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

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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 past sensory event with the future motor act. This resulted in a 4-s buffer between the delay covariates and the other covariates corresponding to the delay durations of 12, 14, and 16 s, respectively.

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 \( a = 0.11, \tau_1 = 7.245 \text{s}, f_1 = 0.04 \text{Hz}, \tau_2 = 7.4 \text{s}, \) and \( f_2 = 0.12 \text{Hz} \) (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...
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 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. Similarly, the sample, delays (1 and 2), response, and feedback epochs were also modeled.

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). Essentially, the sample, delays (1 and 2), response, and feedback 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 Materials1 Fig., B for the full plots of lateralized blood-oxygen-level-dependent (BOLD) responses.

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. 2A. Figure 2A 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. 2A]. A statistical map of parameter estimates modeling the evoked response to the selection event from a representative subject is shown in Fig. 1C (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 saccadic 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: \( t(13) = 1.04, N.S. \)]. 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. 2A). 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 \( \leq 30 \) 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 \( [\text{delay 1} - \text{delay 2}] / (\text{delay 1} + \text{delay 2}) \).

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. 2A, that the IPS signal dropped after selection by a disproportionate amount compared with that in the FEF (Fig. 2B).

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. 2A) 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 \( \sim 15\% \) 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
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...
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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REFERENCES


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