Reference Frames for Reach Planning in Human Parietofrontal Cortex

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INTRODUCTION

To reach to a visual object, a local pattern of retinal stimulation caused by the object must be transformed into a correct set of muscular contractions of the arm and hand. It is generally believed that at some stage(s) of this visuomotor transformation, the brain computes the difference vector between target and hand location (the hand–target movement vector), which it then further parses into motor commands by processing independently the amplitude and direction of this vector (Ghez et al. 1997; Rossetti et al. 1995; Vindras and Viviani 1998; Vindras et al. 2005). A complexity in the computation of the difference vector is that the sensory representations of target and hand positions may be coded in different reference frames, depending on contextual conditions and task constraints (Sainburg et al. 2003; Sober and Sabes 2003, 2005). Vision reports the locations of targets relative to the retina, i.e., in a gaze-centered frame of reference. The initial location of the hand can also be extracted visually, when in view, or can be derived from proprioceptive information from the arm, which is coded somatotopically, as relative joint angles in body-centered coordinates (Gardner and Costanzo 1981). To calculate the difference vector in a spatially consistent manner, it has been argued that the brain must code target and hand locations in the same reference frame (Andersen and Buneo 2002; Buneo et al. 2002; Flanders et al. 1992).

Previous literature proposed that the brain computes the difference vector in body-centered coordinates, an operation that requires target location to be transformed into a body-centered reference frame (Flanders et al. 1992; McIntyre et al. 1997). More recent findings, however, have challenged this notion by providing evidence for a hand–target comparison in gaze-centered coordinates (Beurze et al. 2006; Blangero et al. 2007, 2010; Buneo et al. 2002; Pisella et al. 2009).

For example, from behavioral findings on reach errors it has been inferred that reaching movements in visual space are planned in gaze-centered coordinates and updated across eye movements (Beurze et al. 2006; Henriques et al. 1998; Medendorp and Crawford 2002; Van Pelt and Medendorp 2008). Single-unit recordings in monkeys and functional imaging studies in humans have shown an influence of gaze in specific reach-related areas of the parietal cortex (Batista et al. 1999; Bédard et al. 2008; Medendorp et al. 2003). Furthermore, Prado et al. (2005) showed activation differences in the human brain when participants reached toward central or peripheral visual targets, which is another argument for the importance of gaze coordinates. Buneo et al. (2002) showed that position of the hand relative to gaze modulated the neuronal activity in area 5 of the posterior parietal cortex (PPC), whereas Pesaran et al. (2006) discovered that reach-related activity in neurons in the dorsal premotor cortex depends on hand, eye, and target positions. Finally, unilateral and bilateral optic ataxia patients with damage in the PPC show reach deficits that reflect the use of gaze-centered coordinates (Blangero et al. 2007, 2009, 2010; Buxbaum and Coslett 1997, 1998; Jackson et al. 2009; Khan et al. 2005a,b; Pisella et al. 2009).

Although all of these findings are consistent with the idea of a comparison of target and hand location in gaze-centered coordinates, a more direct test of this scheme may require an investigation at the neural population level. Under the assumption that information processes with similar structure and constraints are implemented in spatially contiguous patches of cortex (Graziano and Aflalo 2007), here we address the cerebral relevance of gaze-centered computations in sensorimotor transformations, compared with body-centered contributions. More specifically, we tested human subjects in 3T functional magnetic resonance imaging (fMRI), while they planned (and
performed) goal-directed reaching movements starting from various initial hand positions while keeping gaze fixed in various directions.

We hypothesized that brain areas that compute a difference vector in gaze coordinates respond more strongly when target and hand are both at peripheral coordinates in the gaze frame than when either of these is at the origin of the gaze-centered coordinate frame (Jackson et al. 2009). The motivation for this hypothesis is shown in Fig. 1: when the target is foveated (the most naturalistic situation), the difference vector from hand to target is simply the inverse of the vector that defines the hand position in gaze-centered coordinates (Fig. 1A). By the same token, when the hand is foveated, the difference vector simply equals the vector representing the target in gaze-centered coordinates (Fig. 1B). However, computing a difference vector for a reaching movement to a peripheral target with peripheral hand position requires the brain to simultaneously represent the spatial location of the target in gaze-centered coordinates and the initial position of the hand in gaze-centered coordinates (Fig. 1C), which increases the computational demands, and thus the metabolic cost, compared with the conditions of Fig. 1, A and B. Note that, in the experiment, several combinations of target, hand, and eye positions (see Fig. 2C) were used to isolate the gaze-centered integration effects.

