Spatial and effector processing in the human parietofrontal network for reaches and saccades

Running head: Parietofrontal activation for reaches and saccades

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# figures: 6
# tables: 3
# pages: 40

18 February 2009

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Abstract

It is generally accepted that interactions between parietal and frontal cortices subserve the visuomotor processing for eye and hand movements. Here, we used a sequential-instruction paradigm in 3-T fMRI to test the processing of effector and spatial signals, as well as their interaction, as a movement is composed and executed in different stages. Subjects prepared either a saccade or a reach following two successive visual instruction cues, presented in either order. One cue instructed which effector to use (eyes, right hand); the other signaled the spatial goal (leftward vs. rightward target location) of the movement. During the first phase of the prepared movement, after cueing of either goal or effector information, we found significant spatial goal selectivity but no effector specificity along the parietal-frontal network. During the second phase of the prepared movement, when both goal and effector information were available, we found a large overlap in the neural circuitry involved in the planning of eye and hand movements. Gradually distributed along this network, we observed clear spatial goal selectivity and limited, but significant, effector specificity. Regions in the intraparietal sulcus and the dorsal premotor cortex were selective to both goal location and motor-effector. Taken together, our results suggest that the relative weight of spatial goal and effector selectivity changes along the parietal-frontal network, depending on the status of the movement plan.
Introduction

The process of motor control is assumed to be organized in a hierarchical fashion, at multiple levels of abstraction, with motor selection followed by movement planning, which in turn operates before the muscular contractions that move the effector (Bernstein 1967; Cisek et al. 2003; Grafton and Hamilton 2007; Tresilian 1999). To date, a comprehensive understanding of the neural substrate that underlies the processing at these different levels is still lacking, particularly with regard to the control of multiple effectors.

Consider, for example, the planning of eye and hand movements. While eye movements obviously involve different muscles with different dynamics than hand movements, and thus require different neural commands at the muscular level, it is less clear whether the parietal-frontal circuit involved in planning and selecting eye movements is different from that of hand movements (Andersen and Buneo 2002; Colby and Goldberg 1999; Levy et al. 2007).

According to heuristic reasoning, if motor planning is organized merely in relation to the effector to be moved, one could expect segregated neural circuits for planning of eye and hand movements (Andersen et al. 1997). In contrast, if motor planning is organized more in relation to the goal to achieve (Hamilton and Grafton 2006; Hommel et al. 2001), one could expect overlapping neural circuitry to be recruited in the planning of eye and hand movements.

Monkey neurophysiological data are interpreted in favor of either view. The prevailing interpretation is that distinct effector-specific modules exist in the parietal-frontal network. More specifically, according to this account, neurons in
the lateral intraparietal area (LIP) are thought to encode eye movement plans (Gnadt and Andersen 1988) while neurons in the parietal reach region (PRR) are responsive to impending reaching movements (Snyder et al. 1997). Similar distinctions have been proposed in the frontal cortex, with the frontal eye fields (FEF, Schall 1991) and the dorsal premotor area (PMd, Wise et al. 1997) coding for eye and reaching movements, respectively.

More recent notions, however, emphasize that this separation is not so strict. For example, neurons in the various regions described above also respond for the non-preferred effector (Boussaoud et al. 1998; Calton et al. 2002; Fujii et al. 2000; Lawrence and Snyder 2006; Oristaglio et al. 2006; Snyder et al. 1997; Thura et al. 2008). Also recent human fMRI studies, which assess the overall computations of larger neuronal populations, noted limited effector specificity in the parietal-frontal network during movement planning (Connolly et al. 2007; Hagler et al. 2007; Levy et al. 2007; Medendorp et al. 2005).

We reasoned that an adequate test of these conflicting views would require independent experimental manipulations of effector selection and goal processing. Most of the studies mentioned above, however, collapsed these two control parameters into a single explanatory variable, and focused on the steady states toward which neural activity evolves, rather than on the more informative transient dynamics leading to those states (Durstewitz and Deco 2008).

Here we have studied the planning and execution of eye and hand movements, by partitioning them over spatial goal, motor effector, and time (Beurze et al. 2007; Hoshi and Tanji 2000). By using fMRI to characterize the
temporal evolution of neural activity, we tested the contributions of different portions of the motor system to the processing and integration of effector and spatial goal information, in the context of saccadic or reaching movements. Our results show that the degree of spatial and effector selectivity varies gradually over the parietal-frontal cortex, changing over time during the built up of the movement plan. For further comparison, we related these results to the findings of our previous study on right-hand vs. left-hand movement, using the same paradigm (Beurze et al. 2007).

Methods

Subjects and ethics approval
Fourteen healthy, right handed subjects with normal or corrected-to-normal vision participated in this study (seven male, seven female). Their mean age was 26 ± 4 years. All subjects gave their written informed consent in accordance with the institutional guidelines of the local ethics committee (CMO Committee on Research Involving Human Subjects, region Arnhem-Nijmegen, the Netherlands). One or two days before scanning, all subjects practiced the task using a mock set-up in order to familiarize themselves with the experimental requirements. Also, they performed a couple of monitored practice runs inside the scanner prior to the actual experiment. Two subjects (authors) were aware of the purpose of the paradigm.

