

NeuroImage

www.elsevier.com/locate/ynimg NeuroImage 34 (2007) 1209-1219

Effector-specific fields for motor preparation in the human frontal cortex

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Received 15 November 2005; revised 27 September 2006; accepted 2 October 2006 Available online 28 November 2006

We investigated the neural correlates of advance motor preparation in two experiments that required a movement in response to a peripheral visual stimulus. In one experiment (the memory delay paradigm), subjects knew the target location during a preparatory 'memory delay' interval; in the other experiment they did not know the target location during a 'gap period' (the gap paradigm). In both experiments we further varied the effector that was instructed, either the eye or the forelimb. An area that codes motor preparation should exhibit increases during the memory delay and gap period and such increases should predict some attribute of performance (planning to use the eye or the forelimb). We first identified the frontoparietal visuomotor areas using standard fMRI block designs. Subjects were then scanned using event-related fMRI. With the exception of primary motor cortex (M1), all areas (putative lateral intraparietal area (putLIP), dorsal premotor cortex (PMd), frontal eye field (FEF), ventral frontal eye field (FEFv), supplementary motor area (SMA)) showed gap and memory delay activation for both saccades and pointing. Gap activity in the frontal areas was higher than in the parietal area(s) investigated. The observation that 'memory delay' activity was equivalent or less than gap activity in all areas suggests that what is commonly considered to be memory-related responses largely represents advance motor preparation. Certain areas showed increased activation during the gap or memory delay intervals for pointing (PMd, FEF, FEFv) or saccades (SMA, putLIP). These observations suggest an important role of the frontal cortex in advance motor preparation. © 2006 Elsevier Inc. All rights reserved.

Keywords: Saccade; Reach; Functional magnetic resonance imaging; Preparatory set; Oculomotor control; Event related

Introduction

It is commonly believed that the mechanisms that underlie advance motor preparation and by extension, behavioral flexibility, lie within the cerebral cortex. Our use of the term 'advance motor

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E-mail address: doug@eyeml.queensu.ca (D.P. Munoz). Available online on ScienceDirect (www.sciencedirect.com). preparation' specifies that the timing of the neural activity changes must occur during a delay or warning period just before the motor act and should predict some attribute of performance, such as planning to move the eye or the forelimb (Requin et al., 1991; Riehle and Requin, 1993; Dorris and Munoz, 1998; Snyder et al., 2000).

We used two event-related fMRI paradigms to identify the areas that code advance motor preparation. In the gap paradigm, a period of darkness between disappearance of the central instruction cue which specifies the type of movement to be made (move toward or away from the target with either the eye or the forelimb) and the appearance of the peripheral target provides a warning (Saslow, 1967). We also tested a memory delay paradigm (Hikosaka and Wurtz, 1983), during which the target was flashed before the preparatory period so that subjects knew the target location during the delay period. Comparing these two paradigms allows us to make conclusions not only about an area's relative involvement in advance motor preparation with or without spatial target information, but also allows us to determine whether the commonly observed delay activity is "memory-related", i.e., represents short term encoding of spatial information, or instead represents a form of advance motor preparation (or some combination of the two).

We have shown previously using a saccadic eye movement version of the gap task that activity is present in the frontal eye field (FEF) during the gap period but not in the putative human homologue of the monkey lateral intraparietal area (putLIP) (Connolly et al., 2002, 2005). This observation suggests that frontal areas code advance motor preparation (Hebb, 1972; Evarts et al., 1984). FEF signals further predict both the type of movement (either look toward or away from the target) and the subsequent reaction time (Connolly et al., 2002, 2005; Everling and Munoz, 2000). These results, however, do not tell us whether such preparatory signals further distinguish between the type of effector the subject is planning to use. By identifying the neural substrates of effector-specific motor preparation, we will also be identifying the brain areas that underlie behavioral flexibility and contribute, more generally, to decision making.

The posterior parietal cortex has been most implicated in the visuospatial guidance of movements (Jeannerod et al., 1995; Andersen et al., 1997; Connolly et al., 2002). The relative

^{1053-8119/\$ -} see front matter ${\rm \textcircled{C}}$ 2006 Elsevier Inc. All rights reserved. doi:10.1016/j.neuroimage.2006.10.001

involvement of putLIP in spatial (memory delay) over nonspatial (the gap task) motor preparation is not clear. For example, in memory delay tasks, neurons recorded from monkey LIP typically have stronger activity when monkeys are planning saccades rather than reaches, indicating that a large component of this delay activity may be related to saccade planning (for review, see Snyder et al., 2000). Additional evidence in the monkey indicates that parietal cortex may show effector-specific preparatory activity even in the complete absence of spatial target information (Stoet and Snyder, 2004; Dickinson et al., 2003). The present experiments are designed to address the relative role of human putLIP in these two types of processes.

Importantly, recent work on the effector-specific properties of the parietal lobe should not be used to deemphasize the wellknown role of the frontal cortex in motor preparation (Everling and Munoz, 2000; Passingham, 1993; Mesulam, 1990; Connolly et al., 2002). For example, Pierrot-Deseilligny and others have argued on the basis of studies in neurological patients that the human frontal lobe is more important for intentional saccades whereas the parietal lobe is more important for reflexive saccades (Pierrot-Deseilligny et al., 1995; Heide and Kompf, 1998). It is therefore reasonable to speculate that there may be important differences between the parietal and frontal premotor areas across tasks that probe nonspatial as compared to spatial motor preparation.

