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Human Parietal "Reach Region" Primarily Encodes Intrinsic Visual Direction, Not Extrinsic Movement Direction, in a Visual–Motor Dissociation Task

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Posterior parietal cortex (PPC) participates in the planning of visuospatial behaviors, including reach movements, in gaze-centered coordinates. It is not known if these representations encode the *visual goal* in retinal coordinates, or the *movement direction* relative to gaze. Here, by dissociating the intrinsic retinal stimulus from the extrinsic direction of movement, we show that PPC employs a visual code. Using delayed pointing and event-related functional magnetic resonance imaging, we identified a cluster of PPC regions whose activity was topographically (contralaterally) related to the direction of the planned movement. We then switched the normal visual–motor spatial relationship by adapting subjects to optical left/right reversing prisms. With prisms, movement-related PPC topography reversed, remaining tied to the retinal image. Thus, remarkably, the PPC region in each hemisphere now responded more for planned *ipsilateral* pointing movements. Other non-PPC regions showed the opposite world- or motor-fixed pattern. These findings suggest that PPC primarily encodes not motor commands but movement goals in visual coordinates.

Keywords: pointing, precuneus, reaching, reversing prism adaptation, visuomotor learning, visuomotor transformation

Introduction

When we reach for a visual stimulus, the brain initially codes the target in eye-fixed retinal coordinates but the final output command is coded in muscle coordinates. A central problem in neuroscience is how and where the central nervous system achieves the transformation between these visual and motor representations (Soechting and Flanders 1992; Pouget and Snyder 2000; Andersen and Buneo 2002; Crawford et al. 2004). Perhaps the most fundamental, yet unanswered, question that visuomotor scientists can ask is at what stage in the transformation is the transition made from a visual representation to a motor representation?

Primate neurophysiology has revealed a network for visuomotor transformations that includes the posterior parietal (PPC) and premotor cortices (Kalaska and Crammond 1992; Colby and Goldberg 1999; Snyder 2000; Andersen and Buneo 2002). The PPC can be further divided into several functional subregions (Colby and Goldberg 1999; Andersen and Buneo 2002). In particular, the lateral intraparietal (LIP) sulcus encodes intended saccades (Snyder et al. 1997; Dickinson et al. 2003), whereas the medial intraparietal region often called the "parietal reach region" (PRR), is more active during arm movements (Snyder et al., 1997;Batista et al., 1999; Calton et al., 2002). Both regions encode the target and the action in contralateral space relative to the gaze pointing direction, that is, in a gaze-centered frame like the retina (Duhamel et al. 1992; Stricanne et al. 1996; Batista et al. 1999; Colby and Goldberg 1999).

Recent functional magnetic resonance imaging (fMRI) experiments suggest that human PPC probably has a similar functional organization. Human PPC contains a region (or regions), perhaps analogous to monkey LIP that selectively code for contralateral saccades (Sereno et al. 2001; Medendorp et al. 2003; Schluppeck et al. 2005). Some regions within PPC are also activated during contralateral pointing movements and are modulated by eye position in a manner consistent with the physiology of monkey PRR (DeSouza et al. 2000; Medendorp et al. 2003; Medendorp, Goltz, Crawford, et al. 2005; Medendorp, Goltz, Vilis, 2005). Specifically, Connolly et al. (2003) have identified a dorso-medial area of PPC within the precuneus that they called the human PRR.

Moreover, some of these saccade and pointing regions, like the corresponding monkey regions (Duhamel et al. 1992; Batista et al. 1999), appear to represent space in a gaze-centered frame, and update these representations when the eyes rotate (Medendorp et al. 2003; Merriam et al. 2003). This has recently been confirmed causally: Optic ataxia patients with PPC damage show reach deficits in a gaze-centered frame that is updated with each saccade (Khan, Pisella, Rossetti, et al. 2005; Khan, Pisella, Vighetto, et al. 2005). Thus, spatial activity in human PRR is not tied to the initial retinal input but instead provides a dynamic, gaze-centered representation (Khan, Pisella, Vighetto, et al. 2005).

However, the more basic question remains unanswered: It is not known if this gaze-centered signal encodes the visual goal of the movement (upstream from the vision-to-motor transformation) (Gottlieb and Goldberg 1999) or the direction of the movement (downstream from this transformation) (Kalaska 1996; Eskandar and Assad 1999; Zhang and Barash 2000). This fundamental question has practical importance because PRR is one of the regions that is currently being investigated as a possible neural interface for prosthetic devices (Musallam et al. 2004).

This is a difficult question to address experimentally because the visual goal and movement direction are normally aligned. When subjects are asked to look or point in the direction opposite to the visual target ("antisaccades" and "antipointing") neural activity sometimes shows a transient visual response but ends up aligned with the movement direction (Kalaska 1996; Eskandar and Assad 1999; Connolly et al. 2000; Zhang and Barash 2000). This shows that PPC activity can be dissociated from the visual stimulus. However, these antipointing and antisaccade tasks instruct the subject to imagine a *goal* opposite

to the stimulus, so they probably do not truly dissociate the goal from the movement.

A better way to specifically dissociate the retinal coordinates of the goal from the corresponding motor command is to train subjects to point while looking through optical reversing prisms (Kohler 1962; Sugita 1996). A recent study has shown that this produces a simple visuomotor adaptation that does not generalize to other motor tasks (Marotta et al. 2005). Because this optical manipulation reverses the normal spatial contingency between the proximal retinal stimulus and the direction of movement, we can now ask if human PRR encodes the intrinsic direction of the goal in retinal coordinates, or the extrinsic direction of movement relative to gaze.

Here we localized parietal areas active during a pointing task in an initial fMRI block design experiment. Subsequently, using an event-related fMRI design, we mapped those areas active during 2 specific components of the pointing task: the spatial memory delay and the motor pointing. Finally, we tested the activity of those areas in the reversing prism condition.

Materials and Methods

Participants

Nine right handed subjects participated in these experiments (3 females and 6 males, 29.6 ± 5.4 year, mean ± standard deviation [SD]). All subjects provided informed written consent and experimental protocols were approved by the York University Human Participants Review Subcommittee and the University of Western Ontario Ethics Review Board.

