

# A Common Network in the Left Cerebral Hemisphere Represents Planning of Tool Use Pantomimes and Familiar Intransitive Gestures at the Hand-Independent Level

Gregory Króliczak<sup>1</sup> and Scott H. Frey<sup>1,2</sup>

<sup>1</sup>Psychology Department and <sup>2</sup>Lewis Center for Neuroimaging, University of Oregon, OR, USA

**Evidence from neuropsychology and neuroimaging implicates parietal and frontal areas of the left cerebral hemisphere in the representation of skills involving the use of tools and other artifacts. On the basis of neuropsychological data, it has been claimed that 1) independent mechanisms within the left hemisphere may support the representation of these skills (transitive actions) versus meaningful gestures that do not involve manipulating objects (intransitive actions), and 2) both cerebral hemispheres may participate in the representation of intransitive gestures. Functional magnetic resonance imaging was used to test these hypotheses in 12 healthy adults while they planned and executed tool use pantomimes or intransitive gestures with their dominant right (Exp. 1) or nondominant left (Exp. 2) hands. Even when linguistic processing demands were controlled, planning either type of action was associated with asymmetrical increases in the same regions of left parietal (the intraparietal sulcus, supramarginal gyrus, and caudal superior parietal lobule) and dorsal premotor cortices. Effects were greater for tool use pantomimes, but only when the right hand was involved. Neither group nor individual analyses revealed evidence for greater bilateral activity during intransitive gesture planning. In summary, at the hand-independent level, transitive and intransitive actions are represented in a common, left-lateralized praxis network.**

**Keywords:** apraxia, gesture, parietal cortex, praxis, tool use

## Introduction

Much of what we know about the neural substrates of the skillful use of tools and other artifacts comes from investigations of patients with acquired brain injuries. For more than a century it has been known that damage, particularly to the left parietal cortex, can lead to apraxia: an impairment in the representation of acquired skills that cannot be attributed to difficulties in linguistic, sensory or lower-level motor functions (Liepmann 1900; Geschwind and Kaplan 1962; Heilman and Rothi 1997). Classically, apraxic patients are impaired at pantomiming the uses of familiar tools or other manipulable objects (i.e., transitive actions) in response to verbal commands and/or imitation (Leiguarda and Marsden 2000). (Several different subtypes of apraxia have been defined and debated actively, and difficulties with tool use pantomime and/or intransitive gestures have been interpreted in various ways by different authors. In an attempt to avoid confusion, we have elected to use the generic term “apraxia” throughout the manuscript. For consistency with existing literature, we have chosen to use the term “tool use pantomime” to refer to tasks in which participants are required to manually pantomime the common uses of familiar tools and other manipulable objects;

i.e., transitive actions). The ability to pantomime such transitive actions to verbal command has long been considered a critical test for apraxia because it isolates the retrieval of stored action representations in response to minimally informative stimuli (Liepmann 1900; Goldenberg 2003a, 2003b). Often apraxics perform better when allowed to actually manipulate objects (De Renzi et al. 1982; Goldenberg et al. 2004), however, some of these patients also commit errors under these circumstances (De Renzi et al. 1982; Clark et al. 1994; Poizner et al. 1995).

There are at least 2 points of convergence between these patient data and the results of recent functional neuroimaging studies of tool use pantomime. First, although the precise regions implicated vary somewhat depending on the tasks used, both sources of evidence implicate left parietal and/or frontal mechanisms in the representation of skills involving objects. A widely cited study based on gesture imitation found maximal lesion overlap within and adjacent to the left intraparietal sulcus (IPS), including both the ventral extent of the superior parietal gyrus (SPG) and extending into the inferior parietal lobule (IPL), and/or the left middle frontal gyrus (MFG) and/or premotor cortex (Haaland et al. 2000). Recently, the left inferior frontal cortex (including adjacent insular and ventral premotor cortices) has been implicated as being critical to the production of tool use pantomimes (Goldenberg et al. 2007). Likewise, preparation and/or execution of these actions is consistently associated with increases in neural activity in the left parietal cortex within and along IPS, and in left premotor and/or prefrontal cortex (Moll et al. 2000; Choi et al. 2001; Ohgami et al. 2004; Rumiati et al. 2004; Johnson-Frey et al. 2005; Hermsdorfer et al. 2007). Depending on the control conditions employed, planning tool use pantomimes in response to pictorial (Choi et al. 2001) or linguistic cues (Johnson-Frey et al. 2005; Hermsdorfer et al. 2007) is also associated with increased activity within the left caudal middle temporal gyrus (cMTG). This is likely attributable to the activation of conceptual representations of manipulable objects and/or their associated actions (Martin et al. 1996; Chao and Martin 2000; Mahon et al. 2007; Weisberg et al. 2007). Damage in this vicinity is known to affect performances on tasks that require accessing conceptual knowledge of actions (Tranel et al. 2003).

Second, both patient and neuroimaging data demonstrate that these left-lateralized mechanisms participate in the construction of *hand-independent* representations of skills involving the use of tools and objects. As a result of their injuries, apraxic patients typically have right hemiparesis, and thus often receive their diagnoses on the basis of performances with their ipsilesional left, and typically nondominant, hands. Similarly, increased activity in left parietal, frontal and often

posterior temporal cortices is found when preparing and/or executing tool use pantomimes with either limb (Moll et al. 2000; Choi et al. 2001; Ohgami et al. 2004; Johnson-Frey et al. 2005; Hermsdorfer et al. 2007).

On the basis of these findings, we hypothesized that the human left hemisphere supports of distributed praxis representation network (PRN) that includes the aforementioned regions of parietal, frontal and temporal cortex (Johnson-Frey 2004; Frey 2008). Further, we postulated that left parietal cortex may be the critical node for the integration of distributed conceptual and sensory-motor representations into contextually appropriate action plans (Johnson-Frey 2004; Johnson-Frey et al. 2005; Frey 2007).

### ***Transitive versus Intransitive Actions***

One important issue that remains unresolved is whether or not the role of this PRN is exclusive to skills involving the use of objects (i.e., transitive actions). Despite their difficulties with tool use pantomimes, apraxics are typically less impaired when performing familiar intransitive gestures, such as waving goodbye, or signaling thumbs-up (Roy et al. 1991; Foundas et al. 1999; Haaland et al. 2000); however, cf. Belanger et al. (1996). At least 2 case studies of apraxic patients report a complete preservation of the ability to perform intransitive gestures despite substantial impairments of tool use pantomime following left hemisphere lesions (Rapcsak et al. 1993; Dumont et al. 1999). This evidence suggests that the left hemisphere might support independent mechanisms for the representation of familiar transitive versus intransitive skills. This hypothesis has a long history (Morliss 1928; Leiguarda 2005) and figures prominently in current theories of praxis (Rothi et al. 1991; Cubelli et al. 2000; Buxbaum 2001). Yet, evidence for a clear double dissociation between the *production* of transitive versus intransitive gestures is lacking. Reports of deficits confined to intransitive gesture production are few, and those cases that have been described are confounded by the presence of aphasia and the use of verbally cued tasks only for intransitive testing (Cubelli et al. 2000). Some apraxic patients with frontal lesions do show equal impairments for transitive and intransitive gesture recognition (Pazzaglia et al. 2008), but the same does not appear to hold for production. This raises the possibility that tool use pantomime may simply place higher demands on a representational system shared by both transitive and intransitive actions.

Although impairments of tool use pantomime are more commonly associated with left hemisphere lesions (Heilman et al. 1982; Buxbaum 2001; Goldenberg et al. 2003, 2007; Heilman and Rothi 2003), some studies indicate that the ability to perform intransitive gestures can be equally disrupted by damage to either cerebral hemisphere (Heath, Roy, Black, et al., 2001; Buxbaum et al. 2007). This suggests that intransitive gestures may depend on mechanisms distributed across both hemispheres, or that compared with transitive actions there is a higher degree of individual variability in the lateralization of these representations. However, other results suggest that impairments in the performance of both tool use pantomime and intransitive gesture are more likely following left versus right hemisphere damage (Hanna-Pladdy et al. 2001).

Because familiar intransitive gestures often serve important symbolic and/or communicative functions, determining whether the PRN supports both transitive and intransitive

actions has potentially important implications for our understanding of the relationship between 2 fundamental human cognitive specializations, tool use and language (Bradshaw and Nettleton 1982; Gibson 1993; Frey 2008). Given the significance of this issue, direct comparisons of these 2 types of actions in the neuroimaging literature are surprisingly scarce. Results of a single functional magnetic resonance imaging (fMRI) study demonstrate that planning either familiar tool use pantomimes or intransitive gestures engage largely the same regions—referred to above as the PRN—of left parietal, frontal, and also posterior temporal cortices (Fridman et al. 2006). Fridman and colleagues find that only left caudal ventral premotor cortex (cPMv) is significantly more active during the preparation of tool use pantomimes versus intransitive gestures. This difference is interpreted as evidence that this region may uniquely support representations of acquired skills involving objects (p. 425). Yet it is important to note that, relative to resting baseline, even cPMv shows significantly increased activity when planning both transitive and intransitive actions. Therefore, although more demands may be placed on cPMv when planning tool use pantomimes, this area also appears to contribute to the representation of intransitive gestures. This result is particularly interesting in light of the recent findings mentioned above which indicate that production of tool use pantomimes is particularly vulnerable to left inferior frontal damage, including PMv (Goldenberg et al. 2007).

A potentially important limitation of the study by Fridman and colleagues (Fridman et al. 2006) is that actions were only planned for and executed with the right hand. Thus, it is impossible to determine whether these left-lateralized effects are attributable to the engagement of *hand-independent* action representations (Moll et al. 2000; Choi et al. 2001; Ohgami et al. 2004; Johnson-Frey et al. 2005), or whether they reflect processes specific to the use of the contralateral, right, and dominant hand. In fact, a recently published study that used the Fridman et al. paradigm (Fridman et al. 2006) found stronger responses in left parietal and premotor cortex when planning intransitive versus transitive gestures, irrespective of the hand involved (Bohlhalter et al. 2008). This result is difficult to reconcile with the earlier study, and also seems incompatible with the existing neuropsychological evidence discussed above.

In short, the existing evidence indicates a high degree of overlap in patterns of increased brain activation when individuals plan either tool use (i.e., transitive) pantomimes or intransitive gestures (Fridman et al. 2006). Yet, the high degree of overlap in activity associated with transitive and intransitive action planning seems incompatible with evidence suggesting that left hemisphere lesions may selectively impair transitive actions (Rapcsak et al. 1993; Dumont et al. 1999), and with observations that impairments of intransitive gestures are equally likely to occur following left or right hemisphere damage (Heath, Roy, Black, et al. 2001; Buxbaum et al. 2007). Further, these findings suggest the possible need for a re-interpretation of previous neuroimaging studies of tool use pantomime; activity in the PRN may actually reflect mechanisms that play a more general role in representing meaningful actions, including gestures that have symbolic and/or communicative functions but that are not associated with the manipulation of objects.

Here, we seek to clarify the role of the PRN in the representation of planning meaningful actions. Is this network specific to the representation of skills that involve tools and

other objects (i.e., transitive actions)? Or, does it constitute a more general domain neural substrate for the representation of meaningful actions regardless of whether or not they involve objects (i.e., transitive and intransitive actions)? In Exp. 1 we examined the similarities and differences in neural activity associated with planning familiar tool use pantomimes versus intransitive gestures for subsequent production with the dominant right hand. In Exp. 2, the same individuals performed identical tasks with their nondominant left hands. Comparisons across both experiments within the same regions of interest (ROIs) allowed us to make inferences about the typical organization of hand-independent representations of familiar transitive and/or intransitive actions.

