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Handedness-dependent and –independent cerebral asymmetries in the anterior intraparietal sulcus and ventral premotor cortex during grasp planning

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Abstract

When planning grasping actions, right-handers show left-lateralized responses in the anterior intraparietal sulcus (aIPS) and ventral premotor cortex (vPMC), two areas that are also implicated in sensorimotor control of grasp. We investigated whether a similar cerebral asymmetry is evident in strongly left-handed individuals. Fourteen participants were trained to grasp an object appearing in a variety of orientations with their left and right hands and with a novel mechanical tool (operated with either hand). BOLD fMRI data were then acquired while they decided prospectively whether an over- or under-hand grip would be most comfortable for grasping the same stimulus set while remaining still. Behavioral performances were equivalent to those recorded previously in right-handers and indicated reliance on effector-specific internal representations. In left-handers, however, grip selection decisions for both sides (left, right) and effectors (hand, tool) were associated with bilateral increases in activity within aIPS and vPMC. A direct comparison between left- and right-handers did reveal equivalent increases in left vPMC regardless of hand dominance. By contrast, aIPS and right vPMC activity were dependent on handedness, showing greater activity in the motor-dominant hemisphere. Though showing bilateral increases in both left- and right-handers, greater increases in the motor dominant hemisphere were also detected in the caudal IPS (cIPS), superior parietal lobule (SPL) and dorsal premotor cortex (dPMC). These findings provide further evidence that regions involved in the sensorimotor control of grasp also participate in grasp planning, and that for certain areas hand dominance is a predictor of the cerebral organization of motor cognitive functions.

Keywords

hand dominance; action planning; anterior intra-parietal sulcus; ventral premotor cortex; fMRI; grasping; tool use

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Introduction

The left cerebral hemispheres of the vast majority of humans are dominant for manual sensorimotor control, and this is reflected in their preference for use of the right hand (Kimura and Archibald, 1974). Left cerebral asymmetries are also apparent in neural activity associated with a variety of motor-related cognitive functions including: the representation of acquired skills (Johnson-Frey et al., 2005; Kroliczak and Frey, 2009; Moll et al., 2000; Rumiati et al., 2004), motor imagery (Gerardin et al., 2000), action selection (Rushworth et al., 1998; Schluter et al., 2001), and motor attention (Rushworth et al., 2001; Rushworth et al., 1997). Due to the exclusion of left-handed participants, however, our understanding of the relationship between these cerebral asymmetries and variations in motor dominance is quite limited (Kroliczak et al., 2011). To address this issue, we focus on the motor-cognitive functions involved in planning grasping actions.

Representing grasping actions

There is considerable evidence for similarities between monkeys and humans in the neural organization of grasp (Castiello and Begliomini, 2008; Grafton, 2010). In monkeys, the anterior intraparietal area (AIP) and ventral premotor cortex (F5) (Jeannerod et al., 1995; Sakata et al., 1997) are critically involved in sensory-motor transformations for grasping. In monkeys, AIP and F5 are reciprocally interconnected (Luppino et al., 1999), and a similar pattern of connectivity may exist in humans (Rushworth et al., 2006). Likewise, a growing number of functional neuroimaging studies demonstrate involvement of the human anterior intraparietal sulcus (aIPS), and in some studies ventral premotor cortex (vPMC), in the control of grasp (Binkofski et al., 1999; Binkofski et al., 1998; Culham et al., 2003; Ehrsson et al., 2001; Johnson-Frey and Grafton, 2005; Kroliczak et al., 2008).

In addition to their involvement in sensorimotor transformations, these inferior posterior parietal and ventral premotor regions also appear to contribute to grasp planning. Macaque AIP (Murata et al., 2000) and F5 (Murata et al., 1997) contain visual neurons that respond selectively to the observation of 3-D shapes even when no hand movements are involved. Effective stimuli are typically of a shape that is compatible with the particular cell's preferred hand configuration, suggesting the possible involvement of these units in the selection of appropriate grasping actions (Murata et al., 1997; Murata et al., 2000). Results from a recent investigation of prospective grip selection in humans are consistent with these observations. When required to select the most comfortable way (over- vs. under-hand) to precision grasp differently oriented objects while remaining still, right-handed humans showed clear behavioral evidence of relying on representations that accurately captured the unique biomechanical properties of the left and right limbs. Importantly, these prospective grip selection decisions were accompanied by left-lateralized increases in aIPS and vPMC regardless of the hand involved (Jacobs et al., 2010). After practice grasping stimuli with a formerly novel handheld tool, participants' prospective grip selection decisions showed evidence of relying on internal representations that captured the unique mechanical and dynamical properties of the instrument (Arbib et al., 2009). Critically, the left aIPS and vPMC again showed increased activity during these decisions. These findings suggest that in addition to their roles in sensorimotor control of grasp, the human left aIPS and vPMC participate in effector-specific grasp planning (Frey, 2010).

Human specializations

Despite apparent similarities in their functional architecture, human grasping behaviors are distinguishable from those exhibited by monkeys in at least two key ways. First, humans demonstrate a strong population-level preference for using their right hands to grasp objects. Interestingly, many left-handers also exhibit a right hand preference in precision grasping

tasks (Gonzalez and Goodale, 2009; Gonzalez et al., 2007a). Like right-handers, they are also less affected by visual illusions when grasping objects with their right hands (Gonzalez et al., 2006). These findings have been interpreted as evidence that the left hemisphere is specialized for grasping regardless of hand dominance. However, these predictions are not easily reconciled with recent fMRI findings that indicate bilateral increases in aIPS when right- or left-handers actively grasp objects with either hand (Begliomini et al., 2008). As with many investigations of visually-guided grasping in humans, increases in vPMC were not detected (Caciello and Begliomini, 2008). The aIPS increases were greater in both hemispheres for right- vs. left-handers, but only when using their dominant right hands. Left-handers, by contrast, showed no differences in aIPS activity between hands. One unexplored possibility is that, like right-handers (Jacobs et al., 2010), left-handers might show evidence of a left-cerebral asymmetry in aIPS and vPMC activity during the planning of precision grasping actions.

