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Multisensory and Sensorimotor Representations for Action  
in Human Posterior Parietal Cortex investigated with functional MRI

A dissertation submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

in

Cognitive Science

by

Flavia Filimon

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Professor Martin I. Sereno, Chair  
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Professor Geoffrey M. Boynton  
Professor Andrea Chiba  
Professor Joan Stiles  
Professor Emanuel Todorov

2008

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University of California, San Diego

2008

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## ABSTRACT OF THE DISSERTATION

Multisensory and Sensorimotor Representations for Action  
in Human Posterior Parietal Cortex investigated with functional MRI

by

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Doctor of Philosophy in Cognitive Science

University of California, San Diego, 2008

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The posterior parietal cortex of human and non-human primates has been implicated in sensorimotor transformations, whereby sensory input (vision, touch, sound) is converted into motor commands. For instance, visual information regarding a target can be used to appropriately guide reaching movements towards the relevant part of space. These sensorimotor and multisensory representations suggest that the role of the posterior parietal lobe is to implement perception for action, rather than create a passive, purely perceptual representation of space.

This dissertation consists of three different studies that map such multimodal and sensorimotor representations in the human brain, using functional magnetic resonance imaging (fMRI). The first study shows that observation, imagery, and execution of reaching rely on similar neural substrates in the posterior parietal lobe,



specifically involving more superior (dorsal) areas. These 'mirror neuron' activations are in agreement with macaque parieto-frontal circuits underlying reaching movements, and differ from the more ventral (inferior) activations for grasping or for hand-object interactions. This suggests that (visuomotor) mirror neurons are specific to the hand action that is executed (reaching versus grasping). The second study attempts to dissociate visual and proprioceptive feedback from the reaching hand, to identify visuomotor and proprioceptive-motor areas involved in the control of reaching. Reaching without visual feedback from the moving hand involves more anterior and medial parietal areas than reaching with visual feedback. This indicates a posterior-to-anterior organization for sensorimotor representations that use visual versus somatosensory input, respectively, within posterior parietal cortex.

Finally, the third study investigates tactile and visual representations of target location. Identifying target location using exploratory hand movements in the absence of visual input activates similar intraparietal and superior parietal areas as does visual identification of spatial location. The common activation by visual and tactile input suggests multisensory processing in these areas.

Together, the experiments reported in this dissertation extend our knowledge of the functional organization of human posterior parietal cortex.

## **Chapter 1.**

### **Introduction**

### **Posterior Parietal Cortex - sensory, motor, or sensory-motor?**

Research in nonhuman primates has suggested that the posterior parietal cortex serves as a sensory-motor interface for guiding specific actions. These sensory-motor representations are specific to different effectors such as the eye, hand, or head (Colby, 1998; Andersen and Buneo, 2002; Colby and Goldberg, 1999; Buneo and Andersen, 2006). The posterior parietal cortex is located posterior to primary somatosensory cortex (SI) and anterior to the occipital lobe, and is heavily interconnected with frontal premotor areas (Matelli and Luppino, 2001). Importantly, neurons in these posterior parietal areas have both sensory and motor responses, e.g. they may respond both during sight of a target and during a particular movement to that target (Buneo and Andersen, 2002). Many of these neurons are multisensory, responding to stimulation in more than one sensory modality (Colby and Goldberg, 1999).

While recent research in humans has attempted to uncover a similar functional organization and sensory-motor role for human posterior parietal cortex, functional imaging studies to date have investigated simplistic and limited motor tasks. This is due to difficulties in studying certain sensory-motor tasks with functional neuroimaging techniques (Culham et al., 2006). For instance, arm and hand movements are technically challenging to implement in a magnetic resonance imaging (MRI) scanner environment, whereas saccades are relatively easily studied with functional

MRI (Culham et al., 2006). This is due to the critical need to hold the head stable while moving the hand. As such, a majority of studies attempting to uncover reach-related mechanisms in human posterior parietal cortex have instead studied pointing or smaller movements rather than reaching (e.g. Hagler et al., 2007; Simon et al., 2002; Astafiev et al., 2003). This has made it difficult to establish a similar functional organization as in the macaque, where reach regions and saccade regions are relatively segregated, or at least where different posterior parietal regions exhibit different effector *preferences* (Andersen and Buneo, 2002). Since true reaching has not really been compared with saccades in humans, the current literature has remained unclear as to whether there might be reach-specific or reach-dominant regions in human posterior parietal cortex. A related question is whether reach representations in humans are also activated by observation and imagery of reaching. Are human posterior parietal sensory-motor representations also activated by imagery and observation of actions? How much overlap is there between parietal sensory-motor representations informed by different modalities, such as the haptic or visual modality?

This dissertation comprises several fMRI experiments attempting to shed more light on sensory-motor functions of the human posterior parietal cortex. The studies reported here attempt to identify human posterior parietal regions that carry both sensory, e.g. visual or somatosensory, and motor, e.g. hand movement-related, signals. This dissertation extends existing fMRI research to the study of reaching and reach-related tasks such as imagery and observation of reaching. It also provides new

evidence for reach-dominant parietal areas, independent of visual input from the hand, as well as for overlaps in saccade- and reach-related representations. Finally, evidence is provided for overlapping visual and somatosensory representations of locations, perceived either visually or by touch using exploratory hand movements. The emerging view is one of human posterior parietal cortex using information from multiple sensory modalities for the purpose of guiding actions in a variety of sensory-motor tasks.

To allow us to study larger hand movements, including actual reaching, we obtained each individual subject's dental impression to create a 'bite-bar' for each subject. This bite-bar was attached to a plexiglass support that could be rotated in three different dimensions and tightened for the duration of the experiment, thus reducing head motion. Foam was also packed around the head, allowing for hand movements while keeping the head still. Also, whereas most previous experiments have used a mirror for stimulus presentations, which means subjects would not move their hand directly to the targets, we used a direct-view setup for the reaching experiments described in Chapters 2 and 3. This involved tilting the head forward in the head coil, with padding support behind the head, and with subjects obtaining a direct view of stimuli presented on a screen at the mouth of the scanner bore. Thus hand movements were carried out directly towards targets in the studies described in Chapters 2 and 3. In Chapter 4, subjects had a horizontal head position with the arm extended towards the mouth of the bore.

## **Neurophysiological and anatomical studies in macaques**

A multitude of different anatomical and functional areas exist in macaque posterior parietal cortex, which includes the superior parietal lobule anterior to the intraparietal sulcus (IPS), the IPS itself, as well as the inferior parietal lobule posterior to the IPS (Cavada, 2001). The majority of these areas contain neurons with both sensory and motor properties pertaining to actions with specific body parts. Their response properties indicate that they may well serve as a sensory-motor interface.

Neurons in area MIP (medial intraparietal) respond to stimuli within reaching distance and range from purely arm somatosensory in the dorsal bank of the sulcus to bimodal to visual in the fundus of the sulcus (Colby and Goldberg, 1999). The more dorsal neurons become active around the time of movement of the arm, while more ventral neurons show selectivity around the time of the stimulus. Visual receptive fields of bimodal MIP neurons expand when a tool is used that can reach farther than the limb. Bimodal visual and somatosensory neurons with receptive fields on the arm and which are selective for the direction of arm movements have also been found in superior parietal area 5 (Jeannerod, 1997; Mountcastle et al., 1975) and area 7a (MacKay, 1992). The latter neurons respond during particular phases of a reach movement, such as reach onset or arm return (MacKay, 1992). Medial parieto-occipital cortex, including area V6A, also includes neurons that respond during reaching either in the dark or in light (Fattori et al., 2001).

Neurons in the anterior intraparietal area (AIP) are activated by specific hand movements. Reversible inactivation of AIP neurons leads to deficits in accurately pre-shaping the hand for grasping, but not in reaching (Colby and Goldberg, 1999).

The ventral intraparietal area (VIP) also has bimodal neurons, whose visual receptive fields are aligned with corresponding somatosensory receptive fields on the head and face. Its connectivity with premotor area F4, which contains neurons with similar response properties, suggests that VIP is involved in planning actions in perioral space, via visually-guided head movements (Colby and Goldberg, 1999).

Lateral intraparietal cortex (LIP) contains neurons that respond to visual targets for saccades. Responses are generated when the stimulus appears, during an instructed delay, and around the time of a saccade to the stimulus (Andersen and Buneo, 2002; Colby and Goldberg, 1999). Area LIP is discussed in more detail below.

The areas described here have specific projections to frontal cortex, with AIP connecting to ventral premotor area F5, area MIP connecting to dorsal premotor area F2, and area LIP connecting to the frontal eye fields, FEF (Matelli and Luppino, 2001). This connection pattern to premotor regions suggests a role in sensory-to-motor transformations for these posterior parietal regions.

A related line of work has been examining a different class of visuo-motor neurons, namely mirror neurons (Rizzolatti et al., 1996). These neurons have been primarily studied in macaque ventral premotor cortex (F5) for grasping actions. Mirror neurons respond both during sight of an action (e.g. grasping observation) and

execution of the same action (e.g. grasping execution). Although most studies have focused on ventral premotor cortex, mirror neurons for grasping actions have also been found in inferior parietal areas (Fogassi et al., 1998). Auditory mirror neurons, which recognize actions by sound, have also been found in macaque F5 (Kohler et al., 2002). Virtually no macaque studies to date have investigated the presence of mirror neurons *outside area F5* for reaching or non-grasping actions, in which the hand does not interact with an object. Given the relative segregation of grasping and reaching circuits, one might predict the existence of mirror neurons for reaching in more dorsal areas. The presence of sensory-motor neurons coding a variety of actions in the posterior parietal cortex also begs the question of whether mirror neurons may be found all over the parietal cortex of the macaque, provided that they are tested with the right action.

## Attention

Some researchers have suggested that the saccade-related responses observed in the lateral intraparietal area, area LIP, do not reflect the planning or control of saccades but rather reflect visual attention to the targets (Colby and Goldberg, 1999). One reason cited is that LIP neurons give strong on-responses to stimuli that are not saccade targets. However, Andersen and Buneo (2002) have argued that such on-responses are transients followed by sustained activity during a delay period which reflects either an intended saccade or an intended reaching movement. Snyder et al. (1997) have shown that in areas MIP (medial intraparietal), 7a, and PO (parieto-



occipital), neurons fire in response to cues that signal that a reaching movement is to be executed after a brief delay, but not when the cue signals an impending saccade. The reverse was true of LIP neurons, where the majority of neurons preferred planning saccades over planning reaches to the same targets. Such motor specificity during the planning stage has been interpreted as evidence for a motor intention, rather than attention to the target. In experiments that use two sequential cues to switch from a preferred movement plan to a non-preferred plan, reach-related neurons increase their firing rate when the cue instructs a reaching movement, then decrease their firing rate if the second cue changes the plan to a saccade, and vice-versa, even though either the saccade or the reaching movement would eventually be executed towards the same spatial location (Andersen and Buneo, 2002). While both cues elicited transient firing increases, the sustained firing during the delay period distinguished planned saccades from planned reaches. Since no movement has yet occurred in the planning stage, it would be difficult to argue that increased firing to reaches is due to reaching execution requiring more attention than saccades. Note that the differential firing in LIP and MIP/PO/7a also persists during the execution of the movement. Calton et al. (2002) have also shown that reach-related cells increase their firing rate after an instruction to prepare a reach, but not after an instruction to prepare a saccade, even before the spatial location of the target for the movement is known. While cells selective for the spatial location of the target, but not for the movement, were also found, this suggests that at least some cells in the posterior parietal cortex of the macaque show movement

preparatory activity, not just sensory activity. Buneo and Andersen (2006) have labeled areas such as LIP a sensory-motor interface, meaning a shared boundary between the sensory and motor systems.

The specificity of deficits produced by reversible inactivation of AIP in monkeys, which leads to deficits in shaping the hand prior to grasping but not to deficits in reaching (Andersen and Buneo, 2002) also suggests that general visuospatial attention cannot account for the variety of responses found in the posterior parietal cortex. Rather, specific sensory-motor representations for specific actions are being implemented in different areas of the posterior parietal cortex of the macaque.

Thus, rather than asking ‘is activity in response to a target confounded by attention?’ one could ask ‘is a covert movement plan being formed without being executed?’. The latter view has become known as the pre-motor theory of attention (Rizzolatti et al., 1994), which holds that attention and saccades rely on common brain networks. This view is supported by functional imaging studies in humans, as noted below.

In summary, neurophysiological studies in monkeys have revealed sensory as well as motor functions in diverse areas of the posterior parietal lobe which are, if not effector-specific, at least effector-dominant. These areas show specific connection patterns with areas in premotor cortex. Finally, visual attention does not explain the neuronal responses in most of these posterior parietal regions, with a debate still ongoing regarding area LIP.

## **Functional imaging studies in humans**

The issue of whether posterior parietal activations reflect sensory attention signals versus motor intention signals has been addressed in the human neuroimaging literature as well. fMRI studies of covert attention and saccades in humans have revealed that a common network of parietal, frontal, and superior temporal cortical areas is activated by both visuospatial attention and saccades (Corbetta et al., 1998; Beauchamp et al., 2001). This overlap between visuospatial attention and oculomotor responses supports the pre-motor theory of attention, i.e. of covert attention reflecting the preparation of an oculomotor response, rather than being a purely spatial, sensory signal.

Some studies have specifically compared attention to visual targets with eye as well as hand movements to those targets (Astafiev et al., 2003; Simon et al., 2002). Those studies have consistently shown that both planning and execution of hand movements activate certain posterior parietal and dorsal premotor regions more than either covert attention or saccades. This suggests a clear motor role for posterior parietal cortex, not just a visuospatial role.

Human fMRI studies have attempted to identify functional homologues to the mosaic of posterior parietal areas identified in the macaque (for a review, see Culham et al., 2006; Culham and Valyear, 2006; also see the individual Chapters in this dissertation). While there appears to be a lot more overlap between activations elicited

by different effectors, several putative homologues have been proposed.

fMRI studies of grasping compared to reaching in humans have revealed an anterior intraparietal area (AIP) which, just like in the macaque, is more active during grasping than reaching (Culham et al., 2006). Human AIP is also activated during hand pre-shaping and hand manipulation in the absence of vision, again suggesting a motor role rather than a purely sensory role (Culham et al., 2006). Studies of eye movements (e.g. Sereno et al., 2001; Hagler et al., 2007) have identified human homologue(s) of macaque LIP. A somatosensory and visual area responding to air puffs on the face and visual stimulation near the face has also been identified as a possible human homologue of VIP (Sereno and Huang, 2006). Unlike in macaques, it has been difficult to identify reach or hand-specific regions in human posterior parietal cortex. Studies of hand movements (Astafiev et al., 2003; Simon et al., 2002; Connolly et al., 2003; Levy et al., 2007; Hagler et al., 2007) have shown wide-spread activations both for small, pointing-like movements and larger reaching movements (Filimon et al., 2007, included in Chapter 2). Most of these activations overlap extensively with eye movement areas such as LIP and the frontal eye fields. Reaching activations also overlap with grasping activations (Culham and Valyear, 2006). While this suggests that functional areas in the human posterior parietal cortex are less distinct than in the macaque, there are also differences in the strength of activation for particular actions in different areas, as we show in this dissertation. On the other hand, it is also possible that neurophysiological research has over-emphasized the distinctness between different posterior areas in the

macaque, as indeed is evidenced by the fact that LIP neurons do fire above baseline during reaching movements too (see figures in Andersen and Buneo, 2002).

In short, human functional imaging studies have revealed similar sensory-motor representations for actions in the posterior parietal lobe, although these representations overlap more than in the macaque. Despite the finding of such sensory-motor representations for actions, several important questions remain regarding the organization of human posterior parietal cortex. This dissertation attempts to address some of those questions.

**Aim of the present dissertation: extending evidence for sensory-motor representations in human posterior parietal cortex to novel tasks**

The goal of the present dissertation is to advance our understanding of the sensory-motor roles of human posterior parietal cortex. Specifically, this dissertation addresses the following questions, using fMRI:

1) Chapter 2: Are there sensory-motor neurons for actual reaching in human intraparietal and superior parietal cortex, and are they also activated by observation and imagery of reaching? Our study shows that, consistent with findings in the macaque, reaching activates superior parietal and intraparietal areas, in conjunction with dorsal premotor cortex. Moreover, the same premotor and posterior parietal regions also respond to imagined and observed reaching.

2) Chapter 3: Do different posterior parietal areas represent reaching with and

without visual feedback from the hand? Which posterior parietal areas preferentially respond to either kind of reaching compared to saccades? Our results show that the anterior precuneus, as well posterior parietal cortex medial to the intraparietal sulcus, is equally active for reaching with or without visual guidance, and is significantly more active for reaches than for saccades. This suggests proprioceptive input to the anterior precuneus, which is used for the guidance of unseen reaches. Most posterior parietal areas are equally active for visual and non-visual reaches, while the superior parieto-occipital sulcus region is more active during reaching with visual feedback.

3) Chapter 4: Finally, does the posterior parietal cortex participate in tactile exploration of external targets in the absence of any vision? Are the same posterior parietal regions that are responsive to tactile location exploration also activated by visual location perception? Our results show that parietal regions involved in tactile location exploration also represent visual locations, suggesting multisensory representations. An expanded preview of each dissertation chapter follows.

## Chapter 2: Mirror neurons for reaching in the superior parietal cortex

Chapter 2 of this dissertation brings together the mirror neuron literature, which has focused primarily on ventral premotor cortex, with the literature on visuomotor and more generally sensory-motor properties of the posterior parietal lobe. The literature on parieto-frontal connections in the macaque suggests that a dorsal parietal pathway, connecting MIP/V6A to dorsal premotor cortex, subserves

reaching. By contrast, a more ventral pathway from the anterior intraparietal area (AIP) and inferior parietal lobule to the ventral premotor cortex subserves grasping (Matelli and Luppino, 2001). Mirror neurons for grasping have been found in the ventral pathway in both frontal and inferior parietal regions (Rizzolatti et al., 1996, Fogassi et al., 1998). We reasoned that if mirror neurons are sensory-motor neurons specific to particular hand actions, there should be mirror neurons for reaching in the dorsal circuit, i.e. in the dorsal premotor cortex and the superior parietal lobule. While functional MRI does not record signals from individual neurons, several recent fMRI studies have interpreted overlapping activations for observation and execution of hand actions as evidence for mirror neuron-like networks in the human brain (Grèzes and Decety, 2001). Thus, evidence for overlapping activations in the dorsal circuit for execution, observation, and imagery of reaching movements would suggest mirror neuron networks for actions related to reaching. This is indeed what we found. Specifically, in our article “Human cortical representations for reaching: Mirror neurons for execution, observation, and imagery” we showed that such mirror neuron-like activations are found for executed, observed, and imagined reaching, specifically in the intraparietal and superior parietal cortex as well as in dorsal premotor cortex. This article was published in *NeuroImage* (37) in 2007 and is included in full in Chapter 2. It is the first fMRI article to compare execution, imagery, and observation of true reaching, rather than pointing or grasping movements. Previous fMRI studies had investigated grasping or local hand movements, guided by the focus on ventral

premotor cortex and object-manipulation movements in the macaque (Grèzes and Decety, 2001). Our research is also the first to compare all three conditions, i.e. execution, observation, and imagery, for the same hand action. Our data show that several sensory-motor processes related to reaching, including execution, observation, and imagery of reaching, activate similar superior parietal and intraparietal regions in the human posterior parietal lobe. Although reaching and grasping activations do overlap (Culham et al., 2003, 2006), the important point here is that mirror neuron activations for reaching were not found in Broca's area, the putative human homologue for macaque ventral premotor area F5 (Rizzolatti et al., 1996), or solely in the inferior parietal lobule. Instead activations were found in more dorsal premotor and superior parietal areas, consistent with macaque parieto-frontal circuits for reaching, rather than grasping (Matelli and Luppino, 2001).

The lateralization pattern seen in actual, observed, and imagined reaching, with stronger parietal activations contralateral to the reaching hand, suggests that these activations are specific to the hand being moved, rather than being due to general visuospatial attention. Reach targets were presented in both left and right visual fields. If visual attention to the location of the targets had been responsible for the parietal activations observed, then we would have expected bilateral frontoparietal activations (Beauchamp et al., 2001), perhaps even stronger activations in the right hemisphere (Corbetta et al., 1998). In contrast, activations were stronger on the left, consistent with the right hand being moved, observed, or imagined moving. This stronger



contralateral activation pattern in the superior and intraparietal lobule relative to the hand moved has also been shown with PET studies for either hand (Kertzman et al., 1997).

In Chapter 2, reaching was executed under visual guidance with visual feedback from the arm and hand. Thus the shared superior parietal and intraparietal activations for observed and imagined reaching may reflect a visual, i.e. sensory, representation, rather than a motor role. However, the same regions were also activated during motor imagery, which is essentially a form of motor planning and shares many of the same mechanisms for motor planning and control (Johnson et al., 2001). Reaching imagery did not activate visual areas relative to baseline, suggesting motor imagery is distinct from visual imagery, in agreement with the literature (Johnson et al.). Thus the intraparietal and superior parietal activations obtained here for reaching imagery suggest a motor, not just sensory, role for the posterior parietal cortex.

Chapter 3: Reaching versus saccade representations in human posterior parietal cortex: visuo-motor or proprioceptive-motor?

The findings described in Chapter 2 raised several important questions. Only visually guided reaching was studied in that experiment. Would similar posterior parietal activations be obtained for non-visually guided reaching, or would some areas be more active for reaching under visual guidance compared to reaching without visual feedback from the hand?

The posterior parietal cortex has been claimed to serve as a visuomotor interface for visually guided movements (e.g. Iacoboni, 2006). However, some areas of the posterior parietal lobe are also activated by hand actions such as precision grips in the absence of vision (Culham et al., 2006). A direct comparison of activations for hand movements with and without visual guidance did not yet exist in the literature. In addition, previous fMRI studies had yielded inconclusive results regarding hand-specific or hand-dominant regions in the posterior parietal lobe, when comparing activations for pointing and saccades. Some studies had reported that the same posterior parietal areas were activated by either pointing or saccades (Hagler et al., 2007; Levy et al., 2007), whereas other studies had claimed more medial parietal activations for pointing (Connolly et al., 2003). A recent study found greater medial intraparietal activations for reaching-to-point (i.e., with the index finger) than for saccades, in the absence of visual input from the hand.

In the 3 experiments reported in Chapter 3, we therefore compared visual and non-visual reaches with saccades, to see if there is any dominance for true reaching in human posterior parietal cortex and to see if there is modulation from sight of the hand. Experiment 1 compared reaching under visual guidance with saccades to the same visually-presented targets on a screen. Experiment 2, carried out in the same scanning session, compared reaching on a plate hidden from view with saccades to visual targets presented on a screen as in Experiment 1. Finally, Experiment 3 compared visual and non-visual reaches as well as saccades to the same fiber-optic targets displayed in front

of the subject. To render the hand invisible in the non-visual condition, reaching was carried out in darkness, with the exception of the extremely dim fiberoptic targets. For the visual condition, a bright fiberoptic light source illuminated the hand.

Our findings showed that antero-medial posterior parietal cortex, including the anterior precuneus, is not sensitive to visual feedback from the hand, responding equally strongly during reaching with or without sight of the hand. Given the fact that the precuneus is not a motor area in the sense that primary motor cortex (M1) is, some sensory information must be available to guide movement. A candidate source of sensory information that could be used to guide reaches in the absence of vision is proprioception from the moving arm. In fact, recent neurophysiological recordings in the macaque superior parietal lobule have shown the presence of somatosensory cells sensitive to passive joint-rotation in area PEc (Breveglieri et al., 2006). These cells were also responsive during active reaching, with or without visual stimulation. Area PEc is located in a similar anatomical location as human precuneus, i.e. posterior to the cingulate sulcus and anterior to the parieto-occipital sulcus. The involvement of these cells in reaching, as well as their sensitivity to passive joint rotations, suggests a proprioceptive-motor role for this posterior parietal region. We suggest a similar proprioceptive-motor role for human precuneus. Interestingly, area PEc is located immediately medial of areas MIP and V6A, which have been labeled the macaque ‘parietal reach region’ or ‘PRR’ (Andersen and Buneo, 2002; Buneo and Andersen, 2006). In the macaque, PRR neurons respond more during planned and executed

reaches than to saccades. Likewise, we found greater anterior precuneus fMRI activations for both kinds of reaching than for saccades, consistent with a more reach-dominant role for this area. Greater strength of reach-related activations compared to saccade activations was also found in anterior IPS and in regions medial of the IPS in our subjects. This is consistent with pointing and planned pointing versus saccade studies in which the wrist and hand were moved in addition to the finger (e.g. Astafiev et al., 2003). The large overlap between hand and eye movement activations in most of the IPS and superior parietal cortex is consistent with the literature on pointing (Simon et al., 2002) and reaching-to-point (Levy et al., 2007; Prado et al., 2005) compared to saccades. Surprisingly, almost all of the posterior parietal cortex responded equally for visual and non-visual reaching, although some of these areas were also strongly activated by saccades. The main difference between visual and non-visual reaching was found in a region at the superior end of the parieto-occipital sulcus (POS). It is possible that visual information from the moving hand is used to calculate the distance to the target in this area. The greater activation for visual reaching than non-visual reaching in the POS region is consistent with findings in macaque parieto-occipital cortex. Neurons in area V6A also respond more during reaching in light compared to in darkness (Fattori et al., 2001).