### General Method

Twelve adult native English-speaking volunteers (6 females), ranging in age from 19 to 41 years (mean age = 27 years) participated in 2 fMRI testing sessions and were compensated financially for their time. All participants were strongly right-handed—as measured by the revised Edinburgh Handedness Inventory (Oldfield 1971)—and had normal or corrected-to-normal visual acuity. Both experiments reported in this paper were approved by the Ethics Committee for Research Involving Human Subjects at the University of Oregon, and were carried out in accordance with the principles of the Helsinki 1964 Declaration.

### Practice Phase

Prior to scanning, participants undertook a series of training trials presented on a computer. Each trial began with an instructional cue (IC) consisting of a centrally presented gerund verb (see Appendix 1). Verbs denoting physical transitive (e.g., typing) or intransitive (e.g., beckoning) actions were followed by a clip of an actor performing the corresponding unimanual pantomime or gesture, once with her right and once with her left hand. A centrally presented movement cue (MC) instructed subjects to reproduce the observed gestures using their right and then left hands. On trials with verbs denoting nonphysical actions (e.g., thinking), no actions were presented and subjects were instructed to remain still. After completing this initial practice session, subjects undertook 2 additional practice runs inside a mock MRI scanner that replicated the experience and constraints of the actual MRI testing environment. Here and again immediately prior to each fMRI testing session, it was emphasized that 1) movements must be performed as accurately as possible, 2) the upper arm should remain still, and 3) head motion must be avoided. All participants performed at ceiling before being advanced to the first fMRI testing session.

### Test Phase

All participants completed 2 separate experiments on different days; one using the dominant right hand and the other using the non-

dominant left hand. Immediately prior to testing, participants again viewed the training video. Although the order of the tested hand was counterbalanced across the whole sample of participants (including gender, given an equal number of males and females in our study), we will refer to use of the right hand as Exp. 1, and left hand as Exp. 2. Each testing session consisted of 6 functional runs. Throughout each run participants were instructed to maintain fixation on a centrally presented cross. Functional runs consisted of 3 conditions distinguished by their ICs: 1) transitive condition—verbs denoting familiar unimanual transitive actions (e.g., “painting” or “writing”); 2) intransitive condition—verbs denoting familiar unimanual intransitive actions (e.g., “hitchhiking” or “scolding”); 3) linguistic control—verbs denoting mental actions (e.g., “knowing” or “evaluating”). As illustrated in Figure 1, trials of each condition consisted of a 1) visually presented IC (1500 ms), 2) variable length delay interval (2000, 4000, or 6000 ms) for action planning, 3) visually presented MC (4000 ms), and 4) variable duration (2500, 4500, or 6500 ms) intertrial interval (ITI). In the Transitive and Intransitive Conditions, participants were asked to prepare to gesture the actions identified by the IC during the subsequent delay period. At the onset of the MC—a bright green circle presented in the middle of the display, participants were instructed to execute the planned action using only the fingers, hand and forearm while the MC was visible. During the Linguistic Control condition trials, they were asked to relax and neither plan nor undertake any movements.

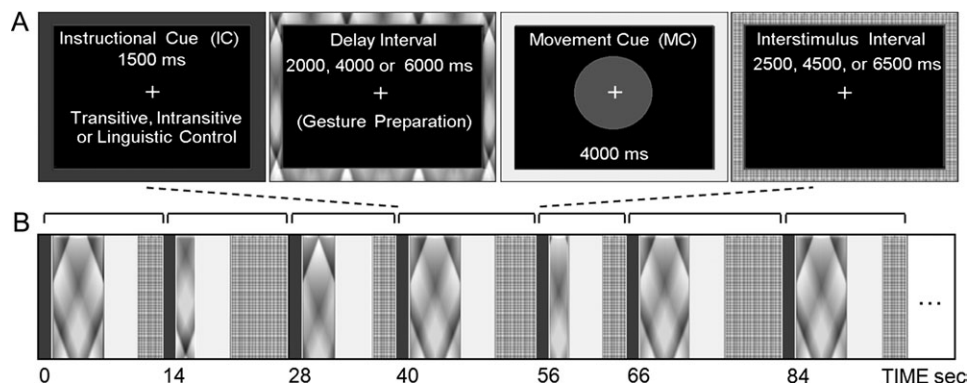
For each condition there were 14 ICs divided randomly into 2 sets of 7 items (Appendix I). Care was used to avoid ICs in which the verbs would be homonymous with the nouns that they were cueing (e.g., “sawing” to cue saw) as such items have unique neural correlates (Tranel et al. 2005).

Each of the 6 functional runs consisted of 21 trials, 1 set from each condition. ICs from each condition were followed equally often by each of the 3 delay intervals. Likewise, ICs from each condition had an equal likelihood of being preceded by either of the 3 ITIs. Finally, the order of runs was randomized across participants.

Stimuli were controlled by Presentation software (Neurobehavioral Systems v. 10.0, Albany, CA; <http://www.neurobs.com>) digitally synchronized with the MRI scanner. The stimuli were back projected on a screen at the back of the magnet bore and viewed via a mirror attached to the head coil. Eye position was monitored throughout each session with an MRI-compatible tracking system (<http://www.a-s-l.com>). Manual performances were monitored by the experimenter and recorded with digital video. Padding was used to immobilize the head and upper arms.

### MRI Procedure

All scans were performed on a Siemens (Erlangen, Germany) 3 Tesla Allegra MRI scanner at the Robert and Beverly Lewis Center for Neuroimaging at the University of Oregon. Before the start of functional runs, Auto Align Scout and True FISP sequences were executed to prescribe the position of slices. The blood oxygenation level-dependent (BOLD) echoplanar images were collected using a



**Figure 1.** (A) Trial structure and timing. (B) Portion of a sample trial sequence within a functional run. The 1500-ms IC was followed by a variable delay Interval during which gestures were planned, and a 4000-ms MC that signaled gesture execution. ISIs were 2500, 4500, or 6500 ms.

$T_2^*$ -weighted gradient echo sequence: time repetition (TR) = 2000 ms; time echo (TE) = 30 ms; flip angle = 80°; 64 × 64 matrix; field of view (FOV) = 200 mm; 33 contiguous axial slices, 3.0-mm isotropic voxels. High-resolution  $T_1$ -weighted structural images were also acquired: magnetization prepared rapid gradient echo (MP-RAGE) pulse sequence: TR = 2000 ms; TE = 4.38 ms; inversion time (TI) = 1100 ms; FA = 8.0°; 256 × 176 voxel matrix size; FOV = 256 mm; 176 contiguous axial slices; 1.0-mm isotropic voxels. To reduce artifacts attributable to magnetic field inhomogeneities, raw image data were first reconstructed using 2-dimensional fast Fourier transform, and converted to NIFTI-1 format using MRI-Convert software (<http://lcni.uoregon.edu/~jolinda/MRIConvert/>). Data were preprocessed and modeled with FSL version 3.2 (<http://www.fmrib.ox.ac.uk/fsl/>).

### fMRI Data Analysis

Statistical analyses were preceded by the following preprocessing procedures: nonbrain removal using brain extraction tool (BET) (Smith 2002); motion correction using MCFLIRT (motion correction with the Oxford Centre for Functional MRI of the Brain's linear registration tool) (Jenkinson et al. 2002); spatial smoothing using a Gaussian kernel of FWHM = 5 mm, mean-based intensity normalization of all volumes by the same factor; high-pass temporal filtering ( $\sigma = 50.0$  s). For a given participant, each fMRI run was modeled separately at the first level. Estimates of the degrees of freedom in the statistical model were corrected for autocorrelation in the data by using the FSL prewhitening technique (Woolrich et al. 2001). Time-series statistical analysis was performed 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. FLIRT (Jenkinson and Smith 2001; Jenkinson et al. 2002) was used to implement registration to high-resolution and standard space images (Montreal Neurological Institute [MNI-152] template). Intersession (level 2), intersubject (level 3), and interexperiment (level 4) random-effects components of mixed-effects variance were modeled and estimated using FLAME Stage 1 (Beckmann et al. 2003). Unless noted otherwise,  $z$  (Gaussianized  $t/F$ ) statistic images were thresholded using clusters not smaller than those determined by FSL default values of  $z > 2.3$  and a corrected cluster significance threshold of  $P < 0.05$  (Worsley et al. 1992). ROI analyses used FSL's Featquery to compute mean percent signal change associated with each of the experimental conditions relative to the resting baseline. Inclusive contrast masking was used to identify areas significantly activated across 2 comparisons.

Planning-related activity in each condition was modeled as the 3500-ms period beginning with the onset of the IC (1500 ms) and lasting through the end of the shortest (2000 ms) delay interval (Fig. 1). Execution-related activity in the transitive and intransitive conditions was modeled as the 4000-ms period during which the MC was visible.

Verification of 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 (2005) using CARET software (Van Essen et al. 2001). Two procedures were used to map volumetric group average data onto the PALs atlas: average fiducial mapping in which standard (i.e., MNI-152) space group average data is projected onto the atlas, and multifiducial mapping in which data is first mapped to a set of 12 individual brains then reaveraged to account for individual variations in cortical topography (Van Essen 2005).

### Exp. 1: Tool Use Pantomimes and Intransitive Gestures with the Dominant Right Hand

On the basis of previous results, we hypothesized that planning tool use (transitive) pantomimes would increase activation within the PRN, a network of areas in left parietal, frontal and posterior temporal cortices (Moll et al. 2000; Choi et al. 2001; Ohgami et al. 2004; Rumiaty et al. 2004; Johnson-Frey et al. 2005; Fridman et al. 2006). If this left-lateralized network is only specialized for the representation of skills involving the use of objects, then these areas should not show significant increases in activity when retrieving and planning intransitive gestures. Any differences between transitive versus intransitive conditions might be particularly evident in left inferior frontal cortex, including PMv (Fridman

et al. 2006). By contrast, if this system plays a more general role in the representation of meaningful skills, then these areas will evidence significantly increased activity during both types of planning.

Our primary objective here and in Exp. 2 was to investigate the mechanisms involved in the retrieval and planning of transitive and/or intransitive actions. Furthermore, no efforts were made to equate the complexity (e.g., amplitudes, velocities, and trajectories) of movements involved in the production of transitive versus intransitive actions. For these reasons our presentation of the results focuses primarily on changes in neural activity associated with the planning phase, that is, the initial 3500 ms of each trial beginning with the onset of the IC (see Method section above).