Second, while extensive training can teach monkeys to grasp with a tool (Umiltà et al., 2008), humans flexibly make use of a variety of instruments (e.g., chopsticks, pliers, tweezers, and tongs) when grasping objects in everyday life. As introduced earlier, recent work from our lab with right-handers suggests that through experience the left aIPS and vPMC come to support effector-specific representations involved in planning such tool use behaviors (Jacobs et al., 2010). Whether these areas play a similar role in left-handed individuals is uncertain.

The primary goal of the current investigation is to test the hypothesis that the left hemisphere specialization for motor-cognitive functions observed in right-handed individuals is independent of motor dominance. If so, then we expect that, like right-handers, left-handers will show selective increases in left aIPS and vPMC when performing a prospective grip selection task based on the use of either hand. After training, we predict that these same areas will also show increased activity when planning grasping actions involving use of a formerly novel tool. Alternatively, motor-cognitive functions may be a specialization of the motor dominant hemisphere, as suggested by a recent fMRI investigation of motor imagery in left- and right-handers (Willems et al., 2009). If this is the case, then we expect left-handers to show the opposite pattern of right-handers, i.e., increases in right aIPS and vPMC during prospective grip selection.

Materials and Methods

Participants

Sixty self-identified left-handed adults gave their informed consent and were administered the Edinburgh Handedness Inventory (Oldfield, 1971). Of these, 16 participants (7 females) with normal or corrected- to-normal visual acuity scored in the top quartile of left-hand dominance (Edinburgh Laterality Quotient range = -75 to -100; mean = -89). Two participants were excluded from this study due to an inability to complete all testing sessions. The remaining 14 participants (7 females age range 19 – 45yrs; M = 26yrs) completed all testing described below. None had a history of psychiatric or neurological illness.

Procedures

Behavioral Testing

Assessment of Hand Dominance: Two tasks were used to evaluate performance asymmetries between hands. To assess differences in manual dexterity, participants performed a timed, nine-hole pegboard task. Participants were seated in front of a table with either their left or right index finger (order counterbalanced across participants) depressing a

response button. The pegboard was placed mid-sagittally within a comfortable reaching distance in front of the participant. The task was to use the instructed hand to as quickly as possible: release the button and remove all nine pegs one-by-one, place them into the holding container, reinsert the individual pegs into the pegboard, depress the button. Completion times (CTs) were recorded as the time between when the button was released at the start of the trial and when it was depressed at the end. This task was completed a total of four times, alternating hands. The identity of the starting hand was counterbalanced across participants.

Maximal grip strength was assessed through use of a hand dynamometer (Stoelting, USA). Participants started with either their left or right hand (counterbalanced) and squeezed the dynamometer as tightly as possible. Three trials were performed with each hand in alternating order with the starting hand counterbalanced across participants. The highest force for each hand was recorded. In order to control for muscle fatigue, a two-minute resting period was inserted between trials.

Participants undertook two main testing sessions. In session 1 they actually grasped stimuli using their hands and a novel mechanical tool, while in session 2 they remained still while making prospective grip selection judgments as detailed below.

Session 1: Overt grip selection (OGS) Task: In order to assess grip preferences, participants were trained to grasp an object that was presented in various orientations in a two-fingered precision grip (Figure 1a). This was undertaken with the hands (using the thumb and forefinger) and with a novel mechanical tool that was 50cm in length from handle to jaw. Importantly, the tool differed from the hand in two critical ways: 1) Participants used a power grip to cause the two jaws of the tool to open or close in a “two-fingered” precision grip. 2) The opposition axis of the tool’s prongs was rotated 90° relative to that of the hand. One jaw of the tool was designated as the “thumb.” For half of the participants the “thumb” was the upper jaw, and for the remainder it was the lower jaw.

Visual stimuli were computer-generated images of spheres that were shaded in a photo-realistic manner to create the appearance of three-dimensionality (Figure 1a). The spheres were half pink and half tan. Each side was shaded to create the appearance of an indented fingerhold indicating where the sphere should be grasped. The spheres were presented on a black background in 24 different orientations so that the midline separating pink and tan rotated with possible orientations ranging from 0–345°, every 15° (e.g. 0°, 15°, 30°). These stimuli were presented on a flat LCD computer monitor that was fitted with a clear Lexan overlay. At the center of the overlay was a clear 20mm thick disc of equivalent size (32mm radius) to the stimuli. This allowed stimuli to be visible through the disc, creating a graspable 3D object extending from the screen (Figure 1b).

Participants completed two runs of 192 trials each. The tool was held by the same hand throughout the first run, and then switched to the other hand for the second run. The opposite hand remained free. Half of the participants started with the tool in the left hand, and the other half with the tool in the right hand. Each run was divided into eight blocks, with the side tested (tool or free hand) alternating across blocks. The first side tested in each block was counterbalanced across participants.