Experimental setup
Subjects were placed in the scanner with their head and shoulders tilted upwards by means of a wooden torso support board, upon which the phased-array receiver head coil was attached. Within the head coil, the head and neck were tilted and stabilized with foam wedges and sandbags. The standard mattress of the scanner bed was replaced with a thinner one, so that subjects were lower in the scanner bore, in order to compensate for the torso tilt. The elbows were positioned on cushions and a foam block was placed underneath the knees for comfort. Subjects were strapped at the level of the chest, just above the elbows, to prevent excessive movements. A magnetic resonance (MR) compatible keypad (MRI Devices, Waukesha, WI) was placed on their lap, a few centimeters away from the body midline, and was pressed by the index finger of the right hand. The keypad served to record the start and finish of the reaching movements.

A stimulus device was attached to a wooden arch of about 40 cm in height that was placed over the subject's hips, so that the device was about 80 cm away from the eyes. The tilted position allowed subjects a direct line of sight to this device, without using mirrors, making the task as natural as possible. The stimulus device contained one central multicolor (red, orange, green) light-emitting diode (LED) and, for target instruction, two peripheral orange LEDs on either side, arranged at an eccentricity of about 7° and at angular elevations of 18 and -18°, respectively, from the central LED. The experiment was performed in complete darkness, so that the only visual input consisted of the LEDs on the stimulus device.
Stimuli were controlled using Presentation software (Neurobehavioral Systems, San Francisco, CA). This program also recorded the reaching data. Furthermore, position of the left eye was recorded using a long-range infrared video-based eyetracker (SensoMotoric Instruments, Berlin, Germany) at a frequency of 50 Hz.

Experimental paradigm
We used a two-stage delayed instruction paradigm to separate right hand movements from eye movements, the same as used in previous studies testing right- versus left hand movements (Beurze et al. 2007). Subjects received two types of information: effector choice (indicated by a color change of the central fixation LED) and target location (a brief flash of one of the peripheral LEDs). The two cues were presented in random order during the experiment, resulting in target-effector and effector-target trials.

As shown in Figure 1, a trial started with the appearance of a central fixation LED, which subjects had to fixate during the entire trial, except when they had to perform an instructed saccade. After a variable delay of 2-4 seconds, the first cue was presented. In the case of a target-effector trial, this cue consisted of a brief flash (250 ms) of one of the peripheral LEDs left or right from the central fixation LED. Then, after another delay of 3-5 seconds, the central LED changed color to either red or green, indicating the use of either the right hand or the eyes for the upcoming movement. Next, 1-5 seconds after the second cue, the central LED changed back to orange, serving as a go-signal for the subject to perform
the instructed movement towards the remembered target, and then back to the hand’s starting position or central eye fixation. After a variable delay of 2-6 seconds, the central LED would turn off and on again, indicating the start of a new trial. Effector-target trials were similar to target-effector trials, but with reversed order of effector and target cues.

Duration of a total trial was jittered between 8 and 20 seconds. To further optimize the paradigm, after every five trials there was a longer (13-17 seconds) period of central fixation to allow the blood oxygen level dependent (BOLD) signal to return to baseline level. The experiment consisted of 160 trials, grouped in blocks of 20 trials. Between two blocks, subjects had a brief pause of 30 seconds, during which they could freely move their eyes. The upcoming start of a new block was indicated 5 seconds beforehand by a three-fold flash of all LEDs on the stimulus device. The total experiment had a duration of 49 minutes.

Behavioral analysis

Trials could be rejected based on the reaching data if 1) subjects made a reaching movement before the go-signal, 2) subjects made a reaching movement when a saccade was instructed, or 3) subjects failed to make a reaching movement when a reach was instructed.

Eye movements in all trials were visually inspected to determine the start time of the saccade toward the target and end time of the saccade back to
central fixation. Trials were rejected if 1) subjects were not able to keep central fixation during the planning phase, 2) subjects made a saccade when a reach was instructed, or 3) subjects made no saccade when a saccade was instructed. Due to technical problems, eye movement data in one subject were missing in 36% of the saccade trials.

We characterized the correct trials by the reaction time (RT) of the movement: the time between the onset of the go-cue and the start of the movement. Also, the mean movement duration time (MT), the time between onset and end of the movement was determined. Statistical tests on behavioral response measures were performed with the type I error set at the 0.05 level (P < 0.05).

*Magnetic resonance imaging (MRI)*

Functional images were acquired on a Siemens 3-Tesla MRI system (Siemens Trio TIM, Erlangen, Germany). Using an eight-channel phased-array head coil, 28 axial slices were obtained by a gradient-echo planar imaging sequence (slice thickness 3 mm, gap = 17%, in-plane pixel size 3.5 x 3.5 mm, TR = 2060 ms, TE = 35 ms, FOV = 224 mm, flip angle = 80°). All 1435 functional images were acquired in one run, lasting 49 minutes. After this, high-resolution anatomical images were acquired using a T1-weighted MP-RAGE sequence (192 sagittal slices, voxel size = 1 x 1 x 1 mm, TR = 2300 ms, TE = 2.92 ms, FOV = 256 mm, flip angle = 8°).
**fMRI data analysis**

Using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands), fMRI data were pre-processed and modeled as in Beurze et al. (2007). Subsequent analyses were performed using Matlab (The Mathworks, Natick, MA) and SPSS (SPSS, Chicago, IL). The first three volumes of each subject’s data set were discarded to allow for T1 equilibration. Functional images were corrected for slice scan time acquisition and motion. Data were temporally filtered by using a high-pass filter of 11 cycles per time course (filter cutoff ± 268 s). The functional images were co-registered with the anatomical scan and transformed into Talairach coordinate space using the nine-parameter landmark method of Talairach and Tournoux (1988). The images were smoothed with an isotropic Gaussian kernel of 8-mm full-width-at-half-maximum.

