, behavioral testing and electrophysiological recordings began at least 60 min after completion of muscimol infusion; the effects of muscimol infusion lasted for at least 4 hr (and potentially up to 24 hr) following infusion, with all data collection being completed well within this time. Inactivation experiments were always separated from one another by at least 48 hr; after 48 hr, no lingering effects of the previous muscimol infusion were observed, and no permanent deficits developed over the series of experiments. Saline infusion sessions were interspersed with inactivation experiments.

The inclusion of the tungsten microelectrode within the center of the drug cannula further allowed us to record the activity of single neurons near the center of the delivered drug volume using conventional recording and filtering techniques. Moreover, we could also use standard electrical microstimulation to confirm at each drug site that saccades could be elicited with low currents and thus that each microinfusion site was within the FEF. To keep the microelectrode from being damaged when inserting the cannula into the brain, the ferrule connecting it to the T-junction could be rotated three-turn counterclockwise, thereby retracting the microelectrode about 1 mm back into the cannula. Once the cannula was well within the brain, the ferrule could be slowly rotated clockwise and tightened, thus positioning the electrode at a known distance beyond the cannula opening. Electrical microstimulation with the microinjectrode consisted of a 100-msec train of biphasic current pulses (0.25 msec pulse duration, 200 Hz) delivered with a Grass stimulator (S88) and two Grass stimulation isolation units (PSIU-6). Current amplitude was measured via the voltage drop across a 1-kΩ resistor in series with the return lead of the current source. All stimulation was delivered via varnish-coated tungsten microelectrodes of 0.2–1.0 MΩ impedance (measured at 1 kHz) contained with the microinjectrode. In each monkey, the FEF was first localized on the basis of its surrounding physiological and anatomical landmarks and the ability to evoke fixed-vector, saccadic eye movements with stimulation at currents of less than 50 μA. The microelectrode typically extended beyond the beveled tip of the cannula by 50–500 μm. During each experimental recording session, we mapped the saccade vector elicited via microstimulation at the cortical site under study with a separate behavioral paradigm (Moore & Fallah, 2001). In this paradigm, the monkey was required to fixate on a visual stimulus (0.48° diameter circle) for 500 msec, after which time a 100-msec stimulation train was delivered on

half the trials. Evoked saccades had vectors with amplitudes ranging from 5° to 13° eccentricity and angles of 90° to 65° theta (left FEF, monkey H) and 135° to 220° theta (right FEF, monkey S). Landing points of microstimulation evoked saccades were considered to be the center of the response field of the FEF site under study (FEF RF).

Behavioral Tasks and Analysis

Throughout the experimental session, monkeys were seated in a primate chair, and eye position was monitored with a scleral search coil with a spatial resolution of <0.1° (Armstrong et al., 2006) and was digitized at 100–200 Hz.

MGS Task

In the MGS task, a cue appears briefly in one of several locations: The monkey must remember the cue location throughout a variable delay and make saccade to the remembered location upon the removal of the fixation point. The delay duration was adjusted via a staircase paradigm, in which the delay for each trial was incremented up or down based on performance in the previous trial at that location; a correct trial resulted in a juice reward and an increase in the delay at that location, and an incorrect trial gave no reward and a decrease in the delay. Thus, the monkey had to correctly complete trials to receive any reward. Delay values were allowed to become negative (down to −300 msec), with values below zero becoming visually guided saccades. "Maximum achievable delay" was defined as the delay duration that would be reached with perfect performance at a given location, for the number of trials completed there; for example, if the delay started at 300 msec and stepped in increments of 100 msec, then after 10 trials at that location the maximum achievable delay would be 1300 msec. Performance was then quantified in comparison with this theoretical maximum, "fraction of maximum delay": the ratio of the delay the monkey actually achieved to the maximum achievable delay.