Behavioral Paradigms

Block Design Behavioral Paradigm

Block design scans were employed to find parietal regions of interest (ROIs) related to finger pointing and saccades (Fig. 1). Before each scan, subjects were instructed to make either right index finger pointing movements or saccades. With the left eye covered by a cardboard occluder, subjects fixated a central cross with the right eye. Then, a peripheral dot target was presented for 250 ms to either the left or right at random horizontal eccentricities between 10° and 25°. Subsequently, a band of distractors (70° horizontal × 8° vertical; angular eccentricity of the individual dot elements, 0.8°; density, 0.14 dots per square degree) flashed at 5 Hz for 2.5 s, during which the subjects maintained central fixation. Then, at distractor offset, subjects made the previously cued movement—finger pointing or saccade—to the remembered target location and immediately back to center. During the pointing scans, subjects were instructed to maintain central gaze fixation at all times. During the saccade scans, subjects were instructed to maintain visibility of their right index finger and keep it directed at the fixation cross at all times. Pointing movements consisted of finger movements, such that the right index finger pointed to the remembered target location. Topographic saccade regions were determined using 3 scans. Each scan had 10 epochs of 20 s each. Within each scan, 5 leftward and rightward saccade epochs were alternated with fixation epochs. Scans to determine pointing topography had the same structure described above. For both saccade and pointing scans the time between successive movements was 5 s, resulting in 4 movement trials per epoch. Each scan included 2 initial and 2 ending fixation epochs, each 20 s in length. The starting movement direction was varied from scan-to-scan. Subjects were required to maintain sight of the tip of their right index finger at all times because during the event-related fMRI reversing prism adaptation experiment which followed, it would be necessary for subjects to see their finger in order to acquire the adaptation.

Event-Related Design Behavioral Paradigm

Subsequent to the identification of topographically organized areas of PPC for saccades and pointing via the block design experiment, event-related scans were employed. This approach allowed analysis of the response periods separately, most importantly the memory delay period in isolation. This allowed study of parietal activity during the memory delay without contamination of the signals by visual or motor activity. With the left eye covered by a cardboard occluder, subjects fixated a central cross for 4 s with the right eye and with the right index finger pointing to it (see Fig. 2*A*) (Snyder et al. 1997; Batista et al. 1999; Sereno et al. 2001). Then, a peripheral target dot was presented for 250 ms. The dot appeared to either the left or right at random horizontal eccentricities between 5° and 12°, thereby instructing the direction and amplitude of the pointing movement to follow. Subsequently, a band

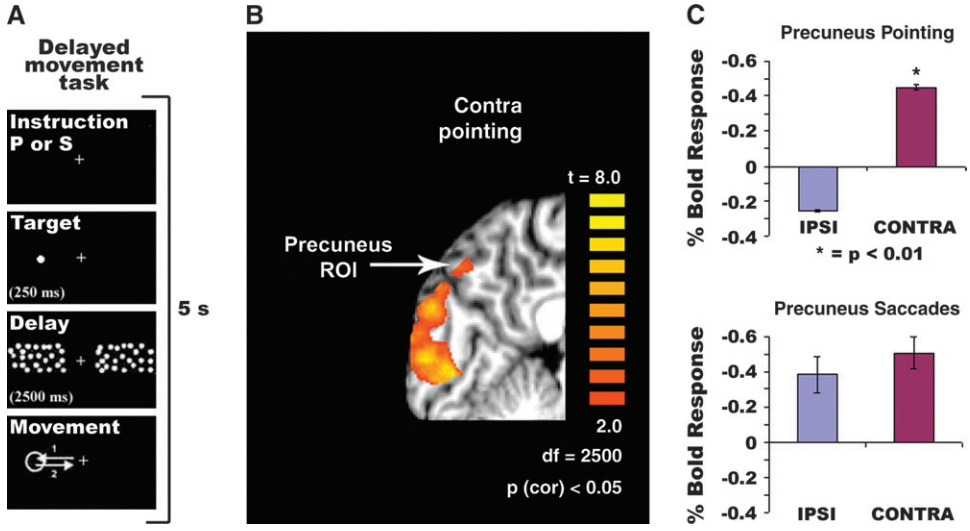

Figure 1. The block design localizer delayed-movement task. (*A*) Subjects were cued to either point or make a saccade before the onset of each scan. Subsequently, subjects fixated a central cross and pointed to the same cross with their index finger. A peripheral dot was presented for 250 ms. After this target disappeared, a horizontal band of distractors dots blinked for 2.5 s. At distractor offset, subjects made a fast pointing or saccade movement to the remembered target location and immediately made a movement back to center. The time between successive movements was 5 s. Subjects made no movements during the fixation and delay periods. (*B*) Medial view of the left hemisphere showing pointing activations within the precuneus. The activity shown is the result of the GLM contrast of rightward movements +, leftward movements − for 6 subjects. The color bar shows the *t*-values associated with the activated voxels. The "*P*" value shown is Bonferroni corrected and is associated with a *t*-statistic. (*C*) Percent signal change in the BOLD response within the precuneus ROI during pointing (top) and during saccades (bottom) while making ipsilateral or contralateral movements. $*P \leq 0.01$ in a Student's paired *t*-test. Error bars are standard error of the mean (SEM).

