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#### INTRODUCTION

It is widely acknowledged that deafferenting injuries to the peripheral nerves or spinal cord induce rapid and profound maladaptive reorganization of primary sensory and motor limb representations in the mammalian brain (1). Recent work in my lab and others demonstrates that dense post-stroke hemiparetics (2-4), upper extremity amputees (5) and spinal cord injury (SCI) (6-9) patients often retain the ability to mentally simulate, or imagine movements of which they are no longer capable. Movement simulation is known to stimulate many of the same brain regions involved in motor planning and control, facilitate the acquisition of new motor skills, and has potential to be a valuable tool in neurorehabilitation (7, 10). In this project we use advanced, non-invasive brain imaging techniques to optimize a set of portable, computer-based, movement simulation tasks previously demonstrated to stimulate sensory-motor representations of the upper limbs effectively (3). We then evaluate the efficacy of these tasks for use in maintaining the integrity of activity-dependent sensory-motor representations during periods of acute limb immobilization, and their potential for re-establishing normal organization in cases with longstanding deafferenting injuries.

**Specific Aim 1:** We will refine a computerized battery of motor simulation tasks to increase their effectiveness in stimulating sensory and motor systems. Functional magnetic resonance imaging (fMRI) will be used to fine tune these modifications with the goal of achieving maximal stimulation within somatosensory and motor areas in the absence of overt movements.

**Specific Aim 2:** Temporary limb immobilization (12 hrs.) induces changes in the organization of somatosensory and motor cortices. We will test the hypothesis that regular performance of motor simulation tasks will maintain the integrity of these activity-dependent limb representations, and lead to faster recovery of function in healthy adults undergoing temporary unlilateral limb immobilization.

**BODY:** This section of the report shall describe the research accomplishments associated with each task outlined in the approved Statement of Work. Data presentation shall be comprehensive in providing a complete record of the research findings for the period of the report. Provide data explaining the relationship of the most recent findings with that of previously reported findings. Appended publications and/or presentations may be substituted for detailed descriptions of methodology but must be referenced in the body of the report. If applicable, for each task outlined in the Statement of Work, reference appended publications and/or presentations for details of result findings and tables and/or figures. The report shall include negative as well as positive findings. Include problems in accomplishing any of the tasks. Statistical tests of significance shall be applied to all data whenever possible. Figures and graphs referenced in the text may be embedded in the text or appended. Figures and graphs can also be referenced in the text and appended to a publication. Recommended changes or future work to better address the research topic may also be included, although changes to the original Statement of Work.

It is widely acknowledged that deafferenting injuries to the peripheral nerves or spinal cord induce rapid and profound maladaptive reorganization of primary sensory and motor limb representations in the mammalian brain (1). Recent work in my lab and others demonstrates that dense post-stroke hemiparetics (2-4), upper extremity amputees (5) and spinal cord injury (SCI) (6-9) patients often retain the ability to mentally simulate, or imagine movements of which they are no longer capable. Movement simulation is known to stimulate many of the same brain regions involved in motor planning and control, facilitate the acquisition of new motor skills, and has potential to be a valuable tool in neurorehabilitation (7, 10). In Stage 1 of this project we use advanced, non-invasive brain imaging techniques to optimize a set of portable, computer-based, movement simulation tasks previously demonstrated to stimulate sensory-motor representations of the upper limbs effectively (3). In Stage 2, we attempted to evaluate the efficacy of these tasks for use in maintaining the integrity of activity-dependent sensory-motor representations during periods of acute (12hr.) unilateral upper-limb immobilization in healthy adults.

#### Year 1

A great deal of the first year of this award was spent preparing and revising human subjects protocols, consents and associated materials in response to feedback both from USAMRMC and our local IRB. We received final IRB approval in the middle of the 4<sup>th</sup> quarter of this fiscal year: from the local IRB on April 15<sup>th</sup>, and from the USAMRMC on April 23<sup>rd</sup>. Despite this lengthy delay in our ability to recruit and test participants, we nevertheless made substantial progress in laying the foundations for this project. During this time we searched for and successfully recruited a post-doctoral research fellow, Dr. Stephane Jacobs. Following his arrival in January of Year 1, Dr. Jacobs and I worked to develop and refine the photo-realistic, computer-graphical stimulus materials for our initial psychophysical and functional magnetic resonance imaging (fMRI) experiments and the computer programs that will deliver these stimuli, and have secured all necessary equipment.