Object DMS Task

Monkeys were trained to fixate within a 1.5–3° diameter error window surrounding a central spot (0.4° diameter). DMS task is depicted in Figure 1A. At 250–750 msec after fixation, a colored photo image (5° diameter) was

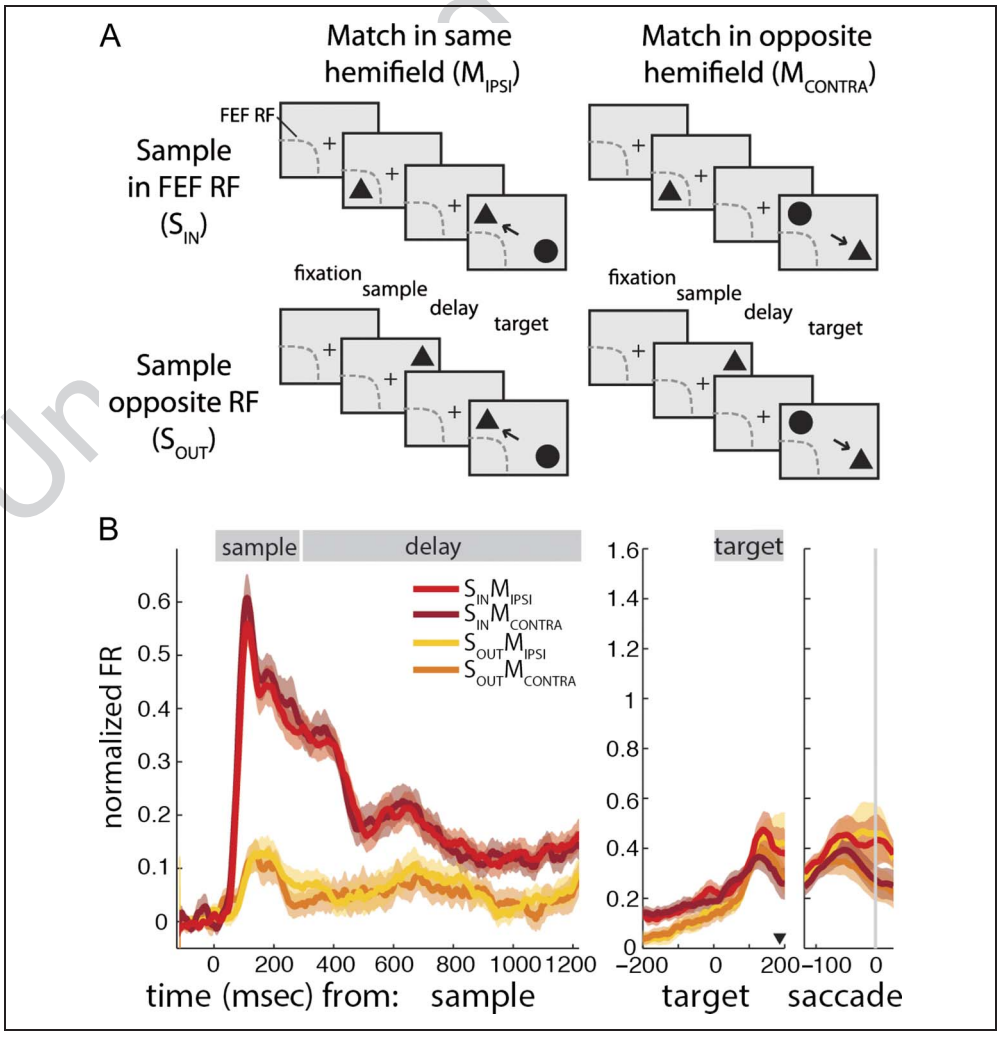

Figure 1. The activity of FEF neurons during the object-based STM task. (A) Object DMS task: Monkey fixates the small central spot. A sample image appears either inside of or opposite the FEF RF for 300 msec (sample period). The monkey maintains fixation throughout a 1-sec delay (delay period) during which only the fixation spot remained on the screen. The match and nonmatch images appear at locations rotated 90° from the FEF RF, and the monkey saccades to the match to receive a reward (target period). The location of the match is randomized with respect to the sample image position. (B) The response of FEF neurons (n = 95) during the object DMS task, when the sample appeared in or out of the FEF RF (reds, S_{IN}; yellow, orange: S_{OUT}) for targets in the same hemifield as the FEF RF (M_{IPSI}: bright red, yellow) or the opposite hemifield (M_{CONTRA}: brick red, orange). The population response is shown aligned to sample image onset (left), target array onset (middle), and onset of the saccade (right). Lines and shading represent mean ± *SEM*.

presented for 300 msec (sample period). A delay period of 1–3 sec followed the sample offset (delay period), after which two images—one match, one nonmatch—appeared (target period), and the monkey was rewarded for making saccades directly to the match. Monkeys were required to maintain fixation throughout the sample presentation and delay; breaks in fixation before the trial was completed immediately terminated the trial, and these trials were not included in the data analysis. Three or four images were used in each experimental session, and all images appeared with equal frequency as the sample/match and the nonmatch. The location of the match was randomized with respect to sample location.

The target array could appear in one of two configurations, with the match and nonmatch appearing either in the two potential sample locations (aligned targets) or in positions rotated 90° with respect to the sample positions (orthogonal targets). In the orthogonal block, once the sample disappeared from the screen, its location was irrelevant for the remainder of the trial: Neither match nor nonmatch ever appeared at the sample location, and saccades to that location were not rewarded. To allow maximum familiarity with the block structure, only two blocks were run in each experimental session: Target positions were held constant for a block of 200–400 trials, then switched for a second block of similar duration. The order of the aligned and orthogonal blocks was randomized for monkey H, whereas the orthogonal block was always