A block started with a centrally presented arrow pointing to either the left or the right. This arrow indicated which side would be used for the forthcoming trials (i.e., the free hand or the tool, depending on the block). Then, 24 trials were presented, one per stimulus orientation in random order for 4000ms each (Figures 2a and 2b). On each trial, participants were instructed to start with their hand in a half-pronated position resting on the table, and to

reach for and grasp the object using the most comfortable posture (i.e. over- or under- hand). They were told to use a precision grip, placing their thumb and forefinger, or the jaws of the tool, on the sphere's fingerholds. Participants were seated at a comfortable distance from the stimuli (as determined by the participant) that allowed them to comfortably grip the sphere with either their hand or the tool, depending on the trial block. Participants were reminded of the necessity to place their fingers, or the jaws of the tool, precisely on the projected indentations and no trials were discarded due to non-compliance. The hand was then returned to the starting posture in preparation for the next trial. At the end of each trial, the experimenter coded the side of the sphere (i.e., pink or tan indentation) on which the thumb or the upper-jaw of the tool was placed. This code therefore indicated whether an over- or under-hand grip was chosen. At the end of session 1, participants also completed two practice runs of the prospective grip selection task detailed below.

Session 2: fMRI testing

Prospective grip selection (PGS) task: Within 48 hours of the OGS task, participants returned for the fMRI (PGS task) portion of the experiment. Each participant performed two practice runs of the PGS task in a mock MRI scanner immediately before the actual fMRI session. In both the mock and actual scanners, participants reclined with their arms along the sides of their body, with their hands in a comfortable, half-pronated (i.e., neutral) position. One hand passively held the tool and it was taped to the participants' leg to provide stabilization without assistance from the participant. Participants were instructed to keep their upper body entirely still. Participants held the tool in the same hand during an entire run, and it was switched to the other hand between runs. The hand holding the tool in the first run was counterbalanced across participants. Therefore, each run was comprised of only two conditions, either Hand Left and Tool Right, or Tool Left and Hand Right. Within each run, the side tested (free hand or tool) alternated across blocks.

Participants performed a *prospective* version of the OGS task while neural activity was recorded from the entire brain using BOLD fMRI (Figure 2). This task was identical to the OGS task except that participants remained still while deciding whether they *would* place their thumb, or the designated thumb of the tool, on the pink or tan indentation when grasping the stimulus object in the most natural manner. Stimulus objects were back-projected onto a screen and viewed through a mirror attached to the head coil. Foot pedals were used to indicate responses, as detailed below.

Participants undertook four fMRI runs. Every run consisted of six blocks, with the left and right sides tested three times in alternating order. Within each block 10, 8000ms long trials were presented in pseudo-random order. Thirty of the trials in each run were based on use of the free hand and the remaining 30 were based on use of the tool. Within a run, 24 trials for each limb involved 2 occurrences of 12 stimulus orientations (from 15°–345°, in 30° increments), and 6 trials were 8000ms null events consisting of a central fixation cross presented on a black background. The side (arrow) cue was presented during the first 2000ms of the block and a small circle at the bottom left or right side of the screen remained visible throughout each block as a reminder of the cued side (Figures 2a and 2b).

PGS trials consisted of four phases optimized for event-related fMRI testing: 1) Stimulus onset occurred at a variable oversampling delay (0, 500, 1000 or 1500 ms) relative to the onset of the acquisition of a volume of functional MRI data (Miezin et al., 2000). 2) A stimulus object was presented in one of the 12 different orientations for a variable duration (i.e., jitter: 3000, 3500 or 4000ms). 3) A 2000ms duration response cue indicating the identity of the mapping between the response pedals (left or right) and colors (pink or tan) denoting the would-be location of the thumb or tool's jaw during the selected grip. Stimulus orientation and the identity of the response pedals were counterbalanced across trials for

each run. Varying the identity of this mapping randomly across trials allowed us to separate neural activity related to grip selection from that associated with foot press selection and execution. 4) A variable length (500 to 3000ms) inter-trial interval was used to make the duration of all trials equal 8000ms. Oversampling and jitter durations were counterbalanced within each run. A central fixation-cross remained visible throughout the entirety of each run (Figures 2a and 2b).

MRI procedure: All scans were performed on a Siemens (Erlangen, Germany) 3T Allegra MRI scanner at the Robert and Beverly Lewis Center for Neuroimaging at the University of Oregon. BOLD echoplanar images were then collected using a T2*-weighted gradient echo sequence, a standard birdcage radio-frequency coil, and the following parameters: TR = 2000ms, TE = 30ms, flip angle = 80°, 64 × 64 voxel matrix, FoV = 200mm, 32 contiguous axial slices acquired in interleaved order, thickness = 3.5mm, in-plane resolution: 3.125 × 3.125 mm, bandwidth = 2605 Hz/pixel. The initial four scans in each run were discarded to allow steady-state magnetization to be approached. High-resolution T1-weighted structural images were also acquired, using the 3D MP-RAGE pulse sequence: TR = 2500ms, TE = 4.38ms, TI = 1100ms, flip angle = 8.0°, 256 × 256 voxel matrix, FoV = 256mm, 176 contiguous axial slices, thickness = 1.0mm, in-plane resolution: 1 × 1mm. DICOM image files were converted to NIFTI format using MRIConvert software (<http://lcn1.uoregon.edu/~jolinda/MRIConvert/>).

Behavioral Data Analyses: As mentioned above, the ending position of the participants' thumb, or the designated jaw of the tool, on pink or tan allowed for coding over- vs. under-hand postures for each stimulus orientation. To enable comparison of data across participants, grip preferences for the tool were coded in terms of the placement of the tool's upper jaw. The proportion of overhand (pronated) grasps for every stimulus orientation was calculated for each participant and condition separately for both the OGS and PGS tasks, and submitted to repeated measures 2 (Effector – Hand or Tool) × 2 (Side – Left or Right) ANOVA as detailed below.

fMRI data analyses: FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied; motion correction using MCFLIRT (Jenkinson et al., 2002); fieldmap-based EPI unwarping using PRELUDE+FUGUE (Jenkinson, 2003, 2004); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 25.0s). Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich et al., 2001). Delays and undershoots in the hemodynamic response were accounted for by convolving the model with a double-gamma basis function. Registration to high-resolution structural and/or standard space images was carried out using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001).