The purpose of this paper is twofold: (1) to determine whether any preparatory responses in the frontoparietal regions predict behavior (eye versus forelimb); and (2) to determine whether there are differences in gap (nonspatial preparation) versus memory delay (spatial preparation) paradigms within the frontoparietal regions. To accomplish this, we studied human subjects using a combination of block design and event-related fMRI. Using the block design, we first identified visuomotor areas that appeared to be dedicated to the eye (the ventral frontal eye field or FEFv), the forelimb (the PMd, the M1), or both (the FEF, the putLIP, the SMA). Using an event-related design, we inserted "gap" periods of 0, 2, or 4 s prior to target appearance. Because no target is on the screen during the gap, and the subject has not yet moved, activation can be argued to represent advance motor preparation (Connolly et al., 2002). We also tested subjects with the memory delay task, in which the target was flashed prior to a variable memory delay interval (0, 2, or 4 s). Using these paradigms in combination allowed us to compare an area's relative involvement in preparing the eye or the forelimb and also in nonspatial and spatial advance motor preparation.

Methods

Subjects, stimulus and tasks

The experiments were approved by The University of Western Ontario Review Board for Health Sciences Research Involving Human Subjects. Eight subjects (6 male, 2 female) provided informed consent and participated in this study. Two subjects, JDC and JSC, were coauthors. Each subject performed two training sessions until they performed the tasks without error (one day before testing and just prior to entering the scanner).

Visual stimuli were generated using Director software (Macromedia, San Francisco, CA) and presented using a computer connected to a video projector (NEC, Japan). The image was projected off a mirror onto a screen secured to the ceiling of the magnet bore. The peripheral and central fixation cues subtended 0.25° of visual angle. Subjects performed a gap paradigm and a memory delay paradigm. Each event-related trial began with 3 s of fixation of a white central cue. This was followed by 3 s of fixation of either the blue (saccade trial) or red (pointing trial) instructional cue (Fig. 1). In the gap paradigm (Fig. 1A), the instructional cue was then extinguished and a 0-, 2- or 4-s gap period of darkness occurred. Subjects were instructed to keep their gaze and hand at the remembered location of the central instructional cue. A white peripheral cue was then flashed along the horizontal meridian (9, 11, 13 or 15° eccentricity) to the right or left of center for 100 ms. Subjects were instructed to look to this location on a saccade trial (blue fixation cue) or point to this position while maintaining central gaze on a pointing trial (red fixation cue) and then to hold their gaze or forelimb position at this location until a white central fixation cross appeared following an additional 2-s interval. During pointing trials, subjects pointed to the target by rotating the index finger about the wrist while maintaining central fixation and fixed arm posture, a paradigm that reliably recruits frontoparietal forelimb movementrelated areas (Connolly et al., 2000; DeSouza et al., 2000; Medendorp et al., 2003).

The memory delay experiment (Fig. 1B) followed the same time course as the gap experiment, except that the target was presented for 100 ms *prior* to the 0-, 2- or 4-s memory delay interval and the central fixation cue *remained visible* as a white spot. The fixation cue was then extinguished instructing the subject to move either their eyes (saccade) or forelimb (point) toward the remembered location of the target.

Subjects returned gaze or index finger position to center immediately following reappearance of the central cross. The cross remained on screen for 12 s and this constituted the intertrial interval, which provided time for the BOLD-fMRI signal to return to baseline following each trial. Each experimental block was 528 s in duration, consisting of 12 saccade and 12 pointing trials. Trial types (saccade versus point) were pseudo-randomly interleaved and the amplitudes and gap/delay durations were balanced for right- and leftward movements. Each subject completed 3 runs of the gap experiment and 3 runs of the memory delay experiment.

Each imaging session began with the saccade and pointing localizer tasks, which consisted of alternating time blocks (30 s) of saccades (or pointing movements) and central fixation. Peripheral targets appeared at a frequency of 2 Hz and stepped to the right or left randomly between 4° and 15°, but never more than 15° from center. During the fixation blocks, subjects fixated on a central cross and no peripheral targets were flashed. The localizer experiment was 360 s in duration, consisting of 6 blocks of saccades or pointing movements and 6 blocks of central fixation only. One run of the localizer experiment for each of the saccade and pointing tasks was collected and the images were analyzed in the control room using the Stimulate software package (Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, MN), in order to select a functional volume that included the frontal premotor areas (PMd, FEF, SMA), M1 and an oculomotor region in the intraparietal sulcus of the parietal lobe (putative Lateral Intraparietal Area or putLIP). Including the 2 separate localizer scans and the 6 experimental scans of the gap and memory delay runs, there were a total of 8 functional runs per session per subject.