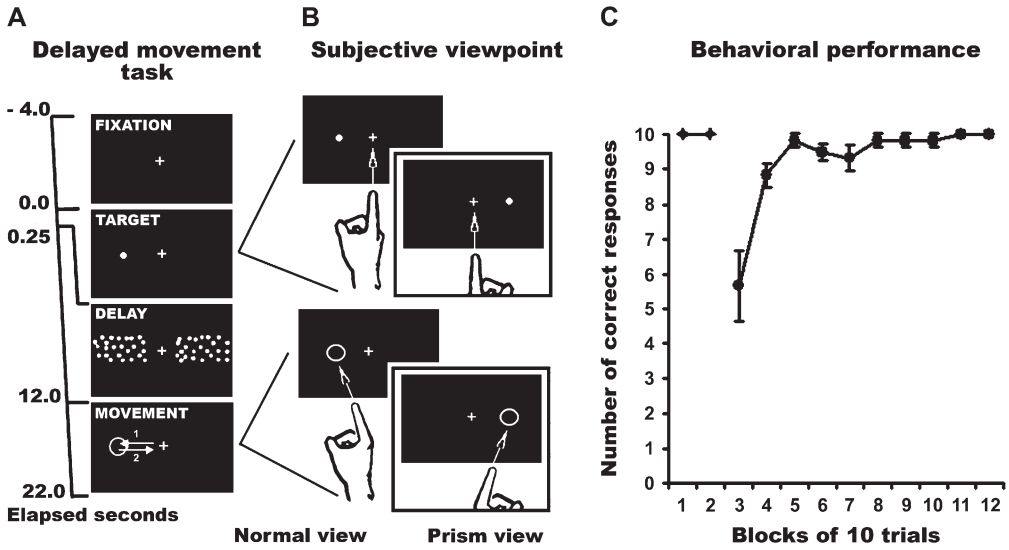

Figure 2. (*A*) Event-related delayed-movement task. Subjects fixated a central cross for 4 s. Then a peripheral dot target was presented for 250 ms toward the right or left at random horizontal eccentricities between 10° and 25°. After this target disappeared, a horizontal band of distractor dots flashed on and off at 5 Hz for 11.75 s. Subsequently, subjects made a rapid pointing movement with the right index finger to the remembered target location and then immediately pointed back to center. The total trial length was 26 s. (*B*) Viewpoint from the subject's perspective. The prism-pointing task was identical to the previous task except that the subjects had to point while looking through a left–right reversing prism. When looking through the prism the subject's view of the index finger and the actual movements that they made appeared to be reversed. This reversed view of the pointing finger caused subjects to adapt their pointing movements to the opposite direction (shown here) after the first few incorrect trials. The diagrams within the boxes are renderings of the subject's view through the prism. The circles represent the remembered location where the subject had to point in order to perform the task correctly. (*C*) Behavioral data collected from 6 subjects in a task identical to that reported here but performed outside of the MRI bore. The figure shows the mean number of correct responses while pointing without (diamonds) and with prism (circles). The data are binned in blocks of 10 trials each. Errors bars are SEM.

of distractors (70° horizontal × 8° vertical; angular eccentricity of the individual dot elements, 0.8°; density, 0.14 dots per square degree) flashed at 5 Hz for 11.75 s, during which the subjects maintained central fixation (this memory period was designed to isolate activity related to the stored visuospatial movement plan (Sereno et al. 2001; Medendorp et al. 2003). At distractor offset, subjects made the instructed pointing movement with the right index finger to the remembered target location and immediately pointed back to center while maintaining continuous fixation. This movement period was given 4 s in the analysis, and was followed by an additional 6 s of control fixation to allow the blood oxygen level–dependent (BOLD) response to return to baseline levels. The next target was presented after another 4 s of central fixation. The whole trial lasted 26 s. On average, we recorded 24 leftward, and 24 rightward trials per subject in this condition. Subjects were instructed to maintain central gaze fixation at all times while keeping sight of the tip of their right index finger. The starting pointing direction was varied from scan-to-scan for each subject.

Prism Event-Related Behavioral Paradigm

The prism task was identical to the event-related paradigm described above except that the subjects looked through a left–right reversing dove prism 25 × 105.7 × 25 mm. The reversing prism was carefully centered on the eye to prevent tonic positional shifts of the fixation point (as occurs with displacing (wedge) prisms—not used here—which produce positional shifts when fixating a centered point). Prism training was performed with subjects positioned normally within the MRI, after acquisition of fMRI data for control pointing was complete. No scanning was conducted during the training period, given the need to communicate with the subjects and the fact that the adaptation took a small number of trials, and had large variability across subjects that it was unlikely to produce statistically significant results on analysis of the fMRI signals. It was necessary for subjects to see their finger moving through the prism in order to produce the stimulus for visuomotor adaptation (see Fig. 2*B*). Training was continued until subjects attained 10 consecutively correct trials. fMRI recordings were then resumed with the prism still in place so that the visuomotor reversal was maintained for the remainder of the experiment. Performance was monitored online via an infrared-sensitive charge coupled device video camera at the back of the magnet bore which provided an unobstructed view of both the subject's right index finger and the visual stimulus displayed on the top of the magnet bore. An additional behavioral experiment was done in 6 subjects in a task identical to that reported here but performed outside of the MRI bore (Fig. 2*C*). Eye tracking was not performed inside the magnet because the prism apparatus used completely occluded the eyes, however, ocular responses outside the magnet using conventional eye tracking apparatus confirm that the subjects were capable of maintaining fixation and produce correct pointing responses while doing our task (Medendorp et al. 2003). Moreover, in-magnet eye tracking was used in a similar prior study of topography and antisaccades (Medendorp, Goltz and Vilis 2005).

Imaging Methods

Data were collected with a 4.0-Tesla Varian/Siemens hybrid whole-body imaging system. To maximize the signal-to-noise ratio of our recordings we used an occipito-parietal radio-frequency quadrature surface coil (15.5 × 11.5-cm elements), which was centered over the posterior parietal lobe. The size of the coil elements and the placement of the subjects' heads with respect to this coil limited the recordings to the back half of the brain because it was designed to image only occipital and parietal regions effectively, with a rapid fall-off of signal outside its physical margins. In an additional experiment we tried repeating these procedures with a "full head coil" to simultaneously image parietal and frontal cortices but the head coil used did not yield sufficient signal to demonstrate the basic left–right topography required for these experiments. More trials or a newer style phased array coil would likely make this possible.

Subjects viewed stimuli generated with Macromedia Flash MX Professional 2004 software (San Francisco, CA) and presented using a computer connected to an Avotec SV-6021 LCD projector (resolution 1024 × 768 pixels, refresh rate, 60 Hz). The stimulus images were projected off a first-surface mirror onto the top of the magnet bore in front of the subject's eyes. Seventeen contiguous axial-oblique slices were used to image the entire parietal cortex as well as portions of the occipital lobe. Functional data were obtained using navigator echo-corrected T_2*-weighted segmented spiral imaging (time echo [TE], 15 ms; flip angle [FA], 40°; field of view [FOV], 19.2 × 19.2 cm; volume acquisition time, 2 s [time repetition (TR) = 1 s × 2 shots]; in-plane voxel size, 3 × 3 mm; thickness, 4 mm). Functional data were superimposed

onto high-resolution inversion-prepared three-dimensional T_1-weighted anatomical images of the brain (typically 128 slices; 256 × 256; FOV, 19.2 × 19.2 cm; TE, 3.0 ms; TR, 50.0 ms; in-plane voxel size 0.8 × 0.8 mm, 1-mm thickness) using a phase reference image that corrected for high-field geometric distortions. In separate sessions, subjects were rescanned using a birdcage-style head coil to obtain full-brain anatomical images. A high-resolution inversion-prepared three-dimensional T_1-weighted sequence was used (FA, 15°; voxel size, 1.0 mm isovoxel; 256 × 256; 164 slices; TR, 0.76 s; TE, 5.3 ms). Surface coil images were aligned manually to head coil images.

Analysis was performed using Brain Voyager 4.96 software (Brain Innovation, Maastricht, The Netherlands). Full-brain anatomical images for each subject were segmented at the gray–white matter boundary, rendered and inflated for visualization purposes only. Time-courses corresponding to each voxel were corrected for linear temporal drift. Anatomical and functional images were transformed into Talairach space to obtain stereotaxic coordinates for the ROIs. All scans were screened for subject head motion. In the analysis of the block design functional data, we excluded from further analysis 44 trials (5 s each) out of 1440 trials due to motion artifacts (across all subjects). Similarly, in the event-related functional data analysis, we excluded 30 trials (26 s each) out of 1018 trials (across all subjects) because of head motion.