The primary objective of Stage 1 was to develop and refine a set of tasks that reliably evoke neural activity in sensory-motor representations. This was an iterative cycle with data collection and analysis driving task modifications, which were then evaluated behaviorally and using fMRI testing.

live visual feedback of their own hand movements or substitute pre-recorded video to provide "feedback" even when movements were not being executed by the actor. The system that we developed allows us to rapidly switch between these states, enabling direct comparisons between activation of sensory-motor structures associated with actual movement, imitation, motor imagery, and action observation. In addition, this system allows us to parametrically manipulate the viewpoint of actual or simulated visual feedback to better simulate conditions under which an individual might be taught a series of movements by another (e.g., therapist).

Dr. Kristen Macuga replaced Dr. Jacobs as the post-doctoral fellow in charge of this project. Further details of a subset of these findings can be found in the manuscript attached as **Appendix 1.** A second manuscript is in final stages of preparation for submission.

This work yielded several key results of potential relevance to neurorehabilitation:

1) Activation of common left hemisphere sensory-motor structures by movement, movement observation, movement observation and movement imagery. As illustrated in **Figure 1**, we identified a distributed network of brain regions that can be activated significantly during the a) execution of aurally-paced bimanual hand movements with live visual feedback (MOVE condition); b) execution of aurally-paced bimanual hand movements with temporally synchronized pre-recorded visual "feedback (IMITATE condition);" c) imagination of bimanual hand movements during observation of pre-recorded visual "feedback (IMAGINE condition);" d) passive observation of previously recorded bimanual hand movements (OBSERVE condition).



The common activation of parietal and premotor structures in the left hemisphere establishes that these areas can be modulated even under circumstances where movement is impossible (e.g., amputation or limb injury, spinal cord damage, brain injury). It is well-established that these brain areas or critical for the sensory-motor transformations that underlie manual activities such as reaching, grasping and object manipulation and use. Note that the left hemisphere is visualized on the left side; i.e., neurological convention.

**Figure 1.** Brain areas activated by MOVE, IMITATE, IMAGINE and OBSERVE conditions of the Stage 1 experiment (see text for details). Images are oriented radiologically (i.e., left hemisphere on the right side and right hemisphere on the left side). In the motor dominant left cerebral hemisphere, ventral premotor (blue arrow), dorsal premotor (green arrow) and superior parietal lobule extending into the intraparietal sulcus (red arrow) showed increased activity across all four conditions vs. resting baseline.

2) Increased activation in right hemisphere sensory-motor structures during movement with self-generated visual vs. pre-recorded visual feedback. **Figure 2**, shows that the ventral premotor (blue arrow) and parietal (supramarginal gyrus and anterior intraparietal sulcus; red arrow) in the right hemisphere are sensitive to subtle differences between live visual feedback of one's own movements (MOVE condition) vs. movements made in synchrony with pre-recorded visual "feedback" IMITATE condition. These brain areas are known to play an important role in the sensory-motor transformations that occur during visually-guided hand movements. This difference likely reflects sensitivity to subtle differences in spatio-temporal relations between the movement command, proprioceptive and visual feedback by these right hemisphere structures that does not appear present in the left cerebral hemisphere. In addition, the pre-supplementary motor area (Pre-SMA) showed a similar sensitivity.



One possible interpretation of these findings is that right hemisphere parieto-frontal networks are able to differentiate between movements produced by the self vs. another individual. Note that the left hemisphere is visualized on the left side; i.e., neurological convention.

**Figure 2.** Brain areas showing greater responses during bimanual hand movements made with live (MOVE) vs. pre-recorded visual feedback (IMITATE). As discussed in the test, these right hemisphere mechanisms seem more sensitive than those in the left to sublte spatio-temporal differences in between motor commands, proprioceptive and visual feedback.

Right hemisphere regions may differentiate between perceptions arising from movements of the individual vs. those that are generated

1 results, we would expect these later left hemisphere mechanisms (Figure 1) to play a critical role in the ability of motor imagery and observation to serve as effective stimuli for the sensory-motor system in individuals who are immobile.