Data were analyzed using a standard general linear model (GLM). We defined sixteen predictor functions for each of the fourteen subjects (Table 1). Four predictor functions modeled the response to the first instruction (cue1), according to the information conveyed by this cue: leftward target (LT), rightward target (RT), effector eye (E) and effector right hand (H). The second cue (cue2) added further information for building up the movement plan. For example, if the first cue signaled the use of the right hand, the second cue would necessarily instruct a target either in the left visual field or in the right visual field. This results in two possible predictor functions; hand to leftward target (H_LT) and hand to rightward target (H_RT). In this manner, the second cue was modeled by eight different predictors. Finally, the response to the go-signal was modeled by four
different predictor functions: performing a saccade to a remembered target either in the left or in the right visual field, and reaching with the right hand into the left or right visual field, independent of the order of presentation of the cues. To construct each of the predictor functions, we defined a box car function extending over each instance of the corresponding time epoch occurring in each subject’s run, and convolved it with the hemodynamic response function (modeled using a gamma function with a tau of 2.5 s and a delta of 1.5 s). By using these regressors for cue1, cue2 and go/movement, we were able to study separately three stages in the sensorimotor process: the information processing stage (cue1), the movement preparation stage, consisting of further information retrieval and integration of all available information into a movement plan (cue2), and the movement execution stage (after the go-signal). In addition, we incorporated eight predictors of no interest. One regressor captured the error trials, as defined by the criteria described above. Six regressors were designed to represent the head motion, modeled using the six parameters provided by BrainVoyager’s motion correction algorithm. Finally, even with the head perfectly stabilized, the movement of the hand and lower arm near the head coil can induce signal changes in the images (Diedrichsen et al. 2005). Therefore, one regressor was used to model the changes in the mean signal intensity of the cerebrospinal fluid (CSF), representing the magnetic field fluctuations due the hand motion in the magnetic field (Beurze et al. 2007).

GLMs were calculated on individual subject data sets with a correction for serial correlations in the time courses. A random-effects group analysis was
performed to test the effects across subjects. To correct for multiple comparisons, we used the false discovery rate (FDR) controlling procedure with a maximum threshold value of \( q(FDR) = 0.05 \) (Genovese et al. 2002).

Table 1 near here

Statistical inference and regions of interest (ROIs)

Using random-effects group analyses, contrasts relative to the baseline (fixation) were computed individually for each of the 16 regressors, for the three time epochs (cue1, cue2 and movement) and for subsets within these time epochs (e.g. cue 2 for hand movements (cue2_hand) and cue2 for eye movements (cue2_eye)). To compare the activity in areas active for both the preparation of eye and hand movements, we performed a conjunction analysis for cue2_hand > fixation with cue2_eye > fixation. Centered on each point of peak activation in the frontoparietal areas in the resulting map, a region-of-interest was defined as all the contiguous voxels within a cubic cluster of 8 x 8 x 8 mm that exceeded a threshold of \( q(FDR) < 0.01 \). To further characterize these ROIs, mean beta-weights for certain combinations of regressors were computed and used for post-hoc comparative analysis using repeated measures analyses of variance (ANOVA), setting the Type I error at the 0.05 level (\( P < 0.05 \)).

Indexing effector and spatial goal selectivity
In order to further specify the effector selectivity over the parietofrontal cortex, without limiting the analysis to ROIs, we computed index maps, which represented the degree of effector or spatial goal selectivity for each voxel in isolation. We computed these maps for each of the three stages of movement preparation and execution: cue1, cue2 and the movement period following the go-signal. In the effector maps, we only included voxels that had increased activity during the various phases relative to fixation, based on contrast maps for eye > fixation and hand > fixation (qFDR < 0.05). To compare reaches to saccades, the effector index was defined as the difference between the response during saccade trials from that of hand trials, divided by their sum (Stark and Zohary 2008). The index value could thus range from -1 (completely eye-specific) to 1 (completely hand-specific). Spatial goal selectivity maps were computed by subtracting the responses to leftward targets from the responses to rightward targets, and dividing this difference by the sum.