first for monkey S. All sample location, sample/match identity, and nonmatch target identity conditions were pseudorandomly interleaved and were controlled by the CORTEX system for data acquisition and behavioral control. During each experiment, the two sample positions were selected so that one stimulus was positioned inside the RF of the FEF site, based on the endpoints of saccades evoked with microstimulation (5–13° eccentricity). Both monkeys were initially trained exclusively on the orthogonal targets version of the task, and only learned the aligned targets version after reaching criterion (70%) performance with the orthogonal targets. All visual stimuli were displayed on a liquid crystal display monitor (52 cm vertical × 87 cm horizontal) positioned 57 cm in front of the monkey, with a refresh rate of 60 Hz.

Data presented here have been pooled across several variants on the DMS task. The 14 experimental sessions break down as follows: orthogonal target positions, 5 days; aligned target positions, 5 days; orthogonal targets with distractors, 2 days; orthogonal targets with a staircase paradigm for increasing delay duration (performance > 65% at a given sample location resulted in an increase in the delay), 2 days. Most experiments used object photographs as stimuli, but 4 days (one orthogonal, one aligned, one distractor) used four stimuli based on combinations of simple shapes and colors (consisting of a plus symbol and a circle in red and blue). When reporting performance measures for days that used a staircase paradigm, delays were matched for the two blocks; On both days similar delays were reached before and after FEF inactivation. To evaluate the effects of inactivation on DMS performance within a single experimental session, binary logistic regression was used to test the main effects of and interactions between inactivation and sample location on the monkey's ability to maintain object information in the DMS task (binary dependent variable of correct vs. wrong choice).

Experimental Time Course

At the beginning of each day, the microinjectrode was inserted into the FEF based on previously established stereotaxic coordinates and mapping of the recording chamber using eye movements evoked by electrical microstimulation (locations within 1 mm of a site with a saccade threshold of 50 μA or less were considered part of the FEF). First, we ran a baseline block of the MGS task. Then we ran a block of the object DMS task (49–193 trials). We then infused muscimol over a period of 10–15 min. We waited a minimum of 30 min, then ran another block of the MGS task. If no deficit was detected, we waited another 20 min and ran another block of MGS. After a pronounced MGS deficit became visible, we began a second block of object DMS testing (95–254 trials), which continued as long as the animal was willing to perform the task.