For each participant, fMRI runs containing either Hand Left and Tool Right or Hand Right and Tool Left conditions, were modeled separately at the first level. Three explanatory (predictor) variables (EVs) were modeled along with their temporal derivatives. Two EVs coded the experimental conditions, left side grip selection (i.e., Hand Left or Tool Left), and right grip selection (i.e., Tool Right or Hand Right). These were locked to the onset of the stimulus objects and included the subsequent 3000ms (the shortest duration that a stimulus object was displayed). A third EV coded the 8000ms null trials that were used as resting baseline. Orthogonal contrasts (one-tailed t-tests) were used to test separately for differences between each of the four experimental conditions and resting baseline.

The resulting first-level contrasts of parameter estimates (COPEs) then served as input to higher-level analyses carried out using FLAME Stage 1 (Beckmann et al., 2003; Woolrich et al., 2004) to model and estimate random-effects components of mixed-effects variance. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.05$ (Worsley, 2001). First, a whole brain analysis was undertaken in order to identify the cerebral areas that responded significantly to the experimental conditions when compared to resting baseline at the group level. The first-level COPEs were averaged across runs for each subject separately (2nd level), and then across participants (3rd level). Second, in order to test for the main effects of EFFECTOR and SIDE and for the interaction between these two factors, a standard 2 (EFFECTOR: hand, tool) $\times$ 2 (SIDE: left, right) repeated-measures ANOVA (F-tests) was carried out on first-level COPEs. The sensitivity of this analysis was increased by restricting it to only those voxels that showed a significant increase in activity in at least one of the four experimental conditions compared to resting baseline at the group level in the whole brain analysis ($Z > 2.3$, corrected cluster significance threshold of $p = 0.05$).

Anatomical localization was undertaken by manual comparison with an atlas (Duvernoy, 1991) and overlaying activation maps on the population, landmark and surface-based atlas (PALs) of Van Essen (Van Essen, 2005) using CARET software (Van Essen et al., 2001).

Descriptive Region of Interest (ROI) Analysis: Spherical regions of interest (ROIs) were centered on the mean x, y, z coordinates of peak activations in bilateral aIPS and vPMC. These mean coordinates were computed by averaging the locations of peaks detected in the whole brain comparisons of each experimental condition vs. resting baseline (Table 1). Within each participant's ROIs, mean percent signal change was calculated for every condition by taking the ratio of the contrast of parameter estimates (experimental condition $>$ rest) and mean voxel-intensity, and scaling by the peak height of a regressor formed by convolving an isolated three second event with the double gamma hemodynamic response function. This ensures accurate interpretation of the percent change of the COPEs and allows for comparisons across studies (Mumford, 2007).

Results

Behavioral Task Results

Assessments of Hand Dominance—Due to technical difficulties, CTs for the 9-hole pegboard task were not recorded for two participants. For the remaining 12 participants, differences in mean CTs between the left ($M = 17.98$, $SD = 1.83$) vs. right ($M = 18.45$, $SD = 1.15$) hands failed to reach significance, $t(11) = 1.31$, $p = .22$. This is consistent with observations that the precision grasping behaviors of many left-handed individuals are indistinguishable from those of right-handers (Gonzalez et al., 2007b). By contrast, maximum grip strength was significantly greater for the dominant left ($M = 446$ N, $SD = 91$ N) vs. right ($M = 408$ N, $SD = 83$ N) hand, $t(13) = 4.49$, $p = .001$.

Overt Grip Selection Task—The mean proportion of overhand grasps for every stimulus orientation was calculated for each participant and condition separately for both the OGS and PGS tasks, and submitted to repeated measures ANOVA. Inspection of Figure 3 reveals that grip preferences for use of the left side (for both the hand and tool) are mirror reflections of those involving the right side. This is attributable to the fact that the joint constraints on the two upper limbs are 180° out of phase (Mackenzie, 1994). When using their hands, participants showed a consistent preference for overhand grips across all stimulus orientations. The frequency of underhand grips was greatest at 165° and 345° for the left hand, and at 15° and 195° for the right hand.

As expected given the fact that the opposition axis of the tool was rotated 90° relative to that of the hand operating it, grip preferences when using the tool differed significantly from those observed during use of the hand on the same side: left [$F(1,13) = 13.78$, $p = .003$, $SD = 26.26$]; right [$F(1,13) = 23.09$, $p < .001$, $SD = 21.85$]. In contrast to use of the hands, participants preferred underhand (supinated) grips for a wide range of stimulus orientations when using the tool (left side: 0°–75° and 180°–255°; right side: 105°–165° and 285°–0°; Figure 3). Consistent with previous observations in right-handers (Jacobs et al., 2010), this indicates that participants avoided highly pronated postures and instead were able to stabilize the tool against the forces of gravity by using the palm as a supportive platform for its weight. Remarkably, as detailed below, we find evidence that such compensation for the dynamical properties of the tool influenced grip preferences in the prospective version of the task as well.

Prospective Grip Selection Task—Importantly, grip preferences in PGS were highly correlated with those expressed during the OGS task for each of the four conditions: [Tool Left $R = 0.94$; Hand Left $R = 0.94$; Tool Right $R = 0.92$; Hand Right $R = 0.86$, $p < .001$ in all cases]. This high degree of similarity between grip preferences in these two tasks establishes that PGS judgments, in both hand and tool conditions, were based on internal representations that accurately capture the biomechanical properties of the limbs, and the mechanical as well as the dynamical properties of the novel tool.