_Left hand vs. right hand movements_

In a recent study, we applied the same paradigm to study the cortical mechanisms for the planning and execution of left hand vs. right hand movements in a group of 16 subjects (Beurze et al. 2007). Here we use part of those data for purposes of illustration, comparison and validation.
Task performance

Table 2 presents the percentage correct trials, reaction time, and movement duration of saccades and reaching movements to leftward and rightward targets, averaged across subjects, as recorded during the fMRI experiment. On average, subjects scored > 90 % correct responses for all conditions. A 2x2 repeated-measures ANOVA with target location (left/right) and effector (eye/hand) as factors revealed no significant main effect (target location: $F_{(1,13)} = 0.06, P = 0.81$; effector: $F_{(1,13)} = 0.1, P = 0.76$) or interaction effect ($F_{(1,13)} = 0.05, P = 0.82$). This means that there was no difference in performance for saccade versus reaching trials.

Reaction time analysis of the correct responses revealed a mean reaction time of 443 ± 84 ms (mean ± standard deviation (SD)) for saccades and 621 ± 108 for reaches, which is consistent with previous reports (Beurze et al. 2007; Macaluso et al. 2007). The latency differences between saccades and reaches were statistically significant ($F_{(1,13)} = 91, P < 0.01$), irrespective of the location of the target ($F_{(1,13)} = 1.1, P = 0.31$). However, subjects that were fast responders for saccades also had shorter reaction times for reaches and vice versa ($r = 0.71$) and the same was true for the movement durations ($r = 0.75$).

The mean movement duration of a to-and-fro movement was 1025 ± 167 ms (mean ± SD) for saccades and 1487 ± 474 ms for reaching trials, indicating that subjects always had their fixation back to center or their hand returned to the starting position before cue1 of the next trial appeared. Differences between
saccades and reaches were significant ($F_{(1,13)} = 22, P < 0.01$), irrespective of target location ($F_{(1,13)} = 2.4, P = 0.14$).

To allow comparison of fMRI activation for saccades with that for reaches, their differences in reaction time and movement duration were incorporated in the GLM model (see Methods).

Table 2 near here

**fMRI activation data**

To keep connection with previous studies lumping target and effector processing into a single state, we have organized this section by first describing the results of the second stage of our instruction paradigm in order to define the parietofrontal regions involved in movement preparation. Next, we expand on these findings by indexing spatial and effector selectivity of all three stages of the task paradigm; effector information retrieval, motor preparation, and execution, respectively.

**Parietofrontal areas involved in the preparation of saccades and reaches**

Using a random-effects analysis, we first identified regions of the cortex that were activated in the second stage of the paradigm, when preparing either a saccade or a right hand movement. Figure 2A shows an overview of these results, rendered onto an inflated representation of both hemispheres of a single subject,
providing a direct overview of the activated voxels relative to other anatomical landmarks. The map for saccade preparation demonstrates a large overlap with that of reaching, except near the central sulcus. For comparison, Figure 2B demonstrates the activation patterns when planning left-hand movements versus right-hand movements, as collected by Beurze et al. (2007) using the same paradigm (see Methods). As shown, there is also a large overlap in activation during the planning of left hand and right hand movements, although there is a strong preference for the contralateral hand in each hemisphere, most noticeably near the central sulcus. The map for right hand movement preparation resembles the corresponding map in Figure 2A nearly perfectly, as should be the case given the identical task constraints.

To examine the overlap of the saccade and reach-related activation maps, we performed a conjunction analysis the results of which are shown in Figure 2C. Common activation was found bilaterally in the lateral and medial regions both caudally (cIPS) and more anterior (aIPS) in the intraparietal sulcus (Astafiev et al. 2003), as well as in the parieto-occipital sulcus (PO) (Quinlan and Culham 2007). Within the frontal lobe, significant responses were observed in the precentral gyrus and sulcus, which correspond to the dorsal and ventral premotor areas (PMd/PMv) (Picard and Strick 2001). The PMd region showed two separate areas of activation, a more superior (sPMd) and an inferior (iPMd) area. On the medial wall, activation extended from the superior frontal sulcus, corresponding to the supplementary motor area (SMA) (Picard and Strick 2001), into the
posterior rostral and caudal zones of the anterior cingulate sulcus, corresponding to the cingulate motor area (CMA) (Picard and Strick 2001).

Table 3 lists the average Talairach coordinates (in millimeters) of the voxel with peak activation within each parietofrontal region that was defined as region-of-interest (ROI) by the conjunction analysis (Figure 2C), and its t-value across subjects. Additionally, primary motor cortex (M1) (Yousry et al. 1997) was included in the list of ROIs for further comparison, although this region only showed activity for reaches, not for eye movements.

**Effector selectivity during movement preparation**

Although the conjunction analysis revealed the areas commonly involved in planning hand and eye movements, these regions may not necessarily respond in the same manner for these effectors. We computed index maps (see Methods) to address this issue, using only voxels that were significantly active during movement preparation (cue2 > fixation, \(q(FDR) < 0.05\)). The index map was specified by computing for each voxel the difference between its beta value for the two respective movement conditions divided by the sum of these beta values (thus, index = \((\beta_1 - \beta_2) / (\beta_1 + \beta_2)\)). As a result, index values will range between -1 to +1. Using color-coding, Figure 3A shows voxels with a preference for right hand movements in red (index >0) and voxels with a preference for eye movements in green (index < 0). The index map reveals a
preference for hand movements across the parietal-frontal network, except for a region near the parieto-occipital sulcus. It further shows a clear gradient building up from nearly no difference in activity for the two effectors in the back and front of the brain, to a strong preference for hand movement planning in regions surrounding the primary motor cortex. To test the significance of these observations, we performed an ANOVA-analysis on the areas as defined in our ROI-analysis (Figure 2C), pooled across hemispheres. A significant main effect (F(1,13) > 6.0, P < 0.05) for effector was found in SMA, CMA, sPMd, iPMd, cIPS, aIPS and M1, all showing a preference for reaches over saccades.