Stage 2 was, unfortunately, much less successful that Stage 1. Despite several attempts, and enlisting the assistance of a local hand therapist for the immobilization procedure, we were unable to successfully induce reorganization of primary sensory-motor cortex through 12hrs. of limb immobilization in healthy adults. Failure to replicate previously reported changes in motor-evoked potentials led us to also try also try measuring cortical silent periods, to no avail.

#### Key Research Accomplishments Year 1:

- recruitment of post-doctoral fellow
- development and rendering of graphical stimuli
- programming of Stage 1 tasks
- preparation and multiple revisions of human testing protocols and associated materials
- attainment of human subject testing approval from USAMRMC and University of Oregon
- commenced initial pilot testing

#### Key Research Accomplishments Year 2:

- development of hardware and software necessary for implementation of Stage 1 experimental conditions
- completion of the test-revise iterative cycle resulting in final Stage 1 tasks
- completion of fMRI group study data collection on finalized versions of Stage 1 tasks
- application for an receipt of no-cost extension to complete Stage 2 work
- submission of one manuscript and a second in preparation

#### **Reportable Outcomes Year 1:**

• A presentation related to this project was presented: Frey, S.H. "*Contributions of functional magnetic resonance imaging to neurorehabilitation*." Presented at the 17<sup>th</sup> Annual Meeting of the Society for Neuroscience American Institute for Medical and Biological Engineering (AIMBE). Washington, DC (February, 2008).

#### **Reportable Outcomes Year 2:**

- A presentation related to this project was given at the TATRC Product Line Review in February, 2009 (Los Angeles).
- Macuga, K., & Frey, S.H. "Frontal operculum shows sensitivity to live vs. recorded visual feedback to self-produced hand movements." Paper presented at the Annual Meeting of the Society for Neuroscience. Chicago. (November, 2009).
- Macuga, K., & Frey, S.H. "Dissociable cortical networks of action representation for observation, imagery, and execution investigated using fMRI." Paper to be presented at the Annual Meeting of the Society for Neuroscience. San Diego. (November, 2010).
- Macuga, K. & Frey, S.H. (manuscript under review). "Selective responses in right inferior frontal and supramarginal gyri differentiate between observed movements of oneself vs. another".
- Macuga, K., & Frey, S.H. (manuscript in preparation). "Dissociable cortical networks of action representation for observation, imagery, and execution investigated using fMRI."
- Macuga, K., & Frey, S.H. "Dissociable cortical networks of action representation for observation, imagery, and execution investigated using fMRI." Paper to be presented at the Annual Meeting of the Society for Neuroscience. San Diego. (November, 2010).

**Conclusions:** Despite having been delayed as a result of a length human subjects approval process, we have successfully complete Stage 1 of this research. The findings from the Stage 1 fMRI work provide novel and important insights that will contribute in a substantive manner to the science literature on alternative methods of stimulating sensory-motor systems through behavioral tasks. Unfortunately, we failed to observe any reliable changes in the organization of sensory-motor cortex as a result of 12hrs of unilateral

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#### **APPENDIX:**

# Selective responses in right inferior frontal and supramarginal gyri differentiate

# between observed movements of oneself vs. another

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Journal section: Brief Communications (Behavioral/Systems/Cognitive) Abbreviated title: Selective responses in right inferior frontal Number of figures: 4 Contents of supplemental material: 2 figures (S1, S2) Number of pages: 18 Word count: Abstract: 140, Introduction: 414, Discussion: 950, Total: 4499 Keywords: action observation; visual feedback; supramarginal gyrus; inferior frontal gyrus; visual perspective Acknowledgements: We thank Bill Troyer for his contributions to the LabVIEW software development. Grants from USAMRAA (06046002) and NIH/NINDS (NS053962) to S.H.F. supported this work. The fact that inferior frontal (IFg) and supramarginal (SMg) gyri respond to both selfgenerated and observed actions has been interpreted as evidence for a perception-action linking mechanism (mirroring). Yet, the brain readily distinguishes between percepts generated by one's own movements vs. those of another. Do IFg and/or SMg respond *differentially* to these visual stimuli even when carefully matched? We used BOLD fMRI to address this question as participants made repetitive bimanual hand movements while viewing either live visual feedback or perceptually similar, pre-recorded video of an actor. As expected, bilateral IFg and SMg increased activity during both conditions. However, in contrast to mirroring, right SMg and IFg responded differentially during live visual feedback vs. matched recordings. These mirror system areas may distinguish self-generated percepts by detecting subtle spatio-temporal differences between predicted and actual sensory feedback and/or visual and somatosensory signals.