Furthermore, it is important to point out that a gaze-centered movement vector must still be transformed into a body-centered, joint-based motor command to actually execute the movement (Beurze et al. 2006; Blohm and Crawford 2007). This transformation involves an inverse model of the arm (Shadmehr and Wise 2005). Because the internal model requires the actual posture of the arm as input, this transformation likely relies on body-centered, proprioceptive information about hand position (Beurze et al. 2006; Goodbody and Wolpert 1999; Sober and Sabes 2003, 2005). A modulation in the blood oxygenation level dependent (BOLD) signal depending on the position of the hand relative to the body would be indicative of such an effect.

Our results show that the computations of the transformation for reaching in premotor and posterior parietal areas involve locations of target and hand in gaze-centered coordinates. Body-centered hand position effects were also found, in regions closer to the primary motor cortex, which may be related to the implementation of a joint-based motor command.

METHODS

Subjects and ethics approval

In all, 14 healthy, right-handed subjects with normal or corrected-to-normal vision participated in this study (6 male, 8 female). Their mean age was 23 ± 5 yr (range: 19–38 yr). 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). Several days prior to scanning, subjects received written instructions on the paradigm, so that they could familiarize themselves with the experimental requirements. They were trained on the task for ten minutes shortly before they were placed inside the scanner, and performed a number of monitored practice runs inside the scanner prior to the actual experiment. One subject (one of the authors) was aware of the purpose of the paradigm; the others were naive and were paid for their time.
The elbows were positioned on cushions and a foam block was placed beneath the knees for comfort. Subjects were strapped at the level of the chest, just above the elbows, to prevent excessive movements.

Two wooden arches were placed over the subject’s body, one containing the stimulus device, the other containing three touch buttons to record the hand’s onset and movement times. The stimulus device was such that the stimuli were about 90 cm away from the eyes, at the level of the hips. Subjects had a direct line of sight to the stimuli, making the task as natural as possible. The stimulus device contained seven multicolor (red, orange, green) light-emitting diodes (LEDs), spaced either about 2.5° or 5° apart (Fig. 2A). The experiment was performed in complete darkness, so that the only visual input consisted of the LEDs on the stimulus device.

The hand’s button box was attached to the second wooden arch of about 30 cm in height that was also placed over the subject’s body, at the level of the abdomen. It contained three touch buttons measuring 9.7 × 4 cm. The right index finger of the subject rested at one of these buttons during the entire experiment, except when an arm movement had to be made to one of the target LEDs. These buttons served to record the starting and ending times of the instructed movements.

Stimuli were controlled using Presentation software (Neurobehavioral Systems, San Francisco, CA). This program also recorded the visual input consisted of the LEDs on the stimulus device.

The experiment consisted of 160 trials, grouped in blocks of 20 trials. Between two blocks, subjects had a brief pause of 30 s, during which they could freely move their eyes and rest their hand. The upcoming start of a new block was indicated 5 s beforehand by a threefold flash of all LEDs on the stimulus device. The total experiment had a duration of 49 min.

**Behavioral analysis**

Eye movements were visually inspected in all trials, which confirmed that subjects kept the fixation instructions; on average, fixation was broken in <2.5% of the trials. We further characterized trials by the reaction time (RT) of the reaching movement: the time between the onset of the go-cue and the start of the movement. Across subjects, this revealed a mean reaction time of 546 ± 114 ms (mean ± SD), which is consistent with previous reports (e.g., Beurze et al. 2007, 2009; Macaluso et al. 2007). The mean movement duration time (the time between onset and end of the movement) was 510 ± 258 ms.