RESULTS

We performed a total of 14 inactivation experiments in two animals. Each day, we first positioned the microinjectrode within the FEF, then recorded a block of MGS trials and one of DMS trials. Muscimol was infused (as detailed in Methods) and given at least 30 min to take effect. Then we ran another block of the MGS task, looking for spatially localized deficits (Dias & Segraves, 1999; Sommer & Tehovnik, 1997; Dias, Kiesau, & Segraves, 1995). After verifying a deficit on the MGS task, we ran a second block of the DMS task. Figure 2 illustrates the results for a single experimental session. Delay durations in the MGS task increased or decreased based on performance in the previous trial; we quantified MGS performance relative to the maximum achievable delay at a given location—the delay duration that the monkey would reach if he performed all trials at that location correctly. We then looked at the ratio of the actual final delay duration to that maximum, which would have been achieved with perfect performance, the "fraction of maximum delay" (where 1 is perfect performance and 0 indicates the monkey is unable to perform the task with any delay). Performance on the MGS task showed a dramatic, spatially specific deficit following muscimol infusion (Figure 2A). Whereas performance was unaltered for locations 90° away from the infusion site, the animal was unable to correctly perform the task when the sample was presented inside the scotoma (S_{IN}). In contrast to this spatially specific deficit in MGS performance, DMS performance