Imaging and data analysis

Experiments were carried out using a 4.0 T Varian Siemens (Palo Alto, CA; Siemens, Erlangen, Germany) UNITY INOVA



Saccades -Fixation

Saccades + Pointing

Fig. 1. (A) Gap paradigm for the event-related design. Subjects viewed a white fixation point (FP) presented at the centre of the screen for 3 s. The FP turned either blue (saccade trial) or red (point trial) and remained on screen for 3 s. A target (T) was then flashed for 100 ms along the horizontal meridian. The target was flashed 0, 2, or 4 s following offset of the instructional cue. Two seconds following appearance of the target, a central fixation cross appeared and the subject returned gaze (or hand position) to center and maintained central fixation for 12 s. (B) Memory delay paradigm for the event-related design. This paradigm was identical to the gap paradigm, with the exception that the cue was flashed for 100 ms *prior to* a 0, 2, or 4 s memory delay period. The subject then moved to its remembered location following offset of the white fixation cue, 0, 2 or 4 s after target cue appearance. (C) Saccade localizer map used to identify the frontal eye fields (FEF), the supplementary motor area (SMA) and the lateral intraparietal area (LIP). (D) A group average map of all 8 subjects on an inflated left hemisphere brain (contralateral to the instructed hand). The dark patches represent sulci, and the light patches gyri. This map shows a lateral view of the frontal cortex, anterior (right), posterior (left), superior (top) and inferior (bottom). Selective pointing activation is shown in orange, saccades in purple and both types of movements in red. The more medial and superior area was only active during pointing trials (orange activation) and is located at the commonly accepted location of the dorsal premotor area (PMd). Lateral and ventral to this is cortex activated by both types of movements (red), and is at the accepted location of the frontal eye field (FEF). Lateral and ventral to this was cortex activated only by saccades (FEFv) (purple activation). Also shown is the primary motor cortex, situated posterior to the PMd along the central sulcus. (E) An axial slice in a single subject that shows are

whole body imaging system equipped with whole body shielded gradients. Parietal and frontal cortices were imaged using a full head coil. As described above, 15 functional slices were collected for our saccade or pointing localizer tasks to first determine the location of the frontal and parietal motor areas, PMd, FEF, FEFv, SMA, M1 and putLIP that would be activated during either eye or forelimb movements, or both. These data were collected using BOLD (blood oxygenation level-dependent) signal changes related to brain activation (Ogawa et al., 1992) (navigator echo corrected T2*-weighted segmented gradient echoplanar imaging, 64×64 resolution, 19.2 cm in-plane FOV, TE=15 ms, TR=1 s, FA=40° with $3 \times 3 \times 5$ mm voxel size). Once the visuomotor areas were identified in the control room, an axial slice volume was selected centered on the FEF, FEFv, PMd, M1, SMA, and putLIP but including the entire parietal lobe (528 volumes, 10 slices, 64×64

resolution, 19.2 cm in-plane FOV, TE=15 ms, TR=1 s, FA=30° with $3 \times 3 \times 5$ mm voxel size). Functional images were superimposed on anatomical images that were obtained using a T1weighted (3D magnetization-prepared turbo FLASH acquisition, 64 slices, TI=600 ms, TE=5.5 ms, TR=10 ms, FA=11°) image set acquired in the same scan session with the same slice orientation and in-plane field of view.

Analyses were conducted using the Brain Voyager 4.9 and Brain Voyager QX software packages (Brain Innovation, Maastricht, The Netherlands). After co-registering successive fMRI images to reduce motion artifacts, we corrected for linear drift. All data sets were transformed to Talairach space. Activated voxels were identified using a smoothed *t*-test shifted for the hemodynamic delay and corrected for multiple comparisons (Forman et al., 1995) (t>v4.00, cluster of 10 mm³ or > of activation). This *t*-test

was a comparison of saccade (or pointing) with fixation blocks based on our saccade or pointing localizer data sets. These maps were then superimposed and color coded according to whether or not the active voxels overlapped or not for the two types of movements, i.e., those that were activated by both the saccade and pointing tasks (red voxels), and those that were selectively activated by one task or the other (orange for pointing, blue for saccades) (Fig. 1D). The time courses were derived from the single-subject saccade localizer activation maps, rather than the group average map, since a group map would create a 'blurring' of the effects by having inactive regions of cortex in each subject contribute to a time course. These individual subject activation maps were then superimposed onto the gap and memory delay saccade or pointing data sets for each subject, in order to define the premotor areas and putLIP independent of the event-related experiment. It is important to point out that we did not quantify differences between the saccade and pointing activation maps and thus these maps were used as an ROI guide for the event-related analyses. The event-related time courses for each subject corresponding to FEF, PMd, FEFv, SMA, M1 and putLIP were then extracted. Event-related averaged files were generated using the Brain Voyager software package with each line representing an average of all trials of a particular trial type in each subject, as described previously (Connolly et al., 2002, 2005). These time courses were then averaged across subjects (see Fig. 2). For each condition, we collapsed the data across saccade or pointing direction and the signal time courses were then shifted by 3 s to account for the estimated hemodynamic lag (Schacter et al., 1997; Kollias et al., 2000). The event-related files were baselined during the last 4 s of the intertrial interval.



Fig. 2. Event-related time courses for the gap (left panels) and memory delay (right panels) tasks (solid lines: 4 sec gap or memory delay trials; dashed lines: 2 sec gap or memory delay trials; dotted lines: 0 sec gap or memory delay trials; red lines: pointing; blue lines: saccades). The BOLD fMRI signals are aligned on target appearance for both the PMd (A, B), the FEF (C, D), the FEFv (E, F), the SMA (G, H), the M1 (I, J) and the LIP (K, L). Each time bin represents a 1 s interval (functional TR = 1000 ms). FP: fixation point; T: target.