Our studies thus show that for larger reaching movements, medial parietal activations are indeed stronger than for saccades, and that some of these regions may use proprioceptive information to guide the hand, while others, such as the POS, rely

on vision more generally. If we compare the mirror neuron activations for reaching from Chapter 2 with the reach-dominant areas obtained in the non-visual reach versus saccade contrast from Chapter 3, experiment 3, it becomes apparent that the more anterior regions of the superior parietal gyrus and intraparietal sulcus are indeed reach-dominant and could thus contain true mirror neurons for reaching. The more posterior aspect of the overlap for observed, imagined, and executed reaching, namely the posterior intraparietal sulcus and posterior superior parietal gyrus, is also activated by saccades. Hence the posterior aspect of the superior parietal gyrus and intraparietal sulcus may be a more general sensory-motor region, activated equally by saccades, reaches, and imagined and observed reaching.

Taken together, Chapters 1 and 2 of this dissertation show that the human posterior parietal lobe contains not only visuo-motor representations for reaching, but also somatosensory-motor, specifically proprioceptive-motor representations for hand movements. However, the overlap between saccade-related and reach-related activations also suggests a more general, effector-independent sensory-to-motor transformation in many regions of posterior parietal cortex.

One possible concern is that hand movements in an MR scanner may cause magnetic field distortions and artifacts in activation patterns. We have carried out preliminary tests to ensure that distortion of the magnetic field from the hand does not lead to activations that are similar to reaching activations. In a test of magnetic field distortion from the hand held near the head, we found that scattered small spots of

activation did result from the distortion, but not the activation patterns obtained for hand movements, comprising contiguous areas from the parietal to the frontal cortices. This suggests that it is possible to study hand movements, including larger hand movements such as reaching, in an MR scanner.

#### Chapter 4: Tactile and visual spatial representations of external target locations

The findings in Chapter 3 raised additional important questions. In particular, while most of posterior parietal cortex can use either proprioception or visual feedback from the arm for guidance to a target, the targets were always presented visually in all three experiments. This still allows for the possibility that the posterior parietal activations found in both visual and non-visual reaching were due to the visual targets, and were representing the spatial location of the visually-presented targets. This would thus emphasize a role for visual guidance from the visual targets.

The experiments presented in Chapter 4, while not employing reaching movements, show that the posterior parietal cortex (PPC) is activated during exploratory hand movements in the absence of any visual input. In fact, the PPC is activated by movements guided by tactile input from the fingers. Moreover, these tactile representations overlap with visual representations, suggesting multisensory processing. In the study described in Chapter 4, subjects explored raised targets on LEGO platforms with their right hand while blindfolded. The subjects' task was to identify either the location of targets on the platform or the number of targets. Either

task necessitates taking in the somatosensory information and guiding the exploratory hand movement based on that information until the targets are found. The superior parietal and intraparietal cortex was strongly activated in both tasks, in agreement with previous fMRI studies showing a posterior parietal role in tactile processing (Reed et al., 2005; Macaluso and Driver, 2001). Interestingly, tactile location processing activates bilateral superior parietal cortex and especially right intraparietal cortex more than tactile number processing, a pattern found in the visual version of this task as well. The overlap between tactile location and visual location activations could not simply be due to visual imagery, as tactile exploration in each condition (Location and Number) produced minimal visual activations, whereas imagery has been shown to activate occipital areas (Ganis et al., 2004). Also, if there had been a difference in eye movement between the Location and Number conditions in the visual experiment (subjects are blindfolded in the tactile experiment), one would expect differences in visual cortex due to different amounts of visual stimulation between conditions, if stimuli were foveated more in one condition. Instead, there was equal visual activation in both conditions. Thus, this overlap may reflect multisensory processing of target location. Although the tactile task involved exploratory hand movements while the visual task required fixation, activation of parietal and frontal saccade-related areas was observed in the visual experiment, perhaps due to suppressed saccades. This suggests that the multisensory representation found in these superior parietal and intraparietal cortical areas could be used for guiding either movement (eye or hand). The overlap

was located posterior to the reach-dominant areas identified in Chapter 3. Another possibility is that the motor output guided by this multisensory target representation was the left-handed response indicating the spatial location of the tactile or visual target, with far left locations mapped onto the left little finger and far right locations mapped onto the left index finger. Regardless of the contribution of the motor response to these activations, we conclude that the regions identified in this study can take in sensory information in more than one modality, suggesting multisensory representations that may be used to guide hand and eye-movement responses.

### **Overall conclusions**

This dissertation extends the current knowledge of sensory-motor representations for hand actions in the human posterior parietal lobe. We have shown that reach-related representations are found in the superior parietal and intraparietal cortex, in agreement with the macaque literature, and that they can be activated by observation of reaching, by internal motor preparation (reaching imagery), and by execution of reaching. More posterior activations in the intraparietal sulcus or on the posterior end of the superior parietal gyrus are not specific to reaching, as they overlap with saccade activations. However, more medial parietal activations are stronger for reaching than for saccades, and likely carry proprioceptive-motor signals for movement in the absence of visual feedback. Finally, superior parietal and intraparietal regions are also tactile-visual and tactile-motor, in addition to visuo-motor.



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## **Chapter 2.**

**Human cortical representations for reaching: mirror neurons for execution,  
observation, and imagery**

**Abstract**

We used functional magnetic resonance imaging (fMRI) to map the cortical representations of executed reaching, observed reaching, and imagined reaching in humans. Whereas previous studies have mostly examined hand actions related to grasping, hand-object interactions, or local finger movements, here we were interested in reaching only (i.e. the transport phase of the hand to a particular location in space), without grasping. We hypothesized that mirror neuron areas specific to reaching-related representations would be active in all three conditions. An overlap between executed, observed, and imagined reaching activations was found in dorsal premotor cortex as well as in the superior parietal lobe and the intraparietal sulcus, in accord with our hypothesis. Activations for observed reaching were more dorsal than activations typically reported in the literature for observation of hand-object interactions (grasping). Our results suggest that the mirror neuron system is specific to the type of hand action performed, and that these fronto-parietal activations are a putative human homologue of the neural circuits underlying reaching in macaques. The parietal activations reported here for executed, imagined, and observed reaching are also consistent with previous functional imaging studies on planned reaching and delayed pointing movements, and extend the proposed localization of human reach-related brain areas to observation as well as imagery of reaching.



## Human cortical representations for reaching: Mirror neurons for execution, observation, and imagery

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We used functional magnetic resonance imaging (fMRI) to map the cortical representations of executed reaching, observed reaching, and imagined reaching in humans. Whereas previous studies have mostly examined hand actions related to grasping, hand–object interactions, or local finger movements, here we were interested in reaching only (i.e. the transport phase of the hand to a particular location in space), without grasping. We hypothesized that mirror neuron areas specific to reaching-related representations would be active in all three conditions. An overlap between executed, observed, and imagined reaching activations was found in dorsal premotor cortex as well as in the superior parietal lobe and the intraparietal sulcus, in accord with our hypothesis. Activations for observed reaching were more dorsal than activations typically reported in the literature for observation of hand–object interactions (grasping). Our results suggest that the mirror neuron system is specific to the type of hand action performed, and that these fronto-parietal activations are a putative human homologue of the neural circuits underlying reaching in macaques. The parietal activations reported here for executed, imagined, and observed reaching are also consistent with previous functional imaging studies on planned reaching and delayed pointing movements, and extend the proposed localization of human reach-related brain areas to observation as well as imagery of reaching.

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### Introduction

Despite the long tradition of studying space perception from a purely visual perspective, recent research has revealed that motor actions are a key part of space perception. Interactions with the world, such as through eye and hand movements, contribute to a representation of space that is not just visual, but also motor. Mirror neurons for hand actions are one example of such visuomotor representations.

Electrophysiological studies in macaques have identified several frontal areas involved in hand action representations (Preuss et al., 1996; Muakkassa and Strick, 1979; Matelli and Luppino, 2001; Rizzolatti et al., 1988). For instance, both dorsal premotor cortex (PMd, or F2 and F7) and ventral premotor cortex (PMv, or F4 and F5) contain arm/hand representations that are specific to certain motor actions, such as grasping or reaching (Matelli and Luppino, 2001). More specifically, neurons that respond to both hand action execution (e.g. grasping) and hand action observation (e.g. observed grasping) have been found in macaque ventral premotor area F5 (for a review, see Rizzolatti and Craighero, 2004; Rizzolatti et al., 1996a; Buccino et al., 2004a). These “mirror neurons” suggest an observation–execution matching system that allows monkeys to recognize actions performed by other individuals by mapping them onto their own motor representations.

Mirror neurons have also been studied in macaque parietal cortex, in particular in the inferior parietal lobule (Fogassi et al., 1998). Their presence in the parietal lobe is in accord with the many hand/arm motor representations found in monkey parietal cortex, such as the anterior intraparietal area (AIP), which deals with grasping and object manipulation, the medial intraparietal area (MIP), which controls arm movements during reaching, and other arm-related parietal areas, such as areas V6A, 5, and 7 (Johnson et al., 1996; Stepniewska et al., 2005; Fattori et al., 2001; Galletti et al., 1997; Andersen and Buneo, 2002; Buneo et al., 2002; Ferraina et al., 2001; Kalaska, 1996; Battaglia-Mayer et al., 2000; Culham and Kanwisher, 2001). These parietal areas have specific premotor targets: distinct parieto-frontal neural circuits have been found in the macaque brain for grasping (AIP–F5), and reaching (MIP/V6A–F2vr), for instance (Matelli and Luppino, 2001).

Over the last few years, functional imaging studies in humans have begun to explore mirror neuron activations for hand actions in humans (for a review, see Grèzes and Decety, 2001; Decety and Grèzes, 1999; Buccino et al., 2004a). Investigation of the mirror-neuron system in humans has mainly focused on the involvement of ventral premotor cortex and the inferior frontal gyrus (Broca’s area), an area thought to be the human homologue of macaque F5 (Rizzolatti et al., 1996a).

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Several human neuroimaging studies have investigated observation of grasping or of object manipulation (Grafton et al., 1996a; Binkofski et al., 1999; Buccino et al., 2001; Johnson-Frey et al., 2003; Molnar-Szakacs et al., 2006; Tai et al., 2004; Grèzes et al., 2003). Other studies have compared grasping observation with grasping execution or imitation (Rizzolatti et al., 1996b; Grèzes et al., 2003; Hamzei et al., 2003; see also a neuromagnetic study by Nishitani and Hari, 2000), observation versus imitation of simple finger movements (Iacoboni et al., 1999), or observation versus execution of more complex finger movements, such as playing guitar strings (Buccino et al., 2004b). In addition to execution and observation of hand actions, mental simulation (imagery) of hand actions, such as imagined grasping, has also been investigated (Grafton et al., 1996a; Grèzes and Decety, 2001). Finally, there is also a literature on observation of pantomimes and planning of tool use (Decety et al., 1997; Johnson-Frey et al., 2005) as well as execution of pantomimes (e.g. pantomimed grasping compared to actual grasping, and pantomimed reaching to touch an object compared to actual reaching to touch an object; Króliczak et al., 2007).

The majority of these studies involve hand–object interactions, whether through prehension, touching of an object, or preshaping of the hand during a pantomimed interaction with a missing object. In other cases precise, local, finger movement that is limited to the hand was studied, such as finger lifting (Iacoboni et al., 1999). A majority of these studies have found activations in ventral premotor/inferior frontal cortex as well as in the inferior parietal lobe. The frontal activations included Broca's area, the putative human homologue of macaque F5, in most cases. In some cases, the superior parietal lobe, precuneus, and the intraparietal sulcus were also involved, with greater activations in the hemisphere contralateral to the moving hand. Typically studies that involve less of a transport phase in both observation and execution conditions (e.g. Rizzolatti et al., 1996b, where only the final phase of the hand grasping an object was viewed) find activations in the inferior frontal gyrus and the inferior parietal lobule, but not the superior parietal lobule. Tasks that involve a greater transport phase (e.g. Hamzei et al., 2003, where a cup was grasped and moved from the lap to the mouth; Grafton et al., 1996b; Culham et al., 2003) do activate the superior parietal lobule. It is unclear, however, why some studies report superior parietal activations and others do not.

Whereas a number of these studies have focused on hand actions that involve hand preshaping (e.g. during grasping or pantomimed grasping) or precise local hand movements (whether an object is present or not), less is known about which brain areas are involved in the execution, observation, and imagery of hand actions that do not involve object-directed movement, local finger configurations, or touching of an object. For instance, it is unknown if just the transport phase of the hand through space, such as during reaching, activates its own set of mirror neurons during execution, observation, and imagery of reaching. In other words, few studies have investigated whether mirror neuron activations change with hand actions in accordance to the fronto-parietal neural circuits identified in macaques, with AIP–F5 representing grasping-related actions, and MIP–F2vr representing reaching-related actions. Are there mirror neuron activations for reaching (without grasping or touching) in humans, and how do they compare to mirror neuron activations for grasping, hand–object interactions, or smaller finger movements such as finger lifting? Reaching movements are different from the aforementioned hand actions in that only a transport phase of the hand is required, where preshaping of the hand for appropriate hand–object interactions or even touching is not

necessary. For reaching, extraction of the visual properties of the object is not necessary; instead, the hand and arm need guided toward the appropriate point in space, regardless of what is located at that point in space. Buccino et al. (2001) found a somatotopic organization for observation of movements performed with different effectors (hand, mouth, or foot) in both premotor and parietal cortex. This suggests multiple mirror neuron systems in the human brain, dependent on the particular effector with which an action is performed. It remains unclear whether there is a similar systematic differentiation between mirror neuron activations for different types of hand movements, e.g. between reaching movements, and hand–object interactions (including touching) or grasping movements. Observation of static images depicting object prehension versus observation of images depicting object touching results in an increase in activation in bilateral inferior frontal gyrus, suggesting that the less hand–object interaction (touching instead of grasping), the less involvement of the inferior frontal gyrus (Johnson-Frey et al., 2003). It remains unknown whether observation of reaching *without* touching of an object is similar to this static image observation task, in terms of not activating the inferior frontal gyrus. Likewise, it remains unknown which other brain areas, outside Broca's area or premotor cortex, are differentially active for reaching observation relative to grasping observation.

Reaching (defined as involving some arm transport as opposed to just hand/finger movements) has been difficult to investigate with fMRI, due to problems with head motion caused by the moving hand (see Culham et al., 2006). Typically, fMRI studies have investigated a proxy for reaching, such as delayed pointing (Medendorp et al., 2005; Hagler et al., 2007; Connolly et al., 2003; Astafiev et al., 2003; DeSouza et al., 2000) or using a joystick cursor to a visual target (e.g. Grefkes et al., 2004; Lacquaniti et al., 1997). Despite the difficulties, some fMRI studies have investigated reaching-to-point movements (Kawashima et al., 1996; Frey et al., 2005; Desmurget et al., 2001), reaching-to-touch (e.g. with the knuckles) (Culham et al., 2003), or reaching-to-grasp (Chapman et al., 2002; Frey et al., 2005). Prado et al. (2005) investigated actual reaching. The activations reported for these tasks typically include the medial IPS as well as the precuneus, i.e. more medial areas of the superior parietal lobe. Other activations include the parieto-occipital cortex, supplementary motor cortex, and the cingulate sulcus. In addition, an area located at the junction between the anterior IPS and the inferior postcentral sulcus, hypothesized to be the human homologue of AIP (see Frey et al., 2005; Binkofski et al., 1999), is activated during both grasping and reach-to-point tasks as well as during some pointing tasks (Culham et al., 2006). This suggests some overlap between reaching and grasping. Both grasping and reaching activate the hemisphere contralateral to the moving hand substantially more than the ipsilateral hemisphere. In general, activations for reaching tasks tend to be more dorsal and medial in the parietal lobe (medial to the IPS) compared to object manipulation. Studies that involve a transport phase of the hand prior to an executed grasp (e.g. Culham et al., 2003; Grafton et al., 1996b) tend to find superior parietal activations, whereas studies in which the transport phase is not present, involving just local grasping (e.g. Rizzolatti et al., 1996b) tend to find more inferior parietal activations.

According to Culham et al. (2006), reaching-to-point tasks may actually involve preshaping the hand as well as calculating object properties such as the centroid of the shape, and thus may be different from reaching alone. Similarly, pointing may be expected to be different from actual reaching. Areas activated by delayed



pointing activations in humans may thus not be exactly equivalent to macaque reach-related areas. It is also important to note that reaching-to-touch an object still represents a hand–object *interaction*, even if no grasping occurs, and that this task may thus be different from reaching without touching. Likewise, a grasping pantomime, or a pantomime in which an object is implied but not present, also represents an object-directed action: the object is implicit, and the pantomiming hand is preshaped accordingly. Since no preshaping of the hand needs to happen in reaching-only, pantomimed hand–object interactions are still likely to differ from reaching by activating grasping-related neural circuits.

While several studies have investigated the execution aspect of grasping or reaching-like hand actions, we are aware of no studies that have investigated parieto-frontal mirror neurons for reaching *per se*. It is thus unknown which brain areas are involved in both execution of reaching and in observation as well as mental simulation of reaching.

In addition, the majority of previous mirror neuron studies have compared only two types of conditions at a time, i.e. either execution with observation of hand actions, or observation with imagery, or execution/imitation with imagery of hand actions (see Grèzes and Decety, 2001). Since different studies used different hand actions (e.g. object manipulation or finger tapping) as well as different objects, it is difficult to draw general conclusions about which brain areas are involved in *all three conditions* (action execution, observation, and imagery) for a particular hand action. It is also unclear whether there are differences in activation levels between observation, imagery, and execution *within* mirror neuron areas—for instance, whether observing a hand action is more potent at driving mirror neurons than imagining the same hand action.

Here, we compare execution of visually-guided reaching (i.e. reaching directly towards visually presented targets without the use of a mirror) with observed as well as imagined reaching in the same experiment. Since our task involves no explicit touching or grasping of objects, and therefore no preshaping of the hand to match a viewed object shape, mirror neuron activations for observation as well as imagery of reaching should involve more of the reach-related substrates than hand manipulation-related substrates.

## Methods

### Participants

Sixteen subjects (ten males) participated in this experiment (age range 19–48). One subject was discarded due to excessive head motion. All subjects were right-handed and had normal or corrected-to-normal vision. Human subjects' approval was obtained from the UCSD Institutional Review Board. All subjects gave informed consent.

### Stimuli

The stimuli used were photographs of abstract wooden shapes on a black background (see Figs. 1a and c), with five different views taken per shape. The abstract shapes served as targets for the reach, imagined reach, or passive viewing. We chose abstract shapes in order to 1) prevent object recognition/verbalizing, as in the case of common objects such as pens, cups, bananas, etc., and 2) to motivate the reach, since naturalistic reaching usually occurs towards objects rather than simple dots in space. In all photographs, lighting

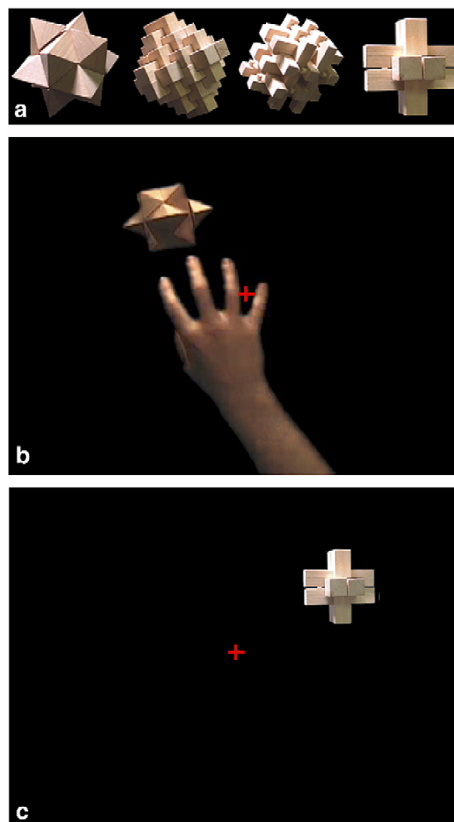


Fig. 1. Stimuli used in the experiment. (a) The four shapes used as visual stimuli. Each shape was photographed from five different angles, yielding a total of 20 stimulus images. (b) Still frame from the observation of reaching video, used in the observed reaching condition. A human hand is seen reaching towards one of the shapes. (c) Example trial during either executed or imagined reaching, or passive viewing of objects (baseline). The subject's task was indicated beforehand with a message.

was held constant (always from the top left), thus giving the objects a three-dimensional appearance.

In addition, video clips of an actor's right hand reaching towards the same abstract wooden shapes (see Fig. 1b) were recorded with a digital camera and edited in Final Cut Pro (version 3.9). The video clips served as stimuli in the observed reaching condition. The hand was seen slowly reaching towards the objects on a black background, with the final hand position being just before the grasp. Only the forearm appeared in all frames. Lighting was as in the photographs. The objects in the video clips used in the observed reaching condition were slightly smaller than the objects presented during the reaching, imagined reaching, and fixation conditions. The video hand was likewise somewhat smaller than subjects' actual hand, so that as much of the transport phase of the reach was observable as possible on a small screen.

Stimuli were projected on a screen inside the scanner ~12 in. in front of the subject's chin, above their torso, such that the subject

could directly view the screen without a mirror and reach directly towards the display without touching the screen. A standard video projector with a 7.38–12.3" focal length Xtra Bright Zoom replacement lens (Buhl Optical, USA) was used to display stimuli running on a PowerBook (500 MHz G3 running Mac OS X) at SVGA resolution. The screen was attached with velcro to the ceiling of the scanner bore. Subjects' heads were tilted forward towards the screen. This ensured that the reaching movement was as far as possible from the subject's head to prevent a disturbance of the magnetic field around the head. In addition, the tilted head position allowed for direct, i.e. visually guided, reaching. The starting hand position was the center of the subject's chest.

The object images were presented at constant eccentricity ( $\sim 10^\circ$ ) from the central fixation cross at a random polar angle. One of the five views of one of the four objects was selected randomly and displayed around the fixation cross. Objects subtended a visual angle of  $\sim 6^\circ$ , while the entire display for all conditions subtended a visual angle of  $\sim 35^\circ$ . Each object was displayed for 4 s, giving subjects enough time to slowly reach and retract their hand, after which the next shape appeared immediately. Subjects were instructed to reach slowly with their open right hand towards the object images without touching the screen and without closing the hand. Movement of the elbow was minimized as it was supported and partially immobilized by foam pads, i.e. subjects mainly moved their forearm. Subjects maintained fixation during the reach and throughout the experiment. To prevent head motion, a custom-made bite-bar was used, consisting of each subject's individual dental impression attached to an adjustable 4-ball-joint yoke. Additional foam pads around the head were used to stabilize the head. Prior to scanning, subjects were trained to reach slowly in a practice session outside the scanner. In addition, their eye movements were monitored during these practice reaching trials, to ensure they were able to reach without visually tracking their hand or saccading to the targets. All subjects were able to reach accurately while maintaining fixation on the fixation cross in the center of the screen. Additional eye tracker data from one subject collected outside the scanner showed that central fixation was maintained during execution, observation, and imagery of reaching, as well as during baseline passive viewing of objects.

#### *Experimental design*

A pseudo-random block design was used. Subjects participated in three experimental conditions and one control condition: 1) actual reaching towards images of objects, 2) observation of reaching towards the same objects, 3) imagined reaching to the visually displayed objects, and 4) fixation with passive viewing of the objects. In 1), 3) and 4) the images of wooden shapes described above were presented randomly around the fixation cross, at fixed eccentricity and random angle, for 4 s each. In the observed reaching condition (2), subjects viewed video clips of a human right hand reaching towards the shapes, while fixating on the central fixation cross, without moving their hand. The object locations and thus possible reach directions in the video clips were randomized and matched the locations of the shapes in the other conditions. For imagined reaching (3), subjects imagined their right hand moving towards the objects at the same speed as their actual reach, while fixating on the central fixation cross. The hand was held stationary on the chest throughout this condition.

A 2-s message (e.g. "Observe") at the beginning of each block of trials indicated to the subject which condition was about to begin.

Each condition was presented for 32 s at a time (block length = 32 s), with each condition being repeated 4 times during an 8 min 32 s run. The order of conditions was pseudo-randomized. Each subject participated in a minimum of two 8 min 32 s runs.

#### *Image acquisition*

Magnetic resonance images were collected with a Varian 3T MRI scanner using an end-capped 23 cm quadrature head coil designed and built by Eric Wong (University of California, San Diego, Center for fMRI). Functional scans were collected using an echo-planar T2\*-weighted gradient echo pulse sequence (28 contiguous axial slices,  $3.75 \times 3.75 \times 3.8$  mm voxel size,  $64 \times 64$  matrix, TR = 2000 ms, 258 repetitions per scan, TE = 27.4 ms, flip angle =  $90^\circ$ , bandwidth = 1950 Hz/pixel). The slice volume included the entire brain except for the inferior tip of the temporal lobes. Stimulus presentation began after the first 2 TRs, which were discarded, to allow the magnetization to reach a steady state. A T1-weighted MPAGE alignment scan ( $1 \times 1 \times 2$  mm, TR = 16 ms, TE = 6.6 ms, flip angle =  $18^\circ$ ,  $256 \times 200$  matrix) was collected in the same scanning session to align the functional images to a previously obtained high-resolution ( $1 \times 1 \times 1$  mm) T1-weighted MPAGE scan collected on a 1.5T Siemens or 3T Varian scanner.