To further validate the efficacy of the index maps in depicting characteristics of the data, Figure 3B illustrates the index maps comparing right and left hand movements. The map demonstrates the distinct preference of each hemisphere for the contralateral over the ipsilateral hand, as already suggested by Figure 2. More lateral brain regions show a stronger contralateral bias than the more medial areas. Furthermore, the index map shows a gradient building up from the precentral to the central sulcus and from the intraparietal sulcus to the central sulcus with a growing preference for the contralateral hand in each hemisphere. Using an ANOVA-analysis, the significance of these differences was assessed in the ROIs defined in Figure 2, in a pooled comparison across hemispheres. A significant interaction effect (F(1,15) > 10.0, P < 0.05) between hemisphere and effector was found in PO, SMA, CMA, sPMd, iPMd, aIPS and M1, confirming the response bias for the contralateral hand in these regions, also reported in Beurze et al. (2007).
Effector selectivity during movement composition

So far, we have described only the neural activity at the second stage of movement preparation, which characterizes the results of the ongoing integration of information about effector and spatial goals. The important next question is, do these regions also respond in an effector-specific manner in the absence of a well-defined goal? And, equally relevant, do these regions sustain such effector-specific activation observed during the second preparation stage during the execution of the planned movement? To answer these questions, we examined the processing of an effector cue in isolation, i.e., during the first stage of movement preparation, by computing the index map for right hand versus eye effector processing as in Fig 3. In the same way, we computed the index map for right hand versus eye movements during the third phase, the execution stage of the movement.

Figure 4 illustrates the index maps at these three stages of movement preparation (A: effector information retrieval, B: movement preparation, C: movement execution). During the first stage (Figure 4A), after signaling the effector cue, but without the spatial goal information available, none of the brain areas shows a clear effector-specific modulation. This was confirmed by an ANOVA-analysis, showing only a significant main effect ($F_{(1,13)} = 9.1, P < 0.05$) in the parietal-occipital sulcus, with a slight preference for the saccade cue. During
the second stage (Figure 4B, which is a replica of Figure 3B), this changes dramatically, with clear effector-specific modulations in many brain regions, as described above. Next, during the third stage, the movement execution phase, there is again a vivid change, with the right hand preference only clearly sustained in the left hemisphere (recall, only right hand movements were made). As the two hemispheres now show different responses, we performed a separate ANOVA analysis per hemisphere. In the left hemisphere, M1 showed a strong and significant preference for reaches ($F_{(1,13)} = 22.1, P < 0.01$). In both hemispheres, the parietal-occipital sulcus was strongly and significantly more activated for saccades than for reaches ($F_{(1,13)} > 19.0, P < 0.01$). No significant differences in effector specificity were found in the other regions-of-interest. Taken together, these phase-related effector-specific modulations suggest that effector-bias is not a fixed property of cerebral circuits involved in supporting different phases of motor control. Rather, effector-bias is a time-varying characteristic of cortical activity as the movement composition goes through different stages.

Figure 4 near here

Spatial goal selectivity during movement composition

The results presented thus far concerned the ‘how’ component during movement composition. In the following analysis, we investigated the ‘where’ component, i.e. the selectivity of the network to the spatial goal of the movement. To assess spatial goal selectivity, both with and without effector information, we computed
index maps comparing responses to rightward and leftward target locations at the three respective stages. During the first stages of movement composition (Figure 5A and B), there is indeed a clear bias toward contralateral targets distributed over each hemisphere. Significant interaction effects (ANOVA, $F_{(1,13)} > 12.0$, $P < 0.01$) between hemisphere and target side were found in PO, cIPS, sPMd, iPMd and PMv. During movement execution (Figure 5C), the preference for contralateral targets remained significant only in PO ($F_{(1,13)} = 9.1$, $P < 0.05$).

Figure 5 near here

*Spatial goal selectivity versus effector selectivity*

A comparison of Figs. 4 and 5 shows regions within the parietofrontal network that are effector-specific, spatial goal-specific, both, or neither. Therefore, a combined assessment would provide more insights in the relations between these characteristics. To visualize the anatomical distribution of spatial goal selectivity in relation to effector selectivity, we plotted their relative weight in the areas of interest, as defined by the conjunction analysis in Fig 2C, pooled across hemispheres. We performed this analysis on the second stage of movement composition only, because no significant effector-specific modulations were found during the first delay period (see Fig 4A). Figure 6 conveys a gradual shift from spatial goal to effector selectivity along the posterior-anterior axis in the parietal cortex (Stark and Zohary 2008) while the opposite gradient appears in the premotor cortex. The premotor cortex also shows an effector-to-spatial
gradient in the medial-lateral direction, with clear effector dominance in SMA to a high degree of spatial-selectivity in PMv. The ANOVA analyses described above indicate that the only two regions showing both significant effector and spatial goal selectivity during the movement preparation stage are PMd and cIPS, which is consistent with our previous report (Beurze et al. 2007). This indicates that these parietal and frontal regions integrate both spatial and effector information, rather than representing either of the single sources (Beurze et al. 2007; Stark and Zohary 2008).