## Results

### Planning Phase

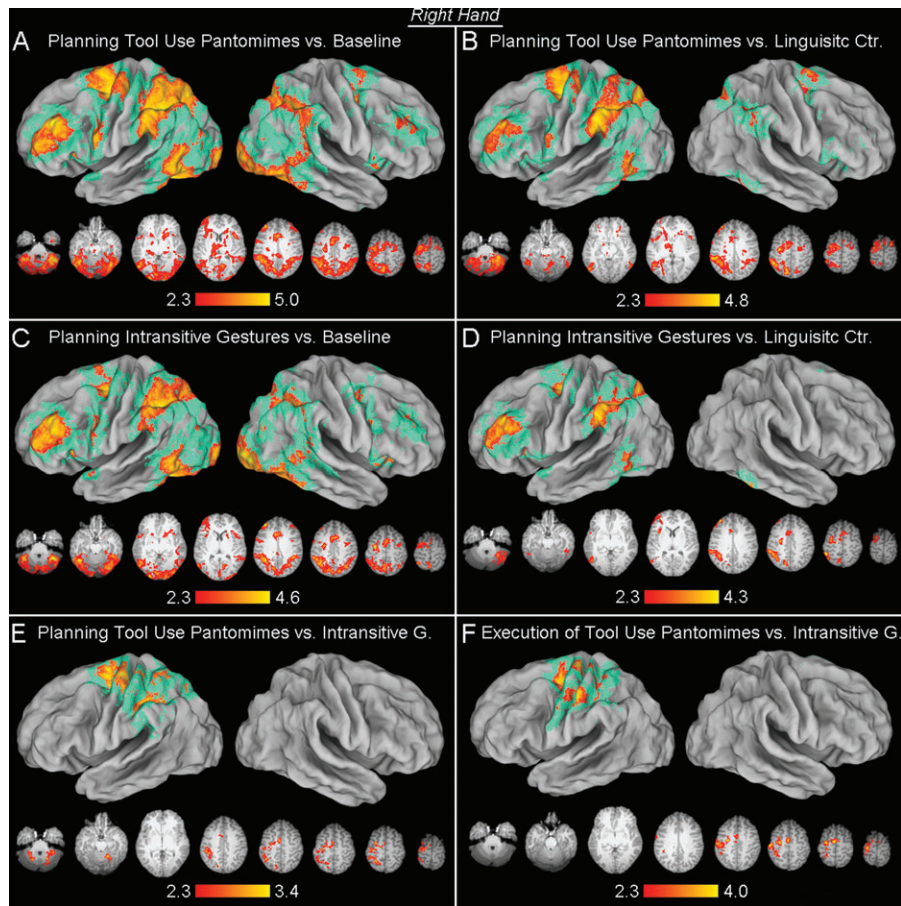
As expected, planning tool use pantomimes was associated with significant increases in activity within parietal, temporal, premotor, and prefrontal cortices relative to the resting baseline, and these effects were more pronounced in the left cerebral hemisphere (Fig. 2A). Increased parietal activity was detected within and along banks of the IPS and extended onto the lateral convexities of the supramarginal gyrus (SMG) and SPG. Similarly, larger increases were detected in the left cMTG, rostral MFG (rMFG), and within and along the dorsal aspect of the precentral sulcus, which we refer to as dorsal premotor (PMd) cortex. A focal activation was also present along the ventral extent of the left precentral sulcus, labeled here as cPMv cortex. Bilaterally increased activity was also detected in the inferior frontal gyrus (IFG) anterior and ventral to cPMv. With the exception of PMd, controlling for linguistic stimulus processing led to a substantial reduction in activity within areas of the right cerebral hemisphere (Fig. 2B; Supplementary Materials Table 1A).

A remarkably similar pattern of increased activity was observed in association with planning intransitive gestures relative to the resting baseline (cf. Fig. 2A,C). Likewise, when contrasted with the linguistic control condition, increases in right rMFG, cMTG, IFG, and premotor cortex no longer achieved significance (Fig. 2D; Supplementary Materials Table 1B).

A direct comparison revealed increased activity during the planning of tool use pantomimes versus intransitive gestures in several regions of the left hemisphere: parietal cortex (within and along left IPS and SPG), PMd, presupplementary (pre-SMA), cingulate (CMA), and primary motor areas (Fig. 2E). A similar effect was also detected bilaterally in the cerebellum. In contrast to previous findings (Fridman et al. 2006), however, activity within left cPMV was not greater for tool use pantomime versus intransitive gesture.

### ROI Analyses

In order to characterize better the conditional responses in areas of the left hemisphere detailed above, ROIs were defined based on the activation peaks ( $z = / > 3.1$ ,  $P < 0.05$ , clusterwise correction for multiple comparisons) identified in the transitive planning versus resting baseline contrast (Supplementary Materials Table 1E). As shown in Figure 3A-I, within left cPMv, transitive, intransitive and linguistic control conditions all increased activity above the resting baseline (Bonferroni-adjusted [BF-]  $P < 0.001$  in all cases), and transitive and intransitive planning increased activity more than the linguistic control (Bf- $P < 0.001$  and 0.05, respectively). However, the



**Figure 2.** Brain areas showing increased activity during the planning (A–E), and execution (F) of tool use pantomimes and intransitive gestures with the dominant right hand. In Figures 2 and 4, the volumetric surface renderings in the upper panels illustrate significant group average effects mapped onto the PALs atlas in Caret 5.5 using the multifiducial procedure (see Methods). Areas showing significant activation after multifiducial mapping are represented in warm hues. Pale green areas were significantly activated in the group FSL analysis, but did not survive the multifiducial correction for intrasubject anatomical variability. Axial slices displayed in the lower panels represent group mean statistical parametric maps (values of the  $z$  statistic) projected onto a single participant's high resolution,  $T_1$ -weighted anatomical scan. All slices are displayed in neurological orientation, that is, right hemisphere on right side, and values correspond to the color bar. (A) Planning tool use pantomimes versus resting baseline. Clusters of significantly increased activity tended to be bilateral, but were stronger in the left hemisphere and included: the inferior (IPS and SMG) and superior (SPG) parietal cortex, cPMv, PMd, rMFG, and cMTG. Slices reveal additional areas of activation in the cerebellum, fusiform gyrus, insular cortex, pre-SMA and thalamus. (B) Planning tool use pantomimes versus the linguistic control condition. Controlling for activity related to linguistic stimulus processing reduced activity, particularly in the right hemisphere where responses in cMTG and rMFG became nonsignificant. (C) Planning intransitive gestures versus resting baseline. Note the similarity to areas showing increased activity during the planning of tool use pantomimes. (D) Planning intransitive gestures versus the linguistic control condition. Here too controlling for linguistic stimulus processing reduced activity particularly within the right cerebral hemisphere. (E) Direct comparison between planning tool use pantomimes versus intransitive gestures. The tool use pantomime condition is associated with greater increases in activity within and along left IPS and extending into the SMG, in SPG, PMd, and M1. The inverse contrast revealed no areas that respond more when planning intransitive gestures versus tool use pantomimes. (F) Direct comparison between execution of tool use pantomimes versus intransitive gestures. Note similarities in activation to (E).

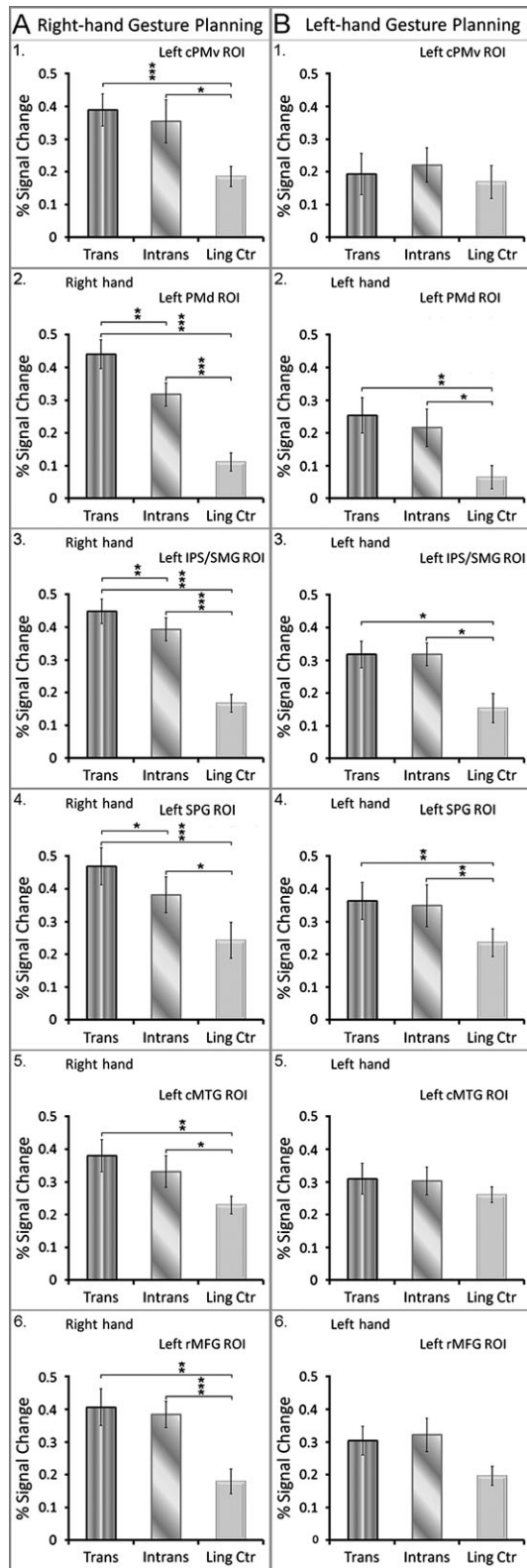
difference between transitive and intransitive planning was nonsignificant,  $Bf-P = 1.0$ . Left cPMv therefore appears to be equally involved in planning tool use pantomimes and intransitive gestures for the right hand.

In left PMd, only transitive and intransitive planning were associated with significant increases above the resting baseline, and responses in both conditions exceeded those associated with the linguistic control,  $Bf-P < 0.001$  in both cases. PMd also responded more during transitive versus intransitive planning ( $Bf-P < 0.01$ ) (Fig. 3A-2). This suggests that planning tool use pantomimes for the right hand places greater demands on this area than planning intransitive gestures.

Within the left parietal ROI, consisting of a large cluster within the left IPS and extending onto the lateral convexity of the SMG, all 3 conditions were associated with increases in activity above the resting baseline ( $Bf-P < 0.01$ ), and transitive and intransitive planning increased activity more than the

linguistic control condition ( $Bf-P < 0.001$  in both cases) (Fig. 3A-3). This area also responded more during transitive versus intransitive planning ( $Bf-P < 0.01$ ), indicating that the planning of tool use pantomimes places greater demands on the left inferior parietal cortex, at least when the right hand is involved. Similarly, all 3 conditions increased activity significantly above the resting baseline in the left dorsal SPG region ( $Bf-P < 0.001$  in all cases), and the effects of both transitive and intransitive conditions exceeded those of the linguistic control,  $Bf-P < 0.001$  and  $0.05$ , respectively (Fig. 3A-4). Here too planning tool use pantomimes for the right hand was associated with significantly greater activation than planning intransitive gestures,  $Bf-P < 0.05$ .

Within the left cMTG, all 3 conditions increased activity above the resting baseline ( $Bf-P < 0.001$  in all cases) and transitive and intransitive planning were associated with larger responses than the linguistic control condition,  $Bf-P < 0.01$  and



**Figure 3.** Region-of-Interest Analyses for Experiments 1 and 2. Mean percent signal change within each ROI is plotted relative to the resting baseline for 3 conditions: planning transitive actions (tool use pantomimes), intransitive gestures, and the linguistic control conditions. (A) Exp. 1. (B) Exp. 2. Asterisks indicate differences with Bonferroni-corrected  $P$  values of at least 0.05 (\*), 0.01 (\*\*), or 0.001 (\*\*\*)

0.05, respectively (Fig. 3A-5). However, similar to cPMv, the difference between transitive and intransitive planning failed to reach significance ( $Bf-P = 0.2$ ), suggesting that planning of both types of actions for the right hand places similar demands on this area.