The saccade or pointing localizer tasks were used to independently identify FEF, FEFv, PMd, SMA, M1 and putLIP in each subject so that the full spectrum of all possible waveform types would be included in the event-related analysis. In other words, a multiple regression analysis was not used because we would only identify voxels with a particular waveform shape. It is noted that our approach was just one possible way to not limit the analysis to a particular waveform shape, for example multiple regression with Fourier sets could also have been employed.

Results

Saccade and pointing "localizer" activation maps

We first employed a block design comparing: (1) saccades and fixation and (2) pointing and fixation, to identify the key frontoparietal areas involved in these two types of movements (Figs. 1C, D). We observed significant activation (p < 0.05corrected) in the frontal eye fields (FEF), the ventral frontal eye fields (FEFv), the supplementary motor area (SMA), the dorsal premotor area (PMd), the primary motor cortex (M1), and an eyemovement-related area in the intraparietal sulcus (putLIP). We then superimposed the saccade and pointing activation maps to determine which areas were activated by (1) both types of movements and (2) those which were activated selectively by one or the other. The FEF, the SMA, and the putLIP were activated equally by both types of movement in the block design. Fig. 1C shows the three areas activated in a single subject during the saccade task. Similar to previous studies, the activation maps for saccades and pointing overlapped almost completely in these areas (Connolly et al., 2000; Medendorp et al., 2003).

Fig. 1D shows the frontal cortex of an averaged left hemisphere (contralateral to the moving forelimb) map for all 8 subjects. The PMd and the M1 were selectively activated by pointing, whereas the FEFv was activated only by saccades. The FEF proper was activated by both pointing and saccades. We included voxels in the PMd locus if they were situated dorsal and medial to the FEF proper (those voxels that overlapped for both types of movements) and were selectively activated by pointing. Voxels situated lateral and ventral to the FEF proper were included if they were selectively activated by saccades. We therefore labeled this region the ventral frontal eye field (FEFv). M1 was situated posterior to the PMd activation along the anterior bank of the central sulcus. In contrast to the group average map (Fig. 1D), M1 represented a separate peak in the single subject maps, with inactive voxels separating PMd and M1 (Fig. 1E).

The mean Talairach coordinates for the different areas activated by: (1) the saccade and pointing tasks; (2) the pointing task only; and (3) the saccade task only, are presented in Table 1. Mean Talairach coordinates for FEF, SMA, and putLIP are consistent with previous studies (Connolly et al., 2000, 2002; Paus, 1996; Toni et al., 1999; Shulman et al., 2002; Sereno et al., 2001).

PMd and M1 were selectively activated by pointing, as determined by superimposing the saccade and pointing activation maps. Area PMd "pointing-only" activation continued medial and dorsal to the FEF, i.e., continued posterior and medial to the superior frontal sulcus (Fig. 1D). The Talairach coordinates for the location of PMd and M1 are consistent with previous studies (Roland et al., 1980; Stephan et al., 1995; Rijntjes et al., 1999; Ehrsson et al., 2000; Ehrsson et al., 2003; for review, see Picard and Strick, 2001).

Table 1

Talairach coo	ordinates for	areas	activated	in	the	block	design	experiment	s

Activated areas	Coordinates								
	Left: X	Y	Ζ	Right: X	Y	Ζ			
Saccade+Pointing									
Putative lateral intraparietal area (putLIP)	-21	-61	41	20	-56	41			
Frontal eye field (FEF)	-28	-7	55	37	-10	55			
Supplementary motor area (SMA)				4	-7	55			
Pointing only									
Dorsal premotor area (PMd)	-27	-14	61	21	-14	61			
Primary motor area (M1)	-34	-25	43						
Saccade only									
Ventral frontal eye field (FEFv)	-48	$^{-4}$	38	28	-8	39			

Activation extended ventral to the FEF proper (FEFv), and this region was selectively activated by saccades. Importantly a dorsomedial to ventral-lateral gradient of forelimb-related activity to saccade-related activity has been reported in the monkey frontal cortex (Roesch and Olson, 2003; Fujii et al., 1998, 2000) (Fig. 1D). Our block design results indicate that a highly parallel organization exists in the human, with the more ventral-lateral activation-FEFv-dedicated to saccades.

Event-related gap experiment

We tracked the event-related time courses of activity in the voxels we identified in PMd, FEF, FEFv, SMA, M1, and putLIP in the separate gap and memory delay tasks (Fig. 2). We first describe the results from the gap task (Figs. 2A, C, E, G, I, K). For all regions studied, the peak in the BOLD response obtained for each of the gap durations occurred at approximately the same time following target appearance and the recovery of the response to baseline followed a similar time course. We ascribe this peak response to the combined visual and motor activation of neurons in these regions that followed target appearance and movement execution (Everling and Munoz, 2000; Gottlieb and Goldberg, 1999; Schlag-Rey et al., 1997; Zhang and Barash, 2000).