Figure 6 near here
Discussion

Overview of main findings

Although it has long been known that parietal and frontal cortices play important roles in motor control, the massively recursive nature of their computational architecture has prevented a clear distinction of their exact functional contributions (Shadmehr and Wise 2005). Here we studied the generation of eye and hand movements, using a sequential-instruction paradigm to isolate spatial goal and effector processing as well as the ongoing integration of this information as the cerebral activity behind a movement unravels over time and runs through different stages.

We found that when effector information (eyes or hand) was presented first, and goal information was left unspecified, a large parietal-frontal network was recruited, but in an effector-independent manner (Fig 4). In contrast, when spatial goal information was presented first, leaving the type of effector unspecified, the activation in virtually the same network depended on the location of the target (Fig 5). Thus, in the first phase of the sensorimotor transformation, spatial goals map onto spatially segregated brain processes, whereas the selection between a saccade and a reach does not.

Spatial goal selectivity along the parietal-frontal network was sustained and extended during the planning phase (Fig 5B), when effector information was added to the movement composition. In this case, i.e., when spatial goal and effector information were both specified, we found a large overlap in the neural
circuitry involved in the planning of eye and hand movements (Fig 2). Strikingly, some areas (SMA, CMA, PMd, IPS) now also exhibited clear preferences for one effector over the other (Fig 3), although none was found to respond exclusively to either effector. This significant effector specificity during the second stage of movement planning is in agreement with previous work (Calton et al. 2002; Levy et al. 2007; Medendorp et al. 2005; Snyder et al. 1997). Because of their effector-specific nature, these co-activations cannot be interpreted as mere sensory or attentional representations (Quian Quiroga et al. 2006).

Based on these results, we conclude that effector-specificity is not a fixed property of the motor system, but rather an attribute whose strength depends on the status of the movement plan. This corroborates the findings by Hoshi and Tanji (2004), showing that effector representations build up and become stronger closer to movement execution in certain motor areas as well as the recent observations that neural variability decreases as the movement approaches in time (Churchland et al. 2006). During movement execution, we found effector specificity for hand versus eye movements sustained in only a few regions, with the contralateral primary motor and somatosensory cortices being entirely hand-specific and a medial occipital region biased to saccade execution (Fig 4). The latter observation is perhaps best explained by an anticipation of the sensory consequences of the eye movements (Medendorp et al. 2003; Merriam et al. 2007).

**Relation to previous work**
We emphasize that no previous fMRI study tested both spatial and effector processing in isolation, using a sequential instruction task. Nevertheless, our observations of widespread spatial goal selectivity confirm previous imaging results on the contralateral representation of target location in parietal and frontal areas (Curtis and Connolly 2008; Hagler and Sereno 2006; Kastner et al. 2007; Medendorp et al. 2006; Schluppeck et al. 2005; Sereno et al. 2001).

Regarding effector specificity, many previous human imaging studies have reported more activation for reaching than saccades, both in regions for which this was expected, such as PMd (Connolly et al. 2007) and M1 (Levy et al. 2007), as well as in regions for which the monkey literature would predict a saccade preference, including the FEF (Connolly et al. 2007) and some regions within the parietal cortex (Levy et al. 2007). The present study found activation related to saccade execution in occipital cortex, which is also in line with previous studies (Levy et al. 2007; Macaluso et al. 2007). Thus, in general, our findings support the notion that human fMRI studies do not simply replicate the somatotopic findings in monkeys, i.e., we do not show clear distinctions between saccade-related areas (e.g. LIP, FEF) and reach-related areas (e.g. PRR, PMd) in parietal and frontal cortex. In this respect, our results support the conclusion by Levy et al. (2007) that the degree of effector specificity is limited in many human cortical areas, transitioning gradually from saccade to reach preference when following the hierarchy of areas in the occipital, parietal and frontal cortices.

In a combined assessment, we showed that the relative contribution of spatial and effector selectivity in movement planning differed along the parietal-
frontal network (Fig 6). The effector-to-spatial gradient observed over parietal cortex is consistent with findings by Stark and Zohary (2008) during grasping movements. The gradient observed in frontal cortex has not been reported before, but is consistent with our previous findings (Beurze et al. 2007). It is interesting to note that cIPS and PMd are in the middle of these gradient axes, consistent with a role in integrating spatial and effector information in sensorimotor control (Beurze et al. 2007; Chang et al. 2008).

Furthermore, for comparison and validation purposes, we have re-analyzed part of the data of our previous study on left hand vs. right hand movements (Beurze et al. 2007). These data support our general conclusion that the degree of effector-specificity depends on the status of the movement plan. A notable difference with the present findings is that effector selection between the right and left hands caused some areas to respond to the hand use cue, even if the effector cue was given as the first instruction. This would suggest that selecting between the two hands and selecting between the eyes and hand involves different neural mechanisms.