Finally, within left rMFG, transitive and intransitive planning increased activity significantly above the resting baseline ( $Bf-P < 0.001$  in both cases), whereas the linguistic control condition did not,  $Bf-P = 0.09$  (Fig. 3A-6). Likewise, rMFG responses were greater during transitive and intransitive planning versus the linguistic control ( $Bf-P < 0.01$ ). However, as in both cPMv and rMTG, the difference between planning tool use pantomimes and intransitive gestures was nonsignificant,  $Bf-P = 1.0$ .

### Individual Variation in Parietal and Ventral Frontal Activity

Given the centrality of the posterior parietal cortex (PPC) in theories of praxis (Rothi et al. 1991; Cubelli et al. 2000; Leiguarda and Marsden 2000; Buxbaum 2001), we sought evidence at the individual subject level for dissociations between representations of transitive versus intransitive actions. This involved overlaying each individual's fMRI results onto their own high-resolution anatomical scans. This was done separately for tool use pantomime or intransitive gesture planning versus the linguistic control condition. Following a procedure described previously (Johnson-Frey et al. 2005), we used anatomical landmarks to determine whether significantly activated clusters were located in SPG, SMG, and/or the angular gyrus (AG).

On the basis of recent findings suggesting that tool use pantomime is affected predominantly by left inferior frontal lesions (Goldenberg et al. 2007), a similar analysis was performed on ventral frontal cortex (PMv, IFG, MFG). Percentages in Tables 1 and 2 reflect proportions based on the total sample of 12 individuals.

All participants showed increased activation of the left PPC during both tool use pantomime (transitive) and intransitive gesture planning. Although no one showed right unilateral activity, 75% did evidence increased activity in the right parietal cortex during at least one condition. Thus, although the left PPC appears ubiquitous in the representation of manual praxis, in most individuals the right PPC also participates in planning these actions, at least when the dominant right hand is involved. We again found no indication, however, that the right PPC is more heavily involved in the representation of intransitive versus transitive actions. Of those 8 individuals (67%) showing right PPC activation, only a single participant demonstrated it exclusively for intransitive gesture planning. Yet, 3 participants (25%) showed increased activity in right PPC during transitive gesture planning. By contrast, half of all individuals showing bilateral PPC activity (33%) did so when planning both transitive and intransitive gestures. Further details on localization can be found in Table 1.

Analyses of individual participants' results in ventral frontal cortex also failed to support the hypothesis that intransitive actions are more bilaterally represented than transitive actions. All participants showed increased activity in left ventral frontal cortex during the planning of transitive and/or intransitive gestures. For 67% of participants, increased activity was detected during both transitive and intransitive gesture planning. Twenty-five percent showed a selective increase in

**Table 1**  
Locations of significant posterior parietal and/or ventral frontal activations in Exp. 1 (right hand) for individual participants during planning of transitive and intransitive gestures, each versus the linguistic control condition

Subject	Right-hand gesture planning																								
	Left hemisphere												Right hemisphere												
	SMG		AG		SPG		PMv		MFG		IFG		SMG		AG		SPG		PMv		MFG		IFG		
	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	
1	*	*	*		*	*		*		*															
2	*	*			*	*		*		*															
3	*	*			*					*															
4	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
5	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
6	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
7	*	*	*		*		*		*	*	*														
8	*	*			*	*	*	*	*	*	*	*					*								*
9	*	*	*	*	*	*	*	*	*	*	*	*				*									
10	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
11	*	*	*		*	*	*	*	*	*	*	*			*			*			*		*	*	*
12	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
%	100%	100%	75%	42%	100%	83%	58%	42%	92%	75%	42%	33%	33%	25%	42%	25%	50%	33%	33%	25%	42%	33%	33%	33%	33%

Note: Asterisks indicate whether significant activations (fixed effects analyses,  $P < 0.05$ , clusterwise correction) were found in the left and/or right SMG, AG, SPG, PMv, MFG, and/or IFG. For a given participant, multiple significant activations can be found. Bottom row summarizes the percentage of individuals showing activation for each area and condition.

**Table 2**  
Locations of significant (fixed effects analyses,  $P < 0.05$ , clusterwise correction) posterior parietal and/or ventral frontal activations in Exp. 2 (left hand) for individual participants during planning of transitive and intransitive gestures (each vs. the linguistic control condition)

Subject	Left-hand gesture planning																								
	Left hemisphere												Right hemisphere												
	SMG		AG		SPG		PMv		MFG		IFG		SMG		AG		SPG		PMv		MFG		IFG		
	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	TR	INTR	
1					*				*								*								
2																									
3			*		*																			*	
4	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
5	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
6	*	*	*		*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
7	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
8	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
9	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
10	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
11	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
12	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
%	67%	58%	58%	50%	92%	67%	25%	17%	75%	67%	33%	42%	50%	33%	42%	42%	58%	58%	17%	25%	33%	33%	42%	33%	33%

the left hemisphere only during transitive planning. A single individual displayed increased activity only during intransitive planning. By comparison, 58% of participants evidenced increased activity in right ventral frontal cortex. For 33% of subjects, this was detected when planning both types of gestures. Two individuals (17%) showed right ventral frontal increases only during transitive planning, and a single participant selectively activated right ventral frontal cortex during intransitive planning. Refer to Table 1 for details on localization.

### Execution Phase

A direct comparison of tool use pantomimes versus intransitive actions revealed increased activity within the left parietal (postcentral gyrus, IPL, and SPG) and frontal (central sulcus extending along the length of precentral gyrus, PMv, PMd, and pre-SMA) cortices, and bilateral cerebellum (Fig. 2F). Though not pictured, the execution of intransitive gestures versus tool use pantomimes was associated with just a single cluster of activity in the left posterior cingulate gyrus.

### Discussion

In summary, planning tool use pantomimes for subsequent production with the right hand increased activity within a distributed network of parietal, frontal and temporal areas. Consistent with previous neuroimaging studies (Moll et al. 2000; Choi et al. 2001; Ohgami et al. 2004; Rumiati et al. 2004; Johnson-Frey et al. 2005; Hermsdorfer et al. 2007), these effects were more pronounced in the left cerebral hemisphere, particularly when activity associated with linguistic stimulus processing was controlled. Similar to the observations of Fridman and colleagues (Fridman et al. 2006), we found that activity within these same regions increased during the planning of intransitive gestures. These effects cannot be explained simply in terms of linguistic stimulus processing demands, as all ROIs (cPMv PMd, IPS/SMG, SPG, cMTG, and rMFG) showed significant increases in activity when planning both tool use pantomimes and intransitive gestures relative to the linguistic control condition. In contrast to this earlier report, however, left inferior (IPS/SMG) and superior (SPG) parietal and PMd cortices showed greater

responses during the planning of tool use pantomimes versus intransitive gestures. Likewise, as will be elaborated in the general discussion section, we failed to detect any differences between these conditions in left cPMv.

The fact that left parietal cortex (IPS/SMG and SPG) is engaged more during the retrieval and planning of tool use pantomimes versus intransitive gestures mirrors the pattern of deficits in apraxia (Roy et al. 1991; Foundas et al. 1999), and is consistent with the hypothesis that the former behaviors place greater demands on this region. Because left parietal activity in our study increases significantly above both the resting baseline and the linguistic control conditions when planning both types of actions, it is not immediately apparent how damage here could selectively impair the performance of tool use pantomimes while completely sparing intransitive gestures (Rapcsak et al. 1993; Dumont et al. 1999). Furthermore, neither whole brain group nor individual analyses of PPC and ventral frontal cortex provided support for the hypothesis that intransitive gestures are more bilaterally represented than tool use pantomimes. This result is inconsistent with reports showing that the intransitive gestures are more likely to be affected by either left or right hemisphere lesions (Cubelli et al. 2000; Heath, Roy, Black, et al. 2001; Heath, Roy, Westwood, et al. 2001; Buxbaum et al. 2007). The present results, however, do fit well with other observations showing greater impairments in both behaviors following left versus right hemisphere injuries (Hanna-Pladdy et al. 2001).

Left dorsal premotor lesions are also relatively common in apraxia (Haaland et al. 2000) and, along with left IPS, PMd appears to play an important role in action selection (Schluter et al. 2001), which is a critical component of both planning conditions. Engagement of PMd here is also consistent with its involvement in representing conditional stimulus-response associations (Grafton et al. 1998; Picard and Strick 2001), such as those established between arbitrary verbal cues and patterns of movement. Further, the observed PMd activation in our task is consistent with previous evidence showing that patients with premotor lesions are impaired when they must retrieve and perform a learned movement in response to a sensory cue (Halsband and Freund 1990).

Finally, we found greater increases in contralateral sensory-motor regions during the execution of tool use pantomimes versus intransitive gestures. This may suggest that these 2 classes of actions are differentially represented at the execution level. However, previous work shows that activity in sensory-motor cortex increases as a function of movement complexity (Gut et al. 2007). Therefore, it is also possible that this difference is attributable to tool use pantomimes simply being more demanding to execute than intransitive gestures.

### **Exp. 2: Tool Use Pantomimes and Intransitive Gestures with the Nondominant Left Hand**

In Exp. 2 we ask whether the left lateralized effects observed in Exp. 1 reflect a true cerebral asymmetry in the representation of praxis, or the engagement of processes contralateral to the involved limb. Testing the left hand is also important because most studies of apraxic patients are based on use of the ipsilesional (and typically nondominant) left hand, a fact often necessitated by their right hemiparesis. The participants and methods were identical to Exp. 1, except that actions were planned for and executed with the nondominant left hand.

## **Results and Discussion**

### **Planning Phase**

Compared with the resting baseline, planning tool use pantomimes for production with the left hand significantly increased activity within many of the same regions identified in Exp. 1: bilaterally within and along the IPS, lateral parietal cortex (IPL and SPG), pre-SMA/CMA and cMTG, right PMd, left rMFG and IFG/insula, and bilateral cerebellum (Fig. 4A). Overall, activations tended to be more strongly left-lateralized (i.e., less bilateral) when planning actions for subsequent production with the nondominant left hand (cf. Fig. 2). As in Exp. 1, this left cerebral asymmetry was even more dramatic when effects related to processing linguistic stimuli were controlled. Significant activity remained only within and along left IPS, bilateral PMd, pre-SMA/CMA, and in the left cerebellum (Fig. 4B; Supplementary Materials Table 1C). In contrast to Exp. 1, activations in left cPMv, rMFG, and cMTG all failed to achieve significance at this threshold (cf. Fig. 2B). Relative to resting baseline, planning intransitive gestures increased activity within the same regions as planning tool use pantomimes, except for right PMd (Fig. 4C). When linguistic processing demands were controlled, effects in the right hemisphere became nonsignificant; only parietal cortex within and along the left IPS, as well as rMFG, and PMd showed significant increases in activity (Fig. 4D; Supplementary Materials Table 1D).