Second, in PMd, FEF, FEFv, SMA, putLIP but not M1, there was an early pretarget activation that occurred during the gap period in advance of target response and the peak response. The onset of this early, pretarget response in the SMA was so early, it in fact preceded the disappearance of the FP. The pretarget rise in activation for 4-s gap trials preceded the rise in activation for 2-s and 0-s gap trials. The magnitude of this pretarget response, measured as the BOLD response for the timepoint immediately prior to the onset of the rise in activity for the motor burst in M1 (and integrated back 6 s or 6 functional volumes in time), is plotted against gap duration for PMd, FEF, FEFv, SMA, putLIP and M1 in the saccade and pointing conditions (Figs. 3A-F). It is therefore the case that the same quantitative approach was used for both the gap and memory delay tasks in calculating the pretarget response. An analysis of variance with gap duration (0, 2, 4 s) and trial type (saccade versus pointing) as factors revealed a significant influence of gap duration on the level of pretarget BOLD activity in PMd (F(2,14)=4.328, p<0.05), FEF (F(2,14)=14.321, p<0.001), FEFv (F(2,14)=7.481, p<0.01), and putLIP (F(2,14) = 8.849, p < 0.01), but not in SMA (F(2,14) = 2.712,



Fig. 3. Quantification of BOLD responses as a function of gap duration (A–F) and memory delay duration (G–L) (blue lines: saccades; red lines: pointing). The pre-movement responses increased with gap duration and memory delay duration, respectively, in the FEF, the PMd, the FEFv, the SMA and the LIP. The percent change was calculated as the BOLD signal (arbitrary units) taken as a percentage relative to the mean of the baseline interval.

p=0.10) or M1 (F(2,14)=1.023, n.s.). Clearly, activation during the gap period was a highly distributed phenomenon throughout the various frontoparietal visuomotor areas. Moreover, there was activation during and prior to the gap in the SMA (Fig. 2G). The reason that the SMA pretarget activation did not reach significance for this measure can be attributed to the fact that the activity increases began very early for all gap durations, well in advance of the other cortical regions, thereby minimizing the difference in positive slope around the time of the gap intervals (Fig. 2).

We did not measure eye or hand movements in the scanner. It is therefore the case that the only area without gap activation. area M1, provides an important control in the present experiment. It cannot be argued that subjects made non-instructed hand movements during the gap intervals because if this were the case, activation would have also been observed in M1 (Figs. 2 and 3). Second, because there was no activation of M1 around the time of the saccade, this simple observation rules out the argument that subjects may have made non-instructed pointing movements during saccade trials. Likewise for FEF, if subjects made noninstructed eye movements during the gap intervals, we would have observed much higher preparatory responses, perhaps even rivaling the motor burst activity around the time of the instructed saccade, i.e., ~1.0% signal changes. It is therefore very unlikely that subjects generated non-instructed saccades during the gap (see Connolly et al., 2002, 2005).

There was also a significant difference in the level of the pretarget BOLD response between saccade and pointing trials in PMd (interaction term: F(2,14)=3.786, p<0.05), FEFv (interaction term: F(2,14)=6.484, p=0.01), SMA (interaction term: F(2,14)=11.156, p=0.001), and putLIP (interaction term: F(2,14)=7.922, p=0.005). Post hoc tests revealed that the pretarget BOLD responses were higher for pointing than saccade trials during the gap in PMd (saccade versus point 0-s gap, t(7)=2.652, p<0.05), and FEFv (saccade versus point 4 s gap t(7)=4.894, p=0.002). In contrast, SMA and putLIP exhibited higher pretarget responses on saccade trials (SMA saccade versus point 2 s gap t(7)=2.618, p<0.05) (putLIP saccade versus point 2 s gap, t(7)=4.659, p<0.005). There was therefore evidence for effector specificity in the different motor fields during the preparatory gap intervals, with higher gap activity in some regions for pointing (PMd and FEFv) and in others for saccades (SMA and putLIP).

The peak of the BOLD response increased with increasing gap duration in PMd, FEF, FEFv and putLIP but not in SMA or M1 (Figs. 4A-F). We measured the magnitude of the peak in the BOLD response, which consistently occurred 2-3 s after target appearance. An analysis of variance with gap duration and trial type as factors revealed a significant effect of gap duration on the peak of the BOLD response in PMd (F(2,14)=3.360, p=0.05), FEF (F(2,14)=12.75, p=0.001), FEFv (F(2,14)=19.279, p < 0.001), and putLIP (F(2,14)=13.957, p < 0.001), but not in SMA (F(2,14)=1.321, n.s.) or M1 (F(2,14)=2.28, n.s.) (Fig. 2). This latter observation confirms the argument that M1 did not exhibit activation during the gap intervals. Moreover, the peak response was significantly higher for pointing as compared to saccade trials in M1 (F(1,7)=13.91, p<0.01) (Fig. 4F), emphasizing the exclusive role of this area in controlling forelimb but not eye movements. There was no significant effect of the type of effector on the peak responses in any of the other areas. There were no significant interactions between gap duration and trial type for the peak response in any of the areas. The finding of an enhanced peak with a preceding gap period in PMd, FEF, FEFv and putLIP is important because the relationship between fMRI-BOLD responses that partially overlap in time has been shown to be an additive one (Pollman et al., 2000). In other words, the increase in peak response in these areas with increasing gap duration was presumably the result of a superposition of an increasing pretarget response with a constant post-target response (Connolly et al., 2002). Indeed, the peak response increased from the 0-s to the 2-s to the 4-s gap trials (Fig. 4).