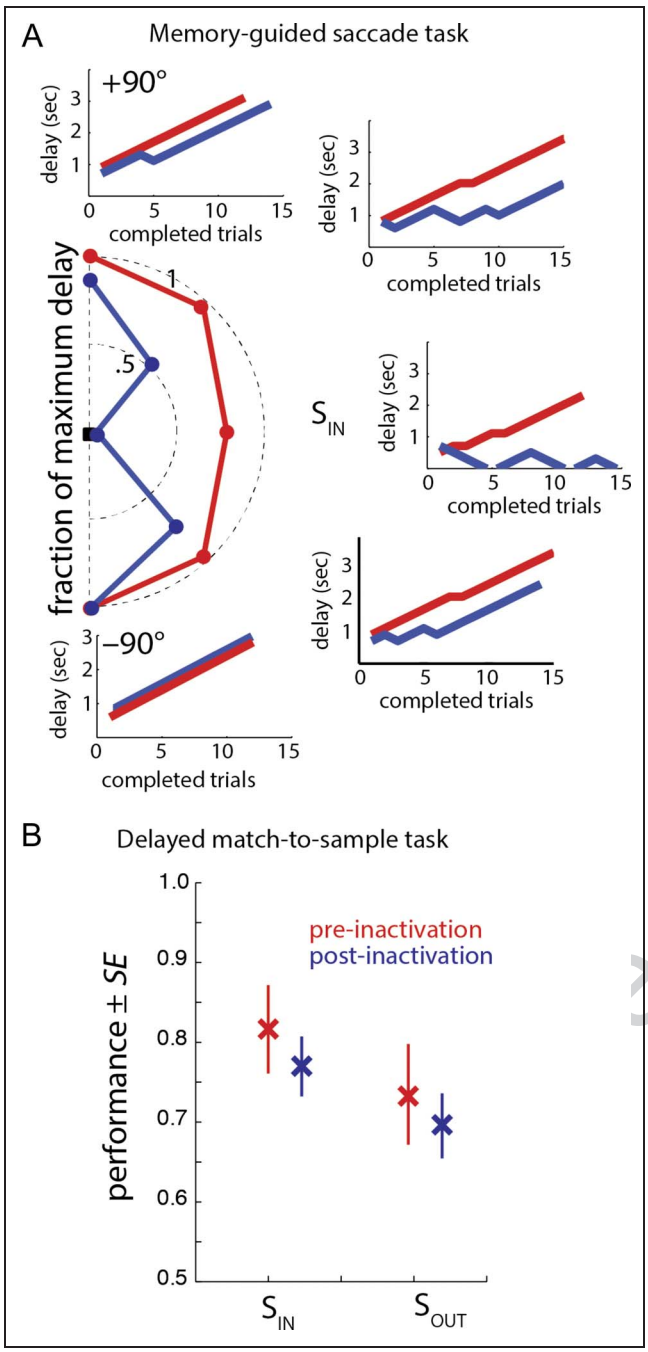

Figure 2. MGS and object DMS performance for a single experimental session. (A) MGS performance at five locations in the hemifield contralateral to FEF muscimol infusion. Each plot shows the delay as a function of completed trials at a given location (correct trials led to an increase in delay, incorrect trials to a decrease), before FEF inactivation (red) and after FEF inactivation (blue). Gaps where the plot dips below zero indicates that the monkey was completing trials with below-0 delay values (visually guided saccades). Performance is quantified in the polar plot (middle) and indicates the delay achieved, expressed as fraction of the delay that would have been reached had the monkey performed perfectly. (B) Object DMS performance for the same experimental session. Plot shows performance (proportion correct) ± standard error for samples appearing in the FEF scotoma (S_{IN}) and in the opposite hemifield (S_{OUT}), before and after FEF inactivation (red and blue, respectively).

was not significantly altered following FEF inactivation for objects presented inside (S_{IN}) or outside (S_{OUT}) the scotoma (Figure 2B; logistic regression, effect of sample location, $p = .001$; effect of inactivation $p = .10$; interaction $p = .41$). Therefore, in spite of spatially selective FEF activity during the DMS task (Figure 1B), suppression of this activity had no spatially specific effects on maintenance of object information during the DMS task (Figure 2B).

In the complete set of inactivation experiments ($n = 14$), performance on the MGS task suffered a significant, spatially selective disruption (Figure 3A). MGS performance at the S_{IN} location, overlapping the inactivated portion of the FEF representation, was significantly impaired following muscimol infusion (Figure 3A, top; fraction of maximum delay, Preinfusion vs. Postinfusion: Wilcoxon signed-rank test, median change = 0.85, $p < 10^{-3}$). Monkeys reached a substantial fraction of the maximum achievable delay before FEF inactivation (median = 0.87, $p < 10^{-3}$). After inactivation, they were essentially unable to remember a cue at the scotoma location for any length of time—delay durations were not significantly different from 0 (median = -9.7×10^{-4}, $p = .94$). In contrast, at a location 90° away from the FEF scotoma, monkeys were able to reach nonzero delays both before and after inactivation (before inactivation, median = 0.52, $p < 10^{-3}$; after inactivation, median = 0.40, $p < 10^{-3}$). Importantly, at this "90°" location, inactivation did not significantly alter the delays achieved (Figure 3A, bottom; fraction of maximum delay attained Preinfusion vs. Postinfusion: Wilcoxon signed-rank test, median change = 0.13, $p = .27$). Across