# Introduction

In monkeys, 'mirror neurons' in the inferior frontal gyrus (IFg) and inferior parietal lobule (IPL) respond both when the monkey executes an action and when it observes that same action made by an experimenter (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996). This discovery provides a potential mechanism to match one's own actions with the actions of others, a link between perception and action via a shared parieto-frontal representation. In these studies, monkeys view their own movements (seen from the 1<sup>st</sup>-person perspective) or those of an actor (seen from the 3<sup>rd</sup>-person perspective).

Functional neuroimaging data indicates that the IFg and the supramarginal gyrus (SMg) of the IPL in the human brain also respond to the observation of others' actions (Grèzes and Decety, 2001; Rizzolatti and Craighero, 2004). With few exceptions (Frey and Gerry, 2006; Jackson et al., 2006; Shmuelof and Zohary, 2008), investigations of this 'mirror system' have tended not to manipulate viewing perspective. Instead, stimuli used in the vast majority of studies have consisted primarily of others' actions as seen from a 3<sup>rd</sup>-person perspective. The effects of perspective change on IFg and SMg, or lack thereof, may provide valuable insights into what is being represented in this system.

On the basis of the mirror system account, one might expect that the IFg and SMg would respond equivalently to visual percepts attributable to our own movements vs. those of another actor. However, it is obvious that the brain is also able to distinguish between percepts arising from these two fundamentally different sources. Is this essential yet overlooked ability attributable to selective responses in IFg and/or SMg, or a separate mechanism? Here we perform the critical test of this hypothesis, by measuring the brain's responses to observation of actions generated by oneself vs. another as seen from both the 1<sup>st</sup>- and 3<sup>rd</sup>-person perspectives.

During the acquisition of whole-brain fMRI data, healthy adults performed aurally-paced, bilateral thumb-finger sequences while viewing either live visual feedback (*Self* condition) or carefully matched pre-recorded video of an actor performing the same task (*Other* condition). We reasoned that if the IFg and SMg are sensitive to subtle perceptual differences between these conditions, then they should exhibit selective responses. Evidence for a right cerebral hemisphere asymmetry in self recognition (Uddin et al., 2007), suggests that these conditional differences might be lateralized. We also varied perspective (1<sup>st</sup>- or 3<sup>rd</sup>-person) in both *Self* and *Other* conditions in an effort to determine the effects of this variable on these responses.

#### **Materials and Methods**

Participants included fourteen healthy, right-handed volunteers (18-36 years, 7 females) with normal or corrected-tonormal vision and no history of psychiatric or neurological disease. Written informed consent was obtained.

# fMRI Design and Procedure

Prior to the experiment, participants were given instructions and performed a short practice set of trials in a mock MRI scanner. Participants rested supine with their heads in the scanner, a cloth draped over their bodies, forearms on thighs and palms aligned in the vertical plane with thumbs facing up. Head and upper arms were padded to reduce motion artifacts. Other than performing the instructed hand movements, participants remained as still as possible.

Participants performed a sequential bimanual thumb-finger sequencing (TFST) task in synchrony with a 1.5 Hz pacing tone under two conditions, *Self* and *Other*. These were distinguished by aural presentation of the word "execute" or "imitate" 2s prior to each block. Blocks of each condition lasted 18s and were followed by a 12s rest interval consisting of a black screen. A central fixation circle was always present. In the *Self condition*, participants viewed their own movements via live video feedback. Images of participants' hands were reflected off an 18" x 18" mirror above the scanner bed. An MRI-compatible, remotely-controlled digital video camera captured this reflection. This video stream was then back-projected onto a screen at the head of the scanner bore and viewed by participants on a 5" x 2" mirror attached to the head coil. In the *Other condition* participants performed the aurally-paced TFST task while viewing a pre-recorded digital video of an actor performing the same task in the scanner. This video was created prior to the experiment using the same setup. Thus, the perspective, FoV, and lighting conditions of the video were matched as closely as possible to the live feedback. Participants were explicitly informed about the difference between *Self* and *Other* and received 15-20mins of practice. To avoid possible confusion between conditions, participants wore green gloves and the actor in the video wore purple gloves. The orientation of the visual stimuli was also manipulated. For both conditions, 50% of counterbalanced blocks presented visual stimuli (live or pre-recorded) from the perspective of the participant (*I<sup>st</sup>-person perspective*), and the remaining 50% were rotated by 180<sup>0</sup> (3<sup>rd</sup>-person perspective) (**Figure 1A**).