In our previous work, we were able to show that during the gap period in the gap paradigm, putLIP was relatively inactive, yet during the memory delay epoch it was highly active (Connolly



Fig. 4. The peak post-target responses increased with gap duration (A-F) and memory delay duration (G-L) in the FEF, FEFv, and putLIP, but not in the SMA, PMd or M1.

et al., 2002). From these results, we concluded that the putLIP does not participate in the generation of preparatory set. Surprisingly, in the present experiment there was evidence that putLIP was mildly active (as compared to frontal regions) during the gap task, when the subjects were now instructed to use one of two possible effectors. It is important to point out that the gap activity level in the putLIP was still much less than that observed in the frontal premotor regions (Fig. 5). Indeed, a direct comparison of the level of gap activity in the FEF versus putLIP (added total across the 2and 4-s gaps) was significant, with the FEF showing a significantly higher level of activity, t(7)=2.65, p<0.05. It is thus likely that the putLIP plays a more minor role in coding preparatory set, as concluded in our previous work, yet does become active during tasks which allow the subjects to choose between effectors.

Event-related memory delay experiment

The memory delay experiment was used to confirm the effector differences observed in the gap paradigm, and provide additional evidence as to whether or not there were differences across the different regions when target location had (memory delay period) or had not (gap period) been specified. In PMd, FEF, FEFv, putLIP, SMA but not M1, there was memory delay activation that occurred in advance of the peak response (Figs. 2B, D, F, H, J, L). The delay period activity rose to higher levels for the 4-s delay trials, compared to the 2-s and 0-s delay trials (Figs. 3G-L). An analysis of variance with memory delay duration (0, 2, 4 s) and trial type (saccade versus pointing) as factors revealed a significant influence of memory delay duration on the level of pre-movement BOLD signals in the FEF (F(2,14)=13.675, p=0.001), FEFv (F(2,14)=12.129, p=12.129)0.001) and putLIP (F(2,14)=9.305, p<0.005). [The pre-movement activity was calculated as the cumulative integral value of 25% of the peak response back in time 6 s (or 6 functional volumes).] There was weaker evidence for an effect in PMd, Interaction term (F(2,14)=9.077, p<0.01, t-test of 0- versus 4-s



Fig. 5. Qualitative comparison of the cumulative percent signal change across the 2 and 4 s gap (solid line) or memory delay periods (dashed line) for all regions. Putative LIP most closely resembles the preparatory activity levels of area M1 (which had little or no preparatory activity), whereas the frontal regions all position to the right of the figure, with high levels of advance preparatory activity. Surprisingly, the memory delay activity appeared slightly less or equivocal to the gap activation in all regions.

memory delay t(7)=2.080, p=0.07). There was no effect of memory delay duration in SMA (F(2,14)=0.838, n.s.) or M1 (F(2,12)=1.023, n.s.) (Fig. 3). The memory delay activation was a distributed phenomenon throughout the visuomotor areas. All areas that showed gap activation also showed memory delay activation. Also similar to the gap task, there was considerable activation during and prior to the memory delay interval in the SMA (Figs. 2H, 3J). Again, the reason that the SMA memory delay activation did not reach significance was owing to the fact that the activation rose exceptionally early for all intervals in this area, well in advance of the other cortical regions, and the relative slope increases were thus relatively shallow across the different memory delay intervals (Fig. 2). This observation provides additional support to the argument that the activation increases were related to advance preparation rather than encoding of the visual stimulus, since in the SMA the activity increases began prior to target appearance. Second, the gap activation levels across all the areas were similar to or higher than the memory delay changes (Fig. 5). If the activity changes were related partially to stimulus encoding we would have seen higher memory delay activity (which we did not). Area M1 did not exhibit any memory activation at all and was only active during pointing movements around the time of the actual movement (Fig. 2J).

There was a significant difference in the memory delay premovement BOLD responses between saccade and pointing tasks in PMd (F(1,7)=F(1,7)=8.388, p<0.05) and FEF (F(1,7)=F(1,7)=12.181, p=0.01), with higher preparatory activity for pointing trials. Since the interaction term was significant in PMd, a post hoc t-test revealed that there was higher delay activation during pointing trials for the 2-s memory delay (t(7)=6.762), p < 0.001). Consequently, there was evidence that both FEF and PMd exhibited higher activity when subjects were preparing to make a future pointing movement. Lastly, although there was no memory delay response in M1, there was some evidence for higher baseline activity for pointing as compared to saccade trials (main effect of effector F(1,6)=10.790, p<0.05; interaction term F(2,12)=4.121, p<0.05; post hoc t-tests pointing higher than saccades 0-s and 2-s memory delay t(6)=2.426, p=0.05and t(6) = 5.893, p = 0.001, respectively).

The peak of the BOLD response increased with increasing memory delay duration in FEF, FEFv, and putLIP but not in PMd, SMA, or M1 (Figs. 4G–L). An analysis of variance with delay duration and trial type as factors revealed a significant effect of memory delay duration in FEF (F(2,14)=4.762, p<0.05), FEFv (F(2,14)=6.748, p<0.01), and putLIP (F(2,14)=7.038, p<0.01), but not in PMd (F(2,14)=0.888, n.s.), SMA (F(2,14)=0.054, n.s.) or M1 (F(2,12)=1.604, n.s.). This observation again confirms the argument that M1 did not exhibit activation during the memory delay intervals.