#### *Data processing and statistical analysis*

Each subject's cortical surface was reconstructed from the high-resolution ( $1 \times 1 \times 1$  mm) T1-weighted MPAGE anatomical scan using FreeSurfer (Fischl et al., 1999a; Dale et al., 1999). The functional images were superimposed on the alignment scan (MPAGE,  $1 \times 1 \times 2$  mm resolution) and then registered with the high-resolution ( $1 \times 1 \times 1$  mm) anatomical image, allowing for functional data to be registered with and painted onto each subject's reconstructed cortical surface. Statistical analyses were carried out using Analysis of Functional Neuroimages (AFNI) (Cox, 1996).

#### *Motion correction*

The functional runs were concatenated, yielding at least 512 TRs per subject, and were corrected for motion artifacts and linear drift using AFNI's volreg (volume registration) function, in which all functional images were registered to the middle of the second functional run. Six estimated motion (3 rotation and 3 translation) parameters were obtained during this registration.

#### *Deconvolution analysis*

Each individual subject's blood-oxygenation-level-dependent (BOLD) activations were analyzed using AFNI's 3dDeconvolve (Cox, 1996; Ward, 2000a) general linear model. Motion parameters obtained during volume registration were added to the baseline model as additional regressors. We used a quadratic polynomial to fit and remove the baseline. Hemodynamic responses were modeled at four different lag times (1, 2, 3, and 4 TRs). 3dDeconvolve uses multiple regression to estimate the goodness of fit between estimated system impulse response functions and the actual fMRI time series data, for each voxel. Program 3dDeconvolve does not assume a specific shape of the hemodynamic response function (HRF) (e.g. a fixed waveform such as a square wave), but instead estimates the shape of the waveform voxel by voxel, based on the data itself, using a sum of scaled and time-delayed versions of the stimulus time series to model the system response. Thus the shape and amplitude of the HRF was allowed to vary at each of the 4 lag points.

Correlation coefficients and  $F$ -statistics were generated for the area under the hemodynamic response function. Six general linear tests were carried out: observed, imagined, and actual reaching each versus baseline, as well as pairwise comparisons (reach versus observe or imagine, observe versus imagine).

#### Group analysis

The group data were analyzed using cortical surface-based averaging algorithms in FreeSurfer (Fischl et al., 1999b). Each subject's reconstructed cortical surface was spherized and morphed to an average spherical surface of 40 subjects using a best-fit sulcus alignment. Individual functional activations and statistics could then be interpolated onto the average sphere and averaged across subjects.

Surface-based smoothing using 16 smoothing steps was performed before resampling coefficients onto the average spherical surface, which corresponds to a full-width, half-max (FWHM) Gaussian filter of approximately 4.9 mm (Hagler et al., 2006). The average activations and  $F$ -stats were then resampled back onto a single subject's inflated cortical surface for display purposes using FreeSurfer. Surface-based averaging across subjects has been shown to yield a better alignment of activations across subjects, leading to less blurring and less loss of signal compared to Talairach methods (Fischl et al., 1999b).

$F$ -statistics and regression coefficients (means) for the group analysis were generated for each condition (observed, imagined, and executed reaching, versus baseline) as well as for pairwise comparisons (executed versus observed reaching, executed versus imagined reaching, and observed versus imagined reaching) using AFNI's mixed-effects, two-factor 3dANOVA2 with repeated measures (within-subject). Condition was treated as a fixed effect with three levels while subject was a random effect.

#### Clustering

To correct for multiple comparisons, surface-based cluster-size exclusion (Hagler et al., 2006) was used for surface-based group-averaged data, with  $t$ -statistics thresholded at  $p < 0.05$ ,  $p < 0.01$ ,  $p < 0.005$ , and  $p < 0.001$ , corresponding to cortical surface clusters of 352, 148, 112, and 60 contiguous vertices, respectively. Clusters with fewer contiguous vertices than the specified cluster sizes were excluded. AFNI's AlphaSim (Ward, 2000b) was adapted to cortical surface data to ensure that the corrected  $p$ -value for these thresholds was 0.05 (Hagler et al., 2006).

#### ROI analysis

Regions of interest (ROIs) were selected according to the following criteria: 1) activated voxels overlapped for observed, imagined, and executed reaching (all three conditions); 2) the overlapping activations had to survive a threshold of  $p < 0.001$  in each of the three conditions, relative to baseline; and 3) voxels were in anatomical regions identified in the literature as being involved in action production as well as observation, namely, premotor and parietal cortices. Two regions emerged that fulfilled each of these criteria: one in dorsal premotor cortex (superior frontal gyrus/sulcus) and one in posterior parietal cortex. The ROIs were saved as surface patches in FreeSurfer, with MATLAB scripts extracting the overlap between the three conditions. Each voxel's time series was normalized by its mean intensity and then averaged together with all voxels within each ROI using MATLAB. Each ROI's normalized time series was then analyzed with AFNI's input -1D 3dDeconvolve option to extract percent signal change coefficients for each condition.

## Results

All three conditions (executed, observed, and imagined reaching) activated a fronto-parietal network when compared to baseline (Fig. 2, Tables 1–3). Fig. 2 shows average group activations displayed on an inflated cortical surface. The activations for all three conditions overlapped in dorsal premotor cortex, as well as in superior parietal cortex and in the intraparietal sulcus (see Figs. 4a and b). Fig. 3 shows activations from 5 individual subjects who are representative of the group of 15 subjects. Note that we are following the terminology used in Duvernoy's (1999) human brain atlas when using the term "dorsal premotor", which is defined as dorsal cortical areas anterior to the precentral gyrus, i.e. in this case the superior frontal gyrus and sulcus.

#### Execution of reaching versus passive viewing of objects

Visually-guided reaching involves motor, visual, as well as somatosensory components, and was therefore expected to activate several brain areas subserving these functions. Indeed, activations ( $p < 0.005$ , corrected) were observed in primary motor and somatosensory cortex, dorsal premotor cortex (superior frontal gyrus and sulcus, extending onto the caudal aspect of the middle frontal gyrus), the inferior frontal gyrus, the supplementary motor area (medial aspect of the superior frontal gyrus), cingulate cortex, the posterior end of the Sylvian fissure, as well as superior and inferior parietal (supramarginal) cortex, the intraparietal sulcus (IPS), and the precuneus. Visual areas including the cuneus, lingual gyrus, superior occipital gyrus, middle occipital gyrus (MT+), the calcarine sulcus, and the posterior end of the superior temporal sulcus (STS) were also activated (see Fig. 2 and Table 1). Most activations were lateralized to or stronger in the left hemisphere, as expected for normal right-handed subjects moving their right hand only. For instance, primary sensorimotor and inferior frontal gyrus activation was present only in the left hemisphere, and dorsal premotor and superior parietal activations were much weaker in the right hemisphere compared to the left hemisphere. Interestingly, ventral premotor and inferior frontal gyrus activations, overlapping with Broca's area, were weaker compared to the dorsal premotor activations (superior frontal gyrus), consistent with the fact that our task involved reaching and no grasping.

#### Observed reaching versus passive viewing of objects

Although observed reaching consisted of simply viewing video clips of a reaching right hand, we expected to find activations not just in visual areas, but also in visuo-motor areas. In particular, we expected activations in premotor and parietal areas, in which mirror neurons have previously been found for observation of hand actions, as well as in areas that represent reaching. As expected, observation of reaching activated the intraparietal sulcus, the superior parietal lobule and precuneus, as well as dorsal premotor cortex (superior frontal gyrus/sulcus) ( $p < 0.005$ , corrected; Fig. 2, Table 2). In addition, observed reaching activated visual areas (superior occipital gyrus, cuneus, middle occipital gyrus), and the posterior end of the superior temporal sulcus. Activations were again stronger in the left hemisphere, with dorsal premotor activations strongly left-lateralized. Notably, no activations were observed in the inferior frontal gyrus (even at  $p < 0.05$ , corrected), which may be due to the fact that there were no interactions between the observed hand and the objects in the videos. This is consistent

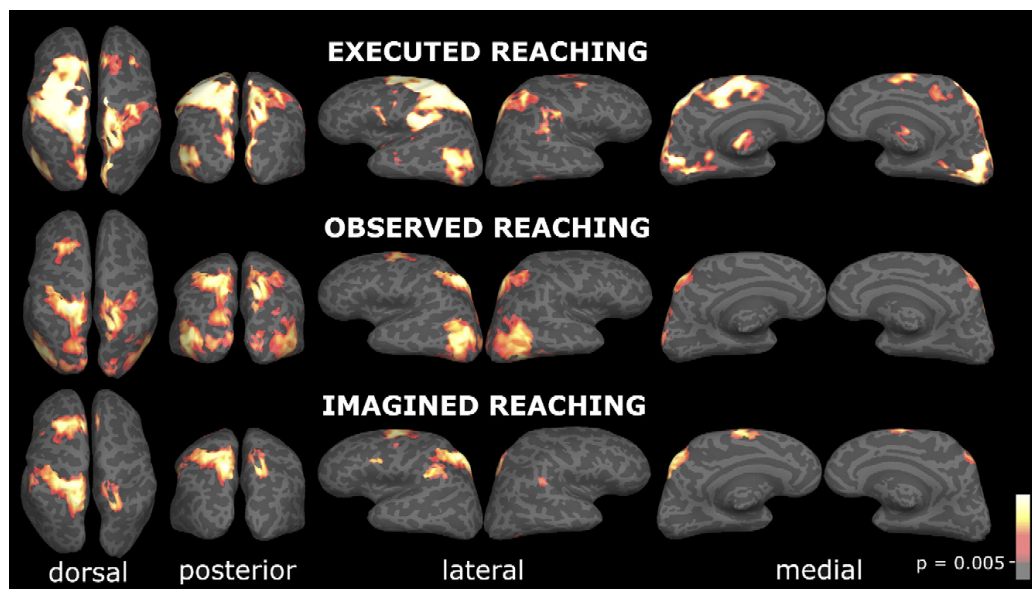


Fig. 2. Group surface-averaged activations for executed, observed, and imagined reaching, versus baseline, from 15 subjects, interpolated onto a single subject's inflated cortical hemispheres, viewed here from dorsal, posterior, lateral, and medial views. All activations displayed are significant at  $p < 0.005$  (corrected). Note the overlap in activations in superior parietal and dorsal premotor cortex (superior frontal gyrus and sulcus), for all three conditions, suggesting the presence of mirror neurons in those areas.

with our hypothesis that ventral premotor/inferior frontal cortex is activated primarily during observation of hand–object interactions as well as hand configurations, rather than during observation of the transport phase of the hand.

#### *Imagined reaching versus passive viewing of objects*

Similar to observed reaching, imagined reaching activated the superior parietal lobule and intraparietal sulcus, the precuneus, as well as dorsal premotor cortex (superior frontal gyrus/sulcus) (see Fig. 2, Table 3). In addition, the inferior parietal lobule (supramarginal gyrus), the posterior end of the Sylvian fissure, and supplementary motor cortex (SMA) were activated, as was the inferior frontal gyrus (Broca's area). The activations ( $p < 0.005$ , corrected) were left-lateralized with the exception of weak superior parietal, supramarginal, and supplementary motor area activations in the right hemisphere. The left-lateralization of imagined reaching activations suggests that imagery of hand movements engages a similar system as actual hand movements, which are also left-lateralized in the human brain. At a lower threshold ( $p = 0.05$ , corrected), a small activation focus emerged within the left anterior occipital sulcus, overlapping with the lateral occipital activations for execution and observation of reaching. Other than this weak anterior occipital sulcus activation at  $p = 0.05$ , no other occipital areas were activated during imagined reaching. This suggests that motor imagery is different from visual imagery, which activates visual areas. Note that since our baseline involved passive viewing of objects, any visual object-related activation unrelated to motor imagery was subtracted out. Although it has been suggested that the STS contains mirror neurons for hand movements (Perrett et al.,

1989), the STS was not activated during imagined reaching, suggesting that this area may respond to visually perceived biological motion, but not to imagined motion.

#### *Overlap between executed, observed, and imagined reaching*

All three conditions activated two main foci (Fig. 4, Table 4): a frontal region in the left dorsal premotor cortex (superior frontal gyrus and sulcus) and a parietal region in the left medial intraparietal sulcus and in the left superior parietal cortex (including the superior parietal gyrus and transverse parietal sulcus). Activations also overlapped in the right superior parietal cortex, although they were much weaker and the overlapping focus was much smaller. The superior parietal overlap in the left hemisphere extended medially into the superior aspect of the precuneus, in an area located anterior to the parieto-occipital sulcus and posterior to the cingulate sulcus (see Fig. 4b). In addition, activations for executed and imagined reaching (but not for observed reaching) overlapped in the left and right medial superior frontal gyrus (SMA), the left and right inferior parietal lobule (supramarginal gyrus), the posterior end of the Sylvian fissure, and the left inferior frontal gyrus. Consistent with previous findings (Grèzes and Decety, 2001), executed reaching activations in the SMA extended more caudally than imagined reaching SMA activations, although there was some overlap between the two. Conversely, activations for executed and observed reaching (but not for imagined reaching) overlapped in the left middle occipital gyrus and surrounding sulci (MT+). This suggests that imagined reaching is more potent than observed reaching at driving motor preparation areas such as supplementary motor cortex. In contrast, observation of reaching drives visual motion areas

Table 1  
Average MNI-space coordinates (in mm) for activations during execution of reaching versus baseline

Brain area	Left				Right			
	x	y	z	No. of subjects	x	y	z	No. of subjects
Lateral fissure, posterior segment	-45	-41	26	14	54	-35	26	13
Superior precentral sulcus	-23	-14	59	14				
Precentral gyrus	-33	-18	70	14	37	-11	64	13
Postcentral gyrus	-37	-30	69	14	34	-38	69	7
Central sulcus	-31	-28	52	14				
Superior postcentral sulcus	-30	-37	54	14	29	-40	53	11
Inferior frontal gyrus, pars opercularis	-52	12	15	13				
Superior frontal gyrus/sulcus	-21	-2	63	14	23	-5	67	12
Middle frontal gyrus	-31	3	64	6				
Superior temporal sulcus	-48	-47	5	9				
Intraparietal sulcus	-33	-46	46	14	26	-52	49	12
Superior parietal gyrus	-27	-55	65	14	20	-59	65	14
Supramarginal gyrus	-57	-38	46	14	60	-31	42	14
Precuneus	-4	-60	57	11	7	-64	58	12
Cingulate sulcus	-10	0	41	13				
Supplementary motor area (SMA)	-5	-5	59	14	7	2	56	14
Superior occipital gyrus	-14	-88	32	14	15	-90	32	14
Middle occipital gyrus/anterior occipital sulcus	-45	-72	8	14				
Lingual gyrus	-3	-74	-1	14	6	-76	-3	13
Cuneus	-2	-88	9	14	5	-86	17	13
Calcarine sulcus	-11	-81	4	13	13	-79	7	13

One subject's MNI coordinates were anomalous (>30 mm different) and were thus excluded from the average of all MNI coordinates. All activations were at  $p < 0.005$  (corrected).

Table 2  
Average MNI-space coordinates (in mm) for activations during observed reaching versus baseline

Brain area	Left				Right			
	x	y	z	No. of subjects	x	y	z	No. of subjects
Superior occipital gyrus	-14	-92	26	13	20	-91	26	14
Intraparietal sulcus	-29	-52	47	13	28	-52	49	13
Superior parietal gyrus (P1)	-29	-57	64	14	21	-62	66	13
Superior frontal gyrus/sulcus	-23	-6	60	14				
Middle occipital gyrus/sulcus	-45	-76	3	14	48	-72	4	14
Superior temporal sulcus, caudal	-45	-58	12	8	51	-50	11	10
Precuneus	-6	-62	52	11	7	-65	52	11
Cuneus	-1	-89	10	12				

All activations were at  $p < 0.005$  (corrected).

Table 3  
Average MNI-space coordinates (in mm) for activations during imagery of reaching versus baseline

Brain area	Left				Right			
	x	y	z	No. of subjects	x	y	z	No. of subjects
Superior parietal gyrus (P1)	-22	-65	62	14	19	-66	61	13
Intraparietal sulcus	-29	-51	45	14				
Superior postcentral sulcus	-28	-40	55	10				
Precuneus	-6	-63	57	12				
Inferior parietal lobule: supramarginal gyrus	-59	-37	41	12	59	-36	43	10
Lateral fissure, posterior segment	-48	-44	26	13				
Superior frontal gyrus/sulcus	-22	-3	61	14				
Superior precentral sulcus	-26	-12	55	14				
Inferior frontal gyrus, pars opercularis	-50	16	15	11				
Supplementary Motor Area (SMA)	-5	-1	59	14	8	6	59	14

All activations were at  $p < 0.005$  (corrected).

(MT+) more strongly than imagined reaching. In addition to MT+, the activation in the middle occipital gyrus and surrounding sulci may include the extrastriate body area, which has been shown to respond to limb movements in the absence of visual input as well as to images of body parts (Astafiev et al., 2004). Astafiev et al. also found that imagery of pointing movements activates the extrastriate body area, although more weakly than actual movement. Our weaker activation ( $p = 0.05$ , corrected) for imagined reaching in lateral occipital cortex is consistent with Astafiev et al.'s findings.

We calculated the percent signal change for voxels ( $p < 0.001$ ) within the two regions of interest (ROIs) defined by overlapping activations in dorsal premotor and parietal cortex shown in Figs. 4a and b. Fig. 5 shows the percent signal change and time course of activation for executed, imagined, and observed, reaching. A one-way ANOVA revealed significant differences between percent signal change means for executed, observed, and imagined reaching ( $p = 0.002$ ) in the parietal ROI. To identify which conditions were different from each other on a pairwise basis, both two-tailed paired  $t$ -tests, and bootstrap resampling were used. In the parietal ROI, Reach was greater than Observe ( $t(14) = 3.25$ ,  $p = 0.0059$ ; bootstrap  $p = 0.0001$ ), and Reach was greater than Imagine ( $t(14) = 3.94$ ,  $p = 0.0015$ ; bootstrap  $p < 0.0001$ ). Observe and Imagine were not noticeably different from each other ( $t(14) = 0.07$ , n.s.; bootstrap n.s.). In the premotor ROI, the trend was also for Reach to be greater than Observe ( $t(14) = 2.58$ ,  $p = 0.0217$ ; bootstrap  $p = 0.0041$ ), and for Reach to be greater than Imagine ( $t(14) = 2.16$ ,  $p = 0.0490$ ; bootstrap  $p = 0.0170$ ). As in the parietal ROI, Observe and Imagine were not significantly different ( $t(14) = 1.77$ , n.s.; bootstrap n.s.). Both the  $t$ -test and bootstrap  $p$  values suggest that in the premotor ROI, the differences between Reach and the other conditions were less strong than in the parietal ROI.

It is possible that execution of reaching drives mirror neuron areas more strongly than observation and imagery of reaching, or that other neurons, in addition to mirror neurons, are active during movement execution but not during observation and imagery.



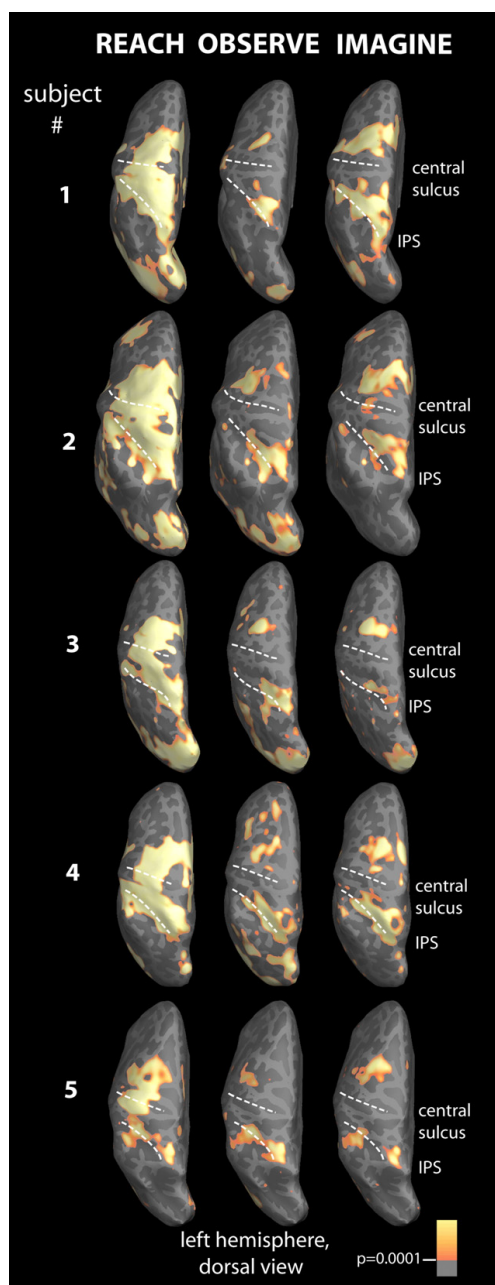


Fig. 3. BOLD activations for executed, observed, and imagined reaching, versus baseline, from five representative subjects. Activations are displayed on the left inflated hemisphere of each subject. Each subject's activations are significant at  $p < 0.0001$ . Note that, despite inter-subject variability, each subject shows overlap in activations between all three conditions in dorsal premotor and superior parietal cortex. IPS=intraparietal sulcus.

Although fMRI cannot distinguish between these two possibilities, the fact that single unit recordings in macaques have found bimodal neurons with both visual and motor properties in premotor and parietal areas suggests that similar bimodal neurons may be involved in humans too, rather than separate populations of neurons.

#### Execution versus observation of reaching

Compared to observed reaching, executed reaching (Fig. 6) activated primary motor and somatosensory cortices, superior parietal cortex, the medial IPS, parts of dorsal premotor cortex (superior frontal gyrus/sulcus), the supplementary motor area, inferior parietal cortex (supramarginal gyrus), inferior frontal gyrus, the cingulate sulcus, cuneus, and lingual gyrus more strongly ( $p < 0.005$ , corrected). These differences were left-dominant. Conversely, compared to execution of reaching, observation of reaching activated the precuneus, the caudal intraparietal sulcus, the superior occipital gyrus, and the angular gyrus more strongly in both hemispheres ( $p < 0.005$ , corrected). Note that neither reaching versus baseline nor observed reaching compared to baseline activated the angular gyrus significantly. Hence the decreased activation in this part of the inferior parietal lobule obtained in the reaching versus observed reaching contrast may be due to a decrease of activation in that region during reaching versus baseline, rather than greater activation for observed reaching compared to executed reaching.

#### Execution versus imagery of reaching

Compared to imagined reaching, executed reaching activated primary motor and somatosensory cortices as well as the superior parietal lobule and the medial IPS more strongly ( $p < 0.005$ , corrected) (Fig. 6). In addition, the supramarginal gyrus, the middle occipital gyrus (MT+), a small part of dorsal premotor cortex (superior frontal gyrus), the cuneus, and the lingual gyrus were also activated more strongly during executed reaching than imagined reaching. Conversely, imagined reaching activated the caudal intraparietal sulcus, the angular gyrus bilaterally, and the precuneus more strongly than actual reaching. As in the executed reaching versus observed reaching contrast, the angular gyrus was not actually significantly activated during imagined reaching compared to baseline. Instead, it is possible that during actual reaching, activations in the angular gyrus decreased relative to baseline.

#### Observed versus imagined reaching

The only difference in activation between observed and imagined reaching was in the superior occipital gyrus and in the middle occipital gyrus (MT+), with greater activations for observed reaching ( $p < 0.005$ , corrected) (Fig. 6). This was expected, as there was visual movement during observation of reaching due to the moving hand, whereas there was no visual movement during imagined reaching. This difference was bilateral.

#### Discussion

We used fMRI to compare human cortical activations for executed, observed, and imagined reaching with the goal of identifying a mirror neuron system that represents reaching and reaching-related behaviors. Our results suggest that such a mirror neuron system exists, and that it bears both differences and similarities to the mirror neuron system underlying grasping movements and ob-

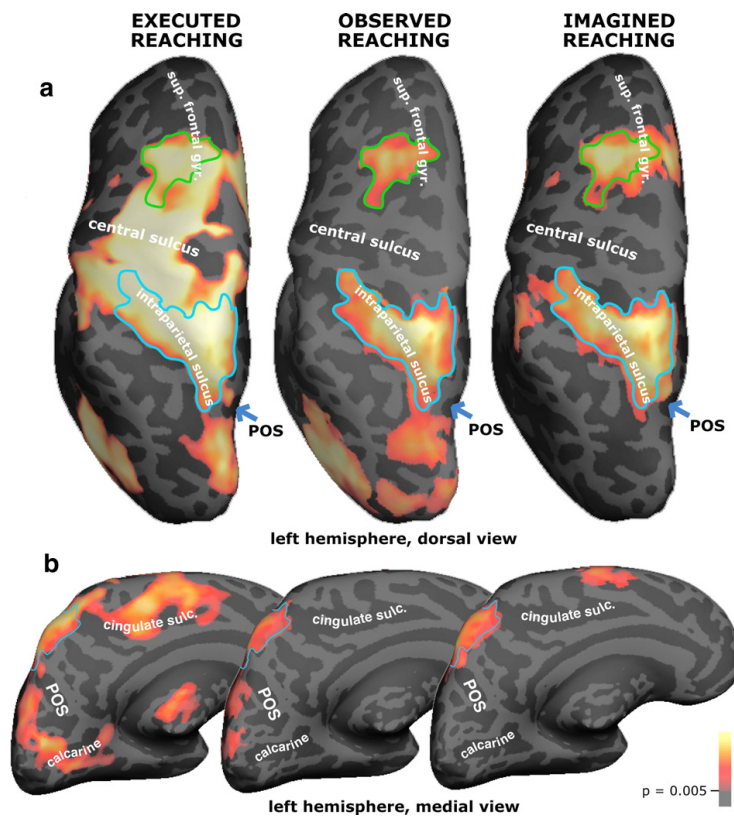


Fig. 4. Outline of overlap between executed, observed, and imagined reaching in left dorsal premotor (superior frontal sulcus and gyrus) and left posterior parietal areas, on group surface-averaged activations from 15 subjects, displayed on one subject's inflated hemisphere. The overlaps in premotor and parietal regions served as regions of interest in the percent signal change analysis. (a) Dorsal view of left hemisphere. (b) Medial view of left hemisphere. Executed, observed, and imagined reaching all activated a medial parietal area located in-between the parieto-occipital sulcus and the posterior end of the cingulate sulcus, outlined in light blue. Sup. frontal gyr.=superior frontal gyrus; POS=parieto-occipital sulcus; calcarine=calcarine sulcus; cingulate sulc.=cingulate sulcus.

ject manipulation. Specifically, mirror neurons for execution, imagery, and observation of reaching are found in dorsal premotor (superior frontal gyrus/sulcus) and superior parietal/intraparietal as well as in more medial parietal cortical areas. Observation of reaching without grasping does not activate Broca's area or the inferior parietal lobule (i.e. areas *below* the IPS, such as the supramarginal gyrus), although both executed and imagined reaching do (to a lesser extent compared to more dorsal areas). The dorsal premotor and posterior parietal activations we report here for executed

reaching are consistent with previous studies of execution of reaching-to-point or reaching-to-grasp movements as well as of pointing movements (Culham et al., 2006; Culham et al., in press; Medendorp et al., 2005; Frey et al., 2005; Grafton et al., 1996b; Astafiev et al., 2003, Prado et al., 2005).