**Magnetic resonance imaging**

Functional images were acquired on a Siemens 3-Tesla magnetic resonance imaging (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 × 3.5 mm, repetition time [TR] = 2,060 ms, echo time [TE] = 35 ms, field of view [FOV] = 224 mm, flip angle [FA] = 80°). All 1,435 functional images were acquired in one run, lasting 49 min. After this, high-resolution anatomical images were acquired using a T1-weighted
MP-RAGE sequence (192 sagittal slices, voxel size = 1 × 1 × 1 mm, TR = 2,300 ms, TE = 3.03 ms, FOV = 256 mm, FA = 8°).

\textbf{fMRI data analysis}

fMRI data were analyzed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). 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 = 0.268 s). The functional images were coregistered 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 one predictor function for placing the hand on the initial position (HP) and one for moving the eyes to their initial position (EP). The target (T) and reaching (R) epochs and the associated predictor functions were subdivided into 12 possible trial conditions, depending on the relative positions of the hand, eyes, and target in each trial (Table 1, Fig. 2C).

To construct the predictor functions for HP, EP, and the movement period, 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 (HRF), modeled using a gamma function with a tau of 2.5 s and a delta of 1.5 s. For the predictor function after target presentation (T), we modeled a block function of 1 s to cover the time interval that was consistently present in all trials before movement execution (instead of the real jittered time duration of each specific trial) and convolved it with the HRF.

In addition, we incorporated eight predictors of no interest. One regressor captured the times of the breaks between the blocks. Six regressors modeled the head motion, modeled using the six parameters provided by BrainVoyager's motion correction algorithm. Head motion occurred predominantly as a translation along the long body axis and a pitch rotation but was always <4 mm and 1.5°, respectively. 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 to the hand motion in the magnetic field (Beurze et al. 2007).

GLMs were calculated on individual subject data sets; 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).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Regressor & Initial Hand Position & Initial Gaze Position & Target Position & Target Relative to Gaze & Hand Relative to Gaze & Hand Relative to the Body \\
\hline
1 & 4 & 5/6 & 2 & Peripheral & Peripheral & Central \\
2 & 4 & 4 & 2 & Peripheral & Central & Central \\
3 & 4 & 4 & 2 & Peripheral & Peripheral & Central \\
4 & 4 & 4 & 2 & Peripheral & Peripheral & Peripheral \\
5 & 4 & 2 & 2 & Central & Peripheral & Central \\
6 & 2 & 2 & 2 & Central & Peripheral & Peripheral \\
7 & 7 & 6 & 6 & Central & Peripheral & Central \\
8 & 4 & 6 & 6 & Central & Peripheral & Central \\
9 & 7 & 4 & 6 & Peripheral & Peripheral & Peripheral \\
10 & 4 & 5 & 6 & Peripheral & Peripheral & Central \\
11 & 4 & 4 & 6 & Peripheral & Central & Central \\
12 & 4 & 2/3 & 6 & Peripheral & Peripheral & Central \\
\hline
\end{tabular}
\caption{Overview of the regressors of interest}
\end{table}

Regressors are numbered and characterized by LED position (see also Fig. 2A) used for the selection of initial hand position, gaze position, and target position. The other columns reflect the positions (central vs. peripheral) of target relative to gaze, hand relative to gaze, and hand relative to the body.

\textbf{Statistical inference and regions of interest}

Contrasts were computed using random-effects group analyses. We restricted our analysis to voxels of the cortical reach network only, including those with preparatory and movement-related responses. We independently but liberally selected \( P < 0.05 \), uncorrected for multiple comparisons, to select the voxels strongly activated during movement execution. We then used a false discovery rate (FDR) procedure with a maximum threshold value of \( q(\text{FDR}) = 0.05 \). To further characterize the activation of these ROIs, we computed peak values for each ROI to determine the extent of the regions activated in the specified reach network. To identify these regions within the specified reach network, we therefore computed a contrast image based on the summed parameter estimates (beta weights) of all predictor functions representing a planned movement with both the hand and target locations peripheral relative to the gaze direction (1, 3, 4, 9, 10, 12) and all predictors presenting a planned hand movement with either hand or target central relative to gaze (2, 5, 6, 7, 8, 11) (see Table 1, Fig. 2C). Centered on each point of peak activation in the areas in the resulting map, a region of interest (ROI) was defined as all the contiguous voxels within a cubic cluster of \( 8 \times 8 \times 8 \) mm (to match the size of the smoothing kernel) that exceeded a threshold of \( q(\text{FDR}) < 0.05 \). To further characterize the activation of these ROIs, we computed peak values for each ROI to determine the extent of the regions activated in the specified reach network. To identify these regions within the specified reach network, we therefore computed a contrast image based on the summed parameter estimates (beta weights) of all predictor functions 5 and 8 (i.e., hand starting position on body midline) versus all predictors 6 and 7 (initial hand location on body midline) for foveal and peripheral targets and between the beta weights of predictors 1, 3, 10, and 12 (hand body midline) versus regressors 4 and 9 (hand peripheral from body midline) for nonfoveated targets.
(see Table 1, Fig. 2C), pooled across hemispheres. Again, mean beta weights for these combinations of regressors were subjected to post hoc comparative analyses. Because of the positioning of our targets (left or right from the body midline) we could not perform an analysis of body-centered target–hand integration effects like the gaze-centered integration effects.