In short, the psychophysical data show clear evidence that, like right-handers, left-handed individuals based their PGS performances on effector-specific representations of the hands or a recently mastered tool. The question of whether this prospective planning involved the same left-lateralized aIPS – vPMC circuit as in right-handers was addressed by the fMRI data collected during performance of this PGS task.

fMRI Results

In order to identify brain areas modulated by the PGS task, an initial whole brain analysis separately compared each of the four experimental conditions (Hand Left, Hand Right, Tool Left, Tool Right) against resting baseline. As summarized in Figure 4, all four conditions were associated with a highly similar pattern of increased activity. Consistent with results from right-handers (Jacobs et al., 2010), these included vPMC, dorsal premotor cortex (dPMC), and posterior parietal cortex within and along the IPS (including aIPS and caudal IPS (cIPS)) extending to the parieto-occipital sulcus (POS) and into the SPL. Importantly, activations in left-handers were decidedly more bilateral in both vPMC and aIPS. We return to this key aspect of our findings shortly.

As in earlier prospective grip selection studies, increased activity was also observed in lateral cerebellum, pre-supplementary motor area (pre-SMA) and left rostral middle frontal gyrus (rMFG) (Jacobs et al., 2010; Johnson et al., 2002). These regions may play more general roles in action planning, preparation and selection (Vogt et al., 2007), a point elaborated in the upcoming discussion section. Increased activity in occipital regions is likely associated with visual stimulus processing.

Repeated measures ANOVA—In order to increase sensitivity to possible differences between conditions, a 2 (effector: hand vs. tool) $\times$ 2 (side: left vs. right) repeated measures ANOVA was performed on only those voxels that showed significantly increased activity in at least one of the four experimental conditions vs. rest. We failed to detect any areas that showed significant main effects of either the effector or side used, or for the interaction between these factors ($z > 2.3$, cluster-corrected $p = .05$ in all cases). In sum, consistent with earlier findings in right-handers, results of both the whole brain analysis and more targeted

ANOVA are consistent with the hypothesis that, after training, the very same network of parietal and premotor areas is involved in planning grip selection based on the hands or the newly mastered tool.

Descriptive Region of Interest Analyses—Finally, region-of interest (ROI) analyses were used to further interrogate areas showing peak increases in activity within bilateral aIPS and vPMC. Mean percent signal change (PSC) associated with each of the four experimental conditions was calculated from within each ROI, and submitted to separate repeated measures ANOVAs (see Method section). As would be expected from the statistical parametric mapping results discussed above, each of the four experimental conditions was associated with significant increases in activity relative to resting baseline in all ROIs, $p < .05$ in all cases (Figure 5).

These more sensitive, post-hoc analyses revealed modest evidence for differences between conditions. Left aIPS showed a significant main effect of effector, $F(1, 13) = 5.41$, Bonferroni $p = .037$ (Figure 5a). This is attributable to a greater increase in activity when using the Hand ($M = .176$, $SD = .14$) vs. the Tool ($M = .139$, $SD = .138$). Similarly, decisions based on the Hand ($M = .196$, $SD = .144$) as compared to the Tool ($M = .159$, $SD = .145$) were associated with significantly greater increases in right aIPS activity (Figure 5b), $F(1, 13) = 5.121$, Bonferroni $p = .041$. Neither area showed a significant main effect of side or an effector $\times$ side interaction.

Left vPMC showed no evidence for either main effect, or an interaction. However, the main effect of effector approached significance for right vPMC, $F(1, 13) = 4.26$, Bonferroni $p = .06$. Similar to aIPS, this was due to a trend for greater activity when grip selection was based on the hand ($M = .145$, $SD = .1$) vs. tool ($M = .101$, $SD = .12$). The main effect of side and the effector $\times$ side interaction were non-significant, $F < 1.0$ in both cases.

To summarize, PGS decisions based either on the hands or tool were associated with bilateral increases in activity within a distributed network of parietal and premotor regions, several of which have been formerly implicated in the representation of grasping actions, including aIPS and vPMC. Targeted analyses of statistical parametric maps failed to detect any regions that responded selectively to either the side or the effector involved, or an interaction. More sensitive, post-hoc ROI analyses found increased activity for PGS decisions based on the hands vs. tool in both left and right aIPS. This hand advantage approached significance for right vPMC as well.

Relative differences between left- and right-handers

As indicated earlier, the OGS and PGS procedures used here were identical to those of a previous study in right-handers (Jacobs et al., 2010). This allowed us to perform direct comparisons between these groups in order to assess differences in performance and/or brain activity related to hand dominance.

Between-group behavioral comparisons—Mean grip preferences for the OGS and PGS tasks were submitted to two separate 2 (effector) $\times$ 2 (side) repeated measures ANOVAs with hand dominance as the single between subjects factor. Neither the main effects nor interactions provided any evidence for differences related to handedness ($F < 1.0$ in all cases). In short, both right- and left-handed participants exhibited similar grip preferences on these tasks.

Between-group fMRI comparisons—Data from all voxels that showed significantly increased activity in association with at least one of the four experimental conditions, in either the study involving left- or right-handers, were submitted to a 2 (effector) $\times$ 2 (side)

repeated measures ANOVA with hand dominance as the single between subjects factor. As expected on the basis of the results from these individual studies, none of the regions involved in prospective grip selection differences exhibited a significant main effect of effector or side. Despite equivalent behavioral performances in the PGS task, however, activity in several key regions differed significantly between left- and right-handers, $Z > 2.3$, corrected cluster significance threshold of $p = 0.05$. As shown in Figure 6, relative to right-handers, left-handers demonstrated greater increases in activity along the right IPS and in right vPMC and dPMC. They also showed greater bilateral activity in the IPL, pre-SMA, insular cortex and lateral cerebellum. By contrast, right-handers showed greater increases along the left IPS and in left dPMC. Equivalent increases in left vPMC activity for both groups account for the absence of relative differences in Figure 6. While right-handers exhibit strong left cerebral asymmetries in vPMC and aIPS when planning grasping actions prospectively, our between-group analyses confirm that these areas are bilaterally engaged when left-handers perform this task at an equivalent level of accuracy.