Block Design Experiments

The block design experiments were conducted to reveal parietal regions demonstrating left–right topography for both saccades and pointing. In order to localize areas for saccades and pointing we pooled all the subjects' data from the block design experiments together into 2 data sets, one for saccades and the other for pointing. For each data set we created predictors for leftward and rightward movements, and we convolved the boxcar function for each of these predictors with a standard hemodynamic response function (TR = 2000 ms; delta = 2.5; tau = 1.25). We then conducted a multisubject general linear model (GLM) analysis on each data set revealing ROIs with a preference for saccades or pointing versus fixation. Subsequently, we conducted contrasts for the activity related to the leftward predictor versus the one related to the rightward predictor (the Brain Voyager technical terminology would be leftward predictor plus, rightward predictor minus) to identify regions exhibiting left–right topography (this contrast will reveal regions with a preference for contralaterally directed movements). This analysis was implemented so that areas activated for both contralateral and ipsilateral targets with the same magnitude would not emerge as significant in the statistical maps. Using the result of this contrast, we generated a statistical map that was used as the ROI for individual subjects (all data were in stereotaxic space prior to analysis). Time-courses were extracted for all subjects individually on a scan-by-scan basis using the statistical map of the ROI generated from the group data. This was done using a maximum ROI size of 10 × 10 × 10 mm, with the statistical threshold for the map set to $P < 0.01$ (Bonferroni corrected for the number of voxels tested), with the additional statistical criterion that a given activated voxel must be adjacent to 6 or more similarly identified voxels (in x, y, or z directions). Percent signal change of the BOLD response was computed using the following formula: (activated BOLD—baseline BOLD/baseline BOLD) × 100, where the activated BOLD was the raw fMRI signal for each predictor and the baseline BOLD was the raw fMRI signal during fixation periods. These blocked experiments were useful for determining the parietal regions exhibiting topography but they did not allow the stimulus, memory delay, and movement components to be analyzed separately. In order to be able to do this, we conducted the event-related study described below.

Event-Related Design Experiments

The block design experiments described above were used to provide the ROIs for parietal regions that exhibited left–right topography for saccades and pointing. The rest of the experiments to be described will focus solely on topography for pointing, first before adaptation to reversing prisms and then subsequent to that adaptation. The scanner imaging parameters were the same as for the block design, with exception of the necessary changes in stimulus timing as described in the event-related behavioral paradigm.

The most important difference between the 2 designs is that we created separate predictors for the rightward and leftward pointing during memory delay and motor response periods for the event-related scans. For each of these 4 predictors we convolved the impulse function for the individual predictor with a standard hemodynamic response function (TR = 2000; delta = 2.5; tau = 1.25). As before, we pooled all data from all subjects together into one data set and conducted a multisubject GLM regression analysis, revealing regions significantly activated during either memory delay or movement periods relative to fixation. After this omnibus GLM, we conducted a predictor contrast between the rightward intended pointing predictor plus, and the leftward intended pointing predictor minus to reveal topographically organized regions within parietal cortex. Specifically, we wanted to find effector-specific areas (Medendorp, Goltz, Crawford, et al. 2005) demonstrating a preference for rightward pointing in left parietal cortex, given the known left–right topography in this region (Medendorp et al. 2003). Using the result of this contrast, we generated a statistical map that was used as the ROI for individual subjects (all data were in stereotaxic space prior to analysis). Using the same approach, a similar statistical map was also generated for the movement period alone using a similar contrast of the movement period predictors.

Time-courses were extracted for all subjects individually on a scan-by-scan basis using the statistical map of the ROI generated from the group event-related data. This was done using a maximum ROI size of 10 × 10 × 10 mm with the statistical threshold for the map set to $P < 0.01$ (Bonferroni corrected for multiple comparisons associated with the number of voxels tested) for the memory delay period and $P < 0.05$ (Bonferroni corrected for multiple comparisons) for the movement period, and the additional criterion that a given activated voxel must be adjacent to 6 or more similarly identified voxels (in x, y, or z space). Percent signal change of the BOLD response was computed using the following formula: (activated BOLD—baseline BOLD/baseline BOLD) × 100, where the activated BOLD was the raw fMRI signal for each predictor and the baseline BOLD was the raw fMRI signal during fixation periods at the beginning (6 s) and end (12 s) of a given scan. This was done for the memory delay and motor periods for each event-related scan and then averaged first within a given subject and finally across subjects, such that each subject's data were given the same weighting in the analysis.

The time-courses obtained represent the percent BOLD signal change in each ROI during specific conditions. For example, we obtained a time-course for left hemisphere PRR during the delay period for stimuli presented to the right visual field and for stimuli presented to the left visual field. Once we obtained the time-courses for those 2 conditions, we subtracted the percent BOLD signal changes obtained from the left condition minus the one obtained from the right condition yielding a percent signal change that represents the topographical activity for stimuli presented to either side (see Figs 5 and S1).

Results

Our localizer pointing task (Fig. 1*B*) confirmed the functional topology that has been previously observed in the PPC (DeSouza et al. 2000; Sereno et al. 2001; Connolly et al. 2003; Medendorp et al. 2003; Merriam et al. 2003). The activated area marked "ROI" corresponds to the precuneus landmarks used previously to localize PRR (Connolly et al. 2003) and was situated along the medial surface of the parietal lobe, medial to the intraparietal sulcus, anterior to the parieto-occipital sulcus, and posterior to the subparietal sulcus (Fig. 1*B*) (Talairach coordinates [TC]: $x = -8 \pm 1.6$, $y = -74 \pm 1.7$, $z = 42 \pm 1.6$).

Our localizer data also provided the novel observation that this ROI showed statistically significant topographical activity for pointing (Student's t-test for ipsilateral vs. contralateral percent BOLD activation, $P < 0.01$) but *not* for saccades (Student's t-test for ipsilateral vs. contralateral percent BOLD activation) (Fig. 1*C*). Therefore, although this region may show the same general activation for saccades as for pointing, this activity does not contribute to the topographic activation that

forms the basis for the experiments below. Henceforth, we will refer to this region as human PRR.

For our main paradigm we used an event-related fMRI design that allowed us to analyze the topographical response during the memory and movement periods of our task separately. The TC of the ROI from our localizer data were used to guide selection of the ROI in the event-related data but the precise extent of the ROI was described in the *event-related design experiments section*. Figure 3 plots the results of statistical contrast of right intended pointing plus, left intended pointing minus data over a posterior–dorsal–medial view of the left hemisphere visualized on an "inflated brain." This contrast is the approach that we have used previously to demonstrate topography (Medendorp et al. 2003) and effector specificity (Medendorp, Goltz, Crawford, et al. 2005). Figure 3(*A*) shows that during the 12-s memory interval of the task, the only region that was significantly spatially selective (Student's *t*-test for ipsilateral vs. contralateral percent BOLD activation; t(peak value) = 8, df = 5460, P[cor] < 0.01) was the ROI corresponding to PRR, that is, left PRR was significantly more activated for rightward than leftward pointing.