Two steps were taken to ensure spatial and temporal correspondence between participants' movements and those of the actor. First, participants' hand postures were matched with those of the actor depicted in the recorded video. Just before the experiment, participants were shown a semi-transparent digital still frame (1<sup>st</sup>-person perspective) of the recorded video overlaid on a live video feed of their hands (**Figure 1B**). They were instructed to align their hands with those of the actor and remain in this position throughout the study. Second, to facilitate synchronization, participants were

instructed to initiate TFST movements beginning with the index finger after two preparatory tones. Hand movements were recorded with digital video for offline verification of compliance.

## [Figure 1 about here]

Participants completed four (8.6min) runs. Each run consisted of 2 blocks of each of the four conditions (2 types (*Self, Other*) x 2 perspectives ( $1^{st}$ -person,  $3^{rd}$ -person). Two other types of blocks (*Observe, Imagine*) will not be discussed here. Condition order was counterbalanced across runs. Runs were counterbalanced across participants.

To control for possible variations in attention across conditions, participants performed a secondary task that required counting features of the observed movements (**Figure 2**). The central fixation circle's color changed periodically (range 18 – 30 times per run) from red to blue coincident with the pinkie finger contacting the thumb. Participants reported cumulative values at the end of each run. The change occurred with equal likelihood during each condition. Participants performed this somewhat difficult task with a mean of 88% correct indicating that they were attending to the movement in all conditions (**Figure S1**).

#### [Figure 2 about here]

## Data acquisition

Scans were performed on a Siemens (Erlangen, Germany) 3T Allegra MRI scanner. BOLD echoplanar images (EPIs) were collected using a T2\*-weighted gradient echo sequence, a standard birdcage radio-frequency coil, and these parameters: TR = 2000ms, TE = 30ms, flip angle = 90°, 64 x 64 voxel matrix, FoV = 220mm, 34 contiguous axial slices acquired in interleaved order, thickness = 4.0mm, in-plane resolution:  $3.4 \times 3.4 \text{ mm}$ , bandwidth = 2790 Hz/pixel. The initial four scans in each run were discarded to allow the MR signal to approach a steady state. High-resolution T1-weighted structural images were also acquired, using the 3D MP-RAGE pulse sequence: TR = 2500ms, TE = 4.38ms, TI = 1100ms, flip angle =  $8.0^{\circ}$ ,  $256 \times 256$  voxel matrix, FoV = 256mm, 176 contiguous axial slices, thickness = 1.0mm, in-plane resolution: 1 x 1 mm. DICOM image files were converted to NIFTI format using MRIConvert software (*http://lcni.uoregon.edu/~jolinda/MRIConvert/*).

Structural and functional fMRI data were preprocessed and analyzed using fMRIB's Software Library [FSL v.4.1.2 (http://www.fmrib.ox.ac.uk/fsl/)] (Smith et al., 2004) and involved several steps: motion corrected using MCFLIRT, independent components analysis conducted with MELODIC to identify and remove any remaining obvious motion artifacts, fieldmap-based EPI unwarping performed to correct for distortions due to magnetic field inhomogeneities using PRELUDE+FUGUE with a separate fieldmap (collected following each run) for each run, non-brain matter removed using BET, data spatially smoothed using a 5mm full-width at half-maximum Gaussian kernel, mean-based intensity normalization applied, in which each volume in the data set is scaled by the same factor, to allow for cross-sessions and cross-subjects statistics to be valid, high-pass temporal filtering with a 100s cut-off was used to remove low-frequency artifacts, time-series statistical analysis was carried out in FEAT v.5.98 using FILM with local autocorrelation correction, delays and undershoots in the hemodynamic response accounted for by convolving the model with a double-gamma HRF function, registration to the high-resolution structural with 7 degrees of freedom and then to the standard images with 12 degrees of freedom (Montreal Neurological Institute [MNI-152] template) at a 2x2x2 voxel resolution implemented using FLIRT, and registration from high resolution structural to standard space was further adjusted using FNIRT nonlinear registration (Andersson et al., 2007).