Discussion

Previous work reported left-lateralized increases in the aIPS and vPMC during grip selection judgments involving use of the hands or a recently mastered mechanical tool (Jacobs et al., 2010). The objective of the current investigation was to evaluate whether this left cerebral asymmetry is independent of motor dominance. If so, then we expected a similar pattern for left-handed (i.e., right hemisphere motor dominant) participants. Instead, we found consistent bilateral increases in both the aIPS and vPMC activity regardless of the side (left, right) or effector (hand, tool) involved. A direct comparison with right-handers revealed equivalent increases in left vPMC for both groups, suggesting that the functional contributions of this region to grip selection are unrelated to handedness. By contrast, only left-handers showed significant increases in right vPMC activity, and aIPS activity for both groups was greater in the motor dominant hemisphere. These results and their implications are considered in greater detail below.

Handedness-independent planning behaviors

Like right-handers, grip preferences expressed by left-handers during all conditions of the PGS task were highly consistent with those adopted when actually grasping objects with the hands or tool (OGS task). In both tasks, grip preferences differed systematically depending on the effector (hand or tool) and side (left or right) involved (Figure 3). Thus, regardless of one's hand dominance, PGS judgments were sensitive to the physical constraints that would be experienced were these movements to be actually undertaken (Johnson, 2000). The effector-specific planning behavior suggests that during the OGS session, participants acquired accurate representations of the formerly novel tool's mechanical and dynamical properties. Along with existing representations of their natural limbs, these newly acquired internal models were then used to perform subsequent PGS judgments during the fMRI testing session. Before addressing the relationship between hand dominance and the neural mechanisms supporting these behaviors, we consider the issue of effector-specificity.

Effector-specificity of aIPS and vPMC responses

It is clear from our behavioral data that both left- and right-handed participants relied on effector-specific representations. Increases in the aIPS and vPMC shown by both groups in association with these grip selection behaviors suggest that these regions support long-standing (hands) as well as newly acquired (tool) effector-specific representations for grasp. However, we cannot rule out the possibility that these neural responses also reflect engagement of effector-independent representations. This possibility might also apply to a recent report of similar responses in the aIPS when participants actually grasped objects with

the hand or a pair of tongs (Gallivan et al., 2009). After extensive training, individual neurons in the monkey PMv (area F5) that code manual grasps come to also represent grasping actions performed with a tool; a finding that can be interpreted as evidence for either the development of goal-based (Umiltà et al., 2008), or effector-independent (Arbib et al., 2009; Jacobs et al., 2010), representations. It is known that different cells within posterior parietal (Fogassi et al., 2005; Hyvarinen, 1982) and PMv (Rizzolatti et al., 1988) cortices exhibit effector-specific and -independent responses.

Our failure to detect differences in neural activity associated with grip selection planning involving the hands vs. tool, at the whole brain level of analysis, contrasts with results of an earlier investigation of action observation. Across several paradigms, it was reported that a distinct rostral sector of the human left IPL responded selectively to observation of tool use actions (Peeters et al., 2009). A potential reason for these differences between investigations is that motor planning may rely on mechanisms distinct from those activated during the perception of actions. More work is necessary to address this possibility. Post-hoc interrogation of data-derived ROIs did detect greater increases in activity in left and right aIPS when decisions were based on use of the hand vs. tool, but showed no sensitivity to side (left, right), or a side $\times$ effector interaction. We can speculate that this hand advantage reflects a greater representation in the aIPS of grasps involving the natural effectors, with fewer units coming to represent actions involving the newly mastered tool. If so, then the effect might be expected to dissipate with additional tool use training.

Handedness-independent responses in left vPMC and handedness-dependent responses in the right vPMC and aIPS

Consistent with earlier findings in right-handers (Jacobs et al., 2010), left-handers showed significantly increased activity in the aIPS and vPMC for all PGS conditions. However, these responses were bilateral for left-handers (Figures 4 & 5). By contrast, in right-handers increases were decidedly left-lateralized; they failed to exceed resting baseline for all experimental conditions in the right vPMC, and for decisions involving the ipsilateral side (i.e., right hand or tool) in the right aIPS (Figure 4 in Jacobs, et al., 2010).

One possible interpretation of the current data is that representations involved in grip selection are bilaterally organized in the aIPS and vPMC of left-handed brain. If this were true, then similar increases might be expected in left vPMC and aIPS for both handedness groups. This is the case for the left vPMC, where direct comparisons between groups revealed comparable increases in activity for left- and right-handers. However, these same analyses showed greater relative increases for right-handers in the left aIPS and, as discussed momentarily, within several other regions of the left parieto-premotor network implicated in grasping, including the cIPS/SPL and dPMC (Figure 6). Conversely, left-handers showed greater activity in these regions within the right hemisphere. This advantage for responses in the motor dominant hemisphere during grasp planning is consistent with results from a recent fMRI study of motor cognition in left- and right-handers (Willems et al., 2009). During a complex imagery task involving the hands, left-handed participants showed right-lateralized increases in dorsal parietal and motor/premotor structures while right-handed participants showed the opposite pattern. No increases in vPMC activity were detected in their investigation.