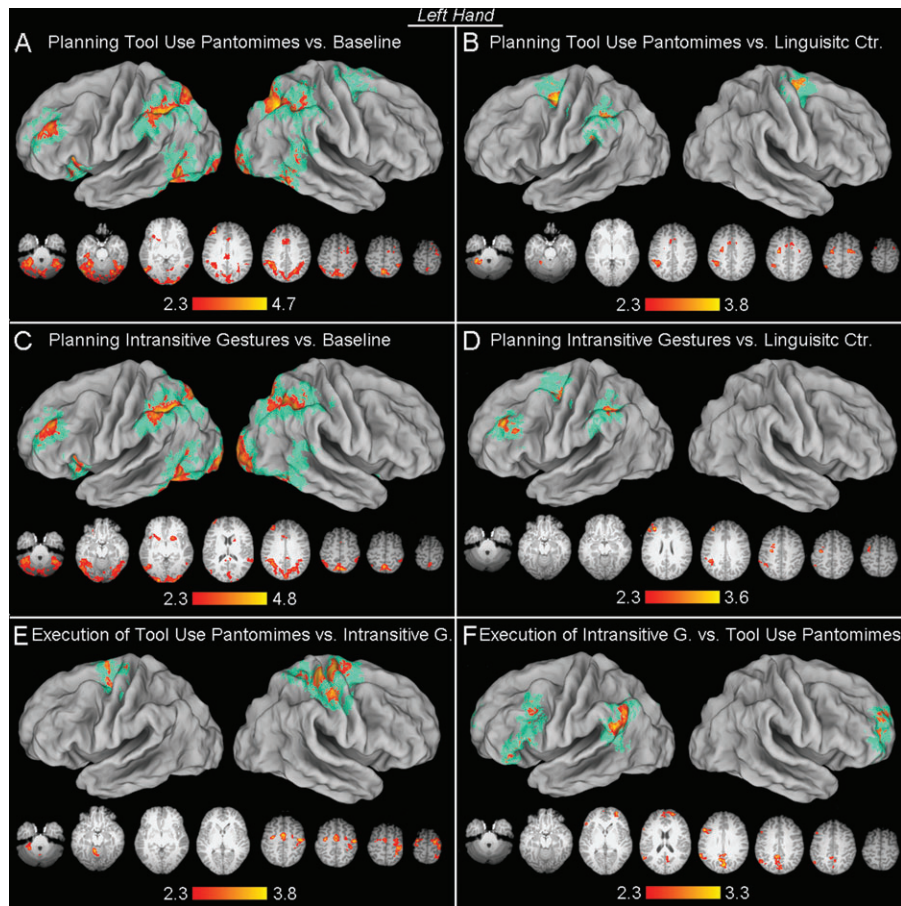
Finally, in contrast to Exp. 1, direct comparisons failed to detect any areas that were significantly more active during the planning of tool use pantomimes versus intransitive gestures. This suggests that these differences within and along the left IPS and PMd were specific to planning actions for subsequent production with the dominant right hand (i.e., hand dependent). Here too, no areas were more significantly activated during the planning of intransitive gestures versus tool use pantomimes.

### **ROI Analyses**

To facilitate direct comparisons across experiments, responses associated with each condition were also analyzed within the same ROIs defined in Exp. 1 (Supplementary Materials Table 1E). In cPMv neither the tool use pantomime (transitive), intransitive gesture, nor linguistic control conditions were associated with significant increases above the resting baseline,  $Bf-P > 0.09$  in all cases (Fig. 3B-1). Transitive planning was associated with a significant increase in activity above the resting baseline in left PMd ( $Bf-P < 0.05$ ), whereas the effects of intransitive planning approached but did not achieve significance,  $Bf-P = 0.07$  (Fig. 3B-2). Effects of the linguistic control condition did not differ from baseline,  $Bf-P = 1.0$ . Both transitive and intransitive planning significantly increased activity above the linguistic control activation ( $Bf-P < 0.05$ ). Though highly significant in Exp. 1, the difference between transitive versus intransitive planning only approached significance here,  $Bf-P = 0.08$ .

By contrast, activity in left inferior parietal cortex (IPS/SMG) during all 3 conditions was significantly higher than baseline ( $Bf-P < 0.05$  in all cases), and both transitive and intransitive planning increased activity more than the linguistic control,  $Bf-P < 0.05$  (Fig. 3B-3). However, in contrast to Exp. 1, responses associated with transitive versus intransitive planning did not differ,  $Bf-P = 1.0$ . Similarly, in left SPG all conditions increased activity above the resting baseline ( $Bf-P < 0.001$  in all cases),





**Figure 4.** Brain areas showing increased activity during the planning (A-D), and execution (E-F) of tool use pantomimes and intransitive gestures with the non-dominant left hand. Overall, planning either type of action for production with the non-dominant hand resulted in less extensive increases in activity (cf. Figure 2). However, several areas detected in Exp. 1 also showed significant increases in activity here. (A) Planning tool use pantomimes vs. resting baseline. Increases were again detected bilaterally in the IPS/SMG, SPL, cMTG, pre-SMA, and cerebellum, as well as right PMd and left rMFG. Compared with Exp. 1 (Figure 2), these activations tended to be more strongly left-lateralized. (B) Planning tool use pantomimes versus the linguistic control condition. With the exception of PMd, controlling for linguistic stimulus processing eliminates activity in the right hemisphere as well as in left cMTG, rMFG, and inferior frontal cortex. (C) Compared with tool use pantomime (A), a nearly identical pattern of increased activity was observed during the planning of intransitive gestures versus resting baseline. (D) Planning intransitive actions versus the linguistic control condition. Again, when linguistic stimulus processing demands were controlled, activity in the right hemisphere became nonsignificant as did the left inferior frontal cortex. Increased activity within the left inferior parietal (along the IPS), PMd, and rMFG remained significant. Note that unlike Exp. 1, we failed to detect any significant differences when comparing tool use pantomime versus intransitive gesture planning conditions directly. (E) Direct comparison between execution of tool use pantomimes versus intransitive gestures. Activation was found bilaterally: in left PMd and pre-SMA, as well as in right SPG, primary somatosensory (S1) and motor (M1) cortices, PMd and pre-SMA. (F) Direct comparison between execution of intransitive gestures versus tool use pantomimes. Activation was also found bilaterally: on the left—in MFG, IFG, and AG/SMG through caudal STG (temporo-parietal junction), and on the right—in rostral MFG.

and the effects associated with both transitive and intransitive planning exceeded those of the linguistic control,  $Bf-P < 0.05$  in each case (Fig. 3B-4). Likewise, there was no difference between the effects of transitive versus intransitive planning,  $Bf-P = 1.0$  in each case.

In left cMTG we again found that all 3 conditions increased activity above the resting baseline ( $Bf-P < 0.001$  in all cases), but they did not differ from one another,  $Bf-P = 1.0$  in all cases (Fig. 3B-5). Similarly, in rMFG, all conditions were above baseline ( $Bf-P < 0.01$  in all cases), but did not differ from one another,  $Bf-P > 0.20$  in all cases (Fig. 3B-6). These results suggest that for the left hand, both cMTG and rMFG were equally involved in planning both types of actions and in processing linguistic stimuli.

#### **Individual Variability in Parietal and Ventral Frontal Activity**

Consistent with Exp. 1, we failed to find support for the hypothesis that intransitive actions are more bilaterally

represented than transitive actions. Analyses of individual variability in parietal recruitment revealed that a single participant (Case 2) showed no significant increases in left or right parietal activity when planning either transitive or intransitive actions (Table 2). This same individual activated left parietal regions exclusively during right hand planning (see Table 1). Consistent with Exp. 1, all other subjects (92%) showed increased activity in left PPC, and 67% engaged right PPC as well. In all of these 8 cases, both right and left PPC showed significant increases. With the exception of a single participant (Case 1), these bilateral increases were observed for both transitive and intransitive planning. Case 1 showed only bilateral SPG increases during transitive planning. Again, we found no participants who showed unilateral right parietal activations in either condition. Details on localization can be found in Table 2.

The pattern of results for ventral frontal cortex was also very similar to Exp. 1. The majority (75%) of participants showed increased activity in left ventral frontal cortex during the

planning of transitive and/or intransitive gestures. For 67% of participants, increased activity was detected during both transitive and intransitive gesture planning. A single individual (Case 1) showed a selective increase in left ventral frontal cortex only during transitive planning. Conversely, 58% of participants evidenced increased activity in right ventral frontal cortex for transitive and/or intransitive gestures. For 33% of subjects, this was detected when planning both types of gestures. Two individuals (17%) showed increased right ventral frontal activity only during transitive planning, and one participant (Case 7) only during intransitive planning.

### **Execution Phase**

Similar to Exp. 1, a direct contrast of tool use pantomimes versus intransitive gestures revealed increased activity contralateral to the involved limb, within the central sulcus extending caudally into the postcentral gyrus, and rostrally into the precentral gyrus and PMd. This was accompanied by ipsilateral increases in all of these frontal regions, and the cerebellum (Fig. 4E). In contrast to Exp. 1, execution of intransitive gestures versus tool use pantomimes was associated with significant increases in the contralateral (right) frontal pole, and in ipsilateral caudal MFG extending into the IFG. Notably, there was also a strong focal increase in the left temporo-parietal junction (Fig. 4F).

### **Discussion**

In summary, relative to the resting baseline, planning tool use pantomimes and intransitive gestures for production with the nondominant left hand increased activity in largely the same regions detected in Exp. 1. Overall, these effects tended to be even more strongly left-lateralized (i.e., less bilateral). As in Exp. 1, this left cerebral asymmetry was magnified when linguistic processing demands were controlled. Here, however, only activations in left parietal cortex (IPS/SMG and SPG) and PMd exceeded those associated with linguistic processing. In contrast to Exp. 1, no areas showed significantly greater responses when planning tool use pantomimes versus intransitive gestures.

As in Exp. 1, we again observed greater activation of contralateral sensory-motor regions during the execution of tool use pantomimes versus intransitive gestures. In addition, transitive actions were associated with significantly greater increases within the left central sulcus extending into precentral gyrus and PMd. Previous work shows increased activity in ipsilateral motor cortex during use of the nondominant left hand (Singh et al. 1998), and these effects increase as a function of movement complexity (Gut et al. 2007). These differences may therefore be attributable to greater motor control demands of tool use pantomimes versus intransitive gestures. In contrast to Exp. 1, execution of intransitive gestures versus tool use pantomimes with the left hand revealed unexpected increases in left ventral frontal cortex and the temporo-parietal junction. The reasons for these differences, peculiar to use of the left hand, are uncertain. However, they are counter to the hypothesis that intransitive actions place greater demands on the right cerebral hemisphere.

### **General Discussion**

The present experiments yielded no evidence for the hypothesis that the left hemisphere supports independent mechanisms for the representation of familiar transitive versus

intransitive skills (Morlass 1928; Rothi et al. 1991; Cubelli et al. 2000; Buxbaum 2001; Mozaz et al. 2002; Leiguarda 2005). Regardless of the hand involved, planning either type of action was associated with increases in the same regions of left parietal (within and along the IPS, SMG, and caudal SPL) and premotor (PMd) cortices. Importantly, this was true even when linguistic processing demands were controlled. These planning-related increases were greater for tool use pantomimes versus intransitive gestures, but only when the right hand was involved. Likewise, neither group nor individual subject analyses of planning-related activity revealed any evidence that intransitive actions are more bilaterally represented than transitive actions. Our findings are therefore consistent with the view that, at the hand-independent level, both types of actions are represented in a common network within the left hemisphere of right-handed individuals (i.e., the PRN). We now consider the main findings in greater detail.

### **Hand-Independent Planning Effects**

As with previous findings (Moll et al. 2000; Choi et al. 2001; Ohgami et al. 2004; Rumiati et al. 2004; Johnson-Frey et al. 2005; Hermsdorfer et al. 2007), planning familiar tool use pantomimes with either the right or left hands increased activity above resting baseline levels within parietal (IPS/SMG, SPG), frontal (PMd, rMFG), and temporal (cMTG) regions. Regardless of the hand involved, these responses were more pronounced in the left cerebral hemisphere (Figs 2A and 4A). Further, we found that the left cerebral asymmetry in activations was more pronounced when linguistic processing demands were controlled (Figs 2B and 4B). This suggests that activity increases within homotopic regions of the right hemisphere were highly associated with the linguistic stimulus processing demands. Region of interest analyses confirm that responses in left parietal cortex (IPS/SMG and SPG) and PMd exceeded those associated with the linguistic control condition, irrespective of the hand involved (Fig. 3). Together, the results of these analyses support the hypothesis that left parietal and premotor cortices support hand-independent representations of transitive actions. The locations of these particular activations are also consistent with areas of high lesion overlap in apraxia (Haaland et al. 2000; Buxbaum et al. 2005).