Finally, to compare the gaze-centered and body-centered effects in these five ROIs, we indexed the sensitivity of the representation in these regions for gaze-centered target location, gaze-centered hand location, and body-centered hand location. The index was computed as the difference between the beta weights characterizing the response during the respective peripheral trials with those of the central trials, divided by their sum (see RESULTS for more details). Table 2 illustrates which regressors were used in these calculations.

RESULTS

Our experimental design identified regions that are involved in integrating target and hand representations in gaze-centered coordinates based on the assumption that the metabolic costs are higher for a comparison with hand and target at peripheral locations in the gaze frame (regressors 1, 3, 4, 9, 10, 12), i.e., nonfoveated, than with either of these at the central location (regressors 2, 5, 6, 7, 8, 11) (Fig. 1). The main result is shown in Fig. 3, illustrating three distinct regions that fulfill this requirement ($P < 0.05$, FDR-corrected), including a region in the left posterior parietal cortex, which corresponds anatomically to Brodmann’s area 7 [PPC, Talairach coordinates (mm): $-20$, $-61$, $58$] and a bilateral region in the dorsal premotor cortex [PMd, Talairach coordinates: $-27$, $-10$, $55$ (left) and $18$, $-7$, $58$ (right)]. A region at a similar position in the right PPC was also activated, but its response pattern did not pass statistical threshold.

To analyze the activation patterns of these regions quantitatively, Fig. 4 illustrates the parameter estimates of the regressors that specify the gaze-centered target–hand integration. We restricted this analysis to conditions in which the hand was positioned on the body midline and the target was balanced over left- and rightward locations relative to the body midline to exclude any possible body-centered effects. In all three regions, there was significantly larger activation for movements planned and performed with hand and target at peripheral locations in the gaze frame (regressors 1, 3, 4, 9, 10, and 12 of Table 1) than when either target position (regressors 2 and 11) or hand position (regressors 5, 6, 7, and 8) was presented centrally ($P < 0.05$). This confirms that the integration effect in these regions is not exclusively due to differential activation for only one of the two variables (target or hand), but rather reflects a computation involving both hand and target position in gaze-centered coordinates. Note, however, in this respect, that this analysis should not be interpreted as if no other hand–target comparisons are involved in the computation of the movement direction (see McQuire and Sabes 2009): the present fMRI paradigm does not entail contrasts distinguishing other comparisons (see DISCUSSION).

Figure 4 further suggests that the most everyday situation, i.e., planning a reach toward a foveally viewed target, has a lower metabolic cost than a reach with a foveally viewed hand position. Indeed, a one-sided paired $t$-test shows that this is the case in right PMd ($P < 0.05$), with a tendency toward this effect in left PMd ($P = 0.06$), but not in PPC ($P > 0.8$).