An alternative interpretation of the current findings is that domain-general task demands engage a common left-lateralized network regardless of handedness, while effector-specific grasp representations are supported in the aIPS and vPMC of the motor dominant hemisphere. Our use of “domain-general” is intended to refer to processes that are not specifically dedicated to representing grasping, but that may be involved in planning a wide variety of actions. Right-handers are known to show hand-independent, left-lateralized

increases in activity along the IPS (including aIPS), inferior frontal sulcus into rMFG, and dPMC (but not the vPMC) when performing choice vs. simple response time tasks (Schluter et al., 2001). The fact that both right- and left-handed participants show increases in activity of these left hemisphere areas during all conditions of the PGS task may be attributable to domain-general action selection demands. If so, then the cerebral organization of these non-specific action selection processes may be similar regardless of one's hand dominance (cf. Schluter et al., 2001). To our knowledge, this hypothesis has yet to be evaluated in left-handed participants.

Although selection among candidate motor programs is inarguably a central component of the PGS task, it is important to recognize that domain-general action selection processes cannot fully explain our data. There is a critical difference between the demands of a choice reaction time task--in which the mapping between a perceptual cue and response is fixed (Schluter et al., 2001), and the PGS task--where selection of a grip is based on an accurate estimation of the physical costs that would be experienced when adopting the under- or over-hand posture for a particular stimulus orientation with the cued side and effector (Johnson, 2000). As discussed later, *effector-specific* representations in the aIPS and vPMC (and possibly also cIPS/SPL, and dPMC) of the motor dominant hemisphere may be involved in representing these costs.

This alternative interpretation does not explain why the left vPMC is activated equivalently for both handedness groups (and thus absent in Figure 6). It is possible that these handedness-independent responses are associated with demands on motor attention. Previous evidence from right-handers indicates left-lateralized increases in IPL and vPMC activity when orienting attention to either hand for an upcoming response (Rushworth et al., 2003; Rushworth et al., 2001). While side-independent motor attention cannot explain the effector-specific nature of grip selection behavior, it is likely engaged in the PGS task when the side cue is presented at the start of a block of trials (see Figure 2a–b). Further, motor attention may continue to modulate neural activity during subsequent grip selection decisions (for possible evidence of this see (Johnson et al., 2002)). It may therefore be the case that increases in left vPMC activity for right-handers in the PGS task reflects both side-independent motor attention and involvement of effector-specific grasp representations, while in left-handers increases in this region would be exclusive to the motor attention demands. If this conjecture is correct, then left-handers should also show left-lateralized increases in IPL and vPMC activity during typical motor attention tasks. As with action selection, we are unaware of any studies that address this issue.

Involvement of other brain regions

Though not the primary focus of our investigation, it is noteworthy that both left- and right-handers showed increased bilateral activity in cIPS (extending to the parieto-occipital sulcus (POS) and into the superior parietal lobule (SPL)) and dPMC during grip selection. For both groups, these increases were detected regardless of the side (left, right) or effector (hand, tool) involved. Direct between-groups comparisons revealed that these effects were greater in the motor dominant hemisphere (Figure 6). As considered in the next section, these responses could reflect coding of hand orientation (actual or anticipated), as has been reported for cells in monkey medial parieto-occipital region (V6A) (Fattori et al., 2009) and the reciprocally interconnected distal forelimb sector of dorsal premotor cortex (PMd or F2) (Raos et al., 2004). Critically, our data indicate that these regions of the dorsal parieto-premotor stream are involved in motor cognition and more specifically grip selection, even in the absence of motor execution.

Finally, both left- and right-handers showed bilateral increases in pre-SMA across all conditions. For reasons that are unclear, these increases were greater in left-handers (Figure

6). Increased pre-SMA activity is commonly observed in a wide range of motor-cognitive tasks (Frey, 2006; Gerardin et al., 2000; Johnson et al., 2002). In macaques, pre-SMA (F6) is richly interconnected with prefrontal regions and plays a role in premovement processes including selection and preparation (Luppino et al., 1991; Luppino and Rizzolatti, 2000). Pre-SMA involvement here is consistent with similar roles in humans (Picard and Strick, 1996).

Feed-forward processing in parieto-premotor circuits and the cerebellum

The fact that aIPS, cIPS, vPMC and dPMC all show increased activity during the PGS task indicates that these areas are not exclusively involved in sensorimotor control. One possibility is that these parieto-premotor circuits represent changes in the effector's state based on feed-forward and/or feedback signals. Earlier work suggests involvement of posterior parietal cortex in state estimation (Desmurget and Grafton, 2000; Wolpert et al., 1995), and transcranial magnetic stimulation of aIPS (Tunik et al., 2005) or cIPS (Desmurget et al., 1999) interferes with the ability to update motor plans based on changing feedback. In the PGS task, the effectors remain immobile and feedback is unvarying. Choice of the most comfortable grip (over- or under-hand) would seem to depend on estimating the costs associated with each candidate action (Johnson, 2000). Computing these cost functions may involve predicting changes in the effector's state in response to a copy of the inhibited motor command (corollary discharge). These feed-forward signals may arise from internal models in the cerebellum (Shadmehr and Krakauer, 2008; Wolpert and Flanagan, 2001), which showed consistent increases in activity across all conditions for both groups. Further, cerebellum appears to be critically involved in supporting internal models of novel tools (Imamizu et al., 2003; Imamizu et al., 2000) and switching between distinct models (Imamizu and Kawato, 2008), as would be required when selecting grips based on the hand vs. tool. Typically, these predictions are viewed as extending over relatively brief periods of time, slightly in advance of actual sensory feedback. Consistent involvement of the cerebellum here and in other prospective planning tasks (Jacobs et al., 2010; Johnson et al., 2002), however, raises the possibility of this structure being involved in forecasting movements' longer range sensory consequences for use in action selection (Frey, 2010).