The dorsal premotor and superior parietal/intraparietal overlap between activations for execution, observation, and imagery of reaching reported here is consistent with a fronto-parietal mirror neuron system for hand actions. Specifically, our results extend previous mirror neuron findings to visually-guided reaching movements in which an object is not grasped, touched, or manipulated. Although grasping activations and reaching activations do overlap, it appears that during reaching, as well as during imagined and observed reaching movements, premotor and parietal activations are more dorsal/superior and more medial, consistent with macaque data on fronto-parietal networks for reaching (Matelli and Luppino, 2001).

In the macaque brain, areas F2 and F7 form the dorsal premotor cortex (PMd). Area F2 is located anterior to primary motor cortex

Table 4  
Average MNI-space coordinates for overlaps between executed, observed, and imagined reaching activations (left hemisphere)

Brain area	x	y	z	No. of subjects
Superior frontal sulcus/gyrus	-22	-2	62	14
Superior parietal gyrus (P1)	-24	-61	60	14
Intraparietal sulcus (IPS)	-30	-49	48	13

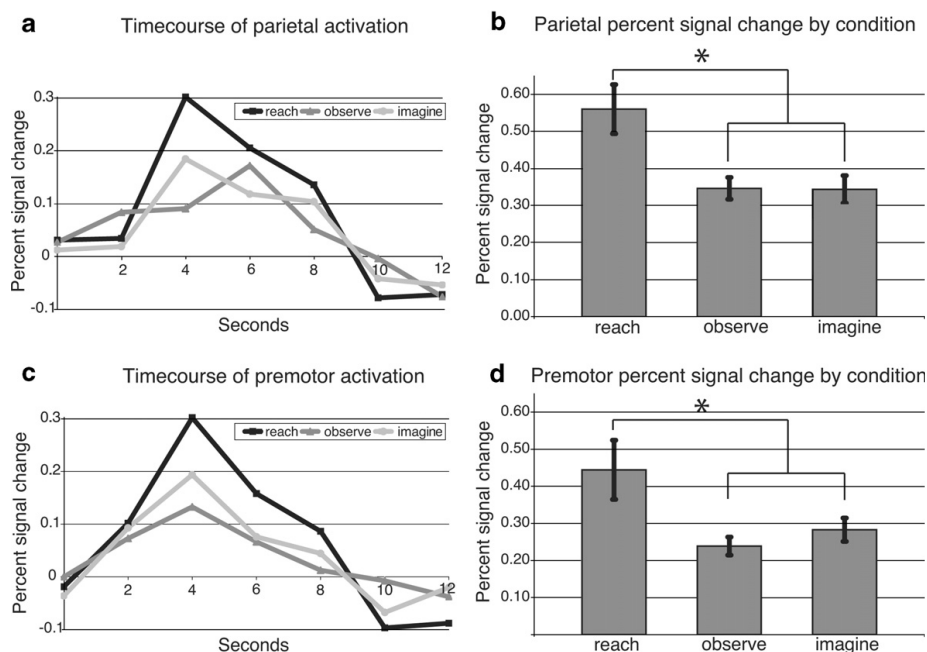


Fig. 5. Time course and percent signal change for parietal and premotor regions of interest (ROIs). (a) Parietal time course of BOLD signal change during executed, observed, and imagined reaching, versus baseline, averaged over 15 subjects. (b) Average parietal percent signal change magnitude for reaching, observed reaching, and imagined reaching, over 15 subjects. Error bars represent standard error of the mean (\* $p < 0.05$ ). (c) Average premotor BOLD time course, as in (a), over 15 subjects. (d) Average premotor percent signal change magnitude over 15 subjects, for executed, observed, and imagined reaching, as in (b). Reaching activations were stronger than observed and imagined reaching activations in both parietal and premotor ROIs.

and contains an arm representation. Within area F2, F2vr contains visually-responsive neurons and is a major target of parietal areas MIP and V6a, both of which contain reach-related bimodal (visual and motor) neurons. The MIP/V6a–F2vr circuit thus represents visually-guided reaching, in particular the transport phase of the hand towards the target (Matelli and Luppino, 2001). By contrast, grasping is represented by connections between the anterior intraparietal area (AIP, an area lateral and rostral in the intraparietal sulcus) and ventral premotor areas F4 and F5 in the macaque. This circuit is more lateral than the reaching circuit. A similar functional specialization of parieto-frontal circuits has recently been found in humans too (see Culham and Kanwisher, 2001; Culham et al., 2006; Culham and Valyear, 2006). Our fMRI results reported here are consistent with macaque fronto-parietal circuits for reaching, as well as with recent human neuroimaging studies on reaching and pointing. We suggest that the dorsal premotor activations obtained during executed, observed, and imagined reaching in the present study are the human homologue of macaque F2vr, and that the parietal activations we see in these three conditions include the human homologue of MIP and V6a.

Our results are consistent with a “direct-matching hypothesis” which states that actions are recognized during action observation by activating one’s own motor representation of those actions (Buccino et al., 2004a). Our findings extend this matching system to imagery of action, and demonstrate that the matching system involved depends on the particular hand action, in our case, reaching. Although there is an overlap between motor substrates for grasping

and reaching, there are also differences between their respective neural representations. The results presented here suggest that the main difference is in dorsal premotor and superior as well as more medial parietal activations, with greater emphasis on more medial/superior areas for reach-related tasks than for object manipulation-related tasks that do not involve a hand transport phase.

#### *Superior versus inferior frontal gyrus activation during observed reaching*

Whereas inferior frontal gyrus activation was present during executed and imagined reaching compared to baseline, observation of reaching versus baseline did not activate the inferior frontal gyrus, but instead only the superior frontal gyrus/sulcus. It is possible that during executed and imagined reaching, subjects may have had the intention to grasp the objects towards which they were reaching or imagining reaching. In fact, a few subjects reported reaching with the intention to grasp (although the object images were 2-dimensional). By contrast, during observation of reaching such an intention was not as obvious because the videotaped hand always stopped before getting to the point of grasping; i.e. only the transport phase was perceived. Hence in executed and imagined reaching, inferior frontal activation (Broca’s area) was present, whereas observation of just the transport phase of the hand during observed reaching failed to activate the inferior frontal gyrus. This lack of inferior frontal gyrus activation is consistent with Johnson-Frey et al. (2003), who found that observation of grasping an object,



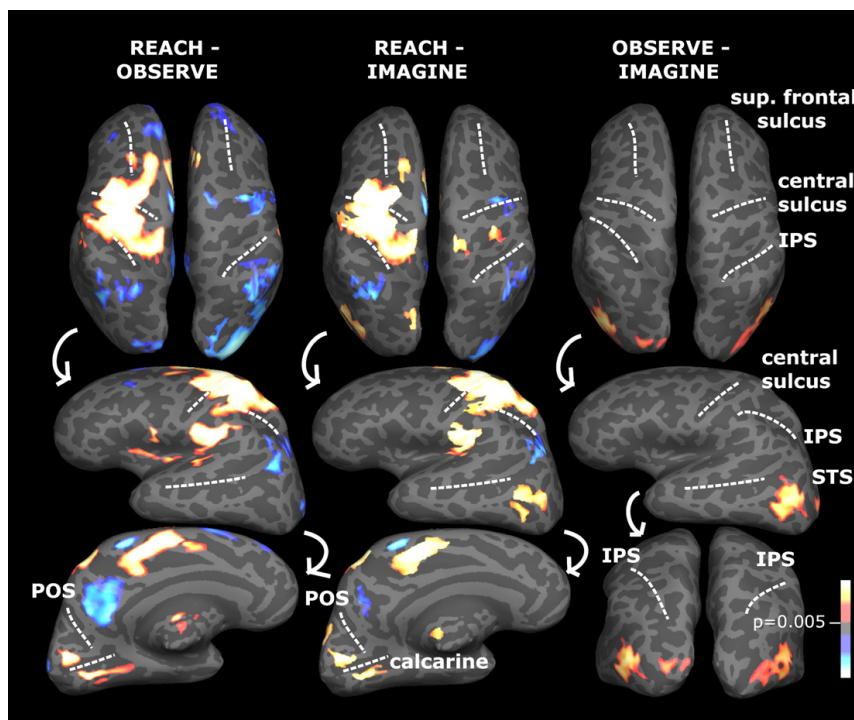


Fig. 6. Comparisons between executed and observed reaching, executed and imagined reaching, and observed versus imagined reaching. Activations are group surface-averages from 15 subjects displayed on a single subject's inflated left and right hemispheres,  $p < 0.005$  (corrected). Red to bright yellow codes for greater activation for the condition subtracted from. Blue activations represent greater activation for the subtracted condition. Note the lack of difference in premotor and parietal cortex for the observed versus imagined reaching comparison, suggesting that parietal and premotor mirror neurons participate equally in observation and imagery of reaching. IPS=intraparietal sulcus; calcarine=calcarine sulcus; sup. frontal sulcus=superior frontal sulcus; POS=parieto-occipital sulcus; STS=superior temporal sulcus.

but not observation of touching the object with the side of the palm (i.e. not with the fingers) activates the inferior frontal gyrus. In all three tasks in our study, the main component was reaching, rather than a putative intention to grasp—hence the strong dorsal premotor activations obtained here. Even if subjects may have imagined grasping at the end of the executed and imagined reach, the small extent of Broca's area activation for executed and imagined reaching compared to the more dorsal premotor activations suggests such an effect was small. The dorsal premotor activations reported here are consistent with activations reported by Culham et al. (2003) for visually-guided reaching as well as reaching-to-grasp, and with dorsal premotor activations for pointing (Medendorp et al., 2005; Astafiev et al., 2003; Hagler et al., 2007).

Our results suggest that in general, ventral premotor areas (including inferior frontal gyrus, middle frontal gyrus) are activated primarily during observation of complex hand movements that involve either pantomimed preshaping of the hand or other local interactions with an object (Grafton et al., 1996a; Buccino et al., 2001, 2004b). If the task is just to observe a hand moving from one location to another as in reaching, more superior or dorsal premotor areas are also activated, such as the superior frontal gyrus, which we see activated in our task.

#### Superior versus inferior parietal activations

Likewise, in parietal cortex, observation of hand–object interactions activates more inferior parietal areas, such as the parietal operculum, whereas observation of reaching without grasping activates superior parietal areas, such as the superior parietal gyrus (P1) within the superior parietal lobule, in addition to the IPS. Although executed reaching activated area AIP in our study (defined as the junction between the intraparietal sulcus and the postcentral sulcus, see Culham et al., 2006; Frey et al., 2005), our activations also extended more medially into the superior aspect of the precuneus compared to grasping-related activations reported by most studies (Grèzes et al., 2003; Rizzolatti et al., 1996b) or activations for local finger actions such as playing the guitar or imitating finger lifting (Buccino et al., 2004b; Iacoboni et al., 1999). This pattern was true for observation of reaching and imagery of reaching as well, suggesting a more dorsal and medial mirror neuron system for reaching-related tasks than for object manipulation tasks. An interesting exception is found by Binkofski et al. (1999), who did find superior parietal activations during complex object manipulation in the dark, in addition to inferior frontal and inferior parietal activations (including AIP). However, the activations depended on the exploration

conditions. When complex objects that were not easily recognized were explored, both left and right superior parietal lobules were activated compared to rest. When more easily recognizable objects were explored, where naming of the objects was possible, the left superior parietal lobule was not activated, whereas the right superior parietal lobule was. Binkofski et al. suggest that the superior parietal lobule is involved in proprioception and that there is a hand/finger representation in the superior parietal lobule. The fact that easily recognizable object manipulation did not activate the left superior parietal lobule suggests that exploration of objects with more complex spatial characteristics will activate this region. This spatial aspect may be important during reaching too, e.g. during the visuomotor guidance of the arm to the appropriate location. It is possible that the superior parietal lobule is involved in multiple motor representations, and not exclusively in reaching. Note that as Binkofski et al. (1999) only investigated the execution aspect of complex object manipulation, it is not known if observation of the same movements would also have activated superior parietal areas. The important finding in our paper, however, is that *mirror neurons* for executed, observed, and imagined *reaching* are located in superior and medial parietal areas, which is consistent with parieto-frontal circuits for reaching in both macaques and humans. The overlap between all three conditions was not found in Broca's area, where mirror neurons for *object manipulation* are found.

While observed and imagined reaching *per se* have not been studied previously, the superior and medial parietal activations obtained here for execution of reaching are consistent with previous neuroimaging studies of execution tasks similar to reaching. Connolly et al. (2003) and Astafiev et al. (2003) propose that the human equivalent of MIP and V6A, also called the parietal reach region (PRR), is located medial to the IPS and on the medial wall of the parietal lobe (precuneus), based on pointing-related fMRI activations in the human brain. The precuneus and medial IPS/superior parietal activations reported here are consistent with their proposed location. Similar parietal activations were also found by Medendorp et al. (2005), Desmurget et al. (2001), Hagler et al. (2007), Culham et al. (in press) and Prado et al. (2005). Culham et al. (in press) suggest that the superior parieto-occipital cortex, broadly consistent with our activations in-between the parieto-occipital sulcus (POS) and the posterior end of the cingulate sulcus (Fig. 4b), may be especially important for the transport phase of the reaching movement. In our study, all three conditions activated areas immediately anterior to the POS, whereas executed and observed, but not imagined reaching, activated presumably more visual areas posterior to the POS. The activation anterior to the POS is consistent with the proposal that the human homologue of macaque V6A is anterior to the POS (Culham et al., in press), which overlaps with what Connolly et al. (2003) call the parietal reach region (PRR). If Culham et al.'s interpretation of this area is correct, our results suggest that this area contains mirror neurons for the executed, observed, and imagined transport phase of reaching. Fig. 6 shows that this area was equally activated during observed and imagined reaching, and that executed reaching activated more superior aspects of this area more strongly than either observed or imagined reaching.

Prado et al. (2005) argue for a dissociation between brain circuits involved in reaching toward central versus peripheral visual targets. Whereas in their study the medial IPS was active in both, activation centered on the parieto-occipital junction (POJ) on the medial wall was present only during reaching to peripheral targets. Our activations for reaching are in agreement with Prado et

al.'s (2005) activations for reaching to peripheral targets. In our study, targets were presented in the periphery, and no saccade was executed towards targets prior to executed, observed or imagined reaching. All three conditions activated an area located in-between the POS and the posterior end of the cingulate sulcus, with reaching and observed reaching extending posterior to the POS as well (see Fig. 4b). While we did not compare reaching towards central and peripheral targets, we can conclude that there are mirror neurons for observed, imagined, and executed reaching to peripheral targets around and slightly anterior to the parieto-occipital junction, consistent with Prado et al.'s (2005) results for reaching to peripheral targets.

#### *Dorsal premotor cortex and eye movements*

Although we monitored subjects' eye movements outside the scanner and confirmed that they maintained fixation, it could be argued that some of the premotor activations reported here may in fact be eye movement-related activations rather than mirror neuron activations for reaching. Several aspects of our results speak against this argument. Firstly, superior frontal gyrus/sulcus activation was absent or very weak in the right hemisphere during observed and imagined reaching (Fig. 2). If indeed subjects had moved their eyes substantially during all three tasks, one would expect *bilateral* and more symmetric activations in dorsal premotor cortex, which we did not find. Secondly, the proposed location of the frontal eye fields (FEF) in humans is at the junction of the precentral and superior frontal sulci (Koyama et al., 2004; Culham et al., 1998), whereas our dorsal premotor focus of activation for observed and imagined reaching was anterior to this junction (see Figs. 2 and 4). The dorsal premotor activation reported here was located partly on the superior frontal gyrus and inside the superior frontal sulcus anterior to the precentral sulcus. According to Blanke et al. (2000), putative human FEF even overlaps with the precentral gyrus, which is well posterior to the proposed mirror neuron activation reported here. Both Koyama et al. and Culham et al. report a second area related to eye movements in the inferior precentral sulcus. In our study, observation of reaching elicited no such inferior precentral sulcus activations, whereas imagined reaching yielded a very small activation in the inferior precentral sulcus (Fig. 2). These findings suggest that the overlap in activations for observed, imagined, and executed reaching reported here is not likely due to eye movements during each of these tasks, even if some eye movement may have occurred. Culham et al. (2003) obtained activations in the FEF during visually-guided reaching and grasping, which they suggested may be due to a subpopulation of neurons in FEF that is activated during arm movements. This would support our hypothesis that part of dorsal premotor cortex in humans represents arm movements. It is possible that some of the dorsal premotor activations reported here partially overlap with such a population of FEF neurons, although as stated above our activations are mainly anterior to the FEF. A similar anterior focus was also obtained by Astafiev et al. (2003) for pointing, consistent with our results.

In conclusion, we have demonstrated the existence of a frontoparietal mirror neuron system for executed, observed, and imagined reaching. Whereas grasping has been studied before, very few fMRI studies have investigated reach-related mirror neuron activations, perhaps due to the difficulty with larger hand movements that involve a transport phase. Our results suggest that reach-related mirror neuron activations are present in the superior frontal gyrus and sulcus, as well as in intraparietal and superior/medial parietal

areas. Reaching drives both areas more than observation and imagery of reaching, whereas activations for observation and imagery of reaching in these two regions are equally strong. The present results help shed light on the complex mosaic of visuo-motor representations in the human brain, and extend previous studies of mirror neuron activations in humans to reaching.

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### **Chapter 3.**

**Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during online reaching**

**Abstract**

Reaching towards a visual target involves at least two sources of information. One is the visual feedback from the hand as it approaches the target. Another is proprioception from the moving limb, which informs the brain of the location of the hand relative to the target even when the hand is not visible. Where these two sources of information are represented in the human brain is unknown. In the present study, we investigated the neural representations for reaching with or without visual feedback from the moving hand, using fMRI. To identify reach-dominant areas we compared reaching with saccades. Our results show that a reach-dominant region in the anterior precuneus (aPRR) is equally active in visual and non-visual reaching. A second region, at the superior end of the parieto-occipital sulcus (sPOS), is more active for visual than for non-visual reaching. These results suggest that aPRR primarily relies on proprioceptive input while sPOS receives visual feedback during reaching. Our results suggest that cortical networks for reaching are differentially activated depending on the reach conditions. This indicates the involvement of multiple parietal reach regions in humans, rather than a single homogenous parietal reach region.

## Introduction

The parietal lobe contains sensorimotor representations that use sensory input, such as vision, to guide our interactions with the environment, such as reaching to a target. Whereas macaque neurophysiology has revealed parietal regions that use various sensory representations (visual, somatosensory) to guide multiple actions (eye, limb, head movements), the human homologues of those sensorimotor representations are an open question (Culham et al., 2006), both in terms of effector specificity (e.g. hand versus eye) of the motor component, and in terms of the sensory input used to drive the action (vision or somato-sensation). During online guidance of a reaching movement, for instance, both visual feedback and proprioceptive input from the moving limb are available. How these two sources of information map onto human parietal reach regions is unknown.

In macaques, several medial posterior parietal areas contain neurons that respond more during reaching than during saccades, including V6A (Galletti et al., 2003; Fattori et al., 2001), MIP (Andersen and Buneo, 2002), area 5 (Kalaska, 1996), and the 'parietal reach region' (PRR -- overlapping V6A and MIP; Andersen and Buneo, 2002).

Functional neuroimaging experiments in humans have yielded inconclusive results as to the human homologue(s) of macaque parietal reach regions. This may be because a majority of studies have used pointing preparation rather than actual reaching (Astafiev et al., 2003; Connolly et al., 2000, 2003; Fernandez-Ruiz et al., 2007; Hagler et al., 2007). Finger pointing is a much smaller movement than reaching,



which may not recruit neurons involved in controlling the arm (e.g. in V6A; Galletti et al., 2003). In natural reaching, hands are not pre-shaped into a fist with the index finger extended, which is more typical of communicative functions (Culham et al., 2006; Culham and Valyear, 2006). Reaching-to-point (with the index finger; Prado et al., 2005; Levy et al., 2007), reaching-to-grasp (Culham et al., in press; Grafton et al., 1996) and reaching-to-touch (Pellijeff et al., 2006; Culham et al., in press) movements activate the medial parietal lobe, although various locations and activation magnitudes (relative to saccades) have been reported. In particular, some studies reported activations closer to the parieto-occipital sulcus (POS), and others more anterior precuneus activations.

Recently, execution of visually-guided reaching without touching, pointing, or grasping (Filimon et al., 2007) was shown to activate all of the precuneus, from the POS to the cingulate sulcus. This raises the important question of whether the precuneus maps visual input from the hand or proprioceptive feedback during movement.

To investigate the cortical representations of visual versus proprioceptive feedback during reaching we compared reaching with the hand visible and reaching with the hand non-visible, in a series of three fMRI experiments. Whereas visual reaching involves both visual feedback and proprioception, non-visual reaching to an external target requires online monitoring of proprioceptive feedback during the transport phase. This information is used to calculate and update where the hand is in space, relative to the target, without vision. Parietal reach-related regions exhibiting

increased activation when the reach is visible compared to when it is non-visible would thus reveal modulation from visual feedback. Parietal regions involved in online reaching that are not modulated by the visual feedback would suggest proprioceptive input. Subjects used non-delayed (immediately executed), direct (i.e., without use of a mirror) reaching (involving the forearm and an open hand) towards external peripheral targets. To identify reach-dominant areas, we also contrasted reaching with saccades.

Our results show that the anterior precuneus is activated equally whether or not the reaching hand is seen, whereas the superior POS responds more during visual than non-visual reaching. This suggests proprioceptive and visual roles for aPRR and sPOS, respectively.

## Materials and Methods

### Subjects

Twenty-nine subjects participated in three fMRI experiments. Ten subjects participated in experiment 1 (7 males and 3 females, age range 19-27); an additional subject's data were discarded due to excessive head motion during scanning. Eleven subjects participated in experiment 2 (6 males and 5 females, age range 19-25); of these, nine had also participated in experiment 1. Eight of the subjects participated in both experiments within the same scanning session. Eight subjects participated in experiment 3 (4 males and 4 females, age range 21-33), two of which had also participated in experiments 1 and 2. All subjects were neurologically intact, right-handed, and had normal or corrected-to-normal vision. All subjects gave written informed consent. The experimental procedures were approved by the UCSD Institutional Review Board.

### Stimuli

In experiments 1 and 2, subjects viewed visual stimuli projected on a screen mounted ~14 inches in front of their chin and above their torso (Fig. 1a and 1b). Subjects' heads were tilted forward towards the screen such that they had a direct view of the visual stimuli, without requiring use of a mirror. The targets were small white squares subtending a visual angle of  $\sim 1^\circ$  displayed around a central fixation cross at  $\sim 8^\circ$  eccentricity. Targets appeared one at a time at one of 12 possible locations around the central fixation cross. The 12 possible locations were spaced at a polar angle of

30° (e.g. 1 o'clock, 2 o'clock, etc.), with target location selected at random. The visual angle subtended by the entire display was ~36°. Two example trials are shown in Fig. 1a. Stimuli were displayed using a stimulus presentation program written in C running on an SGI O2 machine. Stimuli were front-projected on a screen inside the scanner using a standard video projector with a 7.38-12.3" focal length Xtra Bright Zoom lens (Buhl Optical, USA).

For experiment 3, stimuli were five fiber-optic targets mounted on a custom-made black screen (see Fig. 1d for a schematic). The fixation point and each target consisted of the endpoint of a single optical fiber. The other end of each optical fiber (located outside the scanner room) was illuminated by a dim LED controlled by a custom-made circuit board designed by R-S. H. (see Huang and Sereno, in press). The screen was mounted at ~14" in front of the subject, with the subject's head tilted forward for a direct view, as in experiments 1 and 2. The fiber-optic targets were arranged horizontally ~7° apart and ~7° below a fiber-optic fixation point, with the total display subtending ~35°. All other sources of light inside the scanner room were turned off or covered up. The fiber-optic lights were dimmed such that a hand movement executed below each target was not visible to a subject inside the scanner. Each of the fiber-optic targets was turned on at random using a custom-made program on a Shuttle PC running Red Hat Linux.