There was a significant effect of the type of planned effector on the peak responses in FEF (F(1,7)=5.272, p=0.05) and PMd (F(1,7)=9.07, p<0.05), with higher peak responses for pointing trials. This finding likely reflects a carry-over of hemodynamic differences observed during the memory delay intervals in these areas, i.e., higher activity during pointing as compared to saccade trials during the memory delay interval. There were no significant interactions between memory delay duration and trial type in any of the areas.

Finally a comparison of the gap and memory delay premovement activity levels (Fig. 5) revealed that memory delay activity was slightly (non-significantly) decreased or equivalent in all areas (FEF, PMd, FEFv, SMA, putLIP). This was a surprising finding, and suggests that during the memory delay period, some of the observed fMRI-BOLD activity changes may represent advance motor preparation, rather than simply representing the encoding of the stimulus location over time.

Discussion

We have provided evidence showing effector-specific activation of regions of human frontoparietal cortex in different motor preparation tasks. Using a block design, PMd and M1 were activated only by pointing movements whereas the FEFv was activated only by saccades. The FEF, SMA and putLIP were activated by both movement types. Using an event-related design, we observed that gap and memory delay activation was highly distributed throughout frontoparietal cortex. The frontal areas appeared more involved in advance preparation than the parietal area.

Frontal effector-specific advance motor preparation

Nonspatial advance preparation signals were higher in the frontal than in the parietal cortex, a finding that is consistent with monkey neurophysiological experiments that support involvement of the frontal cortex in motor preparation (Everling and Munoz, 2000; Passingham, 1993; Mesulam, 1990; Picard and Strick, 2001). Furthermore, these findings are in line with our previous work showing that preparatory activity profiles in the FEF predict both the latency of an upcoming saccade (Connolly et al., 2005), and whether or not the subject plans to look toward or away from the target (Connolly et al., 2002). Thus, frontal signals predict the effector, the type of eye movement (look toward or away) and subsequent reaction time.

An important finding in the present study was that the SMA showed higher gap activity for saccade trials, confirming that there are separate fields in frontal cortex for preparing movements for either the forelimb (PMd) or the eye (SMA). Because our activation foci overlapped for pointing and saccades, it was not possible to partition the supplementary eye fields (SEF) and the SMA. Nevertheless, it is assumed that at least a portion of the activated region included the SEF. The SEF is well known to be involved in the initiation of saccades based on lesion, TMS, and functional imaging studies (for review, see Pierrot-Deseilligny et al., 2002). A second finding was that SMA gap activity began earlier than in the other eye movement areas (FEF and putLIP). We found the same pattern in a previous report (Connolly et al., 2005). Note that a recent monkey study reported anticipatory activity in monkey SEF that also preceded activity in the FEF and LIP (Coe et al., 2002).

An unexpected finding was that FEF preparatory activity was higher for pointing. We have previously shown that the FEF preparatory responses are higher for anti (look away)- as compared to pro (look toward)-saccade trials (Connolly et al., 2002). Correct performance of the anti-saccade task requires the successful suppression of a reflexive pro-saccade to the peripheral target stimulus (Munoz and Everling, 2004). Neurophysiology experiments in awake monkeys have demonstrated that the FEF saccade neurons are inhibited during anti-saccade trials (Everling and Munoz, 2000). During our present pointing task, subjects were required to inhibit a saccade toward the target of the pointing movement. This task is therefore similar in

this regard to the anti-saccade task. The enhanced activity in the FEF on pointing trials may have been the result of a suppression signal required to inhibit the reflexive glance toward the stimulus.

In addition to effector selection and the decision/trigger (reaction time) to move, nonspatial signals may represent stimulus-response mapping, in which a nonspatial visual instruction stimulus is mapped onto a particular response (Wise et al., 1997). Stimulus-response mapping has been shown to be a principal task computed by PMd neurons. The activity in these neurons reflects, in part, the motor significance of nonspatial visual stimuli. In our study, the colored fixation cue which signals to either point or make a saccade represents a nonspatial cue. These data provide support then for the hypothesis that frontal cortex plays a key role in the selection of action that is based on arbitrary, nonspatial cues (Passingham, 1993). Yet another possibility is that a component of the FEF, the PMd, and the SMA preparatory activity is motor-related. In the present experiments we used a limited number of targets. Singleunit work in monkeys has shown that when multiple movements are possible, each movement type is simultaneously coded in PMd activity (Cisek and Kalaska, 2002). It is thus possible that the preparatory activity in FEF, PMd and SMA reflects the directions of multiple potential future movements, corresponding to the limited possible locations of the visual target.

In addition, it should be pointed out that the activity levels would be the same across the memory delay and the gap intervals if what we are measuring in both cases is largely a pretarget form of preparatory set, such as stimulus response mapping (Wise et al., 1997) or activity increases summed across multiple potential target vector representations, such as those reported by Wise et al. (1997) and also by Cisek and Kalaska (2002) (see also the work of Passingham et al.). Cortex that subserves such a 'nonstandard sensorimotor' mapping would be equally active during either a gap or a memory delay preparatory phase, since in both cases an arbitrary instruction cue is used to prepare a specific effector system. These results therefore provide new evidence to support the argument that a substantial component of the BOLD preparatory signal represents nonstandard mapping.