For movement execution, a movement plan must be converted into intrinsic coordinates, such as joint angles, and ultimately into muscle activations. As pointed out in the INTRODUCTION, this transformation requires an estimate of the joint angles of the arm, i.e., a set of body-centered variables. To examine the role of the dorsal premotor and posterior parietal cortex in this mapping, we also examined their activation patterns for reaches starting from central and peripheral hand positions in body coordinates (initial hand position on the body midline vs. away from it). To exclude in this comparison an obvious contamination or bias by the gaze effects described earlier (see Fig. 3), we first identified the posterior parietal and premotor regions independently, based on their peak activation in our predefined reaching network (HP–EP; see METHODS). In the posterior parietal cortex, this revealed peak activation in the lateral and medial regions, both caudally (cIPS) and more anteriorly (aIPS) in both hemispheres (Table 3). Furthermore, a region in the parietooccipital sulcus (PO) was identified. The
dorsal premotor region also showed two separate clusters of bilateral activation: a superior (sPMd) and an inferior dorsal premotor (iPMd) area (Beurze et al. 2009).

We indexed the sensitivity of each of these regions (cIPS, aIPS, PO, sPMd, iPMd) for gaze-centered target position, gaze-centered hand position, and body-centered hand position. These respective indices were computed by taking the difference between the responses of trials with peripheral and central locations in the particular reference frame, divided by their sum. In this analysis, we also distinguished the body-centered hand position index in relation to foveal and peripheral reaches, following recent findings by Prado et al. (2005). Figure 5 demonstrates the computed indices in a proportionalsized view, i.e., relative to each other (the sum of all is 1).

Stars indicate a significant difference \( P < 0.05 \) between the two conditions (central and peripheral). The index characterizing the selectivity for gaze-centered target position was significant in all regions, except PO, where we found only a significant trend. For the gaze-centered hand position, the index was significant in only the iPMd, cIPS and PO regions, which are indeed the regions closest to the gaze-centered integration areas, described in Fig. 3. With regard to the body-centered hand position, the results were significant for foveal reaches in all regions, but only in superior PMd for nonfoveal reaches, which is the region closest to the primary motor cortex. This indicates that the clearest body-centered effects are found in the superior dorsal premotor cortex.

**DISCUSSION**

To plan a reaching movement, the brain must integrate information about the spatial goal of the reach with information

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**TABLE 3. Premotor and parietal brain regions activated during reach planning and execution (HP–EP)**

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Functional Label</th>
<th>Side</th>
<th>Coordinate</th>
<th>t-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentral sulcus</td>
<td>iPMd</td>
<td>L</td>
<td>−24 −13 58</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>25 −10 58</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>sPMd</td>
<td>L</td>
<td>−26 −13 63</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>21 −13 70</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Intraparietal sulcus</td>
<td>aIPS</td>
<td>L</td>
<td>−24 −52 58</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>24 −51 58</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>cIPS</td>
<td>L</td>
<td>−22 −63 49</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>22 −64 49</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Parietooccipital sulcus</td>
<td>PO</td>
<td>L</td>
<td>−15 −80 37</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>12 −86 30</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

Coordinates (in mm): x (lateral/medial), y (anterior/posterior), and z (superior/inferior) in accord with Talairach and Tournoux (1988). The t-values represent the areas’ statistics across all subjects.

**FIG. 4.** Gaze-centered target–hand integration during reach planning. Comparison of the level of activation (beta weights, in arbitrary units) in left (A) and right PMd (B) and in left PPC (C) for the planning of a reach with target and initial hand positions at different locations in gaze-centered coordinates: 1) target central, hand peripheral (regressor 1, 3, 4, 9, 10, 12); 2) target peripheral, hand central (regressor 2, 11); 3) target peripheral, hand peripheral (regressor 5, 6, 7, 8). Error bars: SE.

**FIG. 5.** Relative contributions of reference frames for target and hand position coding in the posterior parietal (aIPS, cIPS), parietooccipital sulcus (PO), and premotor regions (iPMd, sPMd). Indices computed according to Table 2. Stars (★): indicate a significant difference between the peripheral and central condition \( P < 0.05 \). Activation in iPMd and cIPS is mostly modulated by the gaze-centered target representation. Closer to the central sulcus, in the sPMd and aIPS regions, the body-centered hand representation gains influence. PO represents hand position in both gaze- and body-centered coordinates.
about the position of the hand selected for action. From previous studies (Calton et al. 2002; Hoshi and Tanji 2000), including those from our group (Beurze et al. 2007, 2009), it has become clear that the dorsal premotor and the posterior parietal cortex are involved in the coding of target position and effector selection and in the integration of target and effector information for reaching. In the present study, we studied the role of gaze-centered coordinates in the integration process of target and hand positions.