## Whole brain Analysis

For every participant, each of the 4 fMRI runs containing *Other* and *Self* conditions viewed from either a *1<sup>st</sup>*- or *3<sup>rd</sup>*-*person* perspective, were modeled separately at the first level. Orthogonal contrasts (one-tailed t-tests) were used to test for differences between each of the experimental conditions and resting baseline. Orthogonal contrasts were also used to test for differences between conditions. Because the only differences for contrasts of the 1<sup>st</sup>- vs. 3<sup>rd</sup>-person perspectives were in visual areas, we collapsed across perspective.

The resulting first-level contrasts of parameter estimates (COPEs) then served as inputs to higher-level analyses carried out using FLAME Stage 1 to model and estimate random-effects components of mixed-effects variance. Z (Gaussianized T) statistic images were thresholded using a cluster-based threshold of Z > 3.1 and a whole-brain corrected cluster significance threshold of p = 0.05. First-level COPEs were averaged across the 4 runs for each subject separately (level 2), and then averaged across participants (level 3).

In order to test for the main effects of PERSPECTIVE and TASK and for the interaction between these two factors, a 2 (PERSPECTIVE: 1<sup>st</sup>, 3<sup>rd</sup>) x 2 (TASK: other, self) repeated-measures ANOVA (F-tests) was performed on

Anatomical localization of brain activation was verified by manual comparison with an atlas (Duvernoy, 1991). In addition, the multi-fiducial mapping alogorithm in Caret (<u>http://www.nitrc.org/projects/caret/</u>) (Van Essen et al., 2001) was used to overlay group statistical maps onto a population-average, landmark- and surface-based (PALS) atlas for the human brain (Van Essen, 2005).

## Post-hoc ROI Analysis

Descriptive ROI analyses were also conducted on significant clusters of activation in IFg and SMg identified by the contrast of *Self* vs. *Other* in the whole-brain analysis. Mean percent signal change relative to the resting baseline across all voxels within this functionally defined ROI was calculated separately for each participant and condition using FSL's Featquery. Repeated-measures ANOVAS were conducted to test for differences between conditions in these ROIs.

## Results

# **fMRI** Results

#### Self or other

Self vs. rest and Other vs. rest contrasts. Relative to resting baseline, both Self (Figure 3A) and Other (Figure 3B) conditions were associated with increased bilateral activity within fronto-parietal areas (including both IFg and SMg) as well as other regions traditionally implicated in visually-guided bimanual behavior.

#### [Figure 3 about here]

*Self vs. Other contrast.* Importantly, IFg and SMg showed greater increases in activity for movements accompanied by self-generated visual feedback (*Self*) vs. matched video of another's actions (*Other*), as illustrated in Figure 4. This is consistent with the hypothesis that responses arising from these regions, frequently cited as critical nodes of the mirror system, signal this fundamental distinction. These selective cortical responses were entirely right-lateralized, and were also detected in the superior parietal lobe (SPL), insula, and lateral occipital (LO) cortex (**Figure 4**). Left cerebellum also showed this advantage for *Self*. Our findings provide further evidence for a right cerebral asymmetry in self-related processing (Keenan et al., 2001).

*Descriptive Region-of-Interest (ROI) Analyses.* Activity within regions of the right IFg and SMG that showed greater responses for *Self* vs. *Other* exceeded resting baseline in all four conditions (p < .001 in all cases; **Figure 4, panels A & B**). Consistent with the results of the whole brain analysis (reported below), these more focused tests failed to detect significant effects of the visual perspective manipulation on activity in IFg [F(1,13 = 1.80; p = .20)] or SMg [F(1,13) = 3.99; p = .07)]. There was also an unexpected task by perspective interaction not detected with the whole brain analysis in right IFg, F(1,13) = 6.61; p < .05, with the 3<sup>rd</sup> person perspective producing greater activations for *Self*. By contrast, SMg showed no such interaction, F < 1.0.

*Other vs. Self contrast.* This comparison only revealed increased activity in occipital regions, which may reflect their sensitivity to subtle differences in lower-level aspects of the visual stimuli.

