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Report

Selection and Maintenance of Saccade Goals in the Human Frontal Eye Fields

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[1]*Department of Psychology and Center for Neural Science, New York University, New York, New York; and* [2]*Helen Wills Neuroscience Institute and Department of Psychology, Henry H. Wheeler Jr. Brain Imaging Center, University of California, Berkeley, California*

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Curtis, Clayton E. and Mark D'Esposito. Selection and maintenance of saccade goals in human frontal eye fields. *J Neurophysiol* 95: 3923–3927, 2006. First published February 8, 2006; doi:10.1152/jn.01120.2005. In a delayed-response task, response selection marks an important transition from sensory to motor processing. Using event-related functional magnetic resonance imaging, we imaged the human brain during performance of a novel delayed-saccade task that isolated response selection from visual encoding and motor execution. The frontal eye fields (FEFs) and intraparietal sulcus (IPS) both showed robust contra-lateralized activity time-locked to response selection. Moreover, response selection affected delay-period activity differently in these regions; it persisted throughout the memory delay period following response selection in the FEF but not IPS. Our results indicate that the FEF and IPS both make important but distinct contributions to spatial working memory. The mechanism that the FEF uses to support spatial working memory is tied to the selection and prospective coding of saccade goals, whereas the role of the IPS may be more tied to retrospective coding of sensory representations.

INTRODUCTION

During a classic delayed-saccade task, visual information about a target's location is used to later execute a memory-guided saccade. Persistent neural activity during the retention interval is thought to provide a bridge across time linking the transient sensory stimulus and its contingent motor response (Curtis and D'Esposito 2003; Fuster 2001). The nature of the code carried by this persistent delay period activity remains unknown. A *retrospective* code of the past sensory event could be maintained by the persistent activity. For example, the position of the brief visual cue could be stored in retinal coordinates throughout the retention interval until a saccade is made to the stored location. Alternatively, a *prospective* code of the future motor act could be maintained by the persistent activity. In this case, a saccade is immediately planned to the location of the brief visual cue, and this motor plan is maintained throughout the delay period until the memory-guided saccade is triggered. Evidence for both mnemonic-coding schemes exist (Boussaoud 2001; Constantinidis et al. 2001; Funahashi et al. 1993; Gnadt and Andersen 1988; Quintana and Fuster 1999; Rainer et al. 1999; Takeda and Funahashi 2002).

In trying to understand the factors that influence which coding scheme is implemented, we focus on the effect that response selection has on persistent delay period activity. Successful performance of a delayed-response task requires maintaining an internal representation of the visual stimulus, but only until a response is selected. Once a response is selected, simply maintaining the motor plan becomes a sufficient strategy for bridging the memory delay. Therefore we consider response selection to be the most critical rate-limiting step in the evolution of sensation to action.

Strategically, visual and motor events are separated in time during delayed-response tasks so that the evoked physiological responses to each event can be independently quantified (Hikosaka and Wurtz 1983). Building on this strategy, we designed a paradigm that isolated in time response selection from sensory encoding and motor execution (Fig. 1). Two working-memory retention intervals were used to separate response selection from the visually presented cues and from the execution of the memory-guided saccade. In an event-related functional magnetic resonance imaging (fMRI) study, we isolated evoked activity in the human frontal eye fields (FEF) and intraparietal sulcus (IPS) during response selection and further investigated its impact on the maintenance of visual spatial and motor information.

METHODS

Fourteen subjects (6 female; 12 right-handed; ages range from 19 to 34) gave informed consent and participated in the event-related fMRI study. We used standard scan parameters to acquire single shot gradient echo-planar images (FOV: 224 × 224; MAT: 64 × 64; 18 3.5-mm axial slices; TR: 1,010 ms; TE: 28 ms; flip angle: 20°) with a 4 Tesla scanner and TEM send/receive volume RF coil. We recorded eye position at 60 Hz (Model 504LRO; Applied Sciences Laboratories, Bedford, MA) while brain images were acquired as each subject performed five runs of 12 trials each of the delayed-selection task (60 trials total). Functional images were motion corrected with a six-parameter rigid body algorithm, band-pass filtered (0.001-Hz low-pass and 0.5-Hz high-pass filter) and analyzed with a modified general linear model in which each epoch of the task, including the sample cues, selection, both delays, response, and feedback, was modeled independently. Each of these covariates were convolved with an estimated hemodynamic response function (HRF)