In our paradigm, we capitalized on the idea, put forward by Jackson and colleagues (2005, 2009) based on studies in optic ataxia patients, that gaze-centered integration areas should be able to simultaneously represent and compare the spatial location of the target in gaze-centered coordinates and the starting position of the hand in gaze-centered coordinates. This simultaneous representation of multiple spatial locations that must be directly compared with one another is presumably metabolically more costly than representing only a single location relative to gaze.

Based on this notion, we postulated a higher BOLD signal for reaches into the visual periphery than for reaches directed toward foveally viewed targets. Indeed, both bilateral PMd and an area in the left PPC showed this result, consistent with the notion that they represent target locations in gaze-centered coordinates (Batista et al. 2007; Medendorp et al. 2003, 2005). We followed the same line of reasoning for delineating gaze-centered hand position effects: if the hand is positioned in line with gaze, its position does not need to be separately encoded in gaze-centered coordinates, leading to less brain activation for planning a reach with a foveally viewed initial hand position than for planning a reach with a gaze-peripheral hand position. Again, PMd and left PPC showed clear gaze-centered hand position effects. Taken together, these observations suggest that the PMd and PPC areas have access to both a gaze-centered target and a gaze-centered hand representation. By corollary, these regions are in a good position to be involved in the integration of these two types of information to compute a gaze-centered movement vector.

We also studied the sensitivity of the premotor and posterior parietal cortex for hand position in body-centered coordinates, by examining the differences in activation for reaches that are made with the hand initially aligned with the body midline versus those with the initial hand position away from the body midline. This analysis revealed body-centered hand position effects in both neural structures. Also an area near the parietooccipital junction was sensitive for changes in body-centered hand position. The body-centered effects in the superior part of the PMd (sPMd) were found irrespective of whether the reach was made to a foveal or peripheral target. This mixture of gaze- and body-centered reference frames in sPMd is in line with recent findings in monkeys (Batista et al. 2007; Cisek and Kalaska 2002; Pesaran et al. 2006). Unfortunately, our data set did not allow for a comparison between central and peripheral targets in body-centered coordinates, which means that any body-centered integration effects could not be tested directly. Based on our observations, however, it seems logical that sPMd is involved in the bidirectional transformations between reference frames.

At first sight, it seems odd that the cIPS, aIPS, iPMd, and PO show body-centered hand position effects only in relation to foveal reaches and thus not for peripheral reaches. One explanation is that foveal reaches are coded simultaneously in gaze- and body-centered coordinates and peripheral reaches are not. Another possibility is that, in everyday life, reaches toward initially peripheral targets are almost always preceded by a saccade to foveate the target. Indeed, also in our results (Fig. 4), foveally directed reaches revealed the lowest metabolic costs, perhaps reflecting that these are most typical. Since a gaze-centered movement plan still has to be mapped to body-centered coordinates for reach execution, it may be the case that a body-centered movement plan is more readily available for foveal targets than for nonfoveal reach targets. Testing this possibility requires further experimentation, perhaps involving imaging techniques with higher temporal resolution than fMRI.

The posterior parietal cortex has access to different kinds of sensory information and is thought to be involved in the planning of movements of various effectors (eyes, hand, fingers) (Andersen and Buneo 2002). That only the left PPC was found to be significantly active may be attributed to the fact that the reaches were performed with the right hand (Medendorp et al. 2005; Snyder et al. 2006), but is also consistent with reports suggesting a specific role for the left parietal cortex in arm movement planning (Rushworth et al. 2003; Wheaton et al. 2009).