**Limitations of interpretation**

The present and previous human imaging results do not support the idea of fully distinct effector-specific modules in the brain – the commonly held view based on electrophysiological results in the monkey. We consider it unlikely that this reflects an interspecies difference (Koyama et al. 2004), since the monkey has typically appeared a good model for studying human sensorimotor control. But
one could list other factors that may limit the scope of our findings. First, BOLD-imaging and single unit recording are different techniques, with fMRI informing about local information processing and unit recordings reporting about the output stage of those computations (Bartels et al. 2008; Logothetis 2008). In the monkey, one can simply count the number of neurons active in planning a particular movement, and then determine the effector preference of that region based on the resulting proportions. BOLD-fMRI only assesses the overall activation of the neurons in that region. Although fMRI measurements cannot differentiate the proportion of cells involved in eye versus reaching movements, Levy et al. (2007) used a method of counting the voxels with a preference for either reaches or saccades to determine their effector selectivity, an approach most similar to the monkey studies. Based on this analysis, they still observed a larger proportion of voxels with a saccade preference in the visual areas, and a larger number voxels with a reach preference in the intraparietal areas, FEF and motor cortex, consistent with the present study.

A further reason of why saccadic and reaching activity may be hard to differentiate in fMRI is that the planning of the movement of the one effector may be accompanied with a suppression of the other, non-chosen effector, perhaps due to the random presentation of the effector instructions. We can neither exclude the possibility that subjects in fact planned multiple effector movements and inhibited the non-instructed movements at the moment of execution. Moreover, eye movements are also difficult to distinguish from attentional processing (Rizzolatti et al. 1987), and attention is needed in both effector
conditions. In the monkey PPC, it was shown that a portion of reach-specific neurons was activated when a saccade was instructed and vice versa (Calton et al. 2002; Snyder et al. 1997). However, when these default plans were countermanded by explicit instructions, their activity disappeared again.

One could argue that BOLD-fMRI may not distinguish between effector selection and suppression because the respective excitatory and inhibitory processes both have metabolic demands, which both may result in increases in the BOLD signal (Logothetis 2008). However, recent studies have provided evidence for haemodynamic and metabolic downregulation accompanying neuronal inhibition (Shmuel et al. 2002, Stefanovic et al. 2004), making it unlikely that the effects we report are driven by suppression of the non-relevant effector.

A concern in our comparison of effector-selectivity to spatial goal-selectivity relates to an imbalance in the mnemonic components related to spatial and effector cues, due to technical experimental constraints. In our paradigm, the goal cue was a brief flash that had to be memorized; the effector cue remained present till the go-signal of the movement. Could the latter explain the absence of effector-selectivity (eye vs. hand) after the first cue, as if subjects did not process the information yet? We do not consider this explanation very likely because the same paradigm testing left-hand vs. right-hand movements did reveal effector-specific modulations, also when presented as the first cue. Also, our rapid event-related fMRI design, with the short and variable delay intervals, placed a strong incentive for subjects to start movement preparation after cue presentation. In further support, recent studies have shown that a continually present cue induces
robust motor-related activation, ramping up as the motor plan evolves (Curtis and Connolly 2008).

Finally, we should emphasize that our interpretation regards the selection and integration of effector and spatial goal information for movement planning. While the effector information only concerned ‘how’ to act, we note that the initial position of the effector is also an important variable in the integration process. In this respect, it would be interesting, in future work, to apply the paradigm to distinguish between brain areas linked to the representation of the effector location and those linked to target location (Beurze et al. 2006).

An efficient coding principle?
Because reaches and saccades are naturally coupled in daily life, a regional overlap for the planning of these movements in the brain may be quite viable. In close connection, it has recently been suggested that the topology as found in the motor cortex is not based solely on the separate functions of the body parts, but rather on a clustering of relevant action categories (Graziano and Aflalo 2007), one of which may be eye-hand coordination. Although this does not directly change the current knowledge on how the monkey cortex is organized, it may dispute the principles that led to this organization. In this context, it would be interesting to examine how the planning of movements of other body parts (e.g. the feet) is organized within the parietofrontal network.

From the perspective of parsimonious coding, Levy et al. (2007) suggested that it makes little sense to have separate machinery for coding
similar planned movements that only differ in the effector used to execute them; especially for two effectors that so often accompany each other. Furthermore, the literature suggests that the overlapping circuitry may operate in limb-independent, eye-centered coordinates (Batista et al. 1999; Medendorp et al. 2003; Van Pelt and Medendorp 2008), which would support the idea that the planning of actions from different effectors takes place in a common frame of reference (Andersen and Buneo 2002; Beurze et al. 2006).

In summary, the present study revealed different involvement of parietofrontal areas in the processing of spatial goal and effector information, which changed over time depending on the status of the movement plan. Although these findings provide important insights in the organization of the human parietofrontal network, it remains a challenge for future studies to further clarify the processes in these areas underlying the planning and execution of reaches and saccades. Studies of these processes will not only be important to design realistic models of sensorimotor physiology but also to understand the disorders that arise when damage or dysfunction occurs.