$$h(t) = \exp(-t/\tau_1) \sin(2\pi f_1 t) - a \exp(-t/\tau_2) \sin(2\pi f_2 t)$$

where $a = 0.11$, $\tau_1 = 7.245$ s, $f_1 = 0.04$ Hz, $\tau_2 = 7.4$ s, and $f_2 = 0.12$ Hz (see Polonsky et al. 2000). The delay periods were modeled with a 4-s HRF convolved boxcar centered in the middle of delay 1 or a 4, 6, or 8-s HRF convolved boxcar centered in the middle of delay 2, corresponding to the delay durations of 12, 14, and 16 s, respectively. This resulted in a 4-s buffer between the delay covariates and the other

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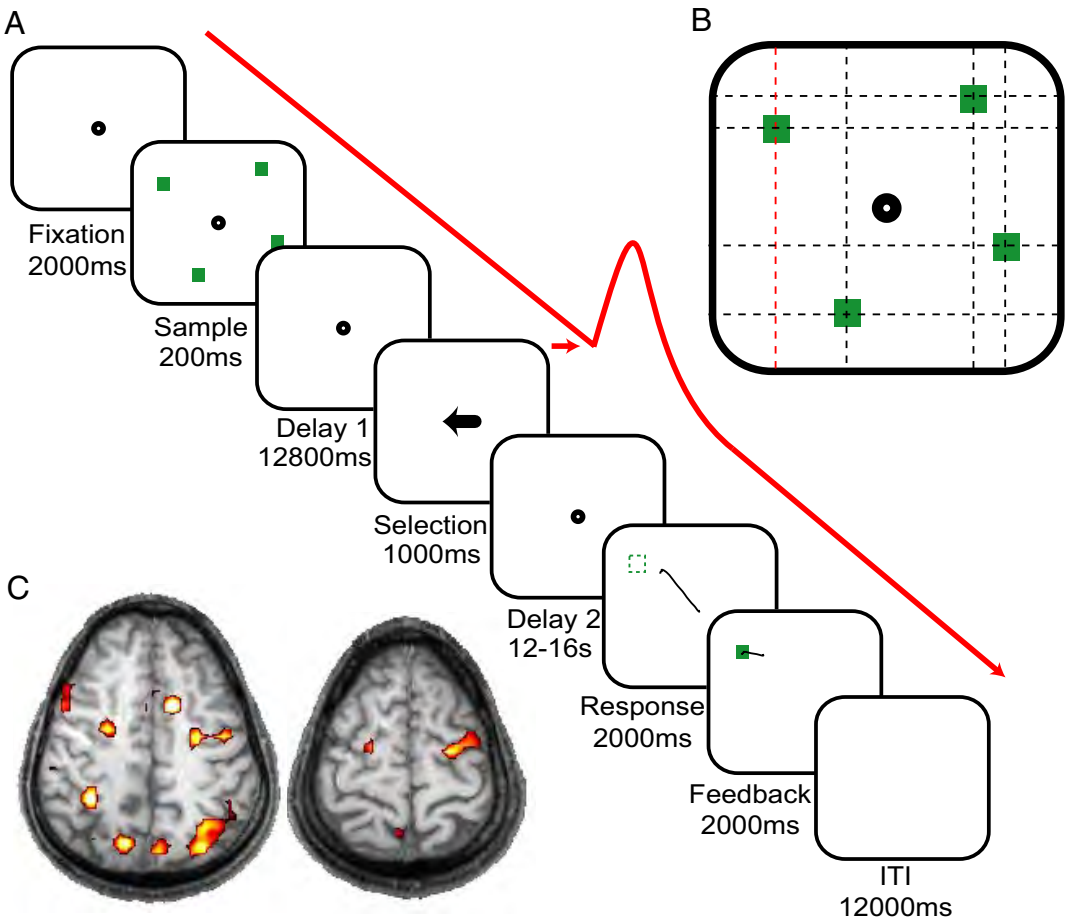