To contextualize the activation in PRR with the concurrent activity in the surrounding visual and visuomotor areas, we relaxed the statistical threshold for the same GLM contrast and observed the broader activity during the memory delay period (Fig. 3*B*). This revealed a network of areas with trends toward spatial selectivity that activated while PRR was active. These regions included one lateral to the intraparietal sulcus that, based on previous studies, we have labeled LIP (TC: x = –26 ± 1.1, y = –68 ± 2.9, z = 41 ± 1.3) (Sereno et al. 2001; Medendorp et al. 2003; Schluppeck et al. 2005). Similarly, we labeled more posterior "visual" regions as a putatively V7 homologue (TC x = –27 ± 0.9, y = –79 ± 1.4, z = 29 ± 1), and V3 (TC) x = –28 ± 0.5, y, –83 ± 1.8, z = 14.6 ± 0.9) (Shipp et al. 1995; Schluppeck et al. 2005). We also observed a more anterior parietal area of activation that corresponded anatomically to Brodmann's area 7 (BA7) (TC x = –12 ± 0.8, y = 60 ± 1.1, z = 57 ± 1.6), which is thought to function in the storage of motor sequences in spatial working memory during finger movements (Sadato et al. 1996). All of these regions were more activated for contralateral pointing than ipsilateral pointing. These areas' coordinates agree with previous studies (Sereno et al. 2001; Connolly et al. 2003; Merriam et al. 2003).

We did a mirror image analysis for right parietal cortex and qualitatively found the same results, that is, a similar network of ROIs was activated but now with the contrast leftward pointing movements plus, rightward pointing movements minus (see Fig. S2 for single subject examples from 2 individuals). However, right cortical activation never reached Bonferroni-corrected significance because our subjects always used their right hand. Previously we showed that the maximal cortical activation for pointing in the delayed pointing task occurred in the cortical hemisphere that is contralateral to both the goal and the effector (here the right hand) (Medendorp, Goltz, Crawford, et al. 2005). Consistent with this, the only area with significant directionally selective activation during the memory interval was PRR in the left hemisphere (Fig. 3*A*). Therefore, we will focus our analysis on the statistically significant left hemisphere parietal responses.

When a similar analysis was performed on the *movement* phase of the task, a different pattern of activation emerged (Fig. 3*C*). PRR remained active but activity in the other parietal areas decreased, consistent with previous findings (Connolly et al. 2003). During the movement phase, another region located along the angular gyrus (AG) (TC, x = –39 ± 0.5, y = –65 ± 2.5, z = 40 ± 0.6) became significantly activated. AG has previously been associated with manual pointing, tool use, and other visuospatial functions (Astafiev et al. 2003; Johnson-Frey et al. 2005). Other more frontal cortical areas were probably also activated during the movement phase but could not be imaged in our experiment (see Methods for explanation).

Pointing with Reversing Prisms

After completing data acquisition in the normal delayed pointing task, we trained subjects to point with the prism placed in front of their right eye. Complete adaptation (involving all visuospatial behaviors) to reversing prisms takes considerable time but in a previous behavioral experiment we found that rapid adaptation can be achieved by employing a very simple set of horizontal visual targets (Marotta et al. 2005). This type of reversing prism adaptation does not appear to be achieved

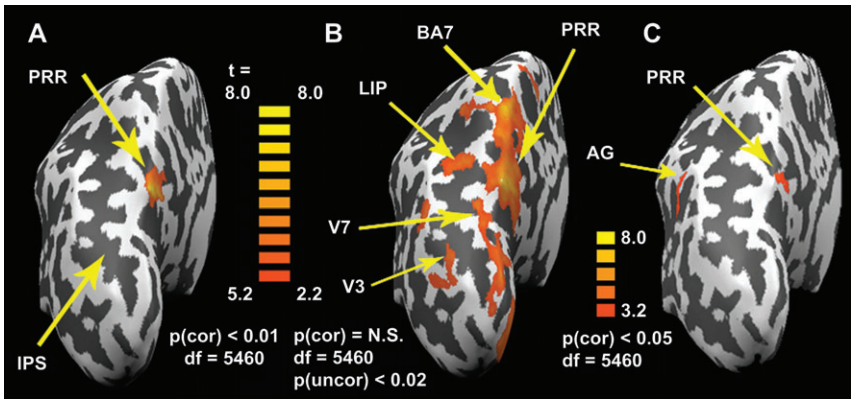

Figure 3. Cortical ROIs. Rear-medial views of the left hemisphere are rendered as "inflated brains," that is, with unfolded sulci (darker areas) and gyri (lighter areas). Locations of the cortical activation (group-averaged fMRI BOLD responses were determined using GLM regression analysis in 9 subjects) across 2 different task periods in the event-related task. Statistical significance of the cortical activation is proportional to the color scale shown for each hemisphere (*t*-scores). (*A*) The topographical activation obtained during the *delay period* before pointing, when the target had been projected to the contralateral side (GLM predictor contrast of rightward intended movements +, leftward intended movements −, $P < 0.01$). (*B*) Same as (*A*) but at a reduced threshold (*t*-value of 2.2 instead of 5.2) to view a broader functional network. (*C*) Similar to (*A*) but data collected during the *movement period* (*t-value of 3.2*). N.S. = not significant, V3 = Visual area 3, V7 = visual area 7, IPS = Intraparietal sulcus.

through a general cognitive reversal strategy because the learned pointing response does not generalize to other visuospatial behaviors, such as perceived orientation (Marotta et al. 2005). The subjects took around 30 trials to completely adapt to the reversing prisms (Fig. 2*C*). Once adapted, subjects reported that they were unaware of the adaptation. Here, as confirmed in our video analyses within the scanner and in our quantitative behavioral controls (Fig. 2*C*), subjects also showed a very rapid pointing adaptation (within approximately thirty pointing movements, on average). Subsequent to this adaptation, we resumed our fMRI recordings with the prism in place for comparison between the normal data and the optically reversed data.