Relation to previous work

Recently, Filimon et al. (2009) described two medial parietal areas with a visuomotor role in goal-directed reaching movements: the superior parietooccipital sulcus (sPOS) and the anterior precuneus (aPCu). The latter area seems to correspond to the parietal area described by Pellijeff et al. (2006) and has been implicated in the dynamic representation of a body schema because of its sensitivity to postural changes of the arm. The sPOS region is very close to the region at the parietooccipital junction, described by Prado et al. (2005) to be active specifically for peripheral reaches, not for reaches into central vision. Filimon et al. (2009) found the sPOS more strongly activated for reaches with than without vision of the hand and therefore assigned it a role in the visual monitoring of reaching movements. In our study, where subjects planned and performed reaching movements in complete darkness without visual feedback from the hand, this area did not show up in our gaze-centered hand–target integration contrast, suggesting that sPOS can compute this vector based only on visual input from both target and hand. Our area PO, close to Filimon et al.’s sPOS area, represented the position of the hand in gaze-centered coordinates and in body-centered coordinates when the target is foveated. This would be in correspondence with the suggestion from Filimon et al. (2009) that the area codes the “visual” distance from the hand to the target.

The gaze-centered integration area we found was located very close to the combined aPCu–medial intraparietal sulcus network, as described by Filimon et al. (2009). As Filimon et al. (2009) speculated, this area might comprise multiple populations of neurons, some visuomotor and some proprioceptive-motor, which would explain both their own finding that the region is similarly activated for reaches with and without the hand visible and the finding of Pellijeff et al. (2006) that it reflects postural changes. Our results suggest that the aPCu area might use gaze-centered coordinates to bring these neuronal populations in alignment.
Our results are also compatible with results in patients with optic ataxia (OA), who have damage in the posterior parietal cortex (Karnath and Perenin 2005; Perenin and Vighetto 1988). In fact, the basic premise of the present paradigm is based on the interpretation by Jackson et al. (2009) of the deficits in nonfoveal OA patients. In OA, the disorder of visually guided reaching movements cannot be attributed to a basic motor or sensory deficit (Bálint 1909; Perenin and Vighetto 1988; Rizzo and Vecera 2002), but seems a higher-level impairment in spatial integration of information from both vision and proprioception (Blangero et al. 2007; 2009; Khan et al. 2005a,b; Pisella et al. 2009). According to Jackson et al. (2009), these deficits result from an impaired ability to simultaneously represent multiple spatial locations that must be directly compared with one another. In our study, in the case of a peripheral target, gaze direction and target location had to be represented simultaneously, whereas for a reach to a central target, these directions matched. The region in the posterior parietal cortex showed more activation for the preparation of reaches to peripheral targets, suggesting this area might be involved in such a simultaneous representation of multiple spatial locations.

The notion that PMd reflects gaze-centered signals as well as a body-centered hand representation corresponds closely to studies by Cisek and Kalaska (2002). Interestingly, although gaze-related modulations were found in a large percentage of PMd cells, their overall effect on cell activity was only modest. Instead, total cell activity was more strongly related to the intended movement expressed in body-related coordinates. This supports the hypothesis that PMd is involved in the transformation of the movement plan into body-centered coordinates.

Limits of interpretation

The working hypothesis of this study was that separate gaze-centered and body-centered coordinate frameworks exist for reach planning. The evidence for gaze-centered coordinates in this study was based on two assumptions: 1) that the calculation of a gaze-centered reach signal is computationally more costly when the gaze is not aligned with the hand or the target than when it is directed to either of these and 2) that this computational load will result in a stronger BOLD signal. To the best of our knowledge, there are no electrophysiological experiments in nonhuman primates that could support these assumptions. This emphasizes the novelty of the present results and indicates the need to investigate the issue further with higher resolution electrophysiological techniques. But are there alternative explanations for greater activity when the direction of gaze is not on the target or the hand?

For example, if metabolic costs are higher for more uncertain representations and more uncertain representations reflect more peripheral locations, this could explain the patterns that we see in the data. Nevertheless, this still leaves unchanged the notion that peripheral is defined relative to gaze, i.e., reflecting processing in a gaze-centered reference frame. Along the same lines, could the increase in activation be simply due to the representation of two nonfoveal spatial locations (hand and target) independent of any calculation of the reach signal in a particular reference frame? We also consider this explanation unlikely since all the voxels based in our analysis were pre-defined based on their involvement in reaching movements. As a side note, because of this definition of the reach network (reaches > saccades), it should also be realized that our analysis did not reveal similar effects in areas that respond equally to eye and hand movements (see Beurze et al. 2009; Levy et al. 2007).