Importantly, we found comparable hand-independent responses within these same parietal (IPS/SMG and SPG) and frontal (PMd) areas when participants planned intransitive gestures (Figs 2C,D and 4C,D). As discussed below, we did observe greater activity in left parietal and premotor areas when planning transitive versus intransitive actions, but only for the right hand (Fig. 2E). No regions showed gesture-specific differences, irrespective of the hand involved. The fact that responses during intransitive gesture planning, within the same parietal and premotor ROIs, also exceeded those observed in the control condition indicates that they too cannot be explained in terms of linguistic stimulus processing (Fig. 3). These results support the hypothesis that these left-lateralized regions represent both transitive and intransitive actions at the hand-independent level. Our results are consistent with a very recent study demonstrating consistent hand-independent increases in left parietal and premotor cortices when planning both transitive and intransitive gestures (Bohlhalter et al. 2008). However, in contrast to this report, we do not find that left parietal and premotor cortices are more highly activated when planning intransitive versus transitive gestures, irrespective of

the hand involved (Bohlhalter et al. 2008). This difference was not anticipated on the basis of either the results of neuropsychological investigations or a previous neuroimaging study demonstrating greater left cPMv activation for transitive versus intransitive gesture planning for the right hand (Fridman et al. 2006). The reason(s) for our failure to replicate the Bohlhalter and colleagues result (Bohlhalter et al. 2008) is (are) unclear. One possibility is the use of different paradigms in these investigations. Bohlhalter and collaborators employed a design similar to that of Fridman and colleagues and, as detailed below, the results of this task may be more sensitive to linguistic stimulus processing demands.

There is considerable evidence that left parietal cortex plays a specialized role in the sensory-motor transformations underlying hand-object interactions (Sirigu et al. 1995; Buxbaum et al. 2003, 2005). However, we find that at the more abstract level demanded by classic apraxia tasks (verbally cued tool use pantomime and intransitive gesture), this region participates equally in the representation of previously acquired skills regardless of whether or not they involve objects, or of the hand involved.

Involvement of PMd in these tasks likely reflects its role in computations that are fundamental to many volitional movements including action selection and/or the representation of conditional stimulus-response associations (Grafton et al. 1998; Picard and Strick 2001). This point is discussed further below with regard to the implications of these findings for the hypothesized PRN.

Recent findings indicate that the performance of tool use pantomimes (with the ipsilesional left hand) are particularly sensitive to damage within the left inferior frontal cortex—that is, left IFG including adjacent insular cortex and PMv (Goldenberg et al. 2007). The ability of these patients to produce familiar intransitive gestures was not examined. We found that 9 of the 12 participants in the present experiments did show increased activity in left inferior frontal cortex (IFG and/or PMv) during the planning of tool use pantomimes for the right and/or left hand. However, only 42% did so regardless of the hand involved, and in 3 (25%) instances significant hand-independent increases were also present for intransitive gesture planning (Tables 1 and 2). On the basis of these findings, and the vast majority of previous neuropsychological results, we would expect patients with left inferior frontal lesions to be impaired to some degree on both tasks.

It can be argued that we failed to detect differences between tool use pantomime and intransitive gesture conditions because participants here received training in gesture production prior to testing (in order to minimize interindividual variation). Although we have no basis for suspecting that these relatively brief experiences caused 2 initially independent representational systems to merge, it is worthy of note that patients do not typically receive training prior to such testing, and that those who do sometimes benefit (Cubelli et al. 1991; Smania et al. 2000). The issue of how neural representations of these actions are affected by practice has potentially important rehabilitation implications and deserves additional attention.

Another possibility is that hand-independent representations of transitive and intransitive gestures are implemented within distinct subregions of left parieto-frontal cortex, but that they simply cannot be differentiated with conventional fMRI activation paradigms. If so, then it seems unlikely that dissociations would be observed following naturally occurring brain lesions,

which tend to be quite large as compared with significant clusters of activity in fMRI. Nevertheless, this question might be entertained through use of fMRI adaptation, which exploits the phenomenon of repetition suppression. This method is believed to allow inferences about the selectivity of neural populations at a finer scale than traditional subtraction approaches (Grill-Spector et al. 1999; Grill-Spector and Malach 2001). Indeed, fMRI adaptation paradigms have been successfully extended to investigations of both observed and executed actions (Shmuelof and Zohary 2005; Dinstein et al. 2007; Krolczak et al. 2008).

#### *Hand-Dependent Planning Effects*

Although no brain areas showed significantly greater responses when planning tool use pantomimes versus intransitive gestures independent of the hand involved, 3 regions (IPS/SMG, SPG, and PMd) did show this effect for the right hand (Figs 2E and 3A). These results are consistent with those of an earlier report showing increases in left parietal and premotor activity when planning either familiar transitive or intransitive actions for the right hand (Fridman et al. 2006).

Together these findings suggest that at the hand-dependent level of representation, there may indeed be differences between neural representations of transitive versus intransitive actions within the left hemisphere. These may be experience dependent; that is, participants had considerably more experience undertaking these actions with their dominant right hands. As a result, the left hemisphere may have developed a more highly differentiated system of praxis representations specific to use of the right hand. If so, then we would expect to observe the reversed pattern in strongly left-handed individuals. These findings also raise the possibility that left hemisphere injuries could differentially impact tool use pantomimes versus intransitive gestures performed with the right hand. That is, left hemisphere lesions may cause apraxic-like symptoms that are only manifest with the contralesional hand. Testing for such possible effects in apraxic patients would be very challenging, though, due to the prevalence of right hemiparesis. Nevertheless, the presence of these hand-dependent differences does suggest a need to be cautious when drawing conclusions based on testing of a single hand.

In contrast to the results of Fridman et al. (2006), we did not find evidence for greater activation of left cPMv activity between planning tool use pantomime and intransitive gesture conditions, even when the right hand was involved (Exp. 1). This may have to do with differences between the linguistic demands of the tasks employed in these studies and/or the analyses performed. Fridman et al. used sentences as cues and looked for a transient BOLD response coincident with stimulus onset. By contrast, the present study sought to identify responses developing over the 3.5-s period following the onset of single stimulus verbs. Consequently, it is possible that their results were more influenced by differences between the linguistic processing demands of the sentence stimuli, and less by action planning. Indeed, left inferior frontal cortex (including PMv) is known to show increased activity during tasks such as naming tools (Grafton et al. 1997) or generating action words (Martin et al. 1995). Consistent with this interpretation, we did find increased activity, relative to resting baseline, in the left IFG (anterior and ventral to cPMv) when planning either tool use pantomimes or intransitive gestures for subsequent production with either hand (cf. Figs 2 and 4). However, these

effects were reduced when linguistic stimulus processing demands were controlled.

### *The Issue of Bilateral Representations of Intransitive Gestures*

We also find no clear evidence that intransitive gestures are represented more bilaterally than transitive actions, as suggested by some (Heath, Roy, Black, et al. 2001; Heath, Roy, Westwood, et al., 2001; Buxbaum et al. 2007), but not all (Hanna-Pladdy et al. 2001), studies of brain-injured patients. Irrespective of the hand involved, no brain regions in either hemisphere were significantly more active when planning intransitive gestures versus tool use pantomimes (or vice versa).

Analyses of individual participants' data also failed to support this hypothesis. In parietal cortex, half of all participants showed a hand-independent increase in right PPC, and this was always accompanied by left parietal activity (i.e., bilateral parietal activation). For 3 individuals these bilateral hand-independent increases occurred when planning both transitive and intransitive gestures. Two participants only showed these effects for transitive gestures, and one only for the intransitive condition (Tables 1 and 2).

A similar pattern was evident in ventral frontal cortex (IFG, PMv, MFG), where significant increases in the right hemisphere were always accompanied by increases in the left hemisphere. Across both studies, only 2 individuals showed increased right hemisphere activity exclusively for intransitive planning, whereas 4 participants did so for transitive planning.

### *Implications for Dissociations in Apraxia*

On the surface, our findings may seem at odds with the long-standing observations that patients with left hemisphere lesions often perform better at intransitive gestures than tool use pantomimes. One reason for this apparent discrepancy may be the different levels of analysis involved in these approaches. Functional neuroimaging data reflects relative activity in the brain's gray matter, whereas behavioral deficits experienced by apraxic patients may also result from damage to white matter tracts (Geschwind 1965; Cubelli et al. 2000; Hanna-Pladdy et al. 2001). Likewise, we have primarily focused on activity associated with the planning of actions prior to movement onset. By contrast, studies of patient behavior reflect not only the integrity of premovement processes, but also functions involved in linguistic stimulus processing and sensory-motor execution. When focusing exclusively on premovement planning, we find patterns of activity that show less cerebral asymmetry when demands of linguistic stimulus processing are not controlled. It is also worth noting that movements were executed in our study without visual feedback (i.e., open loop), whereas apraxia testing is typically done with full vision (i.e., closed loop). This may also contribute to the apparent differences between imaging and lesion-based results. One such example might be the fact that left inferior frontal lesions affect tool use pantomime in patients (Goldenberg et al. 2007), yet this area fails to increase activity significantly during the execution of these actions here.

Previous work demonstrates that the mechanisms involved in planning versus execution of familiar transitive and/or intransitive actions only partially overlap (Johnson-Frey et al. 2005; Fridman et al. 2006). It is therefore possible, that stored representations of both tool use pantomimes and intransitive

gestures reside in the same network, but that their production engages dissociable mechanisms. For instance, it may be that—at least in some individuals—the production of intransitive gestures relies more heavily on right-lateralized mechanisms than does the execution of transitive pantomimes. This might explain why left unilateral damage often affects tool use pantomimes more than intransitive gestures, and why some studies find that right hemisphere lesions impact intransitive gestures more than transitive actions. Yet, these conjectures are not supported by our results. We find no evidence that production of intransitive gestures versus tool use pantomimes places greater demands on right hemisphere mechanisms independent of the hand involved.

Alternatively, our work suggests that, at the hand-independent level, both types of familiar actions are represented in a common left parieto-frontal network. The reason that patients often demonstrate greater difficulties with tool use pantomimes (Roy et al. 1991; Foundas et al. 1999; Haaland et al. 2000) may simply be that transitive actions place greater demands on this shared representational system. On the execution side, production of tool use pantomimes versus intransitive gestures with either hand was accompanied by larger increases in activity within classic motor regions, similar to what has been reported previously when tasks differ in complexity (Gut et al. 2007). There are reasons to suspect that similar differences in difficulty exist on the planning side as well, and that these may be responsible for reports of single dissociations between performances on tool use pantomime and intransitive gestures.

In order to minimize cues for retrieval, the classic test of apraxia (adapted here for fMRI) requires participants to retrieve previously acquired skills exclusively on the basis of learned associations with arbitrary verbal cues (Heilman and Rothi 1997). These circumstances differ dramatically from the situations in which these tool use representations were acquired and in which they are typically performed. As previously noted, this tool use pantomime task demands that representations be reactivated in the absence of the objects that normally provide contextual cues (Rapcsak et al. 1993), and physical constraints on subsequent performances (Buxbaum 2001; Goldenberg et al. 2004). Providing apraxics with visual and/or haptic access to the objects with which these actions are associated can often improve their performances (De Renzi et al. 1982; Goldenberg et al. 2004; Hermsdorfer et al. 2006). By contrast, accessing intransitive representations in response to verbal cues recreates the circumstances under which they were acquired and typically performed (Rapcsak et al. 1993; Mozaz et al. 2002).