#### Experiment 1 task

In experiment 1, subjects were instructed to either 1) reach towards the peripheral targets in front of them while maintaining central fixation; 2) saccade to the

peripheral targets and return their eyes to the central fixation cross while keeping the hand motionless on their chest; or 3) fixate (no targets present) while keeping the hand motionless (baseline). A pseudo-random block order of the reach, saccade, or fixate conditions was used, with on average 15-16 blocks per random order (functional run). Each block of trials lasted on average 32s (Fig. 1a). Each reach trial took ~4 s and each saccade trial took ~2s. A 2-second message at the beginning of each block of trials instructed subjects as to the condition they were to begin. A fixation cross appeared at the beginning of each trial for 250-500 ms. Note that since subjects could see their hand during the reach, the reach condition in this experiment involved a visually-guided direct reach to targets. Reaching involved moving the right forearm with an open hand towards the targets from the center of the chest and back, without touching the screen (Fig. 1b). The elbow was supported and partially immobilized by foam pads. All subjects reached with their right hand only. Subjects were trained outside and inside the scanner prior to scanning. Subjects' eye movements were monitored during the training session outside the scanner. All subjects were able to maintain central fixation during reaching and during fixation trials.

### Experiment 2 task

In experiment 2, subjects participated in the same conditions as above (reach, saccade, fixate), with the visual targets displayed as before. Importantly, the right hand was shifted towards the right side of the subject and blocked from view. Reaching was performed on a plate supported with foam on the subject's right side. Subjects moved their hand from the center of the plate, which was marked with a velcro patch, toward

the location that corresponded to the visual stimuli in front of them and back - e.g. a target presented at 12 o' clock led to an upward movement on the plate; a 6 o'clock target led to a downward movement on the plate (Fig. 1c). Since subjects could not see their reaching hand in this experiment, the reach was an indirect, non-visual reach. Subjects were trained prior to scanning. Subjects were able to reach accurately without seeing their hand, as well as maintain fixation.

### Experiment 3 task

In experiment 3, subjects were instructed to either 1) reach in the periphery while maintaining central fixation, 2) saccade, or 3) fixate, as in experiment 1. The targets were very dim fiber-optic points located horizontally below the fixation point (Fig. 1d). This was necessary in order to allow for reaching to just below each target, such that the hand would not obstruct the visual target or fixation point and thereby provide visual feedback as to its location. Subjects were instructed not to touch the screen. Reaching was done either in darkness, with no visual feedback from the hand (non-visual direct reach), or in light, for which a bundle of optical fibers attached to the scanner bore above the subject's chest was turned on. A bright LED located inside the console room illuminated the bundle of optical fibers. The light illuminated the subject's hand during the reach thus providing visual feedback (visual direct reach). Both kinds of reaching were executed directly towards the screen, in the same plane. A pseudo-random block order of visual direct reach, non-visual direct reach, saccade, and fixation trials was used. Each block of trials lasted 30s, with each reach trial lasting 4s, and each saccade trial lasting 2s. A 2s auditory message at the beginning of

the block indicated which condition was about to begin. Each functional run consisted of 20 blocks total.

#### MRI data acquisition

Magnetic resonance images were collected on a GE 3T scanner at the Center for fMRI, University of California, San Diego, using an 8-channel head coil. Functional images were collected using an echo-planar T2\* gradient echo pulse sequence (32 contiguous axial slices, 3.44 x 3.44 x 4 mm voxel size, 64 x 64 matrix, TR = 3000 ms (experiments 1 and 2) or 2000 ms (experiment 3), 165 TRs per scan for experiments 1 and 2 and 300 TRs per scan for experiment 3, TE = 30 ms, flip angle = 90°, band width = 62.5 kHz). The slice volume included the whole brain. The first 4 volumes in each scan series were discarded automatically, to allow the magnetization to reach a steady state. Experiments 1 and 2 each consisted of at least two functional scans each; experiment 3 consisted of at least 3 functional scans. In addition, a T1-weighted FSPGR alignment scan (1 x 1 x 1.3 mm voxel) was collected in each scanning session to align the functional images to a previously obtained high-resolution (1 x 1 x 1 mm) T1-weighted FSPGR anatomical scan. To prevent head motion, each subject's head was stabilized using individual dental impressions (bite bars) supported by a 4-ball-joint yoke. In addition, foam was packed around the head inside the head coil, and the upper arm was immobilized with foam pads.

## fMRI data analysis

(f)MRI data were analyzed using FreeSurfer (Fischl et al., 1999a, Dale et al., 1999) and AFNI (Cox, 1996) (see Filimon et al., 2007 for detailed procedures). Each subject's cortical surface was reconstructed from the separately-obtained high-resolution T1-weighted anatomical scan using FreeSurfer. Functional images were superimposed on the T1-weighted alignment scan collected during the functional session and then registered with the high-resolution anatomical scan from which the cortical surface was reconstructed. This allowed functional activations to be painted onto each subject's reconstructed cortical surface. Functional runs were concatenated using AFNI's 3dTcat function. Slice-timing correction was implemented using AFNI's tshift function. Motion correction was implemented using AFNI's volreg (volume registration) function, registering images to the middle TR of the middle functional run (in cases where only 2 runs were available, the middle TR of the second run was chosen). In a small number of subjects (5 out of 29) there was residual whole-head motion resulting in "spikes" in the raw signal time series which could not be corrected during volume registration (volreg). The TRs affected by head motion artifact were removed from the raw data using AFNI's censor function. On average, 4.22% of reach TRs and 4.24% of saccade TRs were excluded from those five subjects' data in order to remove motion artifact. The percent of TRs (brain volumes) removed per reach, saccade, and rest (fixation) conditions in order to eliminate motion artifact, were as follows: Subject one: 1.83% (reach), 1% (saccade), 1.67% (rest); Subject two: 3.78% (reach), 2.22% (saccade), 9.33% (rest); Subject three: 7.67%



(reach), 1.67% (saccade), 7.67% (rest); Subject four: 1% (reach), 0% (saccade), 2.67% (rest); Subject five: 6.83% (reach), 16.33% (saccade), 10% (rest). Subject five was the only subject with more head motion during the saccade condition compared to the reach condition. Since the activation pattern for each condition was the same as in other subjects even after removing the noisy TRs, subject five was still included in group analyses. The pattern of activation was not different between these five subjects and the remaining subjects, suggesting that motion artifact was successfully removed.

BOLD responses to each experimental condition were analyzed using AFNI's 3dDeconvolve (Cox, 1996; Ward, 2000) general linear model (multiple regression), with a regressor of interest for each condition. A quadratic polynomial was used to fit the baseline. The 6 motion parameters obtained from volume registration were included as regressors in the baseline model to account for variance due to motion. Hemodynamic responses were modeled at four different lag times (1, 2, 3 and 4 TRs). Correlation coefficients and F-statistics were generated for the area under the hemodynamic response function. In experiments 1 and 2, (visual or non-visual) reach and saccade were each contrasted with the baseline (fixation), as well as with each other (visual reach versus saccade in experiment 1; non-visual reach versus saccade in experiment 2). In experiment 3, visual reach, non-visual reach, and saccade, were each contrasted with the fixation baseline, as well as with each other (visual reach versus saccade; non-visual reach versus saccade, visual reach versus non-visual reach).

## Group analysis

Each subject's reconstructed cortical surface was sphered and registered to an average spherical surface atlas in FreeSurfer using a best-fit sulcal alignment (Fischl et al., 1999b). Each subject's coefficients and F-statistics were interpolated onto the average spherical surface after using 16 steps of surface-based smoothing, equivalent to a full-width, half-max (FWHM) Gaussian filter of approximately 5 mm (Hagler et al., 2006). Activations were averaged across subjects in this spherical coordinate system. A one-way, repeated measures ANOVA was carried out using AFNI's mixed-effects, two-factor 3dANOVA2, to generate means and F-statistics of activations for each condition versus baseline (visual direct reach and saccade in experiment 1, non-visual direct reach and saccade in experiment 2, and visual direct reach, non-visual direct reach, and saccade in experiment 3), and for pairwise comparisons. Condition was a fixed effect (with 2 levels in experiments 1 and 2, and 3 levels in experiment 3), while subject was a random effect. Averaged activations and F-statistics were resampled back onto an individual subject's inflated cortical surface for display purposes. To correct for multiple comparisons, we used surface-based clustering (Hagler et al., 2006). Clusters of contiguous vertices were identified for t-statistics thresholded at  $p < 0.05$  for the group-averaged data and  $p < 0.001$  for individual subjects.

## Region of interest analysis

We defined parietal ROIs within each subject based on both anatomical and functional criteria. ROIs consisted of contiguous voxels located on the medial parietal surface, between the POS and the cingulate sulcus. Each subject's data set was divided in two, with ROIs identified in one half of the data, and percent signal change and time series analyses performed on the other half. Since the aim was to identify medial parietal regions that are activated by reaching, and compare reach-related and saccade-related activations within those areas in order to establish whether reaching is dominant, voxels activated by reaching versus baseline in each experiment (visual reaching versus baseline in experiment 3), were selected. Only contiguous voxels significant at  $p < 0.005$ , corrected, were included. This yielded a precuneus region of interest in all three experiments. An additional region of interest was identified in experiment 3 based on the pattern of activations for visual and non-visual reaching compared to saccades around the parieto-occipital sulcus (POS). The region was situated in-between the superior end of the POS and the subparietal sulcus. These anatomical criteria were used in addition to the same functional criteria as above to define an sPOS region of interest in half the data, with calculations performed as noted above on the other half of the data. ROIs were saved as surface patches in FreeSurfer. Voxels within each patch were normalized by their mean intensity and averaged within the ROI using MATLAB. Percent signal change coefficients were calculated for each condition from the normalized time series within the ROI.

## Results

Fig. 1 shows the experimental setup for the different experiments. Note that “visually-guided reaching” could refer either to reaching guided by a visual target or to reaching with the hand visible. Here, we refer to reaching with the hand visible as “visual reaching” and to reaching with the hand non-visible as “non-visual reaching”. We refer to reaching executed directly towards the peripheral visual targets as “direct” reaching, and to reaching executed on the plate as “indirect” reaching. In experiment 1, subjects executed visual direct reaches or saccades to peripheral visual targets in front of them. In experiment 2, subjects reached indirectly on a hidden plate, or saccaded to visual targets as in experiment 1. In experiment 3, subjects executed visual and non-visual direct reaches or saccades to peripheral visual targets in front of them.

Experiment 1: Execution of visual direct reaching, compared to saccades or fixation.

To identify brain regions involved in visual reaching in experiment 1, BOLD fMRI signals were collected as subjects reached to peripheral visual targets with the hand visible while fixating on a central fixation cross. As shown in Fig. 2a (top row), a number of brain regions were significantly activated by visual direct reaching compared to fixation ( $p < 0.05$ , corrected). A fronto-parietal ring of activations was observed, including dorsal premotor cortex (superior and middle frontal gyri), the supplementary motor area, cingulate sulcus and gyrus, primary sensorimotor cortex, the posterior parietal cortex (including all of the intraparietal sulcus; superior parietal gyrus, precuneus, and supramarginal gyrus), the posterior end of the Sylvian fissure,

as well as visual areas, especially V1 (calcarine sulcus), the cuneus and lingual gyrus, and the superior and middle occipital gyri (MT+). The wide extent of activations was expected, as reaching towards visual targets with the hand in sight provides visual, somatosensory, and skeletomotor stimulation. Activations were bilateral but stronger in the left hemisphere, with primary sensorimotor activations entirely left lateralized, as expected for right-handed subjects moving their right hand only. Precuneus (medial parietal) activations extended bilaterally from the posterior end of the cingulate sulcus through to the parieto-occipital sulcus (POS), and continued into the cuneus.

Saccades activated a fronto-parietal network of brain regions which partly overlapped with reaching activations (Fig. 2a, middle row). Saccade activations were bilateral and included the frontal and supplementary eye fields (superior frontal sulcus/gyrus), the inferior precentral sulcus/gyrus, the intraparietal sulcus and superior parietal gyrus (parietal eye fields), and the occipital cortex, including V1, the cuneus, lingual gyrus, and superior occipital gyrus. The right inferior central sulcus was also more active for saccades compared to baseline, corresponding to the sensorimotor eye representation. The precuneus was weakly activated by saccades in the left hemisphere (activations survived a threshold for  $p < 0.05$ , corrected, but did not survive at  $p < 0.01$ , corrected; Fig. 2a, middle row, shows the weaker threshold). Saccade activations were stronger in the right than in the left precuneus.

To identify reach-dominant areas, we subtracted saccade-related activations from visual direct reaching activations (Fig. 2a, bottom row). A number of regions were significantly more active for visual reaching than for saccades ( $p < 0.05$ ,

corrected), including dorsal premotor cortex, the inferior precentral gyrus, primary sensorimotor cortex, supplementary motor cortex, the cingulate sulcus and gyrus, the posterior parietal lobe (including IPS, the superior parietal lobule, inferior parietal cortex, the supramarginal gyrus), and middle occipital areas (MT+).

Our hypothesis was that a possible human homologue of the macaque parietal reach region, located on the medial surface of the parietal lobe, would also be more active during visual reaching than during saccades. Indeed, visual direct reaching activated the precuneus and the superior parieto-occipital sulcus significantly more strongly than saccades (Fig. 2a thresholds activations at  $p < 0.05$ , corrected, but precuneus activations survived even at  $p < 0.001$ , corrected). Visual reaching also activated the dorsomedial aspect of the occipital lobe (cuneus) more than saccades (Fig. 2a, bottom row, medial view). Compared to reaching, saccades activated V1 more strongly. This was expected, as saccades resulted in foveating the visual targets, whereas reaching in the visual periphery provided no foveal visual input. In addition, the right inferior central sulcus was more active for saccades than for reaching. Fig. 2b shows the time course and percent signal change of BOLD responses for visual direct reaching and for saccades in the left precuneus. Percent signal change in the left precuneus was significantly greater for visual reaching than for saccades ( $t(9)=3.34$ , two-tailed  $p = 0.008$ ).

Experiment 2: Execution of non-visual indirect reaching compared to saccades or fixation.

To identify brain regions that respond to execution of non-visual reaching, e.g. reaching out of sight, we carried out a second fMRI experiment in which reaching was performed on a plate. The plate was shifted to the right side of the subject and was blocked from view. Targets were displayed visually on a screen in front of the subject, as before, but instead of reaching directly to the targets, subjects reached indirectly from the center of the plate towards corresponding locations on the plate (Fig. 1c). Saccades were executed to the visual targets as before.

As Fig. 3a shows, non-visual, indirect reaching activated a similar fronto-parietal network as visual, direct reaching in experiment 1 ( $p < 0.05$ , corrected), which included the intraparietal sulcus, superior parietal cortex, and the precuneus. Activations were stronger in the left hemisphere than in the right. In contrast to visual direct reaching, non-visual indirect reaching did not activate V1, confirming that subjects could not see their hand during the reach on the plate. Fig. 3a (top row, center) shows that non-visual, indirect reaching did also activate the superior part of the parieto-occipital sulcus (see arrows), although qualitatively less strongly than visual reaching (experiment 1, Fig. 2a). Saccade activations (Fig. 3a, middle row) were almost identical to experiment 1, including frontal and parietal eye fields, and occipital areas. Saccades also activated the superior aspect of the POS (sPOS), but not the anterior part of the left precuneus. Saccades weakly activated the right precuneus.

To identify non-visual reach-dominant regions on the medial parietal surface, we subtracted saccade activations from non-visual reach activations (Fig. 3a, bottom row). A precuneus region, anterior to the POS and posterior to the cingulate sulcus, was significantly more active during non-visual reaching than during saccades ( $p < 0.05$ , corrected; Fig. 3a, bottom row, center). This difference was stronger in the left hemisphere than in the right, i.e. contralateral to the right reaching hand. This region overlapped with the medial parietal reach region identified in experiment 1, although its extent was somewhat reduced, including only the anterior portion of the precuneus. We refer to this region as aPRR (anterior precuneus reach region).

Thus in experiments 1 and 2 both visual and non-visual reaching activated aPRR. In contrast, the sPOS activation did not differ significantly between non-visual reaching and saccades (see arrows, Fig. 3a). Fig. 3b shows the time course and magnitude of percent signal change for non-visual reaching and saccades in left aPRR. Non-visual reaching activated the left aPRR significantly more than saccades ( $t(10)=5.62$ , two-tailed  $p=0.0002$ ). More posterior activations in the IPS and superior parietal gyrus for non-visual reaching were not significantly different from saccades, thus revealing a non-reach-specific role for those areas (Fig. 3, dorsal view). Qualitatively, activations on the medial parietal wall for non-visual reaching in experiment 2 seemed more restricted in extent than the visual reaching activations in experiment 1. This could be due to several reasons. Removing the reaching hand from sight by shifting the reach onto a plate eliminated visual feedback from the moving hand in experiment 2. However, reaching movements in experiment 1 were performed



in a vertical plane, whereas the movements in experiment 2 were performed horizontally on a plate, and not directly towards visual targets. This may have contributed to the more restricted non-visual reaching activation in experiment 2. We addressed this issue in experiment 3.

Experiment 3: visual and non-visual direct reaching to targets compared to saccades or fixation.

Experiment 3 made use of very dim fiber-optic targets arranged in front of the subject (Fig. 1b, d), with reaching performed either in darkness or light. Subjects reached from below towards the dim targets, without moving the hand on top of the targets, so that no visual feedback could be gained from obstructing the light source. All subjects confirmed that they could not see their hand in the non-visual condition. During the visual reach condition, a bright fiber-optic light taped to the ceiling of the scanner bore illuminated the subject's moving hand. This allowed for a direct comparison of visual direct reaching with non-visual direct reaching to the same targets, in the same reach plane.

Fig. 4 shows group-average activations ( $p < 0.05$ , corrected) for visual direct reaching, non-visual direct reaching, and saccades, versus fixation. Both kinds of reaching elicited a very similar pattern of fronto-parietal activations compared to baseline, including dorsal and medial premotor, primary sensorimotor, intraparietal and superior parietal activations. This pattern was qualitatively very similar to the reaching pattern in experiments 1 and 2. As shown in the central panel of Fig. 4, the

anterior precuneus reach region (aPRR) was bilaterally activated by both visual and non-visual reaching. Both visual and non-visual reaching, as well as saccades, activated the superior aspect of the POS bilaterally, with stronger activations for visual reaching. As expected, visual reaching and saccades strongly activated area V1, the lingual gyrus, precuneus, lateral and superior occipital gyri. Occipital activations during non-visual reaching were greatly reduced medially compared to visual reaching, and did not extend into the calcarine sulcus or lingual gyrus. A certain amount of occipital activation during non-visual reaching was expected, as the fiber-optic targets provided visual stimulation even when the hand did not. A posterior region of the lateral occipital gyrus (including MT+; Fig. 4, dorsal and posterior views) was activated during non-visual reaching as well as during visual reaching, consistent with tactile input to parts of MT+ (MST; Beauchamp et al., 2007); this region may also represent the extrastriate body area, which responds to hand movement (Astafiev et al., 2004). Saccades elicited a pattern of fronto-parietal activations almost identical to experiments 1 and 2. Saccades also activated aPRR bilaterally, although weakly (Fig. 4, bottom center).

Fig. 5a shows direct contrasts between visual reaching and saccades (top row); non-visual reaching and saccades (middle); and visual and non-visual reaching (bottom). Visual and non-visual reaching both activated the same aPRR area bilaterally more than saccades, as in experiments 1 and 2. Analysis of more stringent thresholds ( $p < 0.001$ ; not shown) revealed that aPRR activations for non-visual reaching versus saccades were stronger in the left hemisphere than the right; i.e.,

contralateral to the moving hand. Visual reaching also activated the medial occipital lobe and superior POS more strongly than saccades ( $p < 0.05$ , corrected) (Fig. 5a, top). In contrast, sPOS activations did not differ significantly between non-visual reaching and saccades (Fig. 5a, middle, see arrows). Occipital activations were stronger for saccades than for non-visual reaching, as expected, especially in the right hemisphere (Fig. 5a, middle row, right). Both visual and non-visual reaching activated the dorsal and supplementary premotor cortex, primary sensorimotor and secondary somatosensory cortices, and anterior intraparietal cortex (AIP) more than saccades. Activations in the posterior IPS and in much of the superior parietal gyrus were not significantly different between non-visual reaching and saccades, revealing non-reach-specific roles.

A direct comparison between visual and non-visual reaching activations in aPRR shows no significant difference, bilaterally (Fig. 5a, bottom row). To confirm that our statistical correction was not overly stringent, we also compared visual and non-visual reaching activations at the uncorrected 0.05 level, which still yielded no difference in aPRR. Fig. 5b shows the time course and magnitude of percent signal change for visual and non-visual reaching and for saccades in the left aPRR ROI. Percent signal change in BOLD signals for visual and non-visual reaching in aPRR did not differ significantly ( $t(7) = 0.44$ , n.s.). The magnitude of BOLD signal change in aPRR was significantly less for saccades than either for visual reaching ( $t(7)=6.98$ , two-tailed  $p = 0.0004$ ) or for non-visual reaching ( $t(7) = 3.61$ , two-tailed  $p = 0.01$ ). In contrast to aPRR, the superior POS was activated more by visual than by non-visual

reaching (black arrows in Fig. 5a, bottom row, center), with greater activation in the right hemisphere. Fig. 5c shows the percent signal change in the left sPOS for visual and non-visual reaching and for saccades. Percent signal change in BOLD signals in the left sPOS was significantly greater for visual reaching than for non-visual reaching ( $t(7)=3.34$ , two-tailed  $p=0.01$ ) and than for saccades ( $t(7)=3.71$ , two-tailed  $p=0.004$ ). Non-visual reaching and saccade percent signal change did not differ in the left sPOS ( $t(7) = -1.41$ , n.s.). This pattern is consistent with sPOS having a largely visuomotor role, and aPRR a predominantly proprioceptive-motor role, in reaching. Table 1 shows the average x y z coordinates for the two ROIs from Experiment 3.

In addition to sPOS, visual and non-visual reaching (Fig. 5a, bottom) differed in the occipital lobe, with the cuneus, calcarine sulcus, lingual gyrus, superior and lateral occipital gyri (including MT+) being significantly more active during visual direct reaching than during non-visual direct reaching ( $p < 0.05$ , corrected). This is consistent with the greater visual stimulation provided by the visual reach than the non-visual reach. Also, visual reaching weakly activated an area medial of the left IPS just anterior to the parieto-occipital junction (Fig. 5a, bottom row, dorsal and posterior views) more than non-visual reaching. This difference did not survive  $p < 0.01$ , corrected. Since that region was activated equally for saccades, it likely represents an effector-independent visual representation of visual stimuli (whether a hand or other stimulus). Note that the frontal eye fields (FEF) were equally active for both visual and non-visual reaching, thus arguing against the possibility of more eye movement during visual reaching than non-visual reaching.

Fig. 6 shows activations ( $p < 0.0001$ , corrected) from 3 representative subjects from experiment 3. Every subject showed significantly greater activation in aPRR for visual and non-visual reaching compared to saccades, bilaterally. Fig. 6 also shows greater sPOS activation for visual versus non-visual reaching.

Experiment 3 thus shows that aPRR was activated equally whether there was visual feedback from a reaching hand or not. The superior POS, on the other hand, responded more during reaching with visual feedback than with no visual feedback. Whereas the extent of aPRR activations for reaching in experiments 1 and 2 seemed to differ qualitatively, this could have been an effect of the different plane of movement in experiment 2. Experiment 3 compared direct reaching movements, both executed in the vertical plane, in the presence or absence of visual stimulation from the hand. When the reaching movement was held constant, aPRR responded equally strongly during visual and non-visual reaching. This suggests a proprioceptive input from the moving arm in aPRR. sPOS, by contrast, is likely involved in the visual monitoring of online reaching, or in calculating visual distance of an effector from the target.

## Discussion

The present three experiments were designed to identify the sources of sensory input to human medial parietal reach regions during direct, non-delayed, reaching movements that were either visible or non-visible to subjects.

Based on the macaque literature on reaching, we hypothesized that homologous reach-dominant areas (activated more strongly by reaching than by saccades) would be located in medial aspects of the posterior parietal lobe. We found an anterior medial parietal area that responded significantly more to visual and non-visual reaches than to saccades. This area was located in the anterior precuneus (BA 7 medial) (Figs. 2-6). We refer to this region as the anterior precuneus reach region (aPRR). Its involvement in guiding reaching in the absence of visual feedback suggests proprioceptive input during the transport phase of the reach.

A second, more posterior area, located at the parieto-occipital junction at the superior POS (BA 7, medial and lateral), was more active during visual than non-visual reaches. This sPOS area was also modulated by saccades, suggesting that it is less effector-dominant than aPRR and may be involved in monitoring the visual distance of more than one type of effector to the target. Visual reaching activated the sPOS more than saccades or non-visual reaching, perhaps because it is easier to perceive the distance between a visible effector (the hand) to a visual target than between the eye and the target. This suggests the sPOS processes visual feedback from the hand during online reaching.