Figure 4 qualitatively illustrates the main finding in our experiment (the magnitude of these effects will be illustrated in Fig. 6). Figure 4(*A*) shows left PRR activation during the *memory* period (P corrected < 0.01), overlaid on a sagittal structural MRI "slice" through the posterior left hemisphere. Again, the left PRR was more activated for intended rightward pointing movements (Medendorp et al. 2003) (Fig. 4*A*), and conversely, it was less activated for intended leftward pointing movements. The comparable "prism" data (Fig. 4*C*) are shown immediately below the normal data. Now (comparing panels, *A* with *C*), if PRR codes extrinsic movement direction, its directional selectivity should remain the same (i.e., A = C), whereas if PRR codes intrinsic visual direction, its directional selectivity should reverse (i.e., A $\neq$ C)

PRR clearly showed the reversed "visual" pattern. Remarkably, *left* PRR was now activated during intended ipsilateral movements to *leftward* targets (in physical space), and showed diminished activity during intended rightward movements (Fig. 4*C*) (see Fig. S3 for 2 representative individual subjects). Results for right parietal cortex were qualitatively similar but did not reach significance (Fig. S2 for 2 representative individual subjects). In other words, PPC activity remained fixed with respect to the intrinsic visual direction, and reversed with respect to the extrinsic movement direction of the intended movement.

In contrast, when *movement*-related activity recorded from area AG was compared between normal trials (Fig. 4*B*) and prism trials (Fig. 4*D*), it did not show the vision-related reversal but instead stayed fixed to the extrinsic direction of the pointing target. This demonstrates that fMRI can identify brain areas that are differentially selective for either the intrinsic or extrinsic visual coding schemes.

Our task was designed to minimize the influence of visual activation on spatially selective activation (Fig. 2*A*) but because the fMRI BOLD signal is delayed by approximately 3–4 s from the stimulus input, it is still theoretically possible that our memory interval data were contaminated by the original visual stimulus. For example, in antipointing and antisaccade tasks, PPC activity may initially encode the visual direction of the stimulus but then completely reverse its topography with the direction of movement (Medendorp, Goltz, Vilis, 2005). Therefore, it is also possible, hypothetically, that in our prism-task PRR data (Fig. 4*C*) a late memory-tuned response was masked by a strong initial visual response.

To control for this, we examined the time-course of directionally selective activation (see Fig. 5 for time-course construction method) in PRR and the other regions for both normal and prism pointing (Fig. 5). Once again, PRR (Fig. 6) showed the most robust activation, and was the only area to show strong sustained activation through both the late memory and subsequent movement phases. More importantly, during the prism task the directionally selective activation of PRR was reversed relative to normal pointing trials throughout its *entire* time-course. Thus, no matter how the BOLD hemodynamic response delay period is estimated (i.e., convolved), one must reach the same conclusion: PRR used intrinsic visual coordinates to plan and execute the pointing movements.

To quantify this memory or intention-related effect in a conservative manner, we measured activation during the final 4 s of the memory delay (Fig. 6*A–E*, shaded blocks), where residual visual contamination was least likely to occur and before any finger movement took place. These data are plotted as bar graphs on the right side of Figure 6. During this period, there was a significant "response reversal" in PRR, BA7, LIP, and V7. Note that the magnitude of the control responses (and the reversed responses) grew as the activity moved from retinotopic visual areas to the more sensorimotor-related parietal regions, suggesting progressively increasing task specificity.

An intermediate possibility that we did not yet consider is that PRR could be composed of some units whose directional selectivity is determined by the coordinates of the visual stimulus and some units whose directional selectivity is determined by the intended movement direction. This model predicts that the overall directional selectivity of PRR would decrease or disappear during the prism task. However, this was not observed. If anything, the directional selectivity of PRR increased during the prism task (Fig. 6*A*) but in the reversed direction.

Finally, it is evident from this plot that in AG (Fig. 5 bottom and Fig. 6*F*), significant activation (relative to the fixation baseline) only occurred during the movement phase of the task, and this activity did *not* reverse in the prism condition. When quantified during the peak of its response (Fig. 6*F*, shaded

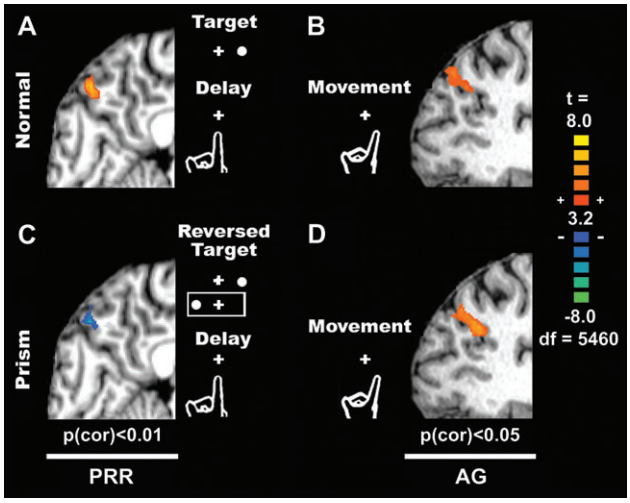

Figure 4. Effect of the reversing prism on PRR response during the memory delay period (*A* and *C*), and absence of prism effect on AG response during the movement period (*B* and *D*). Lateral views of left occipital–parietal region average activations (all 9 subjects) are shown in each condition (panels *A* and *C* Talairach $\times$ coordinate $= -8$; panels *B* and *D*, $x = -39$). Bonferroni-corrected ($P < 0.01$) statistical significance of cortical activation is proportional to the color scale shown (*t*-scores). Top row shows the activations that are the result of the statistical GLM predictor contrast of rightward (intended) movements +, leftward (intended) movements − without the prism, and bottom row shows activations in response to the same contrast after adaptation with the prism in place. Note that the pattern of activation reversed for PRR during the memory period (*A* and *C*) but not for AG during the movement period (*B* and *D*).