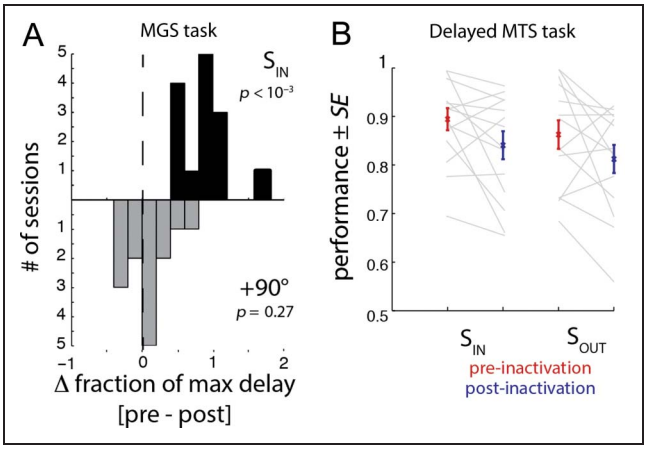

Figure 3. MGS and object DMS performance before and after FEF inactivation across all sessions. (A) Change in MGS performance before versus after FEF inactivation, quantified as fraction of maximum possible delay achieved with a staircase paradigm. Top histogram, memory location corresponding to the S_{IN} position, in the FEF scotoma (black); fraction of delay achieved was significantly reduced following FEF inactivation ($p < 10^{-3}$). Bottom histogram, memory location 90° away from scotoma (gray); no significant change in delay ($p = .27$). (B) Object DMS performance before (red) and after FEF inactivation (blue), for sample locations in and opposite the FEF scotoma (S_{IN} and S_{OUT}).

the population, the inactivation-induced change in delays achieved at the S_{IN} location differed significantly from the changes observed 90° away (Wilcoxon signed-rank test, $p < 10^{-3}$).

Performance on the DMS task decreased overall following FEF inactivation, but there was no difference in the change in performance for samples presented in versus out of the FEF scotoma (Figure 3B; repeated-measures ANOVA with factors sample position and inactivation: no main effect of sample position, $F = 1.35$, $p = .266$; main effect of inactivation, $F = 6.07$, $p = .0284$; no interaction, $F = 0.0062$, $p = .938$). Changes in performance following infusion were comparable in magnitude for the two sample locations (S_{IN} median $\Delta_{\square\square\square\square\square ST} = 0.05$, S_{OUT} median $\Delta_{\square\square\square\square\square ST} = 0.06$; Wilcoxon signed-rank test ΔS_{IN} vs. ΔS_{OUT}, $p = .58$). Comparing performance for the two sample locations before and after infusion within each session, there was never any significant difference in the effect of inactivating FEF on samples presented in versus out of the FEF scotoma (logistic regression based on sample position and preinfusion vs. postinfusion, Bonferroni corrected, no significant interaction terms). For the 5 days in which targets appeared in and opposite the FEF scotoma (aligned targets condition), the animal's choices and performance were not significantly altered based on target location, although there was a trend toward a decrease in the probability of choosing the target in the scotoma (repeated-measures ANOVA with factors target position and inactivation: target position, $F = 5.33$, $p = .082$; inactivation, $F = .017$, $p = .903$; interaction, $F = 5.62$, $p = .077$). However, RTs for saccades to the target appearing in the FEF scotoma were slowed following inactivation. Mean RTs for targets in the scotoma were 190 msec before versus 211 msec after, ΔT_{IN} 21 msec, whereas for targets opposite the scotoma, they were 186 msec before versus 187 msec after, ΔT_{OUT} 1 msec. An ANOVA on RTs for each day revealed main effects of target position and block and a significant interaction between the two (all $p < .0168$). Thus, the inactivation continued to impact saccades into the scotoma during the DMS task, but it did not measurably impact object memory performance based on sample location.

DISCUSSION

We previously reported the existence of persistent, sample location-selective activity in the FEF during the delay period of an object-based STM task (Clark et al., 2012). Here, we tested whether this activity contributed to object memory performance by inactivating a portion of the FEF with muscimol. Consistent with previous reports (Sommer & Tehovnik, 1997; Dias et al., 1995), the muscimol infusion produced dramatic, spatially specific deficits on an MGS task. In contrast, this inactivation did not impact object memory performance for samples presented in versus opposite the FEF scotoma. Thus, the persistent FEF activity observed during the object STM task does not appear to contribute to task performance.