FIG. 1. *A*: schematic of delayed-selection task. Four locations were sequentially cued (50 ms each) for maintenance over a delay interval (delay 1). Then an arrow appeared instructing the subject to select 1 target among the 4 cued locations. The selected location was the goal of a saccade made after another long and variable delay (delay 2). If necessary, a corrective saccade to the re-presentation of the correct cue was made during the feedback interval. The 2 delay periods served to temporally disassociate selection from the presentation of the visual cues and the saccadic response. *B*: during the selection event, subjects selected the cued position that was most eccentric in the direction indicated by the arrow. In this example, the subject should select the cue at the upper left. All 4 cues were potential targets on all trials. *C*: significant activation in the frontal eye field (FEF) and intraparietal suclus (IPS) was evoked during selection in a representative subject ($P < 0.05$, mapwise corrected). Red line in *A* depicts the model used to estimate the hemodynamic response time-locked to selection. Similarly, the sample, delays (1 and 2), response, and feedback epochs were also modeled.

trial covariates allowing for greater temporal specificity of the individual trial covariates.

We specified FEF and IPS regions of interest (ROIs) by a two-step procedure. First, anatomical masks were drawn to include gray matter in and around the dorsal precentral sulcus at the junction of but not extending along the superior frontal sulcus for the FEF ROI and along the sulcus that separates the superior and inferior parietal lobules for the IPS ROI. Second, we selected voxels within these structural ROIs that showed a significant main effect of the linear combination of all the task covariates. These voxels showed some consistent deviation from baseline during the task without being biased by any task component. Similar to the way electrophysiologists first identify neurons that respond to the task and then subject those neurons to further study, our combination structural-functional criteria identified task related voxels in regions that were the basis of study in this report.

To test hypotheses about lateralized activity, we combined activity from both hemispheres of each ROI in the following way. Contralateral activity was defined as left ROI activity when the selected target fell in the right visual field plus right ROI activity when the selected target fell in the left visual field. Similarly, ipsilateral activity was defined as left ROI/left visual field plus right ROI/right visual field. Although we find the same results when we analyze each hemisphere ROI separately, this procedure allowed us to pool data across hemispheres to increase our statistical power. Because separate delay durations were used and it was necessary to align both the cue and response periods, Fig. 3 required the adjustment of some data points. Specifically, time points 30–31 did not include data from the shortest second delay (12 s) because that time course was simply shifted ahead by 2 s at that point. Similarly, time points 28–29 were cut from the longest second delay (16 s). Together, this allowed the time courses from the three delay durations to be in temporal register for the laterality analyses and plotting of Fig. 3. See Supplementary Materials[1] Fig., B for the full plots of lateralized blood-oxygen-level-dependent (BOLD) responses.

RESULTS AND DISCUSSION

We used a combination of structural-functional criteria to define ROIs in the FEF and IPS, both of which have been shown to play an important role in spatial working memory (Brown et al. 2004; Bruce and Goldberg 1985; Corbetta and Shulman 2002; Courtney et al. 1998; Curtis 2005; Curtis et al. 2004; Gnadt and Andersen 1988; Postle et al. 2000). Essen-

[1] The Supplementary Material for this article (two figures) is available online at http://jn.physiology.org/cgi/content/full/01120.2005/DC1.

tially, we studied voxels that showed some consistent deviation from baseline during the task unbiased by which trial component the deviation corresponded.

We plotted the evoked responses from the FEF and IPS phase-locked to the presentation of the sample cues and saccadic responses in Fig. 2*A*. Figure 2*A* shows summed right and left hemisphere responses on trials in which the selected target fell in the visual field contralateral to the ROI's hemisphere (e.g., right FEF responses when the selected target was in left visual field plus left FEF responses when the selected target was in right visual field). First we considered the cue-locked time courses. Both the FEF and IPS showed strong visually evoked activity that began shortly after the presentation of the four sample cues. Sustained activity in both ROIs was clearly evident at a level above baseline during the first delay. Indeed, parameter estimates modeling delay 1 were significantly greater than zero for both ROIs [FEF: $t(13) = 5.25$, $P < 0.001$; IPS: $t(13) = 8.41$, $P < 0.0001$].