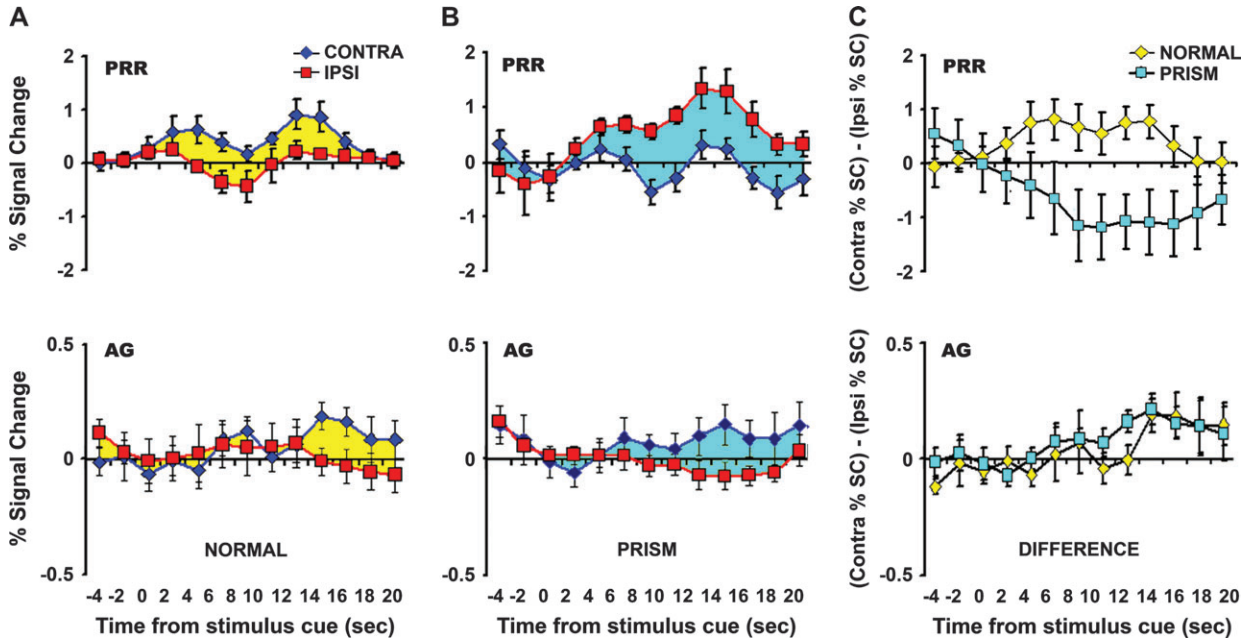

Figure 5. Top. Event-related percent BOLD signal change difference across time (s) in the PRR ROI in the left hemisphere. (*A*) Time-courses with error bars (SEM) for stimuli presented in the contralateral (right) visual field (blue diamonds), and ipsilateral (left) visual field (red squares). (*B*) Same as (*A*) but while viewing through the reversing prism after adaptation. (*C*) Time-course of the resulting percent BOLD signal change difference in PRR after subtracting contralateral activity from ipsilateral activity in normal (yellow diamonds) and prism (light blue squares) conditions. The colored areas in (*A*) and (*B*) represent the magnitude shown in (*C*). Bottom. Same as above but in AG. This method was used to produce all % signal change difference time-courses shown in Figure 6.

block), AG showed preference for the same pointing direction (or world-fixed target direction) both with and without prism.

Discussion

Our event-related fMRI study is the first to show that human PRR—and indeed the entire cluster of human PPC regions associated with manual pointing—shows directionally selective activity that is fixed with respect to the intrinsic retinal coordinates of the remembered goal (Gottlieb and Goldberg 1999), not its physical location in space or the extrinsic direction of the movement. In contrast, another area, AG, appeared to encode the physical location of the goal or the extrinsic direction of the movement. For technical reasons (see experimental procedures) we were not able to simultaneously record spatially selective activation in frontal cortex but it is likely that areas like ventral premotor cortex or dorsolateral prefrontal cortex might show a similar extrinsic pattern (Kakei et al. 2001; Hagler and Sereno 2006). The final stage would be the transformation from extrinsic movement plans to intrinsic muscle commands (Kalaska and Crammond 1992; Kakei et al. 2001).

Data Interpretation

We think our main ROI is task specific because it only showed topography during pointing movements, not saccades. Moreover, our anatomic characterization of this region agrees with previous descriptions of human PRR (Connolly et al. 2003). We also observed a progression of the delay-period activation from early occipital areas to our putative LIP, which ultimately peaks in "PRR" (Fig. 6). This is consistent with previous claims that PRR is task specific for manual reaching and pointing (Calton et al. 2002; Connolly et al. 2003). However, because we did not directly contrast this activation to activations for attention paradigms, we cannot directly exclude the possibility that we were measuring a spatially selective attention response (Merriam et al. 2003; Silver et al. 2005). If so, this would not change our major conclusion but would simply modify it to state that attentional responses in human PRR encode the retinal coordinates of the goal as opposed to the motor coordinates of the movement. However, because we and others have found effector-specific activations for similar PPC regions in this and similar paradigms (Medendorp, Goltz, Crawford, et al. 2005), we do not believe that attention alone can explain our results.

Our PRR results cannot likely be explained away as simple residual visual activation from the stimulus. First, because remapping and antisaccade/pointing paradigms have already shown that reach-related activity in parietal cortex is not locked to the initial visual stimulus (Batista et al. 1999; Medendorp et al. 2003; Khan, Pisella, Vighetto, et al. 2005). Second, in our experiment, PRR showed a robust reversal of activation with the prism that grew during the first half of the 12-second memory delay and was sustained through the second half of this interval right through the actual movement. Conversely, the world-fixed activation observed in AG during the movement phase could not be a trivial by-product of viewing the movement because this would have led to the visual reversal pattern. Finally, PRR and AG showed opposite response patterns in the presence of the prism adaptation. This negates the possibility that the PRR result is the trivial product of sensory input and hemodynamics.

A related question is whether subjects were pointing toward a mentally reversed image, as we have argued is the case in antipointing tasks. Our previous experiments suggest that subjects are not consciously aware of the transformation in