In accordance with the encoding specificity principle (Tulving and Thomson 1973), retrieval of representations of tool use pantomimes in response to verbal cues should be more difficult than the retrieval of intransitive gestures. Consistent with this view is evidence that even healthy adults commit more errors when performing transitive pantomimes versus intransitive gestures in response to verbal cues (Mozaz et al. 2002). The fact that these control subjects also find transitive actions more difficult to discriminate between visually has been used to argue that the transitive versus intransitive difference in performance is not simply due to variations in movement complexity (Mozaz et al. 2002). Yet, assuming that action planning and perception involve common neural representations (Prinz 1997; Rizzolatti and Craighero 2004), differences in

the ease of retrieval would nevertheless be expected to affect performance of both transitive and intransitive tasks. Indeed, recent results indicate that, when confronted with a more demanding speeded imitation task, healthy adults also have greater difficulty imitating transitive versus intransitive gestures (Carmo and Rumiati, 2008). Thus, to the extent that apraxic patients are at or near the performance floor for tool use pantomime, one might expect that manipulations of general cognitive load (e.g., response deadlines) might also have a greater impact on their ability to produce transitive gestures. Consistent with this speculation is previous work indicating that apraxic patients do show greater impairments both in premovement planning and execution (i.e., scheduling and/or timing) of more complex (as compared with simple) sequences of hand postures (Harrington and Haaland 1992).

It is worth emphasizing that the actual use of tools certainly involves a variety of additional demands, including certain sensory-motor transformations, that are absent in pantomime. Indeed, even tool use pantomime may be viewed as a highly symbolic, and depending on the context, and communicative behavior, as discussed by Goldenberg and colleagues (Goldenberg 2003a, 2003b; Goldenberg et al. 2003). This commonality with intransitive gesture may underlie their implementation in a shared representational system. Although pantomime to verbal command has proven useful in isolating praxis functions, it is important to recognize that naturalistic actions will involve a wide variety of other processes and brain areas including those of the right cerebral hemisphere (Schwartz and Buxbaum 1997; Hartmann et al. 2005).

#### *Implications for the PRN*

As noted earlier, it has been hypothesized that the human left hemisphere supports a distributed parieto-fronto-temporal PRN (Johnson-Frey 2004; Frey 2008). The PRN, and particularly the left parietal cortex, is claimed to integrate distributed conceptual and sensory-motor representations into contextually appropriate action plans at the hand-independent level (Frey 2008). Consistent with this hypothesis, our ROI analyses revealed that, regardless of the hand or type of action involved, PMd and parietal (IPS/SMG, SPL) regions showed increases in activation that exceeded that of the linguistic control condition. In other words, these regions seem to be significantly more involved in praxis representation than linguistic processing.

In addition, these results also provided evidence for overlap between the PRN and the linguistic system, at least in right-handers. Activity in left cMTG, and rMFG also increased above resting baseline when planning both types of actions for either hand. However, for the left hand, these increases did not exceed what was detected during the linguistic control condition. Therefore, independent of the hand involved, left cMTG, and rMFG appear to contribute similarly to both linguistic processing and praxis representation. Partial overlap of left hemisphere mechanisms involved in language and praxis is not at all surprising. In fact, although apraxia and aphasia do dissociate they are often comorbid. Likewise, tool use and language (including gesture) are fundamental human cognitive specializations, and have long been suspected of having common origins (Bradshaw and Nettleton 1982; Gibson 1993; Frey 2008).

Furthermore, praxis (tool use and gesture) cannot be understood simply in terms of sensory-motor transformations,

but also requires input from conceptual and perhaps even linguistic functions (Johnson-Frey 2004; Frey 2007). Along these lines, the considerable overlap between areas of the proposed PRN and regions shown to be involved more generally in action selection is worthy of note. Left inferior parietal, PMd, prefrontal cortex (rostral inferior frontal sulcus), and lateral cerebellum all show increased activity during choice versus simple reaction time tasks, irrespective of the hand involved (Schluter et al. 2001). Selection is obviously a fundamental computational demand common to nearly all actions, and undoubtedly plays a role in the left-lateralized activations reported here and in previous studies of praxis. In contrast to studies of praxis, however, the left parietal peak associated with hand-independent action selection appears to be located more caudally (along the AG) and significant activations were not detected in the SPL or cMTG. One possibility is that this left-lateralized action selection network is at the core of the PRN. It may be that when planning familiar praxis skills, left SMG and anterior IPS integrate inputs from areas such as the left cMTG (for conceptual knowledge related to objects uses and/or functions), and SPL (for multisensory representations of the limbs). This information is then passed to the action selection network, resulting in choice of a contextually appropriate action plan.

#### **Conclusions**

In short, the present results do not support the long-standing hypothesis that familiar transitive and intransitive gestures are represented in separate neural systems (Morliss 1928; Rothi et al. 1991; Cubelli et al. 2000; Buxbaum 2001; Mozaz et al. 2002; Leiguarda 2005). Despite employing whole brain, ROI and individual subject-level analyses, it is possible that we have failed to detect subtle evidence of separable networks. However, such subtlety would seem unlikely given the often large and varied brain lesions leading to apraxia. Instead, it appears that at the hand-independent level, both types of action plans are represented in a common left parieto-fronto-temporal network, the so-called PRN. Likewise, neither group nor individual subject level analyses indicate that intransitive gestures are bilaterally represented (Heath, Roy, Black, et al. 2001; Buxbaum et al. 2007). We suggest that the advantage for intransitive gestures found in many cases of apraxia is attributable to the greater difficulty of the tool use pantomime task. This may also account for the absence of cases clearly demonstrating the reverse dissociation.

The present findings are consistent with the view that the human left cerebral hemisphere supports a system that flexibly and dynamically assembles contextually appropriate action plans from sources of information represented in areas distributed throughout the brain (Frey 2008). Depending on the task, these could include linguistic representations, conceptual knowledge about objects and their functions, the intentions and goals of the actor, and interpretations of prevailing task demands. An important question for future research, and one with potential relevance to rehabilitation of higher-level motor disorders, is to explore experience-dependent changes in this system as praxis skills are acquired.

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Address correspondence to Scott H. Frey, 5288 Lewis Center for Neuroimaging, University of Oregon, Eugene, OR 97403-5288, USA.

## Appendix 1: Stimulus Verbs

### 1) Transitive Planning

Dialing, Pounding, Painting, Pouring, Sewing, Scooping, Typing, Unlocking, Writing, Stabbing, Scrubbing, Stirring, Reeling, Cutting.

### 2) Intransitive Planning

Beckoning, Flicking, Hitchhiking, Pointing, Shooing, Snapping, Stopping, Waving, Tickling, Talking, Scolding, Wavering, Conducting, Counting.

### 3) Linguistic Control

Adapting, Being, Devising, Understanding, Evaluating, Innovating, Knowing, Planning, Qualifying, Resolving, Solving, Thinking, Interpreting, Believing.

## References

- Beckmann CF, Jenkinson M, Smith SM. 2003. General multilevel linear modeling for group analysis in fMRI. *Neuroimage*. 20:1052-1063.
- Belanger SA, Duffy RJ, Coelho CA. 1996. The assessment of limb apraxia: an investigation of task effects and their cause. *Brain Cogn*. 32:384-404.
- Bohlhalter S, Hattori N, Wheaton L, Fridman E, Shamim EA, Garraux G, Hallett M. 2008. Gesture subtype-dependent left lateralization of praxis planning: an event-related fMRI study. *Cereb Cortex*. Advanced Access published September 16, 2008, doi:10.1093/cercor/bhn168.
- Bradshaw JL, Nettleton NC. 1982. Language lateralization to the dominant hemisphere: tool use, gesture and language in hominid evolution. *Curr Psychol Rev*. 2:171-192.
- Buxbaum LJ. 2001. Ideomotor apraxia: a call to action. *Neurocase*. 7:445-458.
- Buxbaum LJ, Johnson-Frey SH, Bartlett-Williams M. 2005. Deficient internal models for planning hand-object interactions in apraxia. *Neuropsychologia*. 43:917-929.
- Buxbaum LJ, Kyle K, Grossman M, Coslett HB. 2007. Left inferior parietal representations for skilled hand-object interactions: evidence from stroke and corticobasal degeneration. *Cortex*. 43:411-423.
- Buxbaum LJ, Sirigu A, Schwartz MF, Klatzky R. 2003. Cognitive representations of hand posture in ideomotor apraxia. *Neuropsychologia*. 41:1091-1113.
- Carmo JC, Rumiati RI. 2008. Imitation of transitive and intransitive actions in healthy individuals. *Brain and Cogn*. Advanced Access published October 30, 2008, doi:10.1016/j.bandc.2008.1009.1007.
- Chao LL, Martin A. 2000. Representation of manipulable man-made objects in the dorsal stream. *Neuroimage*. 12:478-484.
- Choi SH, Na DL, Kang E, Lee KM, Lee SW, Na DG. 2001. Functional magnetic resonance imaging during pantomiming tool-use gestures. *Exp Brain Res*. 139:311-317.
- Clark MA, Merians AS, Kothari A, Poizner H, Macauley B, Gonzalez Rothi LJ, Heilman KM. 1994. Spatial planning deficits in limb apraxia. *Brain*. 117:1093-1106.
- Cubelli R, Marchetti C, Boscolo G, Della Sala S. 2000. Cognition in action: testing a model of limb apraxia. *Brain Cogn*. 44:144-165.
- Cubelli R, Trentini P, Montagna CG. 1991. Re-education of gestural communication in a case of chronic global aphasia and limb apraxia. *Cogn Neuropsychol*. 5:369-380.
- De Renzi E, Faglioni P, Sorgato P. 1982. Modality-specific and supramodal mechanisms of apraxia. *Brain*. 105:301-312.
- Dinstein I, Hasson U, Rubin N, Heeger DJ. 2007. Brain areas selective for both observed and executed movements. *J Neurophysiol*. 98:1415-1427.
- Dumont C, Ska B, Schiavetto A. 1999. Selective impairment of transitive gestures: an unusual case of apraxia. *Neurocase*. 5:447-458.
- Duvernoy HM. 1991. The human brain: surface, three-dimensional sectional anatomy and MRI. Vienna, Austria: Springer-Verlag.
- Foundas AL, Macauley BL, Raymer AM, Maher LM, Rothi LJ, Heilman KM. 1999. Ideomotor apraxia in Alzheimer disease and left hemisphere stroke: limb transitive and intransitive movements. *Neuropsychiatry Neuropsychol Behav Neurol*. 12:161-166.
- Frey SH. 2007. What puts the how in where? Tool use and the divided visual streams hypothesis. *Cortex*. 43:368-375.
- Frey SH. 2008. Tool use, communicative gesture and cerebral asymmetries in the modern human brain. *Philos Trans R Soc Lond B Biol Sci*. 363:1951-1957.
- Fridman EA, Immisch I, Hanakawa T, Bohlhalter S, Waldvogel D, Kansaku K, Wheaton L, Wu T, Hallett M. 2006. The role of the dorsal stream for gesture production. *Neuroimage*. 29:417-428.
- Geschwind N. 1965. Disconnexion syndromes in animals and man. II. *Brain*. 88:585-644.
- Geschwind N, Kaplan E. 1962. A human cerebral disconnection syndrome. A preliminary report. *Neurology*. 12:675-685.
- Gibson KR. 1993. The evolution of lateral asymmetries, language, tool-use, and intellect. By John Bradshaw and Lesley Rogers. San Diego: Academic Press, 1992 ISBN 0-12-124560-8. *Am J Phys Anthropol*. 92:123-124.
- Goldenberg G. 2003a. Apraxia and beyond: life and work of Hugo Liepmann. *Cortex*. 39:509-524.
- Goldenberg G. 2003b. Pantomime of object use: a challenge to cerebral localization of cognitive function. *Neuroimage*. 20(Suppl. 1): S101-106.
- Goldenberg G, Hartmann K, Schlott I. 2003. Defective pantomime of object use in left brain damage: apraxia or asymbolia? *Neuropsychologia*. 41:1565-1573.
- Goldenberg G, Hentze S, Hermsdorfer J. 2004. The effect of tactile feedback on pantomime of tool use in apraxia. *Neurology*. 63:1863-1867.
- Goldenberg G, Hermsdorfer J, Glindemann R, Rorden C, Karnath HO. 2007. Pantomime of tool use depends on integrity of left inferior frontal cortex. *Cereb Cortex*. 17:2769-2776.
- Grafton ST, Fadiga L, Arbib MA, Rizzolatti G. 1997. Premotor cortex activation during observation and naming of familiar tools. *Neuroimage*. 6:231-236.
- Grafton ST, Fagg AH, Arbib MA. 1998. Dorsal premotor cortex and conditional movement selection: a PET functional mapping study. *J Neurophysiol*. 79:1092-1097.
- Grill-Spector K, Kushnir T, Edelman S, Avidan G, Itzhak Y, Malach R. 1999. Differential processing of objects under various viewing conditions in the human lateral occipital complex. *Neuron*. 24:187-203.
- Grill-Spector K, Malach R. 2001. fMR-adaptation: a tool for studying the functional properties of human cortical neurons. *Acta Psychol (Amst)*. 107:293-321.
- Gut M, Urbanik A, Forsberg L, Binder M, Rymarczyk K, Sobiecka B, Kozub J, Grabowska A. 2007. Brain correlates of right-handedness. *Acta Neurobiol Exp (Wars)*. 67:43-51.
- Haaland KY, Harrington DL, Knight RT. 2000. Neural representations of skilled movement. *Brain*. 123:2306-2313.
- Halsband U, Freund HJ. 1990. Premotor cortex and conditional motor learning in man. *Brain*. 113:207-222.
- Hanna-Pladdy B, Daniels SK, Fieselman MA, Thompson K, Vasterling JJ, Heilman KM, Foundas AL. 2001. Praxis lateralization: errors in right and left hemisphere stroke. *Cortex*. 37:219-230.
- Harrington DL, Haaland KY. 1992. Motor sequencing with left hemisphere damage. Are some cognitive deficits specific to limb apraxia? *Brain*. 115(Pt 3):857-874.
- Hartmann K, Goldenberg G, Daumüller M, Hermsdorfer J. 2005. It takes the whole brain to make a cup of coffee: the neuropsychology of naturalistic actions involving technical devices. *Neuropsychologia*. 43:625-637.
- Heath M, Roy EA, Black SE, Westwood DA. 2001. Intransitive limb gestures and apraxia following unilateral stroke. *J Clin Exp Neuropsychol*. 23:628-642.