At the time point when subjects were cued to select a response, robust responses were again evoked in both the FEF and IPS [FEF: $t(13) = 5.11$, $P < 0.001$; IPS: $t(13) = 4.41$, $P < 0.001$; Fig. 2*A*]. A statistical map of parameter estimates modeling the evoked response to the selection event from a representative subject is shown in Fig. 1*C* (see Supplementary Materials Fig. A for all other subject statistical parametric maps). These maps confirmed that the FEF and IPS were significantly active when each of the subjects selected a saccadic response from the on-line representation of all potential saccade goals.

Intriguingly, once the response was selected, activity sustained throughout the entire long and variable second retention interval (delay 2) in the FEF but not in the IPS [FEF: $t(13) = 3.75$, $P < 0.01$; IPS: $t(13) = 1.04$, NS]. Activity in the IPS fell below baseline before the memory-guided saccade was made, whereas in the FEF, it remained above baseline throughout the delay until the saccade was generated (Fig. 2*A*). Moreover, the FEF signal sustained despite that the memory load had been reduced by a factor of four and the cued location had been maintained for ≤30 s.

From the time-series data, it appears that selection affected maintenance differently in the FEF and IPS. To quantify and test this possibility, we computed an index of the drop in signal magnitude after selection for each region using the fitted parameter estimates [(delay 1 − delay 2)/(delay 1 + delay 2)]. The magnitude of this index reflects how much the signal fell from the first to second delay period normalized by the responsiveness of the region during the delays. Again focusing on the contralateral data only, the FEF index was significantly smaller than the IPS index, $t(13) = 3.65$, $P < 0.01$, confirming what one intuits from the time-series plot of Fig. 2*A,* that the IPS signal dropped after selection by a disproportionate amount compared with that in the FEF (Fig. 2*B*).

If these signals are indeed related to selection and maintenance, then they should reflect the position of the target and therefore evoke a lateralized BOLD response. Specifically, the BOLD signal should be greater on trials in which the selected target fell in the visual field contralateral to the hemisphere containing the ROI. To test this hypothesis about the spatial selectivity of the BOLD signal, we subtracted the average time courses for ipsilateral from contralateral responses for each subject (Fig. 3). To test for significant differences between the lateralized responses in the FEF versus IPS, we summed over the time points in the trial epochs defined in Fig. 3 (gray boxes). These time points were chosen to capture the peak time-locked BOLD responses (see Fig. 2*A*) to the sample cue (time points 5–7), the selection event (time points 18–20), and the memory-guided saccade (time points 33–35), as well as the two delay periods (delay 1, time points 9–16; delay 2, time points 22–31). As can be seen in Fig. 3, neither the FEF nor IPS showed any spatial bias during the presentation of the four spatial cues or during the first delay period when subjects were maintaining the four cues. During those epochs we did not expect a lateralized response. Because two task-relevant targets were presented in each hemifield and the subject did not yet know which to select, we predicted that the signals should balance. However, as soon as the single target was selected for response, both FEF and IPS activity was greater for contralateral compared with ipsilateral targets. This lateralized response was short-lived in the IPS; it was time-locked to the selection event and possibly during the early part of the second delay period. Lateralized activity in the FEF persisted and even climbed during the second delay. The FEF and IPS showed a similar profile of lateralized activity except during the second delay period when contralateral FEF activity was strongest. Integrating over the second delay period, FEF activity was ~15% higher for contralateral compared with ipsilateral BOLD signal, significantly higher than the 3% differential signal in the IPS [$t(13) = 3.34$, $P < 0.01$].

We derive two important points from these findings. First, both the FEF and IPS show strong activity correlated with response selection independent of visual encoding or motor execution (Gottlieb 2002; Medendorp et al. 2005; Schall and Thompson 1999). Here, we find robust BOLD responses in the FEF and IPS that were time-locked to the selection event and were lateralized according to the position of the selected target. We suggest that these signals reflect the processes involved in selection. In our task, selection likely involves two processes. Once the endogenous cue (i.e., the arrow) appears, one must select the correct cued target among the four stored locations. Then this location must be transformed into a prospective motor plan (i.e., a response must be selected). Although our data do not allow us to disambiguate between these two selection processes, we offer a hypothesis for further study. We hypothesize that the IPS activity we observed time-locked to the selection event reflects visual selection and thereby provides the spatial coordinates of the target (Andersen and Buneo 2002; Goldberg et al. 2002). We further suggest that the FEF activity time-locked to the selection event reflects the processes needed to select among the competing saccade goals (Schall 2002).