# Effects of Perspective (1<sup>st</sup>- or 3<sup>rd</sup>-person)

The manipulation of perspective only affected activity in occipital cortex. Increased activity for the 1<sup>st</sup>- vs. 3<sup>rd</sup>person perspective was detected inferior to the calcarine fissure (**Figure S2**, cool colors), while the opposite contrast revealed effects superior to the calcarine fissure (**Figure S2**, warm colors). Jackson et al. (2006) similarly found increased V1 and V2 activation for 1<sup>st</sup> person perspective and increased lingual gyrus activation for the 3<sup>rd</sup> person perspective. These effects are likely attributable to differential stimulation of the lower visual field (in which 1<sup>st</sup>-person perspective stimuli appeared), or the upper visual field (in which 3<sup>rd</sup>-person perspective stimuli appeared), as illustrated in **Figure 1A**. Critically, responses within regions that have been identified as part of the mirror system were perspective invariant, including those in right IFg and SMg that differentiated between *Self* and *Other*. These perspective invariant responses, including those within right IFg and SMg, may contribute to self-recognition even when seeing one's movements from a 3<sup>rd</sup>-person perspective, as when looking in a mirror. Shmuelof and Zohary (2008) found contralateral anterior SPL for 1<sup>st</sup> person perspective and ipsilateral anterior SPL for 3<sup>rd</sup> person perspective for action observation of either the left or right hand (literally mirror-like).

# Discussion

The discovery of brain regions that respond similarly during the execution of self-generated actions and observation of

(Rizzolatti and Craighero, 2004). We show that responses within two key nodes of the mirror system – right IFg and SMg – differentiate between visual percepts arising from these two conditions. Consistent with previous studies, we find bilateral increases in IFg and SMg when participants receive live visual feedback of their own hand movements (*Self*), or when they move in concert with carefully matched pre-recorded video of an actor (*Other*). Contrary to the mirror system framework, however, right IFg and SMg show greater increases in activity during the *Self* vs. *Other* condition. Accurately distinguishing between these two circumstances is essential to adaptive behavior, and our findings implicate right IFg and SMg in this function. Further, these selective responses were invariant to the viewing perspective, raising the possibility that right IFg and SMg exists in both monkeys (Rozzi et al., 2006) and humans (Rushworth et al., 2006), suggesting that these areas constitute a parieto-frontal circuit. The current results suggest an asymmetry in the perceptual functions of this circuit in the human brain that may be critical to behaviors ranging from self-recognition to action attribution.

Further work is necessary to identify the perceptual information driving this differential response. One possibility is that right IFg and SMg are sensitive to greater spatio-temporal congruency in the *Self* condition between predicted sensory consequences (arising from a feed-forward controller) and actual visual feedback. Another possibility is that greater correspondence between visual and somatosensory feedback (proprioceptive and tactile) in the *Self* condition contributes to this selective response. Sensitivity to either or both of these sources of information may provide a means of distinguishing between visual percepts arising from one's own actions vs. those of other agents.

## Sensorimotor prediction and/or multisensory correspondence

#### Spatio-temporal congruency between predicted and actual sensory feedback

As noted above, increased activity in right IFg and SMg might be attributable to the greater spatio-temporal congruency between predicted sensory consequences and actual visual feedback in the *Self* condition. Motor control involves both feedback and feed-forward (predictive) processes. According to state feedback control theory (Wolpert and Flanagan, 2001; Shadmehr and Krakauer, 2008), an efference copy is generated in parallel with the motor command. The efference copy, along with an estimate of one's current state, serves as input to a forward model that predicts the sensory feedback that should result from the motor command. This internally generated prediction can then be compared with the actual sensory feedback accompanying the movement (Wolpert et al. 1995; Blakemore et al. 1998; Blakemore and Frith. 2003)

then the action can be attributed to another agent (Frith et al., 2000; Blakemore et al., 2003; Sato and Yasuda, 2005). Because we did not require participants to identify movement authorship, our findings are not about agency assignment. We also found increased activity in the cerebellum when participants saw their own movements vs. those of an actor. The cerebellum is widely thought to play a role in predicting the sensory consequences of movements via forward modeling (Wolpert et al., 1998; Blakemore and Sirigu, 2003).

## Spatio-temporal congruency between multimodal feedback sources

Both *Self* and *Other* conditions involved performing the same paced bimanual movements and gave rise to similar proprioceptive feedback. However, use of live visual 'feedback' during the *Self* condition would likely have resulted in greater spatiotemporal congruency of visual and proprioceptive signals. Activity in right IFg and SMg may increase in response to this tighter multisensory coupling.