- Heath M, Roy EA, Westwood D, Black SE. 2001. Patterns of apraxia associated with the production of intransitive limb gestures following left and right hemisphere stroke. *Brain Cogn*. 46:165-169.
- Heilman KM, Rothi LJG. 1997. Limb apraxia: a look back. In: Rothi LJG, Heilman KM, editors. *Apraxia: the neuropsychology of action*. Hove, UK: Psychology Press/Erlbaum (UK), Taylor & Francis. p. 7-18.
- Heilman KM, Rothi LJG. 2003. Apraxia. In: Heilman KM, Valenstein E, editors. *Clinical neuropsychology*. New York: Oxford University Press. p. 215-135.
- Heilman KM, Rothi LJ, Valenstein E. 1982. Two forms of ideomotor apraxia. *Neurology*. 32:342-346.
- Hermisdorfer J, Hentze S, Goldenberg G. 2006. Spatial and kinematic features of apraxic movement depend on the mode of execution. *Neuropsychologia*. 44:1642-1652.
- Hermisdorfer J, Terlinden G, Muhlau M, Goldenberg G, Wohlschlagler AM. 2007. Neural representations of pantomimed and actual tool use: evidence from an event-related fMRI study. *Neuroimage*. 36(Suppl. 2): T109-118.
- Jenkinson M, Bannister P, Brady M, Smith S. 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 17:825-841.
- Jenkinson M, Smith S. 2001. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 5:143-156.
- Johnson-Frey SH. 2004. The neural bases of complex tool use in humans. *Trends Cogn Sci*. 8:71-78.
- Johnson-Frey SH, Newman-Norlund R, Grafton ST. 2005. A distributed left hemisphere network active during planning of everyday tool use skills. *Cereb Cortex*. 15:681-695.
- Kroliczak G, McAdam TD, Quinlan DJ, Culham JC. 2008. The human dorsal stream adapts to real actions and 3D shape processing: a functional magnetic resonance imaging study. *J Neurophysiol*. 100: 2627-2639.
- Leiguarda R. 2005. Apraxias as traditionally defined. In: Freund H-J, Jeannerod M, Hallett M, Leiguarda R, editors. *Higher-order motor disorders: from neuroanatomy and neurobiology to clinical neurology*. Oxford: Oxford University Press. p. 303-338.
- Leiguarda RC, Marsden CD. 2000. Limb apraxias: higher-order disorders of sensorimotor integration. *Brain*. 123:860-879.
- Liepmann H. 1900. Das Krankheitsbild der Apraxie (Motorischen/Asymbolie). *Monatsschrift Psychiatrie Neurol*. 8:15-44, 102-132, 182-197.
- Mahon BZ, Milleville SC, Negri GA, Rumiati RI, Caramazza A, Martin A. 2007. Action-related properties shape object representations in the ventral stream. *Neuron*. 55:507-520.
- Martin A, Haxby JV, Lalonde FM, Wiggs CL, Ungerleider LG. 1995. Discrete cortical regions associated with knowledge of color and knowledge of action. *Science*. 270:102-105.
- Martin A, Wiggs CL, Ungerleider LG, Haxby JV. 1996. Neural correlates of category-specific knowledge. *Nature*. 379:649-652.
- Moll J, de Oliveira-Souza R, Passman LJ, Cunha FC, Souza-Lima F, Andreiuolo PA. 2000. Functional MRI correlates of real and imagined tool-use pantomimes. *Neurology*. 54:1331-1336.
- Morlass J. 1928. Contribution à l'Étude de l'Apraxie. Paris: Amédee, Legrand.
- Mozaz M, Rothi LJ, Anderson JM, Crucian GP, Heilman KM. 2002. Postural knowledge of transitive pantomimes and intransitive gestures. *J Int Neuropsychol Soc*. 8:958-962.
- Ohgami Y, Matsuo K, Uchida N, Nakai T. 2004. An fMRI study of tool-use gestures: body part as object and pantomime. *Neuroreport*. 15: 1903-1906.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 9:97-113.
- Pazzaglia M, Smania N, Corato E, Aglioti SM. 2008. Neural underpinnings of gesture discrimination in patients with limb apraxia. *J Neurosci*. 28:3030-3041.
- Picard N, Strick PL. 2001. Imaging the premotor areas. *Curr Opin Neurobiol*. 11:663-672.
- Poizner H, Clark MA, Merians AS, Macauley B, Gonzalez Rothi LJ, Heilman KM. 1995. Joint coordination deficits in limb apraxia. *Brain*. 118:227-242.
- Prinz W. 1997. Perception and action planning. *Eur J Cogn Psychol*. 9: 129-154.
- Rapcsak SZ, Ochipa C, Beeson PM, Rubens AB. 1993. Praxis and the right hemisphere. *Brain Cogn*. 23:181-202.
- Rizzolatti G, Craighero L. 2004. The mirror-neuron system. *Annu Rev Neurosci*. 27:169-192.
- Rothi LJG, Ochipa C, Heilman KM. 1991. A cognitive neuropsychological model of limb praxis. *Cogn Neuropsychol*. 8:443-458.
- Roy EA, Square-Storer P, Hogg S, Adams S. 1991. Analysis of task demands in apraxia. *Int J Neurosci*. 56:177-186.
- Rumiati RI, Weiss PH, Shallice T, Ottoboni G, Noth J, Zilles K, Fink GR. 2004. Neural basis of pantomiming the use of visually presented objects. *Neuroimage*. 21:1224-1231.
- Schluter ND, Krams M, Rushworth MF, Passingham RE. 2001. Cerebral dominance for action in the human brain: the selection of actions. *Neuropsychologia*. 39:105-113.
- Schwartz MF, Buxbaum LJ. 1997. Naturalistic action. In: Rothi LJG, Heilman KM, editors. *Apraxia: the neuropsychology of action*. Hove, UK: Psychology Press/Erlbaum (UK), Taylor & Francis. p. 269-289.
- Shmuelof L, Zohary E. 2005. Dissociation between ventral and dorsal fMRI activation during object and action recognition. *Neuron*. 47:457-470.
- Singh LN, Higano S, Takahashi S, Kurihara N, Furuta S, Tamura H, Shimanuki Y, Mugikura S, Fujii T, Yamadori A, et al. 1998. Comparison of ipsilateral activation between right and left hands: a functional MR imaging study. *Neuroreport*. 9:1861-1866.
- Sirigu A, Cohen L, Duhamel JR, Pillon B, Dubois B, Agid Y. 1995. A selective impairment of hand posture for object utilization in apraxia. *Cortex*. 31:41-55.
- Smania N, Girardi F, Domenicali C, Lora E, Aglioti S. 2000. The rehabilitation of limb apraxia: a study in left-brain-damaged patients. *Arch Phys Med Rehabil*. 81:379-388.
- Smith SM. 2002. Fast robust automated brain extraction. *Hum Brain Mapp*. 17:143-155.
- Tranel D, Kemmerer D, Adolphs R, Damasio H, Damasio AR. 2003. Neural correlates of conceptual knowledge for actions. *Cogn Neuropsychol*. 20:409-432.
- Tranel D, Martin C, Damasio H, Grabowski TJ, Hichwa R. 2005. Effects of noun-verb homonymy on the neural correlates of naming concrete entities and actions. *Brain Lang*. 92:288-299.
- Tulving E, Thomson DM. 1973. Encoding specificity and retrieval processes in episodic memory. *Psychol Rev*. 80:352-373.
- Van Essen DC. 2005. A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex. *Neuroimage*. 28:635-662.
- Van Essen DC, Drury HA, Dickson J, Harwell J, Hanlon D, Anderson CH. 2001. An integrated software suite for surface-based analyses of cerebral cortex. *J Am Med Inform Assoc*. 8:443-459.
- Weisberg J, van Turennout M, Martin A. 2007. A neural system for learning about object function. *Cereb Cortex*. 17:513-521.
- Woolrich MW, Ripley BD, Brady M, Smith SM. 2001. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage*. 14:1370-1386.
- Worsley KJ, Evans AC, Marrett S, Neelin P. 1992. A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cereb Blood Flow Metab*. 12:900-918.