Second, because delay-period activity following response selection only persisted in the FEF and not IPS, these areas appear to show a preference for maintaining different forms of information (Ploner et al. 1999). We can propose that a brain region plays a critical role in maintenance only when activity persists throughout the entire delay period. After a prospective motor plan became available (i.e., after response selection), the FEF activity persisted throughout the delay until the memory-guided saccade was executed. Moreover, this persistent activity was greater in the FEF contralateral to the direction of the selected saccade and thus may reflect the maintenance of a saccadic plan. FEF neurons do show an enhanced firing rate

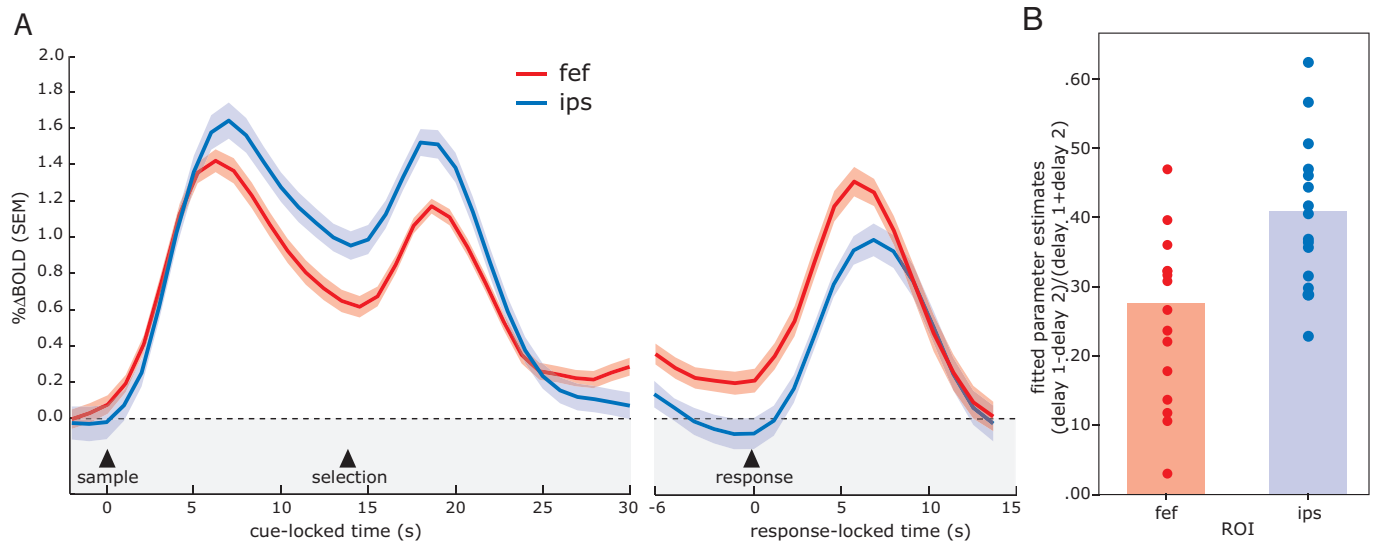

FIG. 2. *A*: group averaged time series (mean ± SE) from the FEF and IPS time-locked to the sample (*left*) and response (*right*). Data plotted are the responses to trials when the selected target fell in the contralateral visual field. Notice how the FEF, but not IPS, signal sustains above baseline even after selection. *B*: change in delay period activity before and after selection. Each dot represents a single subject's index of the change in the magnitude of the fitted parameter estimates from delay 1 to delay 2 for the FEF and IPS, separately. The bars represent the mean drop in delay period activity, which was significantly greater in the IPS than in the FEF ($P < 0.01$).