Activations to reaching additionally included a wide network of dorsal parieto-frontal activations, in agreement with previous reports on reaching (Filimon et al., 2007), reaching-to-grasp (Grafton et al., 1996; Culham et al., 2003, in press), reaching-to-point (Levy et al., 2007; PelliJeff et al., 2006) and pointing (Hagler et al., 2007; Astafiev et al., 2003, 2004; Simon et al., 2002; Connolly et al., 2000; 2003; Fernandez-Ruiz et al., 2007). Saccades activated a subset of these frontal and parietal areas, consistent with previous saccade studies (Sereno et al., 2001; Culham et al., 1998; Koyama et al., 2004; Simon et al., 2002; Connolly et al., 2000). Our study shows differential contributions of medial parietal areas (aPRR and sPOS) to reaching.

#### Area aPRR

Both visual and non-visual reaching activated aPRR. In our study, movements towards targets were executed immediately, allowing no time for planning. Reach-related activations were stronger in left aPRR (contralateral to the moving arm), surviving higher thresholds than the right aPRR, especially in non-visual plate reaching (Fig. 3a), supporting a proprioceptive role. This is consistent with deficits observed in patients with left parietal damage, which include optic ataxia or contralateral proprioceptive impairments (Wolpert et al., 1998; Perenin and Vighetto, 1988). Here, we tested right-handed reaching in right-handed subjects. It is possible that the lateralization would change in left-handed subjects.

In our experiments, the targets were always presented visually. Hence we manipulated the visual presence or absence of the hand, not of the targets. The common visual and non-visual reaching activation in aPRR could be due to the

visually-presented targets, rather than to proprioceptive feedback from the hand. To dissociate the influence of external visual targets from proprioceptive feedback, targets would have to be defined non-visually. In fact, Pellijeff et al. (2006) found that reaching to posturally-defined targets with eyes closed also leads to aPRR activation. Subjects reached-to-point with eyes closed to the contralateral thumb or the chin, with the end-location of the target or the starting location of the reaching hand varying. Anterior precuneus activations were greater during the first reach following a postural change, e.g. after either the starting hand location or the target end location had just changed, than in subsequent reaches. The increased activation following a postural adjustment, as well as the absence of any visual input in Pellijeff et al.'s study, strongly suggest a proprioceptive input to aPRR. Preliminary results from our lab on spatially non-directed arm movements, with eyes closed, also show contralateral aPRR activation. Interestingly, passive vibrotactile stimulation of the hand also activates the precuneus (Beauchamp et al., 2007), suggesting a tactile input in addition to a proprioceptive input. Regardless of the respective roles played by the visual target or by proprioception, the present study shows that *visual feedback from the hand* did not significantly modulate activations in the contralateral aPRR.

The question arises as to whether aPRR may simply represent a purely somatosensory area, rather than also playing a motor role. Supplemental Fig. S1 shows highly significant aPRR activations during imagery of reaching in the absence of proprioceptive input, from a separate experiment (see also Filimon et al., 2007). Imagery of reaching strongly activated aPRR while not activating primary sensory and



motor cortices or visual cortex. This suggests that motor imagery is a form of motor preparation (rather than of visual imagery) and implies a motor role in addition to a sensory role for aPRR. This is consistent with previous studies of hand movement planning, which also activates aPRR despite the absence of proprioceptive feedback (e.g. Astafiev et al., 2003).

Note that passive observation of reaching can also activate aPRR (Filimon et al., 2007). However, precuneus activations for both observation and imagery are weaker than for actual movement, consistent with the greater proprioceptive role. Motor imagery also shows a trend of greater activation in aPRR than does observation of reaching, consistent with aPRR's motor role. This suggests that aPRR may have multiple populations of neurons, some of which are visuomotor, but the majority of which are proprioceptive-motor. The different degrees of aPRR activation in various tasks suggest multiple sensorimotor representations in aPRR. The fact that the present study showed equal aPRR activation for visual and non-visual reaching points to a predominantly proprioceptive-motor representation.

aPRR may represent a human homologue of macaque areas 5 and MIP, which overlap with macaque PRR (Snyder et al., 1997). Another possibility is that aPRR corresponds to macaque PEc, which is located in a similar location in macaques (anterior to POS and V6A), and which responds to joint rotations as well as reaching movements (Breveglieri et al., 2006). PEc neurons respond to postural changes, passively induced or not, suggesting a role in proprioceptive processing during reaching movements (Breveglieri et al.).

## Superior POS

The more posterior activation (sPOS) could, conversely, represent both the location of the visual *target* relative to the visuomotor trajectory, as well as the visual distance from the hand or eye to the target. Visual direct reaching, non-visual direct reaching, and saccades activated the sPOS region bilaterally, although to different degrees. sPOS activations were significantly stronger for visual reaching than for non-visual reaching or saccades. This suggests that the sPOS plays a role in visual monitoring of how far the limb is from the target location, which is dependent on visual feedback. However, non-visual reaching also activated the sPOS region, even though no visual feedback was present. This suggests that the retinal location of the target is also represented, relative to the fovea, in sPOS, as indeed found by Prado et al. (2005). Prado et al. found that the parieto-occipital junction (POJ) was activated during non-visual reaching to peripheral, but not central, targets. POJ activation increased when the target was peripheral rather than foveal. In the present study, both visual and non-visual reaches were made to peripheral targets, with central fixation. Hence involvement of the POJ in our study in both visual and non-visual reaching is consistent with its proposed role in peripheral reaching. Our results suggest that peripheral reaching with visual feedback from the hand leads to greater activation in the POJ than does peripheral reaching without visual feedback, perhaps because the retinal locations of the hand and target are compared.

Additional data on area sPOS from a separate experiment are presented in Supplemental Fig. 1 (S1), which demonstrates that sPOS is not a purely visual area,

but has motor properties as well (see also Filimon et al., 2007). The left sPOS responds very strongly during imagined reaches with the right hand, in the absence of any visual input from the hand. Visual cortex is not activated during reaching imagery, suggesting motor imagery is not visual imagery of a moving hand. This suggests the left sPOS is involved in motor planning. The same area also responds during executed visual reaches, while responding more weakly during passive observation of a moving right hand. The right sPOS, on the other hand, responds more strongly during observation of reaching than imagery of reaching. This could indicate hemispheric differences, with the left sPOS being more motor than the right sPOS, although the pattern could reverse with left-handed reach imagery. These data show that the left sPOS plays a visuomotor role in reaching, and not just a visual role. This is consistent with the present study's finding that non-visual reaching also activates the sPOS, albeit less strongly than visual reaching.

Note that any additional visual stimulation not pertaining to the hand, in the visual condition of Experiment 3, is unlikely to have affected either aPRR or the left sPOS, since both show robust responses to imagery of reaching, when no additional visual stimulation is present. Also, aPRR showed equal activation in the visual and non-visual reach conditions.

Studies of pointing have revealed similar activations anterior to and around the sPOS (Connolly et al., 2003; Fernandez-Ruiz et al., 2007). The sPOS appears to encode planned pointing movements according to the visual location of the target, rather than according to the actual movement direction (Fernandez-Ruiz et al.). Using

reversing prisms, leftward (visible) pointing movements to visual targets on the right appeared rightward, and vice-versa. The sPOS was active when the visually perceived pointing movement matched the visual target location (i.e. a leftward movement that appeared rightward towards a rightward target), instead of being modulated by the actual muscle activation plan (Fernandez-Ruiz et al.). This suggests that the sPOS encodes targets and movement plans in eye-centered coordinates. Consistent with a role in visually-guided reaching, the dorsal POS exhibits a preference for targets in near-space that can be acted upon, rather than for far-away targets (Quinlan and Culham, 2007; Culham et al., in press). This also suggests that sPOS does not passively represent visual information, but instead contains sensorimotor representations for action.

The sPOS region may represent a homologue of macaque V6A, in which neurons are modulated by visual feedback during reaching (Fattori et al., 2001).

### Reaching versus Pointing

In preliminary tests, we have found that the precuneus is less activated by finger movements than by arm movements, with finger activations shifting more laterally. This is consistent with the idea that the superior precuneus contains more neurons representing the arm, thus being more active during arm compared to finger movements. It is thus possible that studies of finger pointing are not a realistic approximation of reaching as done in macaques. This also suggests that pointing ‘PRRs’ may be in somewhat different locations than parietal reach regions for actual reaching. For instance, some pointing studies have labeled sPOS activations as ‘PRR’

(Connolly et al., 2003). The amount of precuneus activation may depend on how much of the hand or arm is moved during pointing. Thus, our greater precuneus activations for reaching than for saccades are consistent with pointing studies in which the wrist (Astafiev et al., 2003) or forearm (Levy et al., 2007) were moved. In contrast, studies of only index finger movement found no difference between pointing and saccade activations in the precuneus (e.g. Hagler et al., 2007). Thus while both pointing and reaching activate the precuneus, it is plausible that reaching leads to stronger precuneus activations than pointing. Note also that to identify all reach-dominant areas it is important to include non-topographical reach activations as well. Macaque *eye-centered* reach neurons do not necessarily imply a *retinotopic* or *topographic* (map-like) arrangement of those neurons. An individual neuron may represent reaches in eye-centered coordinates while being part of a scrambled map of space across all neurons in an area. Our study suggests that overall, reaching activates aPRR significantly more strongly than saccades.

Although we focused on the medial parietal surface to identify reach-dominant areas, other parietal regions were also more active for reaching than for saccades (Figs. 3a, bottom row, and 5a, middle row). These were located in the anterior intraparietal sulcus as well as more laterally in the supramarginal gyrus. These regions likely represent human homologues of other macaque regions, such as area AIP (e.g. Culham et al., 2003, 2006), area 7a, and 7b (Culham and Kanwisher, 2001), which may have been activated by sensory stimulation from the hand. Human homologues for areas involved in arm, rather than hand movements, however, have been proposed

in more medial locations, such as the precuneus or medially of the IPS (Astafiev et al., 2003). The present study confirms the involvement of medial parietal cortex in reaching, and identifies functional differences between more anterior and more posterior regions.

#### aPRR and attention

The precuneus has been previously shown to also respond during increased levels of attention (Beauchamp et al., 2001). This is consistent with attentional modulation in parietal neurons (e.g. in V6A, Galletti et al., 2003). The question arises whether our aPRR reaching activation might be due to greater attention during either type of reaching compared to saccades. This is unlikely for several reasons. First, the precuneus is activated less by covert (non-eye movement) attention than by hand movements (Astafiev et al., 2003). Second, covert attentional shifts activate the precuneus less than overt attentional shifts (when saccades *are* executed) (Beauchamp et al., 2001). In our study, saccades activated aPRR significantly less than reaching, suggesting that attention without a saccade should lead to even weaker activations in aPRR. Finally, studies in macaque PRR have shown that when a target is briefly flashed and attended, the neuronal delay activity reflects the intended hand, rather than eye, movement (Snyder et al., 1997). This effector-specificity suggests that the predominant information being coded pertains to the planned movement, rather than to stimulus attention. In additional tests we found that slow continuous arm, but not finger or non-directional hand movements, activate aPRR with eyes closed, again ruling out greater attention to a continuously moving limb as the source of activation

in aPRR. Thus the aPRR activations found in our study most likely reflect the execution of reaching movements rather than nonspecific spatial attention.

The term ‘parietal reach region’ has been used loosely in the literature, with areas from the sPOS to the cingulate sulcus all termed ‘PRR’. Our results suggest that multiple, functionally distinct posterior parietal sub-regions participate in different aspects of reaching in humans.

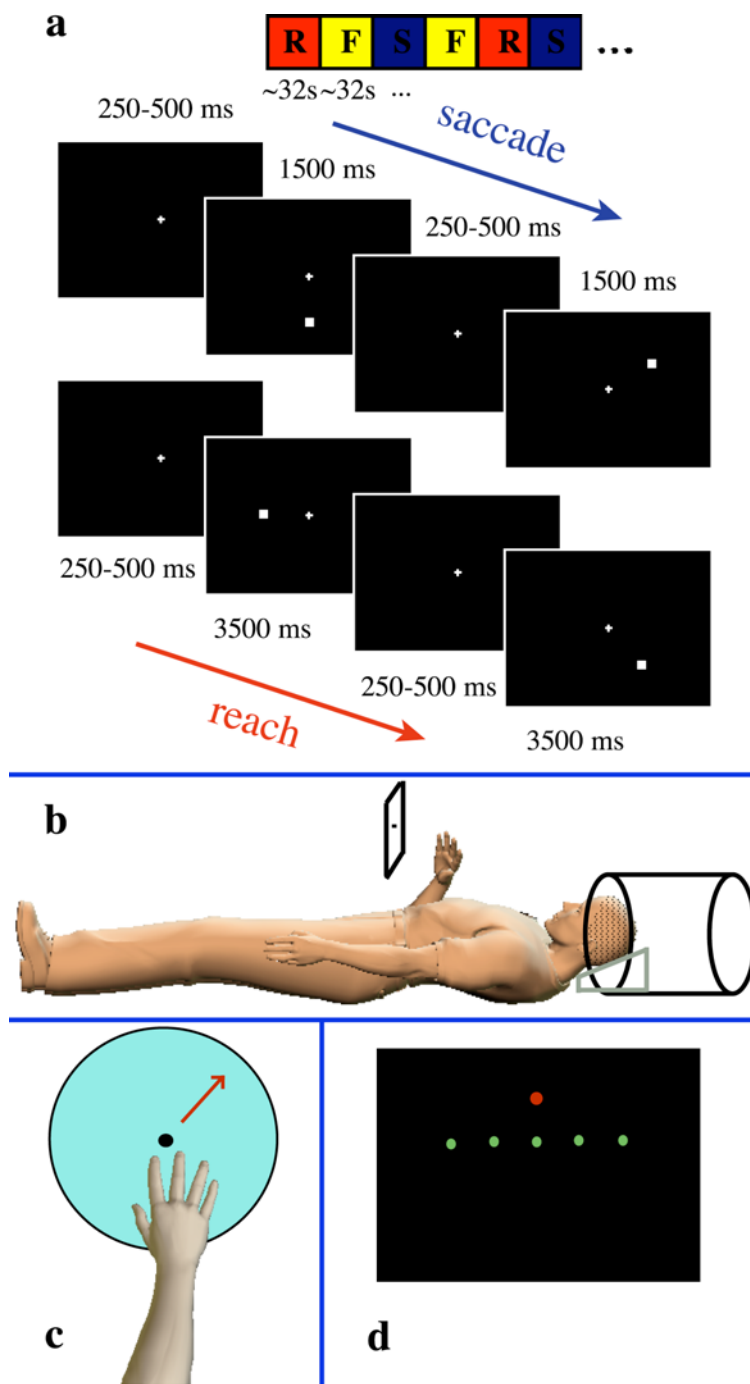
### **Acknowledgment**

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**Fig. 1. Stimuli and experimental design**

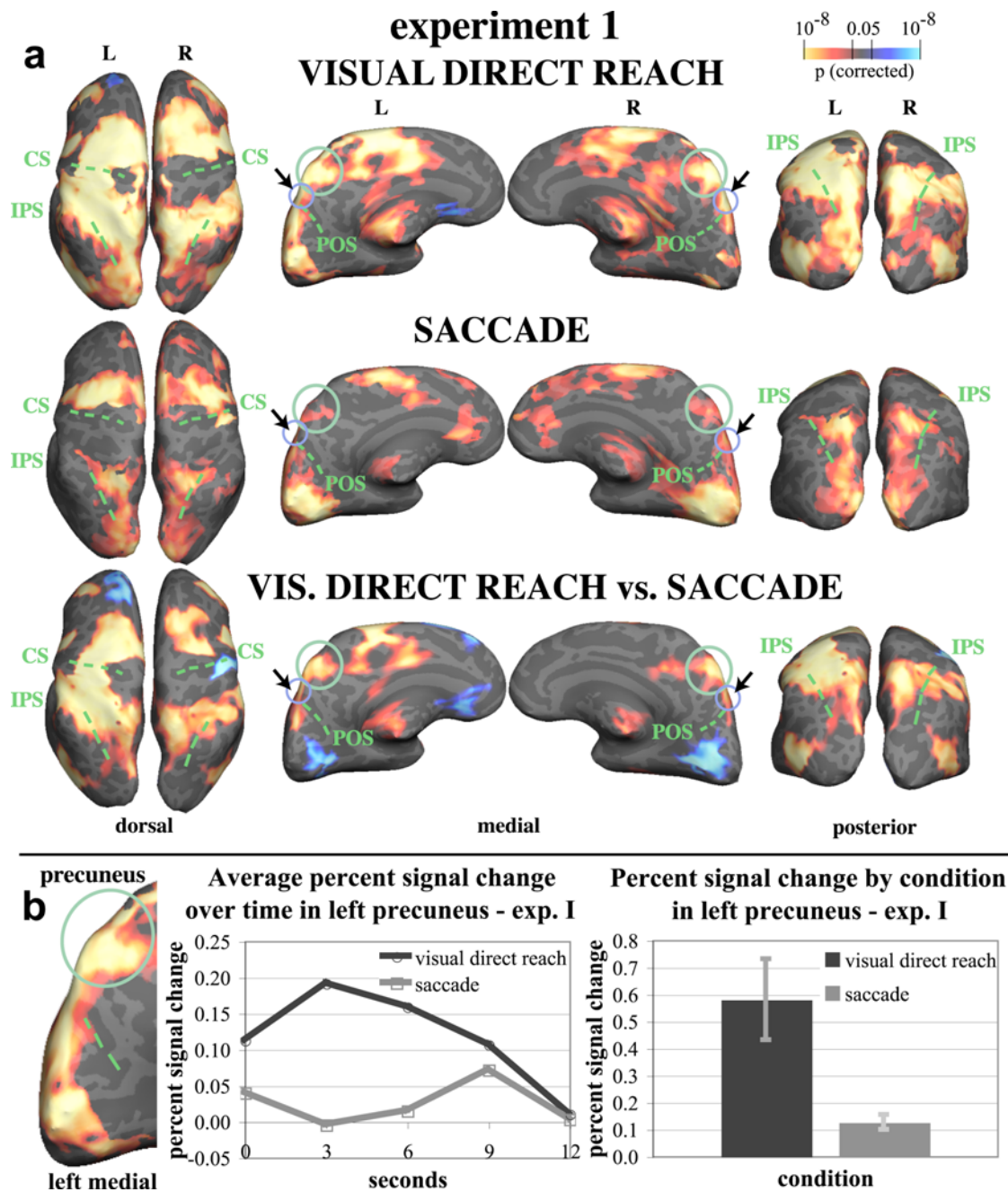
(a) Two reach and two saccade trials illustrating target presentation around a central fixation cross in experiments 1 and 2. A random order of blocks of reaching (R), fixate (F), and saccade (S) trials was used. (b) Subject positioning inside the scanner for all 3 experiments. Subjects lay supine with the head tilted forward for a direct view of the screen. Subjects moved the hand directly towards the screen while fixating in the center in experiments 1 and 3. (c) Reaching as performed in experiment 2. Subjects moved their hand from the center of a plate hidden from view towards locations that corresponded to the visual target locations. (d) Stimulus presentation in experiment 3. A red fiberoptic target served as a fixation point. On a given reach or saccade trial, one of five possible target reach or saccade locations would appear in green.





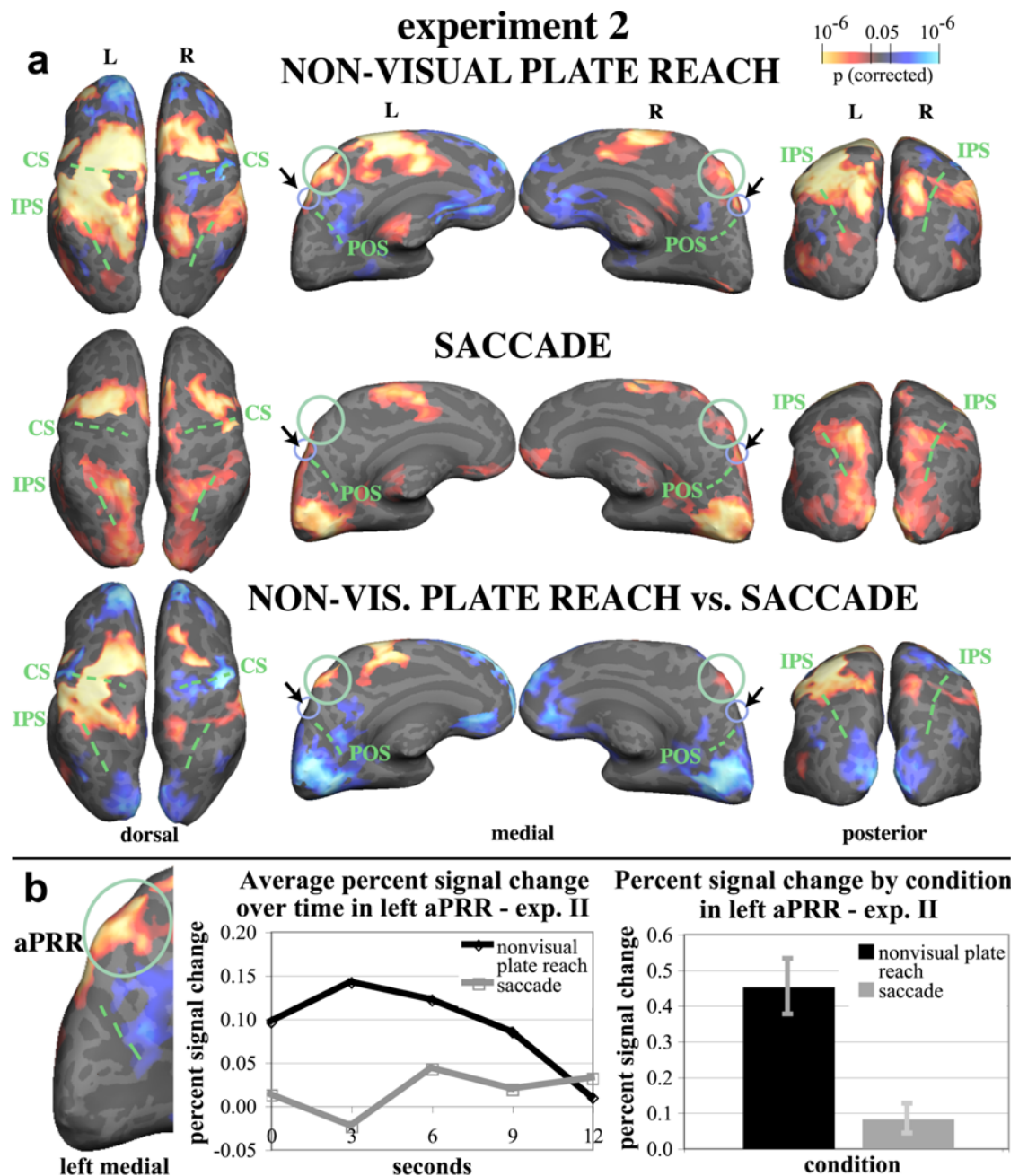
**Fig. 2. BOLD activations for visual direct reaching, saccades, and visual direct reaching versus saccades**

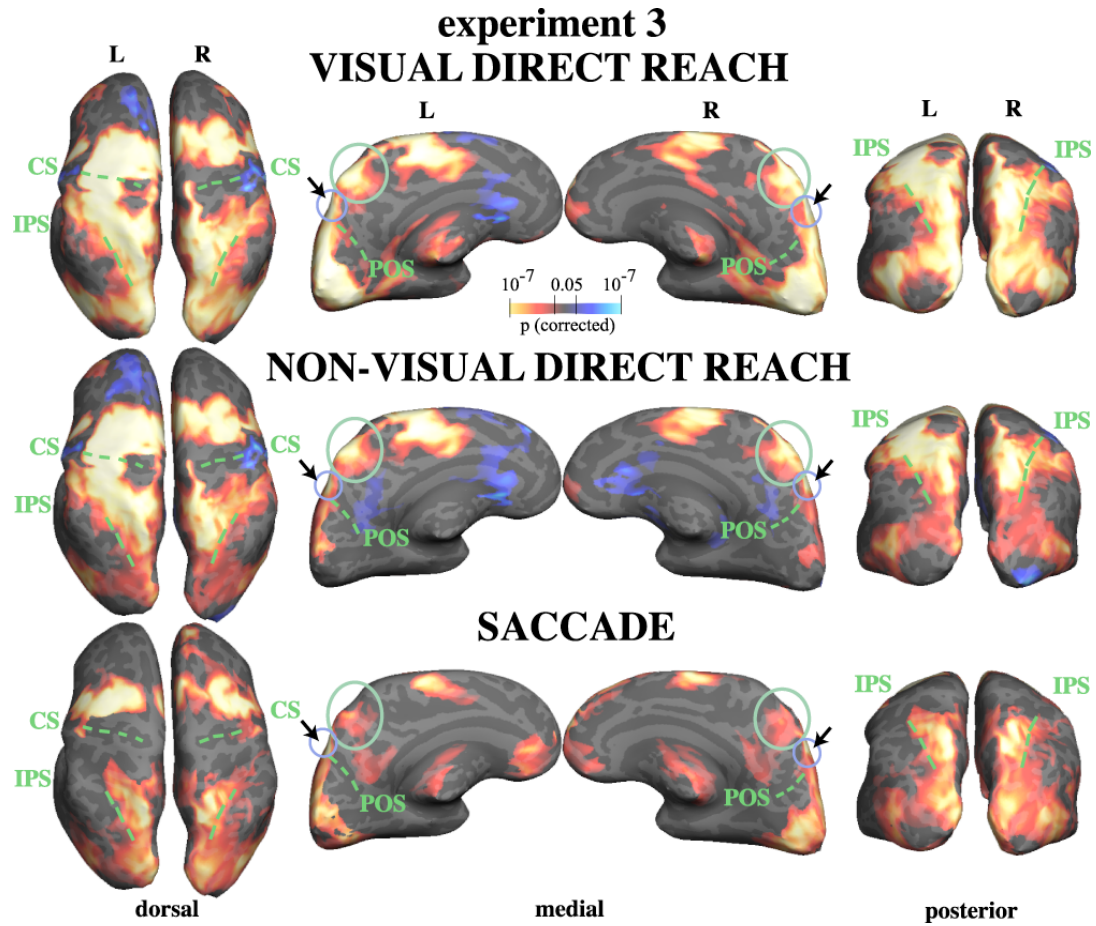
(a). Group surface-averaged activations (n=10) for visual reaching and saccades versus baseline and versus each other from experiment 1 are shown on dorsal, medial, and posterior views of the left and right inflated cortical hemispheres. Activations on the medial surface of the parietal lobe are circled in green. Note the greater activations for visual direct reaching compared to saccades. Activations around the parieto-occipital sulcus are marked with a black arrow and a purple-blue circle. Red to yellow indicates greater activation for reaching than for saccades; blue to light-blue indicates greater saccade than reach activation, in the versus comparison. (b). Average percent signal time course from the left precuneus ROI (left) and relative percent signal change (right) for visual direct reaching and saccades, relative to fixation. Error bars represent the standard error of the mean. Sulci are marked with a dashed green line. CS = central sulcus, IPS = intraparietal sulcus, POS = parieto-occipital sulcus, L = left, R = right.