**Acknowledgements**

We thank the electronic research group and the mechanical engineering group of the Faculty of Social Sciences for excellent technical support. We thank Paul Gaalman for expert assistance during scanning.

**Grants**
This work was supported by a grants from the Netherlands Organization for Scientific Research (VIDI: 452-03-307) and the Human Frontier Science Program to W.P. Medendorp.
REFERENCES


LEGENDS

Figure 1: Sequential instruction paradigm. Subjects fixated a central LED and prepared a movement instructed by two successive visual cues: target location (brief flash of a peripheral LED either left or right) and effector choice (color change of the central LED, indicating the use of either the right hand or the eyes), presented in random order. A go-signal prompted the execution of the movement, which in case of a reach had to be performed while maintaining central eye fixation.

Figure 2: Brain activation during movement planning, presented on the semi-inflated hemispheres of a single subject. A: Saccades (blue voxels) vs right hand movements (red voxels). B: Right hand movements (red voxels) vs left hand movements (green voxels), by a re-analysis of data from Beurze et al. (2007). C: Conjunction analysis; circles indicate the location of peak activation within the regions-of-interest. A parietal-frontal network including the supplementary and cingulate motor areas (SMA, CMA), superior and inferior dorsal (sPMd, iPMd) and ventral (PMv) premotor cortex, regions along the intraparietal sulcus (cIPS, aIPS) and parieto-occipital sulcus (PO) is involved in movement preparation of both hand and eye movements. Primary motor cortex (M1), which was not activated during saccade planning, was included as a region-of-interest in further analyses. All maps, P < 0.01, FDR-corrected.
Figure 3: Index maps representing effector selectivity of the circuitry involved in movement planning (P < 0.05, FDR-corrected). A: Saccades vs. right hand movements. B. Left hand vs right hand movements, using data from Beurze et al. (2007).

Figure 4: Effector selectivity during the three stages of movement generation, comparing saccades and right hand movements. A: First phase, effector cue in isolation: although all voxels show significant activation (P < 0.05, FDR-corrected) to the effector cue, none showed significant effector specificity. B: Second phase, effector selectivity of the circuitry involved in movement planning (replicating Fig 3B). C: Movement execution stage. Effector bias of all voxels showing a significant response during movement execution (P < 0.05, FDR-corrected).

Figure 5: Index maps representing spatial goal selectivity. A: First phase, spatial goal cue in isolation: of all voxels that are significantly activated during this cue (P < 0.05, FDR-corrected), some show a bias to contralateral target locations. B: Second phase, spatial goal selectivity of the circuitry involved in movement planning. The contralateral spatial bias deepens and extends compared to the pattern in A. C: Movement execution stage. Spatial goal selectivity of all voxels showing a significant response during movement execution (P < 0.05, FDR-corrected).
Figure 6: The relative weight of spatial and effector selectivity during movement planning in the region-of-interest, defined in Fig 2C. Gradients of spatial-to-effector specificity can be observed in both parietal and premotor cortex, with the cIPS and PMd selective to both goal location and effector type.
Table 1: Overview of the sixteen regressors of interest in the model. Cue1 signaled either a leftward (LT) or a rightward (RT) target, or the instruction to use the eyes (E) or hand (H) in the upcoming movement. Cue2 conveyed complementary information. Hence, the movement (Mov) instructed either a leftward saccade (sac_L), a rightward saccade (sac_R), a leftward reach (reach_L), or a rightward reach (reach_R). Each movement was instructed in two different ways, depending on information presented by cue1 and cue2.

<table>
<thead>
<tr>
<th>Cue1</th>
<th>LT</th>
<th>RT</th>
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<th>H</th>
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<td>RT_E</td>
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<tr>
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<td>sac_L</td>
<td>reach_L</td>
<td>sac_R</td>
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Table 2: Percentage correct performance, mean reaction times (RT), and mean movement duration times (MT) for each of the four movements. Values are ± SD.

<table>
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<th>Condition</th>
<th>Performance (%)</th>
<th>RT (ms)</th>
<th>MT (ms)</th>
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<tr>
<td>Saccade to leftward target</td>
<td>93.8 ± 3.4</td>
<td>448 ± 91</td>
<td>1012 ± 189</td>
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<tr>
<td>Saccade to rightward target</td>
<td>94.3 ± 6.2</td>
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<tr>
<td>Reach to leftward target</td>
<td>92.7 ± 5.2</td>
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<td>Reach to rightward target</td>
<td>90.2 ± 5.8</td>
<td>619 ± 107</td>
<td>1501 ± 507</td>
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Table 3: Parietofrontal brain regions activated in conjunction during hand and eye movement preparation (cue2). Coordinates in mm: x (lateral/medial), y (anterior/posterior) and z (superior/inferior) according to Talairach and Tournoux (1988). The t-values represent the areas’ statistics across all subjects.

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<tr>
<th>Anatomical region</th>
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<th>x</th>
<th>y</th>
<th>z</th>
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Figure 1. Beurze et al.
Figure 2. Beurze et al.
Figure 3. Beurze et al.
Figure 4. Beurze et al.
Figure 5. Beurze et al.
Figure 6. Beurze et al.