Additional experimentation is necessary to disentangle these two possibilities, which are not mutually exclusive.

# Right cerebral asymmetry for self-referential processing

# Self-recognition and the right hemisphere

The widespread right lateralization of increases in activity associated with the *Self* vs. *Other* comparison compliments the existing literature on the organization of mechanisms involved in self-recognition (Keenan et al., 2001), which emphasizes the contributions of right IFg (Uddin et al., 2005; Uddin et al., 2007; Kaplan et al., 2008). Notably, this included posterior parietal, inferior frontal and the insular cortex among other areas (**Figure 4**). As noted earlier, right IPL has also been implicated in agency detection (Farrer et al., 2003; Uddin et al., 2005). For instance, Farrer et al. (2003; 2007) argue that right IPL (specifically the angular gyrus) is associated with the misattribution of one's own actions to another as well as the degree of mismatch between predicted and actual movements, though their activation increases were not completely lateralized to the right hemisphere. It should be noted, however, that their tasks specifically involved deception and required participants to make a decision about agency. Here, we made no attempts to manipulate or disguise the ownership of the action. There is also evidence suggesting that the right insula is involved in the detection of agency (Farrer and Frith, 2002; Farrer et al., 2003; Tsakiris et al., 2007). Injuries to these areas of the right hemisphere have also been implicated in disorders of agency attribution (Frith et al., 2000).

In contrast to what is predicted by the mirror system hypothesis, our results indicate that right SMg and IFg signal differences, rather than similarities, between the observed actions of oneself vs. another. We conclude that these regions are critical for readily identifying visual perceptions arising from one's own actions. Further work might address the functioning of these areas in the developing brain, or in individuals with impairments of the body scheme.

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# **Figure legends**

**Figure 1. A) Experimental conditions in the fMRI experiment: 2 x 2 factorial crossing task feedback condition (self or other) with perspective (1<sup>st</sup> person or 3<sup>rd</sup> person)**. Within both self and other conditions, 50% of the blocks presented visual stimuli (live or pre-recorded) from a 1<sup>st</sup>-person perspective. Remaining 50% were rotated by 180° for a 3<sup>rd</sup>-person perspective. We did not aim to manipulate agency, so to make conditions distinct, participants always wore green gloves, while the actor in the video wore purple gloves. Conditions presented in a counterbalanced block-design and computer-controlled (National Instruments).

**B) Pre-experiment alignment overlay.** Prior to the experiment, participants aligned their hands with a semi-transparent still frame of the actor's hands from the pre-recorded video.

**Figure 2. Illustrative timeline of task with representative blocks (1<sup>st</sup>-person self and 3<sup>rd</sup>-person other conditions not displayed here.** Aural presentation of the word "Execute" (*Self*) or "Imitate" (*Other*) distinguished conditions 2s prior to each block. Blocks were counterbalanced and lasted 18s followed by 12s rest interval. Central fixation circle always present. Numbers in thought bubbles illustrate participant's running count of the number of times the fixation changed from red to blue coincident with the pinkie finger contacting the thumb. Finger tapping was sequential and '…' symbols indicate skipped taps for illustration purposes. See **Figure S2** for results verifying task compliance measured by this attentional control. Participants performed 4 runs. Each run had 2 blocks the 4 conditions.

**Figure 3.** Areas showing increased activity in association with A) the *Self* condition or B) the *Other* condition vs. resting baseline. In this and subsequent figures, group statistical parametric maps thresholded at Z>3.1 (corrected clusterwise significance threshold p<0.05) and displayed on a partially inflated view of CARET's population-average, landmark- and surface-based (PALS) human brain atlas (see Methods). Data in lower panel are rendered on the group average anatomical image from our sample and oriented neurologically.

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**Figure 4.** Areas showing increased activity for the *Self* vs. *Other* comparison. Right IFg and SMg show greater responses during perceptions of self-generated vs. anothers' actions. Increased activity for this contrast also found in right SPL, insula, LO, as well as left cerebellum. Panels A and B display mean percent signal change relative to baseline for each of the four experimental conditions, extracted from ROIs in the IFg and SMg, averaged across participants. Bars represent standard errors.



В

Overlay



Figure 1



Figure 2





Figure 3



Figure 4