**Fig. 3. BOLD activations for non-visual plate reaching, saccades, and non-visual plate reaching versus saccades**

(a) Group surface-averaged activations (n=11) from experiment 2 for non-visual plate reaching and saccades, compared to baseline and with each other. Medial parietal activations anterior to the parieto-occipital sulcus (POS) and posterior to the cingulate sulcus are circled in green, as before. Black arrows and purple-blue circles indicate the superior aspect of the POS. (b) Activations in the anterior precuneus ROI are greater for non-visual plate reaching than for saccades (aPRR = anterior precuneus reach region). The time course and magnitude of percent signal change from the left aPRR ROI are shown for non-visual plate reaching and saccades, relative to fixation. Error bars represent the standard error of the mean.





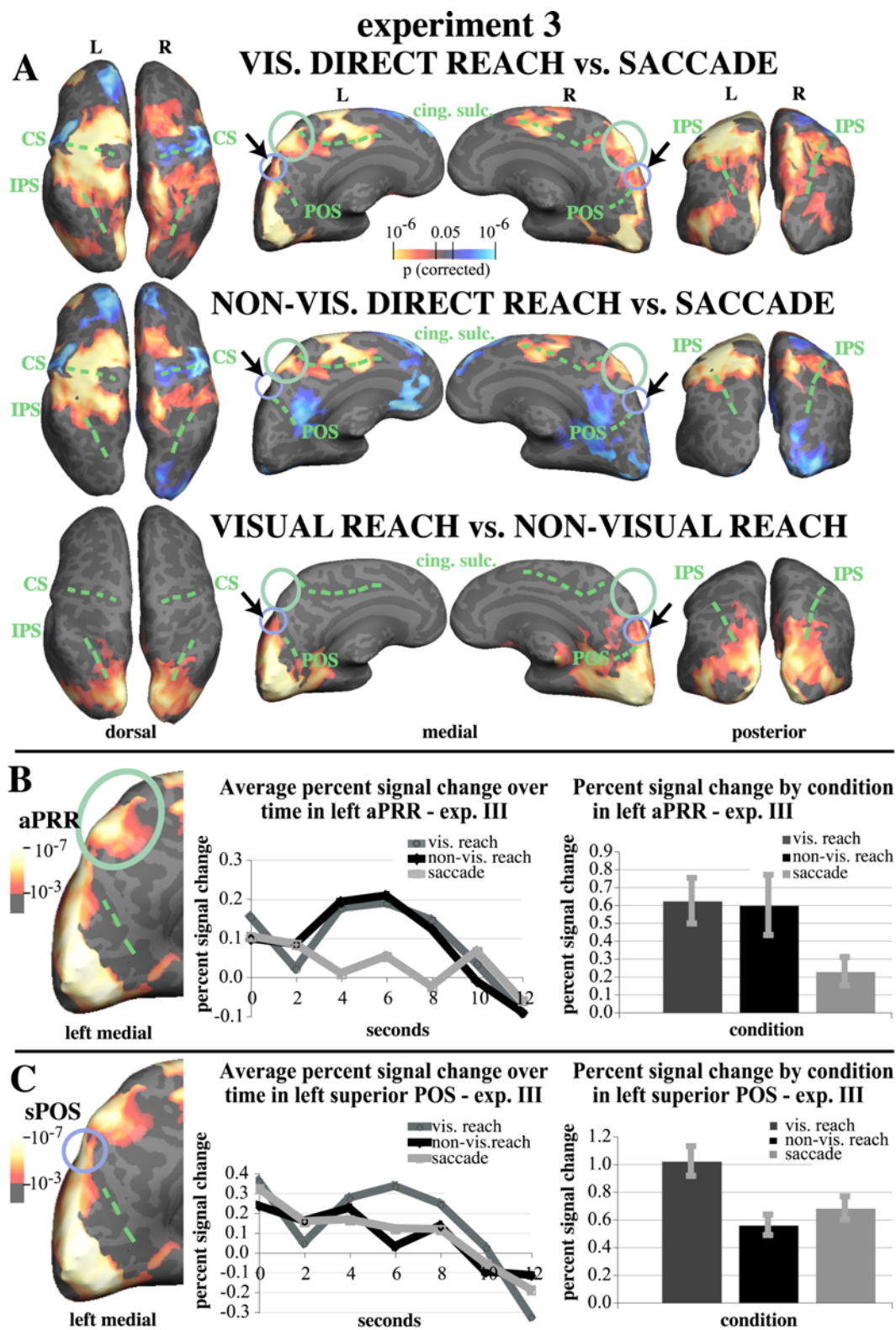
**Fig. 4. BOLD activations for visual direct reaching, non-visual direct reaching, and saccades**

Group surface-averaged activations ( $n=8$ ) for visual and non-visual direct reaching and saccades, versus baseline, from experiment 3. Note the similarity in activation between visual and non-visual direct reaching in the green-circled anterior precuneus region (medial view). Saccade activations in the same precuneus ROI are much weaker. Visual direct reaching also activates the sPOS (see arrows) more strongly than saccades or non-visual direct reaching.

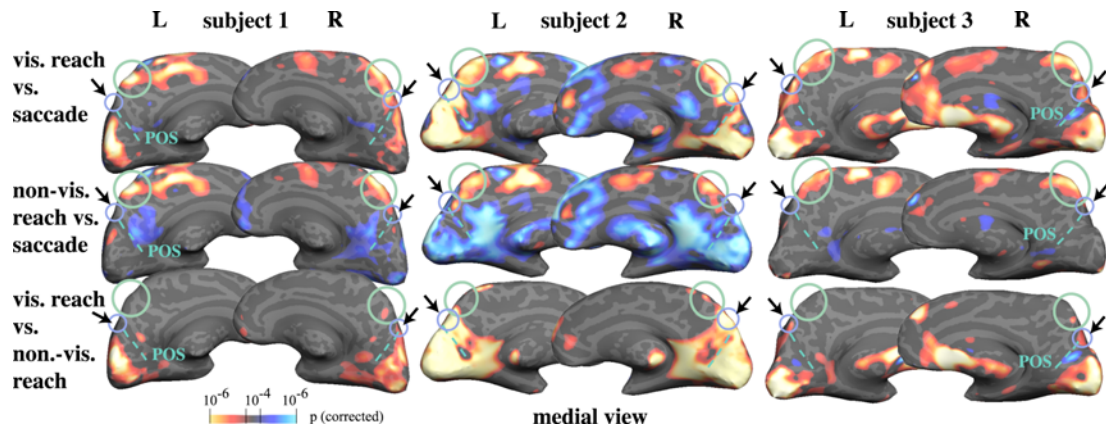
**Fig. 5. Contrasts between activations for visual direct reaching and saccades, non-visual direct reaching and saccades, and visual and non-visual direct reaching**

(a) Contrasts from experiment 3. Note the lack of difference between visual and non-visual direct reaching in aPRR, circled in green (bottom row, medial view). The superior POS is indicated with a black arrow and a purple-blue circle. Note the increased activation for visual direct reaching compared to non-visual direct reaching in the POS region. (b) Percent signal change time course (left) and magnitude (right) in left aPRR for visual direct reaching, non-visual direct reaching, and saccades, compared to baseline. Visual and non-visual direct reaching activations are not significantly different in aPRR and exhibit a similar time course. Both kinds of reaching were significantly different from saccades in left aPRR ( $p < 0.05$ , corrected). (c) Percent signal change time course (left) and magnitude (right) in the left sPOS (superior POS) for visual and non-visual reaching, and saccades. Visual reaching activates the sPOS more than either non-visual reaching ( $p = 0.01$ ) or saccades ( $p = 0.004$ ). Error bars in 5b and 5c indicate the standard error of the mean. Activations to the left of graphs show visual direct reach versus baseline ( $p < 0.001$ , corrected).







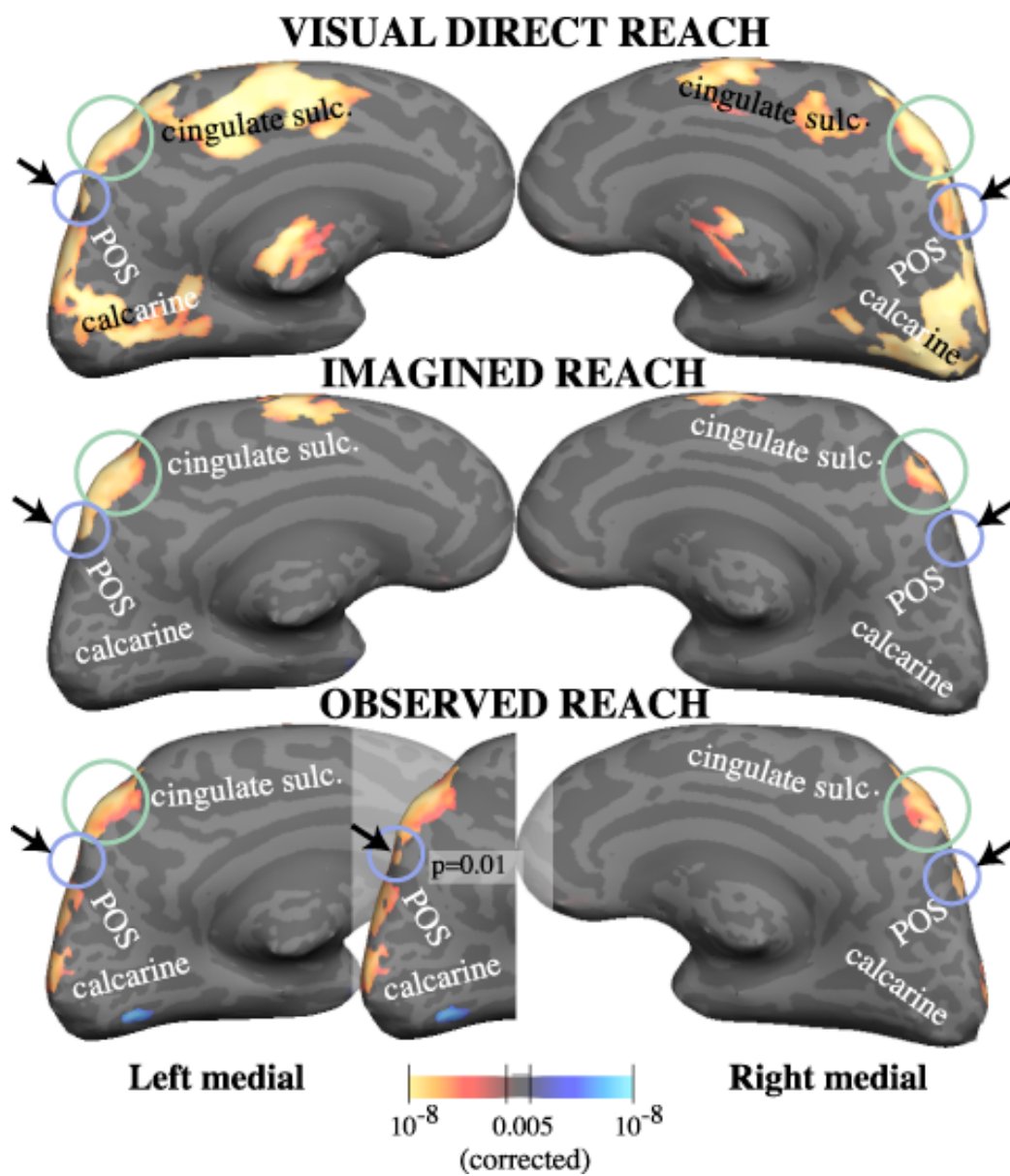


**Fig. 6. Individual data for visual direct reaching versus saccades, non-visual direct reaching versus saccades, and visual versus non-visual direct reaching**

Differences in BOLD responses from three individual subjects from experiment 3. All subjects exhibited greater activations for either type of reach compared to saccades in aPRR (circled in green). Subjects showed variability in the location and amount of superior POS activation in the visual direct versus non-visual direct reach comparison (see arrows). Visual direct reaching compared to saccades (top row) activated the POS region more than non-visual direct reaching compared to saccades (middle row) in 7 out of 8 subjects.

**Fig. S1. Group surface-averaged BOLD activations of 15 subjects from a separate experiment on execution, imagery, and observation of right-hand reaching**

See Filimon et al. (2007). The superior parieto-occipital sulcus (POS) is circled in purple-blue (see arrows), while the anterior precuneus is circled in light green, on the inflated left and right hemispheres, medial view. Note that the left sPOS is strongly activated by imagined reaching and execution of visual reaching, but less strongly by passive observation of reaching (inset). This suggests a visuomotor role for the left sPOS, rather than a purely visual role. The right sPOS appears more visual, although execution of visual direct reaching, in which there is both execution and observation of one's own hand, drives the right sPOS more than passive observation of reaching (see top versus bottom rows). Note the discontinuity between left sPOS and left aPRR and between left sPOS and more posterior, visual areas, in "visual direct reach". Area aPRR (green circle) is also strongly activated by imagined reaching, especially on the left. This points to a motor role in addition to a sensory role. Note that execution of reaching drives aPRR more than reaching imagery (contrast not shown; but see Filimon et al., 2007), supporting a role for proprioceptive feedback as well.



**TABLE 1.** Average MNI-space coordinates (mm) for peak activations in the aPRR and superior POS regions of interest identified in Experiment 3.

Contrast	ROI	x	y	z	No. of sub- jects
Vis. reach > saccade	Left aPRR (anterior precuneus)	-9 ± 1.7	-54 ± 3.1	60 ± 1.2	7
	Right aPRR	11 ± 0.9	-54 ± 2.4	58 ± 2.1	7
Non-vis. reach > saccade	Left aPRR (anterior precuneus)	-11 ± 1.3	-58 ± 3.0	61 ± 1.8	7
	Right aPRR	12 ± 1.2	-57 ± 2.6	60 ± 1.8	7
Vis. reach > non-vis. reach	Left superior POS (parieto-occipital sulcus)	-9 ± 1.9	-77 ± 2.1	46 ± 1.7	6
	Right sPOS	13 ± 1.7	-78 ± 1.7	45 ± 2.8	7

*Note.* The standard error of the mean ( $\pm$ ) is indicated to the right of each x, y, and z coordinate. One of the 8 subjects had anomalous ( $> 30$  mm different) MNI coordinates and was thus excluded. All activations were at  $p < 0.001$  (corrected).

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## **Chapter 4.**

### **Shared neural substrates for tactile and visual processing of external target locations**

**Abstract**

The posterior parietal lobe plays a major role in visuospatial processes and spatial representations. The goal of the present study was to identify spatial representations of external space formed using touch alone, and to compare tactile spatial representations with visual spatial representations. We investigated the neural representations of tactile and visual processing of external target locations using fMRI. Subjects explored LEGO targets on a platform using their right hand while blindfolded, or viewed images of the same LEGO targets. Location identification in either the tactile or the visual modality activated the bilateral superior parietal lobule and the right anterior intraparietal sulcus. The common activation of these posterior parietal areas in the tactile and visual tasks suggests multisensory representations of external space.

## **Introduction**

The visual modality is the dominant sensory modality for humans. Despite our tendency to rely on sight when identifying both objects as well as locations in space, we are nonetheless able to identify objects and locations by touch alone. For instance, we are perfectly capable of reaching inside our pockets or in a cluttered bag to successfully identify our keys or press the appropriate button on a cell phone to silence it, in the absence of visual guidance.

Previous functional imaging studies have shown that in addition to activating primary sensorimotor regions, tactile object exploration and processing activates a network of frontal and parietal areas, especially the inferior parietal lobule and the parietal operculum (SII) (Stoeckel et al., 2003; Deibert et al., 1999; Reed et al., 2004; Jaencke et al., 2001). The intraparietal sulcus is also activated by tactile processing of grating orientation (Zhang et al., 2005; Van Boven et al., 2005).

Whereas several previous fMRI studies have investigated the neural substrates of tactile object processing, or of identification of the location of a grating presented on a finger (Van Boven et al., 2005), very little, by contrast, is known about how the brain processes external spatial locations by touch. Identifying the location of stimulation on the skin (e.g. Macaluso and Driver, 2001) involves monitoring the site of the body that is being touched in a somatotopic fashion. Frequently, however, we are faced with situations in which external rather than body-based spatial locations or

layouts need identified by touch, such as when searching for the light switch in the middle of the night, or when searching for the off button on an alarm clock in the absence of visual input. Instead of taking in the spatial layout using vision, such situations require haptic exploration of locations of targets and the creation of a mental spatial representation based on tactile input.

A recent study (Reed et al., 2005) investigated the neural representations of tactile object identity and tactile object localization, with tactile object identification activating a ventral pathway and tactile location processing activating superior parietal areas. While the superior parietal activations were consistent with brain regions that are also involved in visual spatial processing (Macaluso and Driver, 2001), it is not known if the same anatomical regions are involved in both tactile and visual representations of the external location of identical stimuli or if adjacent, but separate parietal regions are involved in processing tactile space versus visual space.

In the present fMRI study, we were interested in identifying brain regions involved in tactile location identification, and in finding out if the same brain regions are also involved in visual location identification. We used identical stimuli that were either presented tactually or visually, in the same scanning session. Subjects identified the location of clusters of 1-4 LEGO targets on a platform that was either touched with the right hand while subjects were blindfolded, or viewed as an image in the absence of tactile input. As a control in both tactile and visual conditions, subjects reported the number of targets while ignoring the spatial location. We show that the

same parietal regions that respond more during tactile location processing compared to tactile number processing also respond more during visual location processing compared to visual number processing.

## Methods

### Subjects

A total of 15 subjects (age 18-33, nine males) participated in two fMRI experiments: I) tactile exploration of targets on LEGO platforms with their right hand while blindfolded and II) viewing pictures of the same LEGO platforms in the absence of tactile input. Both experiments were conducted in the same scanning session. Twelve subjects participated in the Tactile Experiment and thirteen in the Visual Experiment. Ten of the subjects participated in both the Tactile and the Visual experiments. All subjects were right-handed, neurologically-intact, and had normal or corrected-to-normal vision. Human subjects' approval was obtained from UCSD's Institutional Review Board. All subjects gave informed consent.

### Stimuli and Experimental Tasks

Fig. 1 shows examples of the tactile and visual stimuli used. In the Tactile Experiment, subjects were asked to explore targets on LEGO platforms and determine either 1) the location of the target(s) on the platform (Location condition) or 2) the number of target(s) present (Number condition). Subjects were blindfolded during this experiment. Platforms were 5 x 2 inches (12.7 x 5.08 cm). LEGO platforms were presented one at a time directly underneath subjects' right hand by an experimenter located at the mouth of the scanner bore. Subjects lay supine with their right hand

located to the right side of their body. For the Location condition, clusters of targets could be located either far left, center left, center right, or far right on the platform. Each cluster of targets was composed of 1-4 targets. Subjects touched the platform with their right hand and indicated the corresponding location with their left hand on a four-button response box (left little finger through left index finger). For the Number condition, subjects indicated the number of targets in each cluster (1-4) using the same response mapping. Numbers of targets and locations of targets were independently randomized, such that for example a left little finger response for “far left” was given independent of the number of targets, and a left little finger response for “one target” was given independent of target location, in the respective conditions. A pseudo-random block order of Location and Number trials interleaved with rest blocks was used. Each block of trials lasted 30 seconds, including a 3 second auditory message instructing subjects of the condition about to begin. LEGOs were touched for 3.5 seconds each, with a 1 second inter-stimulus interval and a total of 6 trials per block. Each functional run consisted of 18 blocks of Location, Number, and Rest trials, for a total of 540 seconds (270 TRs). Subjects participated in 2-3 functional runs for the Tactile Experiment. An experimenter located at the bore of the scanner presented the LEGO platforms using a randomized sequence of target locations and numbers for each condition. Subjects were asked to ignore the number of targets when determining the location, and to ignore location while determining the number of targets. In addition to using identical stimuli for the Location and Number tasks, platforms were presented

centered under each subject's hand, such that for both conditions, subjects had to sweep their fingertips across the platform to find the targets, thereby using similar exploratory movements and obtaining similar somatosensory stimulation in both conditions. Subjects were trained on moving the hand equally for both conditions prior to scanning. To prevent head motion, a bite bar as well as head foam were used. The bite bar ensured subjects stayed in the same position for both the Tactile and Visual Experiments.

For the Visual Experiment, subjects viewed pictures of the same LEGO platforms in a mirror mounted on the head coil, and made the same Location or Number decisions about the targets viewed, using their left hand as in the Tactile Experiment. Each visual trial showed one platform at a time, with a fixation cross in the center of the platform. Visual stimuli subtended  $\sim 30^\circ$  visual angle. Visual stimuli were presented using a MacBook (2.16 GHz Intel Core 2 Duo, running Mac OS X) and were displayed on a screen mounted at the front of the scanner bore using a standard video projector at XGA resolution. A pseudo-random order of Location, Number, and Rest blocks was used, as in the Tactile Experiment. Each block lasted 32 seconds, with a 2-second message indicating the condition at the beginning of each block. Each visual stimulus was presented for 1.5 seconds followed by a 0.5 second inter-stimulus interval during which the screen was blank. There were a total of 15 trials per block and 18 blocks per functional run, for a total of 576 seconds (288 TRs). Each subject participated in 2-3 functional runs. Subjects were asked to fixate on a red



fixation cross located at the center of the visual platform while performing the task. Subjects' eye movements were monitored outside the scanner during practice trials.

#### MRI data acquisition

Magnetic resonance images were acquired on a GE 3T scanner at the Center for fMRI, University of California, San Diego, with an 8-channel head coil. Functional images were collected using an echo-planar T2\* gradient echo pulse sequence (31 contiguous axial slices covering the entire brain, 64 x 64 matrix, 3.438 x 3.438 x 4.0 mm voxel size, TR = 2000 ms, TE = 30 ms, flip angle = 90°, band width = 62.5 kHz). Each functional run consisted of 270 and 288 volumes for the Tactile and Visual Experiments, respectively. Each subject participated in at least 2 functional runs per experiment. The first 4 volumes of each functional run were discarded automatically to allow the magnetization to reach a steady state. A T1-weighted (1 x 1 x 1.3 mm) FSPGR alignment scan was collected in the same scanning session to register the functional images to a previously obtained high-resolution (1 x 1 x 1 mm) T1-weighted FSPGR anatomical scan.

#### Data processing and statistical analysis

Each subject's cortical surface was reconstructed from the high-resolution (1x1x1 mm) T1-weighted FSPGR anatomical scan in FreeSurfer (Fischl et al., 1999a; Dale et al., 1999). Functional images were aligned with the T-1 weighted FSPGR

alignment scan collected in the same scanning session and registered to each subject's cortical surface in FreeSurfer (Fischl et al., 1999; Dale et al., 1999).

Functional MRI data were analyzed with AFNI (Cox, 1996). The functional runs were concatenated for each experiment yielding a minimum of 540 volumes per subject for the Tactile Experiment and a minimum of 576 volumes for the Visual Experiment. Within each concatenated run, volumes were motion-corrected by registering all volumes to the middle of the second functional run in AFNI. Six motion parameters (3 for rotation and 3 for translation) were obtained during volume registration. Each subject's BOLD responses were analyzed using a general linear model implemented in AFNI's 3dDeconvolve function, with a regressor of interest for each condition within each experiment. The hemodynamic response function was modeled at 5 different time points, i.e. at 0, 2, 4, 6, and 8 seconds (0-4 TRs), per voxel. A quadratic polynomial was used to fit and remove the baseline. Three general linear tests were carried out within each experiment: Location and Number each versus baseline (Rest), and Location versus Number. Motion parameters were modeled as regressors of no interest. Correlation coefficients and t-statistics were generated for each regressor and for the contrast between Location and Number for the area under the hemodynamic response function.

#### Group analysis

Each subject's reconstructed cortical surface was sphered and morphed to an

average spherical surface using a best-fit sulcal alignment in FreeSurfer (Fischl et al., 1999b). Each subject's deconvolution coefficients were resampled onto the average spherical surface and averaged in this spherical coordinate system. Prior to resampling, smoothing was performed on individual subjects' surfaces using 16 steps of smoothing, corresponding to a full-width, half-max (FWHM) Gaussian filter of approximately 5 mm (Hagler et al., 2006). t-statistics and means were generated on the spherical surface for each condition as well as the contrast between Location and Number, and were resampled back onto an inflated cortical surface for display purposes (see Filimon et al., 2007).