Following FEF inactivation, object DMS performance was slightly reduced for both sample locations. This slight decrease in performance following FEF inactivation might have resulted from reduced motivation and/or increased fatigue throughout the session. It could also reflect the increased effort required to maintain fixation following the muscimol infusion (Dias & Segraves, 1999). Although the reported performance considers only completed trials and thus is not directly affected by changes in the frequency of breaking fixation prematurely, the greater effort required to maintain fixation following infusion may distract from task performance. Nonetheless, even if the significant drop in overall performance can be directly attributed to the FEF inactivation, and not to satiety, fatigue, or increased difficulty to fixate, that nonspatial effect would contrast dramatically with the neuronal effects. The neuronal activity observed in FEF during the object DMS task is sample location specific, whereas the change in performance observed following FEF inactivation is not. This lack of spatial specificity also contrasts with the observed effect of inactivation on MGS performance, in which elimination of similar cue location-selective activity produces a spatially specific deficit.

It is tempting to speculate that the observed FEF activity might contribute to task performance under different circumstances: for example, if the task were more difficult, or if the delays were longer, or if there were distractors present. Although it is true that performance on the object DMS task was generally quite high (median ~90%), the same was true for the MGS task—and yet the latter showed a profound spatially specific disruption, whereas the former did not. Indeed, the frequency and magnitude of the delay activity observed during the DMS is comparable to that seen in spatial working memory tasks (Lawrence, White, & Snyder, 2005; Balan & Ferrera, 2003; Sommer & Wurtz, 2001), in which the effect of inactivation is near total elimination of memory performance. (It should be noted, however, that a two-alternative spatial choice task would be a better task than the MGS for comparing FEF's contribution to spatial vs. object STM.) Studies have previously reported performance deficits on a single-sample color DMS task following prefrontal cooling (Fuster, Bauer, & Jervey, 1985; Bauer & Fuster, 1976); however, in this case delays were much longer (up to 30 sec, with performance deficits emerging at 16 sec for unilateral cooling), and cooling was focused on the principal sulcus, likely inactivating portions of dorsolateral and ventrolateral pFC in addition to FEF. Similarly, large pFC lesions have been shown to impair performance on a covert attention task with feature-defined targets (Rossi, Bichot, Desimone, & Ungerleider, 2007). But again the discrepancy could either be because of the task demands (memory maintenance vs. covert attention) or because of a difference in the inactivated/lesioned cortex. Regardless of whether the FEF might contribute to object memory under other

circumstances, the fact remains that this activity does not appear to contribute to task performance under the conditions in which it was observed.

"Correlation does not imply causation" is a classic phrase in science and statistics that emphasizes that a correlation between two variables does not necessarily imply that one causes the other (Aldrich, 1995). However, in practice, a large number of neurophysiological studies incorporate no causal manipulation while still drawing causal conclusions. Given the high metabolic cost of neural activity (Lennie, 2003), it does seem logical for extraneous neural activity to be kept to a minimum. However, ours is not the only example of neural correlates being present in an area without apparently contributing to the relevant computations or behavior. LIP neurons are modulated by reward, elapsed time, and limb motor planning—yet inactivating LIP does not appear to induce any deficit in these nonspatial task components (Balan & Gottlieb, 2009). Historically, hippocampal activity was shown to precede and predict the behavioral response in eyeblink conditioning, yet hippocampal lesions have no effect on the learning or retention of this conditioned response (Squire, Stark, & Clark, 2004). On a theoretical level, even neurons whose activity correlates with behavioral outcomes across trials need not be causally linked to those decisions (Cohen & Newsome, 2009; Nienborg & Cumming, 2009). Our findings provide a novel example of this in terms of the magnitude and sustained nature of the signal apparently going unused.

Acknowledgments

This work was supported by National Institutes of Health Grant EY014924, National Science Foundation Grant IOB-0546891, the McKnight Foundation, and a Stanford Bio-X Fellowship (K. L. C.). We thank D. A. Aldrich for technical assistance and animal care.

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