It is important to note that the argument could be made that the 'preparatory signals' we are reporting are instead visual responses. Although visual responses may contribute to the preparatory response, we (Connolly et al., 2002) and others have seen greater activation in FEF on anti compared to pro trials and so this early activation is paradigm specific, even though the red and green FPs were matched for luminance. Therefore, the early activation may contain some of the FP disappearance response, it is also composed of preparatory activity. Second, and most importantly, in an earlier set of experiments we (Connolly et al., 2002, Fig. 7) had a control 'fixation' task in which subjects did not make any saccades following varying gap intervals, i.e., they fixated following fixation offset. We reported stable BOLD traces throughout. This helps to rule out the argument that the signal changes were visual in nature.

Parietal effector-specific advance motor preparation

Although more equivocal, there is also work emphasizing the role of the parietal lobe in preparatory set and effector selection, with separate areas dedicated to either the eye (LIP) or the forelimb (the

parietal reach region, or the PRR) (Mountcastle et al., 1975; Andersen and Buneo, 2002; Calton et al., 2002; Connolly et al., 2003). To our knowledge, this is the first work in the human to show consistency with the monkey unit work of Andersen, Snyder and colleagues which showed parietal area LIP shows preparatory specificity for eve over forelimb movements. Recent evidence in the monkey, for example, indicates that parietal cortex may show preparatory activity even in the complete absence of spatial target information (Stoet and Snyder, 2004; Dickinson et al., 2003). However, in our previous work on saccades we did not find evidence for nonspatial preparatory activity in parietal putLIP (Connolly et al., 2002, 2005). This new finding likely reflects the fact that, in the present study, we now had randomly interleaved trials in which one of two possible effectors was instructed. In other words, the reason that we did not see such signals in previous work may have been because we limited our design exclusively to saccades. However, despite this area's activity, frontal areas were once again more active than parietal areas during preparatory periods (see Fig. 5).

Because the frontal preparatory signals are more robust relative to those in the parietal lobe, it is reasonable to conclude that the effector-specific signals in the parietal lobe (for review see Andersen and Buneo, 2002; Snyder et al., 2000; Calton et al., 2002) may be the result of feedback from frontal motor planning areas (Tanne et al., 1995; Shipp et al., 1998). Frontal areas (e.g., PMd, FEF, SMA) are richly interconnected with high-level parietal areas that show effector specificity (e.g., putLIP: eye; PRR: forelimb; Tanne et al., 1995; Shipp et al., 1998). Based on these findings, it can be argued that the frontal cortex may be the main player in terms of both effector selection and more broadly, in the generation of preparatory sets (intention and response readiness). Because the frontal cortex is so heavily interconnected to the actual motor output (i.e., M1—forelimb; FEF—eye), this conclusion makes considerable intuitive sense.

Localizer tasks

We reported event-related activation in the PMd for saccades and in the FEFv for pointing, even though both areas were not active in the saccade (PMd) or pointing (FEFv) localizer tasks. This finding emphasizes the importance of testing both event-related and block designs in combination. Activation in PMd for event-related saccades is at least partly the result of pseudo-randomly interleaving saccade or pointing trials in the event-related experiments, since in the localizer experiments each movement was tested only in isolation. A second reason is the "iceberg" issue inherent to fMRI statistical design. In activation maps there is a point spread function, with a single peak of activity and adjacent cortex gradually becoming less active proceeding away from the peak. The statistical threshold that was set for these maps was somewhat arbitrary. In other words, adjacent areas would fall just under the threshold, but were still in actuality only slightly less active. This means PMd fell just under the threshold for the saccade localizer task, but since it was adjacent to "saccade" FEFv, exhibited substantial saccade-related activity. Nevertheless, there was a pointing to saccade gradient as one proceeds medial to lateral, and this is identical to what has been reported in the monkey (Roesch and Olson, 2003; Fujii et al., 1998, 2000).

Conclusion

The purpose of the present study was to examine whether frontal and parietal areas are involved in nonspatial (the gap task) and spatial (memory delay task) advance motor preparation. We further manipulated the planned effector, to determine whether any preparatory signals predict behavior. We used human fMRI to sample *both* the frontal and parietal cortices simultaneously. Consistent with our previous work, the frontal areas exhibited greater preparatory activity as compared to the parietal area putLIP. However, all areas showed gap and memory delay activity. Memory delay activity was slightly reduced relative to gap activity and based on the idea of pure insertion it follows that "memory" activation is in fact motor preparation rather than encoding of the stimulus cue. Moreover, effector-specific preparatory responses were recorded across all of the different fields. These findings are highly consistent with the classic notion of the frontal cortex subserving motor planning functions (Mesulam, 1990).

Acknowledgments

This research was supported by the Canadian Institutes of Health Research (CIHR) and the Canada Research Chairs Program. We thank J. Gati for assistance with the fMRI scanning. The Robarts Research Institute provided fMRI services. Author JDC is now at New York University, New York, NY, USA 10003; email: jason.connolly@nyu.edu.

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