To conclude, the present results indicate the roles of some parieto-frontal areas in motor cognition are asymmetrically represented in the motor dominant cerebral hemisphere. In the case of prospective grip selection, such handedness sensitivity was observed in the right vPMC, aIPS, cIPS/SPL and dPMC. Conversely, left vPMC appears to play a critical and consistent role in grasp planning regardless of hand dominance. A possibility is that this area is specialized for domain-general motor attention functions regardless of handedness. Therefore, hand dominance is a predictor of the cerebral organization of motor cognitive functions within certain cortical regions. Whether cerebral asymmetries in motor cognition are causally related to hand dominance, or an effect, remains unknown (Sabate, 2004). These findings also indicate that, depending on hand dominance, comparable grip selection behaviors can arise from neural systems that differ in their cerebral organization. Additional work is needed to address the extent to which this pattern holds for other motor-cognitive functions and brain regions. However, recent work from our lab suggests that parietal asymmetries observed during the planning of familiar manual gestures are predicted by frontal asymmetries detected during productive language (Kroliczak et al., 2011). Our results also provide additional evidence that parietal and premotor regions involved in the sensorimotor control of grasp participate in forward grasp planning (Jacobs et al., 2010; Marangon et al., 2011). A topic of ongoing research is the precise contributions of these areas to planning and/or execution of manual grasp (Hansen, 2010).

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Figure 1. Experimental tasks

a.) Sample of stimulus object orientation “widgets” and the hand held novel gripping tool, measuring 50cm in length from jaws to handle.

b.) The Overt Grasp Selection (OGS) task. Widgets of various orientations were presented and participants practiced grasping them with either their left or right hand (pincer grasp), or with the jaws of a novel tool held in their left or right hand, as prompted.

Figure 2. Experiment procedure

a.) Example of a single trial of the Prospective Grasp Selection (PGS) task. After performing the OGS task, participants performed a similar task where they were asked to report how they *would* most comfortably grasp widgets of various orientations using either their hands or the tool, in the absence of movement. Participants responded whether their thumb or the designated thumb of the tool would grasp the pink or tan side of the widget. Foot pedals corresponding to “pink” and “tan” were presented after the stimuli and were randomized, allowing separation of neural activity related to the response. Stimulus onset, over-sampling intervals and inter-trial intervals varied as described in the Methods section. FMRI data analysis modeled the time period associated with planning the grasping selections as shown here, bordered in red. A small circle was present at the bottom of the screen to serve as a reminder of the cued limb (left or right).

b.) Example sequence of events in the PGS task. For a given run, participants held the tool in one hand for the entirety of the 10 trials while an arrow cued the participant as to which side (tool side or empty hand) to base grip preferences decisions. The dot on the screen served as a reminder of the cued side.

Figure 3. Grip preferences during overt (OGS) and prospective (PGS) grasp selection

Polar plots of the average proportion of overhand grasps across participants for each orientation of the stimulus object, as observed in the OGS and PGS tasks. When participants use their hand (either left or right) in either the OGS or PGS tasks, overhand (pronated) grip selections are strongly preferred for the majority of stimulus orientations. When using the tool (either left or right), participants showed limited ROM as well as a 90-degree offset of hand posture due to the mechanical properties of the tool. Participants preferred overhand (pronated) grasps for approximately 50% of the stimulus orientations in the tool conditions.

Figure 4. Figure 4a–d. Group average activation relative to a resting baseline for each condition: a.) hand left, b.) hand right, c.) tool left, d.) tool right, displayed using a multi-fiducial mapping on the PALS template brain (Van Essen, 2005)

Note that significant bilateral increases were detected in all conditions within aIPS, and vPMC, $z = 2.3$, $p = .05$ clusterwise correction.

Figure 5. Figure 5a–d. Results of descriptive region-of-interest (ROI) analyses

Two ROIs were defined bilaterally in the anterior intraparietal sulcus (aIPS) and in ventral premotor cortices (vPMC). Percent signal change (PSC), averaged across participants, relative to a resting baseline were extracted from each ROI. Bonferroni corrected one-tailed t-tests were used to determine the significance of the PSC values in each ROI. Error bars = 1 SEM. * $p < .05$. • $p < .10$.

Figure 6. Differences in activity between left- and right-handers during the PGS task
 Relative to right-handers, left-handers (blue) show greater engagement of several areas in their motor dominant right hemisphere including along the right IPS (including aIPS and cIPS), and in right vPMC and dPMC. Lefties also show stronger bilateral activation across the lateral convexity of the IPL, in pre-SMA and lateral cerebellum. By contrast, right-handers (red) show greater increases along the left IPS (including aIPS and cIPS) and also in left dPMC. Note the absence of left vPMC activity due to similar responses in both groups.

Table 1**Regions of interest**

The center of each spherical region of interest was obtained by averaging these coordinates across conditions. Coordinates (x, y, z) expressed in mm in Montreal Neurological Institute (MNI) standard space.

Condition	Region of Interest			
	L aIPS	R aIPS	L vPMC	R vPMC
	(x, y, z)	(x, y, z)	(x, y, z)	(x, y, z)
Hand Left	-38, -52, 46	38, -50, 42	-54, 6, 32	58, 8, 28
Tool Left	-50, -40, 40	40, -40, 40	-52, 6, 34	52, 4, 26
Hand Right	-38, -38, 32	32, -50, 40	-52, 0, 30	58, 8, 26
Tool Right	-34, -54, 48	34, -40, 38	-58, 8, 24	58, 8, 28
Center of the ROI (Average)	-40, -46, 42	36, -45, 40	-54, 5, 30	57, 7, 27