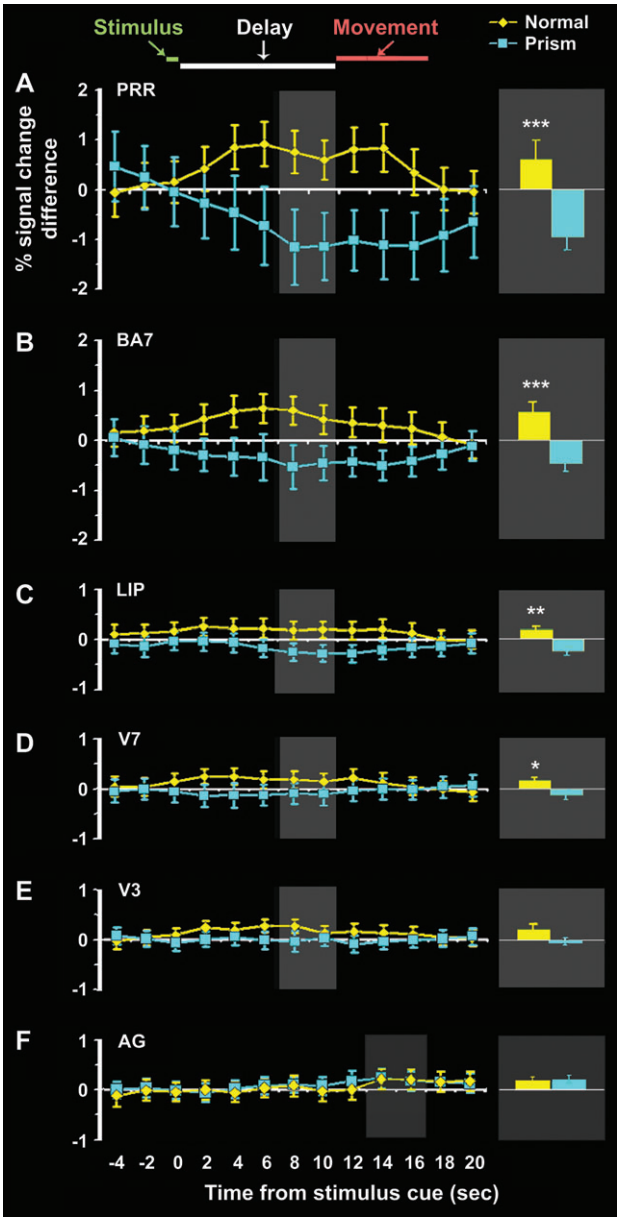

Figure 6. Left. Time-courses of group-averaged percent BOLD signal change right–left differences in the left hemisphere for all ROIs without prism (yellow) and with prism (blue). The prism task resulted in systematic shifts in activation patterns during the memory delay period in areas PRR (*A*), BA7 (*B*), LIP (*C*), V7 (*D*), and V3 (*E*). AG (*F*) was only activated during the movement period and did not show a topographic reversal in activation in the presence of prism adaptation. The % signal change difference was calculated according to Figures 5 and S1. Data were averaged first within subjects and then across subjects. Error bars represent the SEM. Right. Bars in the right column represent the corresponding mean percent BOLD signal change obtained from the shaded blocks of the time-course (2 volumes) in each analyzed cortical region. $*P < 0.05$, $**P < 01$, $***P \leq 0.005$ in a Student's paired *t*-test.

this simple task once it has been learned (Marotta et al. 2005), that is, they did not appear to be using an "antipointing" strategy. Moreover, if PRR were encoding a mentally reversed image, it should have shown a world-fixed pattern of activation, or the visual-to-motor reversing pattern seen in antisaccade/pointing studies (Medendorp, Goltz, Vilis, 2005), not the sustained visually fixed pattern observed here.

A final caveat is that fMRI only shows the "democratic vote" of a large population of neurons as opposed to the exceptions, and probably only shows their explicit codes as opposed to more subtle implicit coding schemes. For example, some neurons in PRR may encode initial hand position (Buneo et al. 2002), which could implicate PRR in the initial stages of calculating a desired hand path. More recently, it has been shown that these signals are even more prevalent in dorsal premotor cortex (Nelson et al. 2005). These observations are not inconsistent with our conclusion that PRR *mainly and explicitly* codes the goal of the movement in retinal coordinates.

Moreover, Zhang and Barash (2000) showed that in an antisaccade task in monkeys, LIP neurons could be divided into different populations whose directional specificity stayed fixed with the visual stimulus or the movement. This was a different task, in a different brain area, and a different species, but one could speculate that the same could be true in human PRR. If so, one might have expected these 2 responses to cancel out during the prism task, leading to a reduced or obliterated directional selectivity. This clearly did not happen in our data. However, an alternative explanation of Zhang and Barash's results—consistent with our data—is that some LIP neurons encode the visual coordinates of the stimulus and some encode the visual coordinates of the imagined goal opposite to the stimulus. If this were also true in human PRR, then these 2 responses should align in the prism task, leading to the completely reversed directional selectivity observed here.

PRR and the Visuomotor Transformation

Because PRR used a visual code in our prism task, it appears that the learned transformation in this task (the visual–motor reversal) was implemented "downstream" from PRR, perhaps between PRR and premotor cortex (Kalaska and Crammond 1992; Kakei et al. 2001). Based on the data shown here, we cannot draw firm conclusions on the detailed neural substrates of this learned transformation. Our behavioral controls and previous study (Marotta et al. 2005) suggest that our prism task induced a simple visuomotor learning rule, so we believe that the learned transformation utilizes "normal" visuomotor mechanisms. Many human behaviors involve very abstract visuomotor transformations (Gorbet et al. 2004). But even if this transformation had a more complex "cognitive" nature, this would not change our main conclusion. Either way, PRR explicitly encoded the retinal direction of the goal, and the new transformation—whatever its nature—was implemented downstream.

What does this tell us about the normal transformation? Our data suggest that PRR encodes targets in intrinsic sensory coordinates. Others have suggested that ventral premotor cortex encodes movements in extrinsic coordinates, whereas dorsal premotor and primary motor cortex encode intrinsic movement directions (Kalaska and Crammond 1992; Kakei et al. 2001). This appears to delineate a logical progression for the visuomotor transformation for arm movements, from intrinsic sensory, to extrinsic, to intrinsic motor coordinates. However, single-unit recording studies show that this transformation is not clean-cut from one region to the next (Buneo et al. 2002; Battaglia-Mayer et al. 2003), so these steps are probably best thought of as relative stages in a progressive sensorimotor gradient.

What is Coded within PPC?

Our analysis focused on memory-related activation in PRR because this phase is important for planning movements

(Andersen and Buneo 2002) and was the least likely period to be contaminated by visual signals in our paradigm. PRR may also be involved in the online monitoring of feedback signals during movements (Pisella et al. 2000; Prablanc et al. 2003). If so, our data would suggest that this is also done in retinal coordinates but this supposition cannot be directly tested using our method because of the rapidity of individual movements relative to the temporally delayed fMRI signals and the possibility of visual contamination during the movement phase.

As confirmed here, PPC also plays an important role in storing target representations for intended movements when the original visual stimulus is no longer present (Snyder et al. 1997; Andersen and Buneo 2002). Moreover, we know from previous studies that this memory-related activity is not hard-wired to retinal input because its activity is updated during eye movements (Batista et al. 1999; Medendorp et al. 2003; Khan, Pisella, Rossetti, et al. 2005) and can reverse (with the exception of some neurons) during antipointing/saccade paradigms (Kalaska 1996; Eskandar and Assad 1999; Connolly et al. 2000; Zhang and Barash 2000; Medendorp, Goltz, Vilis, 2005). The novel finding in the current study is that the directionally selective PPC activity measured with fMRI can also be completely dissociated from movement direction.

Taken together with our new results, these findings suggest that specific PPC regions like PRR *primarily* encode neither vision nor movement per se but rather something more intermediate and abstract: the spatial goal of the movement in retinal coordinates. This places PPC at a point intermediate between visual and motor codes. This provides another piece of information in the understanding of the highly complex workings of the visuomotor transformation and contributes valuable constraint information in the quest to model parietal function (Crawford et al. 2004), interpreting data from patients with parietal damage (Khan, Pisella, Rossetti, et al. 2005), and using PRR signals as neural inputs to drive prosthetic devices in complex behavioral paradigms (Musallam et al. 2004).

Supplementary Data

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

Conflict of Interest: None declared.

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