Another observation reported in the literature, which one might associate with the present findings, is called “foveal sparing.” Mountcastle et al. (1981) reported that visual neurons in area 7A respond more weakly when a stimulus falls on the fovea than when it falls on the retinal periphery (but see Quraishi et al. 2007). We also do not consider this explanation to underlie the present findings, which were obtained in different brain areas, and with remembered stimuli.

Could the increase in activation when gaze is neither on the target nor on the hand simply reflect spatial attention? One theory states that attention can be directed to only one region of space at a time (spotlight theory; see Posner et al. 1980). The spotlight can be expanded or contracted depending on the size of the region to be attended. This model of attention cannot explain our findings. When both target and hand are gaze-peripheral, the focus of attention should spread and thus become more diffuse, resulting in reduced activations, which is not what we found. Another theory states that attention can be divided flexibly to different locations (Müller et al. 2003). With this model at hand, we neither understand how there could be different activations for when the hand is peripheral and the target is central compared with when the hand is gaze-central and the target is peripheral, as our data show (see Fig. 3).

Another factor to mention here relates to the differences in the amounts of hemispheric transfer of spatial information in different trial conditions. We have checked this by comparing the activation in trials at which hand and target were both peripheral relative to gaze, but in opposite visual hemifields versus trials in which hand and target were both peripheral, but in the same visual hemifield. Although we found no significant differences between these types of trials in the IPS, we did find a difference in the PMd region. PMd showed larger activation when hand and target were peripheral in opposite hemifields than in the same hemifield, as if computing the movement plan involving hemispheric transfer is metabolically more costly in this region.

Then, why at all would the brain use gaze-centered coordinates to integrate target and hand position, even in the dark, when the hand is invisible and its position is to be derived from body-centered proprioceptive input? Several ecological explanations can be listed. First, the visual system is the dominant sensory system for spatial input and many brain regions are involved in visual processing. A second reason is related to the difference in spatial resolution of the gaze- and body-centered coordinate frames. The transformation of retinotopic target input into body-centered coordinates might degrade the resolution of the original input. Another argument for a gaze-centered frame may be that it is simpler to orchestrate multiple effectors, such as eye and hand, when they move to the same target. Furthermore, a gaze-centered planning mechanism may facilitate visually based movement corrections. Thus spatial behavior in the dark may not automatically switch off all the gaze-centered computations; the brain could simply use its internal eye position signal to transform between body- and
gaze-centered reference frames and vice versa (Crawford et al. 2004).

As a final note here, we are well aware that we have conceptualized reference frames as very discrete characteristics possessed by certain cortical modules. This is of course an oversimplification of how the brain works (Pouget et al. 2002). There are many studies showing signs of multiple reference frames in many sensorimotor areas (Batista et al. 2007; Khan et al. 2007; Pesaran et al. 2006). It may be possible that the brain compares target and hand positions at more than one level in the visuomotor pathway in multiple reference frames and then integrates all these comparisons in the computation of the movement vector (Blohm et al. 2007; McGuire and Sables 2009). In fact, one could view our findings in Fig. 5 to be consistent with this suggestion. Similarly, the present observations of gaze-centered and body-centered representations do not argue against the existence of representations in other reference frames, such as head-centered, object-centered, or other intermediate coding frames.

To recapitulate, the most novel finding of our study is that areas in the PPC and PMd are more active during reach plans in which starting hand position and final target position are not aligned to the direction of gaze compared with when one of them is in alignment. Although this finding awaits confirmation at the single-neuron level, we have taken it as evidence for a gaze-centered integration mechanism in PPC and PMd and, as such, our study provides a step forward in dissociating reference frames for reach planning in the human brain using fMRI.

Conclusion

To conclude, the present study revealed evidence for gaze-centered target and hand position coding in regions in dorsal premotor cortex and posterior parietal cortex, suggesting that these areas are involved in computing movement vectors in gaze-centered coordinates. We also found body-centered coding of hand positions, which may be related to the subsequent transformation from the gaze-centered movement vector into a body-centered movement plan (in PMd) or to the original transformation of proprioceptive body-centered information into a gaze-centered hand position (in PPC). Although the present findings advance our knowledge about the neural computations for reach planning, it should also be clear that more work is needed in unraveling the computational functions of specific physiological substrates in generating reaching movements.

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Disclosures

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