during the maintenance and preparation of contraversive saccades (Bruce and Goldberg 1985). FEF neurons that code for the metrics of the upcoming saccade may be tonically active as a way to bridge the memory delay. Indeed, microstimulation of monkey FEF neurons at levels below the threshold for evoking saccades during the delay period of an oculomotor delayed-response task biases the direction of the later memory-guided saccade toward the stimulated cell's preferred saccade direction (Opris et al. 2005). Similarly, transcranial magnetic stimulation (TMS) applied to the human frontal cortex during the middle to late phases of oculomotor delayed-response tasks impairs memory-guided saccade accuracy (Brandt et al. 1998; Muri et al. 1996, 2000). However, TMS applied to the human posterior parietal cortex only impairs memory-guided saccade accuracy if it is applied during the first 200–300 ms of the delay, shortly after the visual cue disappears (Brandt et al. 1998; Muri et al. 1996, 2000). Interestingly, TMS may have disrupted response selection processes that operate during this early phase of the delay. These data combined with our observation that the IPS activity does not persist after response selection occurs suggest that the critical role that the IPS plays in spatial working memory involves the maintenance of retrospective spatial cues and the conversion of these cues into a coordinate framework that can be read-out by motor systems for action guidance. Moreover, these data suggest that the FEF contributes to spatial working memory by selecting and maintaining saccade goals. Other evidence from studies of spatial working memory and motor preparation support our conclusion that the posterior parietal cortex and the frontal cortex differ in the degree to which they process visuospatial and visuomotor information, respectively (Connolly et al. 2002; Curtis et al. 2004; D'Esposito et al. 2000; Wise et al. 1997). Finally, we would like to emphasize what Joaquin Fuster has long argued (Fuster 2001): the maintenance of prospective

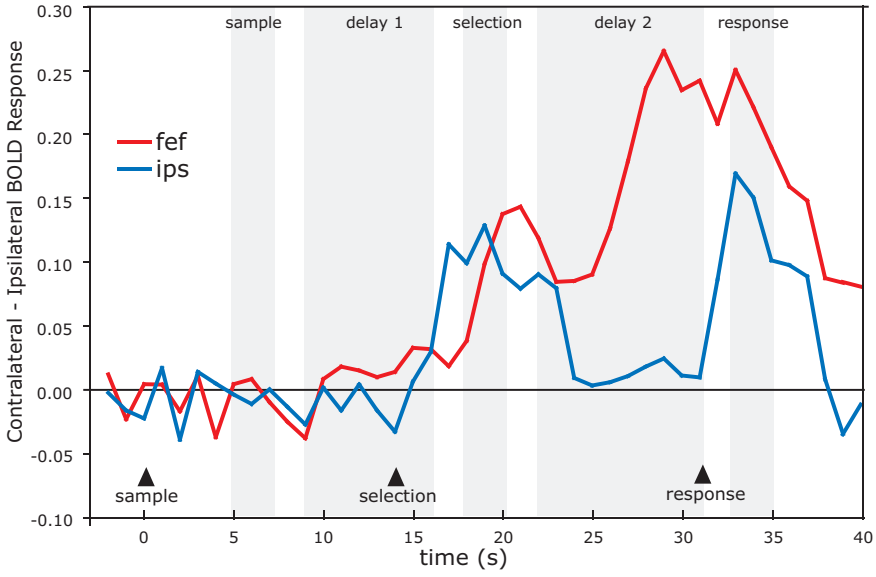

FIG. 3. Spatial selectivity of blood-oxygen-level-dependent signal dynamically evolves after response selection. We first sorted trials based on the direction of the selected target (left/right), and then subtracted the ipsilateral activity from the contralateral activity for each region of interest (ROI; positive values mean greater contralateral than ipsilateral activity; see METHODS). Plotted are the resulting mean differences in time courses across subjects. Notice the absence of lateralized activity until the response was selected (*selection*). Contralateral activity in both IPS and FEF increased just as the response was selected. Then, this difference grew and persisted only in the FEF throughout the 2nd delay period. The only significant difference between the FEF and IPS occurred during the 2nd delay period ($P < 0.01$).

motor plans is no less important of a mechanism for working memory as the more traditional notions of maintenance of past sensory events.

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