#### Multiple comparison correction

To correct for multiple comparisons, we used cluster-size exclusion (see Hagler et al., 2006). Clusters of contiguous vertices were identified for t-statistics thresholded at  $p < 0.005$  for each condition versus baseline in the group-averaged data as well as in individual subjects. T-statistics for the Location-versus-Number contrast in the group-averaged Tactile and Visual data were thresholded at  $p < 0.05$  and clustered with a minimum cluster size of 10 contiguous voxels. Clusters smaller than the corresponding cluster sizes were excluded, achieving a corrected p-value of 0.05.

#### Overlap analysis

Overlapping clusters of voxels that were more active during Location versus

Number in both the Visual and Tactile experiments were calculated in MATLAB. Clusters of voxels from the Location versus Number contrast which survived thresholding at  $p < 0.005$ , corrected, were saved as surface patches in FreeSurfer for all 10 subjects who participated in both experiments. Overlapping surface vertices for contiguous Tactile and Visual voxels that were more active for Location than Number were extracted in MATLAB. MNI coordinates were calculated based on the center of the overlap.

## Results

### Behavioral Results

Fig. 2 shows subjects' accuracy levels (percent correct responses) for the Location and Number tasks in the Tactile (Fig. 2a) and Visual (Fig. 2b) Experiments. Fig. 2c compares the overall accuracy levels between the Tactile and Visual Experiments. As can be seen in Fig. 2a, when relying on tactile information alone, subjects identified both the Location of targets and the Number of targets with very high accuracy. Percent correct responses for Location averaged 93.27%, s.d. 4.25%; percent correct responses for Number averaged 89.35%, s.d. 4.06%. Chance performance for each task was 25%, or one out of four possible responses. A paired two-tailed t-test comparing accuracy levels for the Tactile Location and Tactile Number tasks revealed no significant difference between the two tactile tasks ( $t(11) = 2.16$ , n.s.), indicating that subjects performed both tasks with comparable accuracy.

As seen in Fig. 2b, subjects were highly accurate in the Visual Location and Visual Number tasks as well, with average percent correct responses for Visual Location = 95.95%, s.d. = 3.89%, and for Visual Number = 97.56%, s.d. = 2.45%. A paired two-tailed t-test comparing Visual Location and Visual Number accuracy levels revealed no significant difference in accuracy between Location and Number in the visual modality ( $t(12) = 2.10$ , n.s.). Note that for the Visual Experiment, four subjects (out of 13) mistook the task instruction on 1 block of trials (out of 24-36 blocks) for

the opposite task instruction, and accurately performed the Number task in a Location block or the Location task in a Number block, although the responses were incorrect relative to the true task instruction. Two further subjects switched tasks on 2 out of 36 blocks. This is likely due to the shorter instruction message in the Visual Experiment; the subjects in question reported having missed the instruction on those blocks of trials. Those blocks of trials were excluded from further analysis and were not included in the accuracy levels indicated above and in Fig. 2b or 2c. There was no pattern of one of the two conditions being more frequently switched for the other.

Fig. 2c shows overall performance combined across both Location and Number tasks in the Tactile and Visual modality, respectively. Tactile overall percent correct responses were 91.31%, s.d. 2.72%; Visual overall percent correct responses were 96.75%, s.d. 2.94%. A two-tailed t-test showed that overall Visual accuracy levels were significantly higher than overall Tactile accuracy levels ( $t(23) = 11.96$ ,  $p < 0.0001$ ), as would be expected given the dominance of the visual modality over the tactile modality. Accuracy levels within both the Tactile and the Visual Experiment were significantly above chance ( $p < 0.0001$ , binomial test, for every subject).

#### fMRI results: Tactile Experiment

Fig. 3 shows group cortical surface-averaged activations for the 12 subjects who participated in the Tactile Experiment, displayed on an inflated cortical surface. A bilateral fronto-parietal network of areas was activated for both the Tactile Location

and Tactile Number tasks, as expected for a task requiring active tactile exploration with the right hand and response selection with the left. Activations were significant at  $p < 0.005$ , corrected, and included the primary somatosensory and motor cortex, dorsal and ventral premotor cortices (superior frontal gyrus and sulcus and inferior frontal gyrus), the supplementary motor area (medial aspect of the superior frontal gyrus), cingulate sulcus and gyrus, the secondary somatosensory cortex (SII), the supramarginal gyrus, as well as the superior parietal lobule, including the intraparietal sulcus, superior parietal gyrus, and postcentral sulcus. Weak activation was also observed inside the left calcarine sulcus (primary visual area), for both Tactile tasks, even though subjects were blindfolded during the entire Tactile Experiment. Inspection of each of the 12 subjects' data revealed that 7 of the 12 subjects activated the calcarine sulcus (V1) significantly ( $p < 0.005$ ) during both the Location and Number tasks, while 5 subjects did not show V1 activity in either task. Note that all subjects were blindfolded in the scanner. This differential V1 activation may reflect different strategies or different brain organization in different subjects. In addition, the posterior end of the inferior temporal gyrus in the right hemisphere was activated in both the Location and Number task.

Fig. 5 (top) shows contrasts between cortical surface-averaged activations for the Location and Number tasks. Compared to Number, Location identification by touch activated the superior parietal gyrus significantly more strongly, bilaterally ( $p < 0.05$ , corrected). The anterior intraparietal sulcus, especially in the right

hemisphere, the right lateral occipital gyrus, and the superior frontal sulcus, bilaterally, were also activated significantly more strongly by the Tactile Location task compared to Tactile Number ( $p < 0.05$ , corrected). The lateral occipital gyrus activation may reflect a decrease in activation in the Tactile Number condition relative to baseline, since neither condition significantly activated the lateral occipital gyrus more than baseline, as shown in Fig. 3. Compared to Tactile Location, the Tactile Number condition activated the postcentral sulcus and gyrus, bilaterally, the left precentral gyrus and central sulcus, as well as the anterior cingulate gyrus, especially in the right hemisphere, significantly more strongly ( $p < 0.05$ , corrected). Table 1 lists the MNI coordinates for the cortical regions that differed in activation between Tactile Location and Tactile Number.

Fig. 6 (top) shows 4 representative subjects' activations for the Tactile Location versus Tactile Number contrast ( $p < 0.005$ , corrected). While subjects differed in the extent of activation, all subjects showed significantly greater Location than Number activity in the Tactile Experiment in the superior parietal gyrus bilaterally and in the right anterior intraparietal sulcus. Note that not all subjects showed greater left pre- and postcentral activations for Tactile Number compared to Tactile Location: three of the four subjects shown had relatively weak or absent primary somatomotor activations for Number compared to Location (Fig. 6 top, subjects 1-3), whereas all subjects showed the greater parietal activations for Location versus Number.



## fMRI results: Visual Experiment

Fig. 4 shows cortical surface-averaged activations for 13 subjects from the Visual Location and Visual Number tasks ( $p < 0.005$ , corrected). A similar bilateral fronto-parietal network of cortical areas was activated for both Visual Location and Visual Number tasks, including the superior frontal gyrus and sulcus, the inferior precentral sulcus and gyrus, the medial aspect of the superior frontal gyrus (supplementary motor cortex), the postcentral sulcus, the intraparietal sulcus and superior parietal gyrus, and occipital areas including the occipital pole and posterior calcarine sulcus, the superior occipital gyrus, and the lateral occipital gyrus. In the right hemisphere, primary motor and somatosensory cortex was also activated, in agreement with the left-handed button-presses executed by subjects in both conditions. Intraparietal and superior parietal activations were stronger in the right hemisphere compared to the left for the Visual Location condition, but not for the Visual Number condition.

Fig. 5 (bottom) shows contrasts between the Visual Location and Visual Number conditions. Compared to Visual Number, Visual Location activated the superior parietal gyrus and the anterior part of the intraparietal sulcus significantly more strongly ( $p < 0.05$ , corrected), with activations being stronger and of larger extent in the right hemisphere compared to the left. In addition, Visual Location also activated the right superior frontal sulcus more than Visual Number. The superior parietal and

intraparietal activations for Visual Location compared to Visual Number overlapped with the superior parietal and intraparietal difference activations for Tactile Location versus Tactile Number. No brain regions were significantly more active for Visual Number compared to Visual Location. Fig. 5 (bottom, medial view) also shows the lack of difference in occipital activations between Visual Location and Visual Number, suggesting equal amounts of visual stimulation in both Visual Location and Visual Number. Table 2 lists the MNI coordinates for the brain regions that differed in activation between the Visual Location and Visual Number tasks.

Fig. 6 (bottom) shows the same pattern of activity for Visual Location versus Visual Number contrasts in 4 representative subjects ( $p < 0.005$ , corrected). All subjects showed greater bilateral superior parietal gyrus and right-hemispheric anterior intraparietal activation for Visual Location compared to Visual Number. The 4 subjects shown are the same as in Fig. 6 (top). The Tactile and Visual contrast activations for Location versus Number overlapped in 9 out of 10 and 10 out of 10 subjects in the right and left superior parietal gyrus, respectively, and in 8 out of 10 subjects in the right anterior intraparietal sulcus. Table 3 lists the MNI coordinates for the brain regions showing overlapping activations that were greater for the Location than Number task in both the Tactile and Visual experiment.

## Discussion

The present study attempted to identify parietal regions involved in tactile location processing for external, rather than body-based, targets. In addition, the Visual Experiment aimed to identify whether the same brain regions are also involved in visual location processing. We found two posterior parietal regions that were more active in Location identification during either Tactile or Visual processing, compared to the control condition: the superior parietal gyrus, bilaterally, and the anterior part of the right intraparietal sulcus (IPS). The left IPS also showed greater Location than Number activity, but only in 5 out of 10 subjects.

The involvement of the posterior parietal lobe in tactile perception is in agreement with previous neuroimaging studies on tactile processing (Reed et al., 2005; van Boven et al., 2005; Macaluso and Driver, 2001; Stoeckel et al., 2003; Jaencke et al., 2001; Zhang et al., 2005), and with studies showing disruption of tactile perception following transcranial magnetic stimulation over the posterior parietal lobe (Ro et al., 2004). The anterior intraparietal sulcus has also been shown to be involved in both tactile and visual spatial processing, bilaterally, responding to both air-puff stimulation to the hand and LED light presentation on either the right or left side of space (Macaluso and Driver, 2001). In the left hemisphere, the anterior intraparietal sulcus (aIPS) has also been implicated in tactile perception of grating orientation (Van Boven et al., 2005; Zhang et al., 2005). Our superior parietal lobule activations are also

in agreement with a previous fMRI study of tactile object location processing (Reed et al., 2005).

Our greater posterior parietal, including IPS, activations for Visual Location compared to Visual Number processing are also consistent with previous human and animal studies of visual space perception and the posterior parietal lobe (Colby and Goldberg, 1999; Kastner and Ungerleider, 2000; Astafiev et al., 2003; Haxby et al., 1991; Hagler et al., 2007; Sereno et al., 2001). In our study, posterior parietal activation was greater in the right hemisphere for Visual Location compared to Visual Number. The same right-hemispheric dominance was found here for Tactile Location processing in the anterior part of the intraparietal sulcus, but not in the superior parietal gyrus, where the extent of activation was similar in the left and right hemispheres. In the tactile case, right-hemispheric dominance of the IPS activations may also be due to the fact that stimuli were always presented to the right hand and therefore right side of the subjects. It is possible that the IPS would be activated bilaterally to the same extent for bilateral tactile stimulus presentation, as has been found in the case of air-puff stimulation to either thumb (Macaluso and Driver, 2001).

The high performance accuracy for both the Location and Number tasks in both the Tactile and Visual Experiments shows that subjects were able to perform the tactile and visual tasks well above chance. The fact that there was no significant difference in performance accuracy between Location and Number in both experiments argues against the possibility that subjects might have paid more attention to one

condition than the other or that one condition might have been harder. Subjects reported that distinguishing between 1 and 2 targets was easy, whereas distinguishing between 3 and 4 targets was difficult, in the Number tasks. On the Location tasks, subjects similarly reported that distinguishing between far left and far right was easy, whereas distinguishing between left of center and right of center was difficult. This suggests that the difficulty level in the Number and Location tasks was roughly matched, consistent with the goals in designing the experiments.

While the behavioral data were comparable in both Location and Number tasks, our tactile fMRI results showed greater activation of the left M1 and S1 in the Tactile Number condition compared to the Tactile Location condition, despite the fact that similar exploratory hand movements were performed in both conditions. Due to the way stimuli were presented in the Tactile Experiment, for both the Location and Number tasks, subjects had to sweep their fingers across the platform to find the targets and touch the targets. In fact, the substantial overlap between Tactile Location and Tactile Number activations reflects the overall similarity between the two tasks. However, the greater left M1/S1 activation for Tactile Number may reflect increased stimulation or sensitivity of the fingertips during number identification. Note that this M1/S1 difference activation for Tactile Number compared to Tactile Location does not explain the presence of the greater posterior parietal activations for Tactile Location compared to Tactile Number, for several reasons. Firstly, the same stronger posterior parietal activations for Location are present in the Visual task, where there is no

M1/S1 activation difference in either hemisphere, and where in fact no left M1/S1 activation is present at all during either condition, since the right hand was not moved in the Visual Experiment. The identical pattern of greater posterior parietal activations for Location versus Number present in the Visual Experiment suggests that they are independent of the M1/S1 activations. Secondly, not all subjects (5 out of 12) had greater M1/S1 activations for Tactile Number compared to Tactile Location, while they still displayed significantly greater posterior parietal activations for Tactile Location than Tactile Number; examples of this pattern in individual subjects can be seen in Fig. 6. Thirdly, if the M1/S1 activations were connected to the posterior parietal activations, it is unclear why an increase in M1/S1 activity during the Tactile Number condition compared to Tactile Location should lead to a decrease in posterior parietal activations for the Tactile Number condition relative to the Tactile Location condition. The pattern one would have expected in that case would have been greater posterior parietal activations for Tactile Number compared to Tactile Location, not the opposite as shown in our study.

Another interesting question is whether the superior parietal and intraparietal activations reported here for Location processing compared to Number processing could be due to subjects visualizing the targets more in the Location condition compared to the Number condition. Our results argue against this interpretation: there was no difference of activation in V1 or other occipital areas between the two tactile conditions. Visual imagery has been shown to activate large areas of the occipital lobe

(Ganis et al., 2004), whereas in our data there was no difference in visual activations between the two conditions. Moreover, 5 of the 12 subjects who participated in the Tactile Experiment showed no visual activations at all while still exhibiting greater posterior parietal activations for Tactile Location compared to Tactile Number. This suggests that visual imagery or a difference in visual imagery between the two conditions does not drive the posterior parietal activations for Location.

The congruence between the Tactile and Visual results strongly suggests that the posterior parietal activations obtained here for Location versus Number processing reflect space-related processing rather than low-level sensory or motor differences.

Likewise, in the Visual Experiment, the lack of differences in activation of V1 or other visual areas between the Visual Location and Visual Number conditions argues against any differences in visual attention or low-level visual stimulation due to perhaps a greater need to foveate targets in one condition compared to the other. Subjects' eye movements were monitored outside the scanner, with subjects maintaining fixation in both conditions. The right-hemispheric superior frontal sulcus activation which was greater for Visual Location than Visual Number is anterior to the location of the frontal eye fields (FEF), and overlaps with a similar frontal activation difference found in Tactile Location compared to Tactile Number, where subjects were blindfolded and could not have moved their eyes to any targets. Instead, the parieto-frontal network of activations greater for both Tactile and Visual Location processing compared to Tactile or Visual Number processing reflects a parieto-frontal network for

spatial processing, and is consistent with previous spatial activations reported in the literature (Hagler et al., 2007).

Note that our results do not distinguish between the possibilities that the superior parietal and intraparietal regions found here are multisensory or instead simply process spatial locations in a modality-independent way. Our study does however show that these brain regions are accessed by information coming in through either the visual or tactile modality. Neurophysiological studies in macaques have identified various multisensory areas in the parietal lobe, including upper limb somatosensory and visual neurons in the superior parietal lobule (Breveglieri et al., 2006) and face somatosensory and visual neurons such as in the ventral intraparietal area, VIP (Colby and Goldberg, 1999). fMRI in humans has recently shown the presence of a human homologue of VIP in the posterior parietal cortex, responding to both air puff somatosensory stimulation of the face and visual stimuli close to the face (Serenó and Huang, 2006). It is thus likely that the parietal regions identified in the present fMRI study are also multisensory. This is also consistent with the view that the posterior parietal cortex consists of a mosaic of association areas that respond to multiple modalities (Colby and Goldberg, 1999).

Interestingly, we found no posterior parietal areas that responded more to Visual Number than to Visual Location in the Visual Experiment. Number processing has been previously linked to posterior parietal cortex activations and to implicit spatial processing (Hubbard et al., 2005; Simon et al., 2002). Indeed, Number



activations overlapped substantially with Location activations in the posterior parietal lobe in both experiments. While the Number condition was chosen in this study as a closely-matched control for basic motor, somatosensory, and visual stimulation in both experiments, it is possible that our Location versus control contrast activations would have been even stronger compared to a different control. Regardless of the spatial processing involved in number identification, our results show that actual spatial localization activates the superior parietal gyrus and intraparietal sulcus significantly more than processing of numbers of targets.

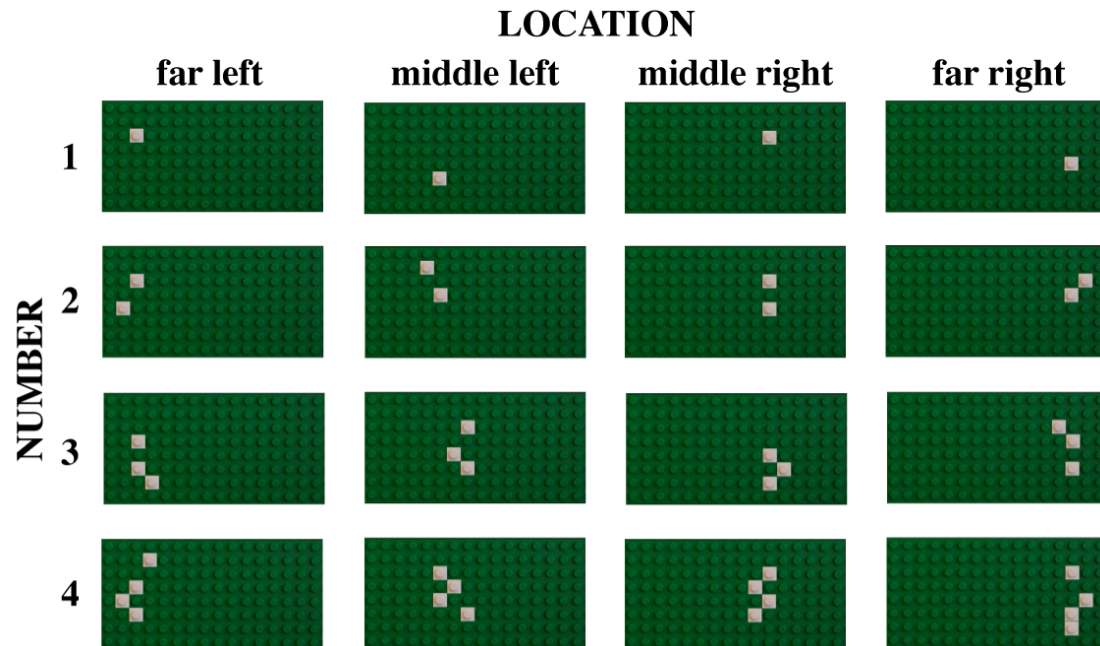
Also, the question arises what spatial reference frame might be used for determining location in either the Tactile or the Visual experiments. Note that in the Tactile Experiment, either an allocentric or an egocentric reference frame could be used. Locations of targets could be defined allocentrically with respect to the platform, i.e. left on the platform, right on the platform, etc. However, since the hand is centered on the platform at the beginning of each trial, locations could also be determined egocentrically: i.e. left of the right hand, right of the right hand, or more towards the right thumb versus more towards the right little finger, which is an egocentric decision. In the Visual Experiment, platform coordinates match eye-centered coordinates, such that target locations could be encoded relative to the fixation point. The fact that the same posterior parietal regions are active in both the Visual and Tactile Experiment suggests a representation not tied to the hand or the eye only, but a reference frame that is extracted from both modalities. It is also possible that the superior parietal and

intraparietal activations reported here represent spatial locations in more than one reference frame.

Taken together, our results suggest that the posterior parietal activations for Tactile Location and Visual Location processing are linked to spatial processing in both modalities. The posterior parietal lobe, however, has also been linked to sensorimotor transformations and motor planning and guidance, with sensory representations being used for the purpose of guiding actions (Colby and Goldberg, 1999; Andersen and Buneo, 2002). Another interesting interpretation of the present results is that, rather than reflecting a purely sensory, albeit multisensory (visual and tactile) representation of space, the posterior parietal activations found here could reflect a (multisensory) *sensorimotor* representation for response selection. In both the Visual and Tactile experiments, the Location task required a response mapping onto the left hand, which had a similar spatial layout (left-most target = left-most finger) as the actual tactile or visual display. Although subjects used the exact same fingers for responses in the Number task, the response finger was not tied to the spatial location of targets in the Number condition. This suggests that the spatial activations observed here could also represent sensorimotor representations for selecting the appropriate response depending on the spatial location of the sensory targets. This sensorimotor representation was similar in both the Tactile and Visual experiments. Our study thus provides evidence for multisensory sensorimotor representations of space, more specifically of actions in space.

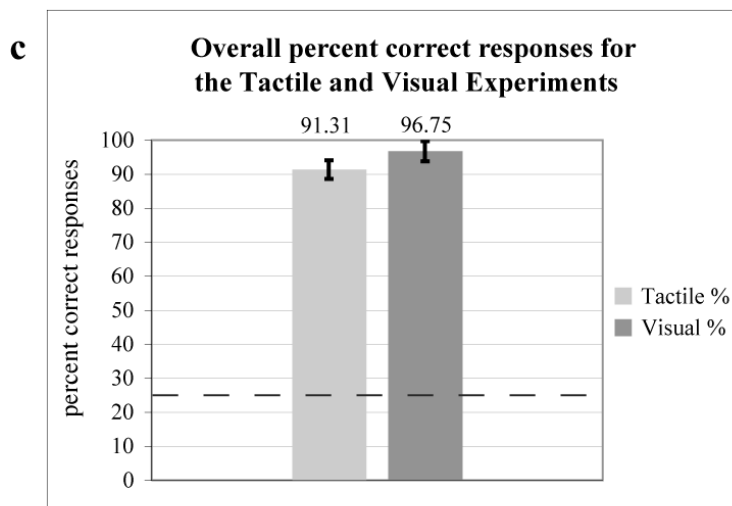
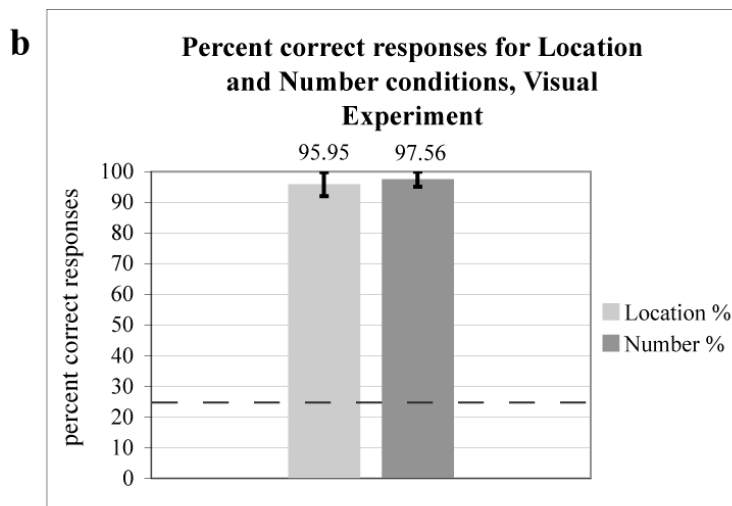
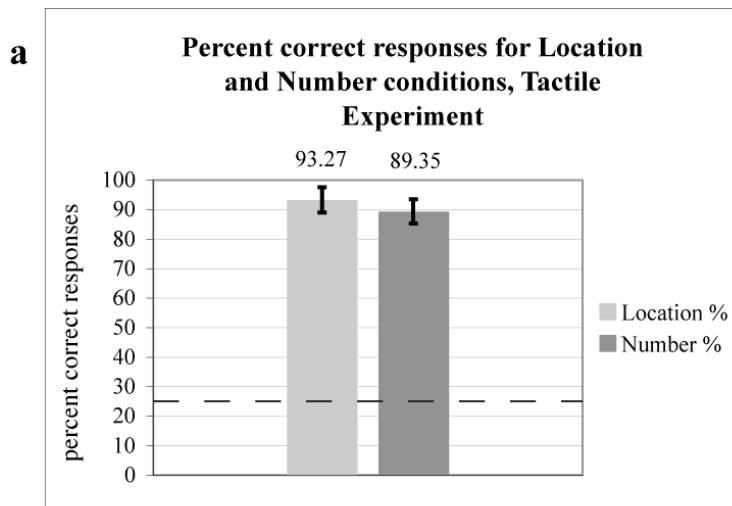
**Acknowledgment**

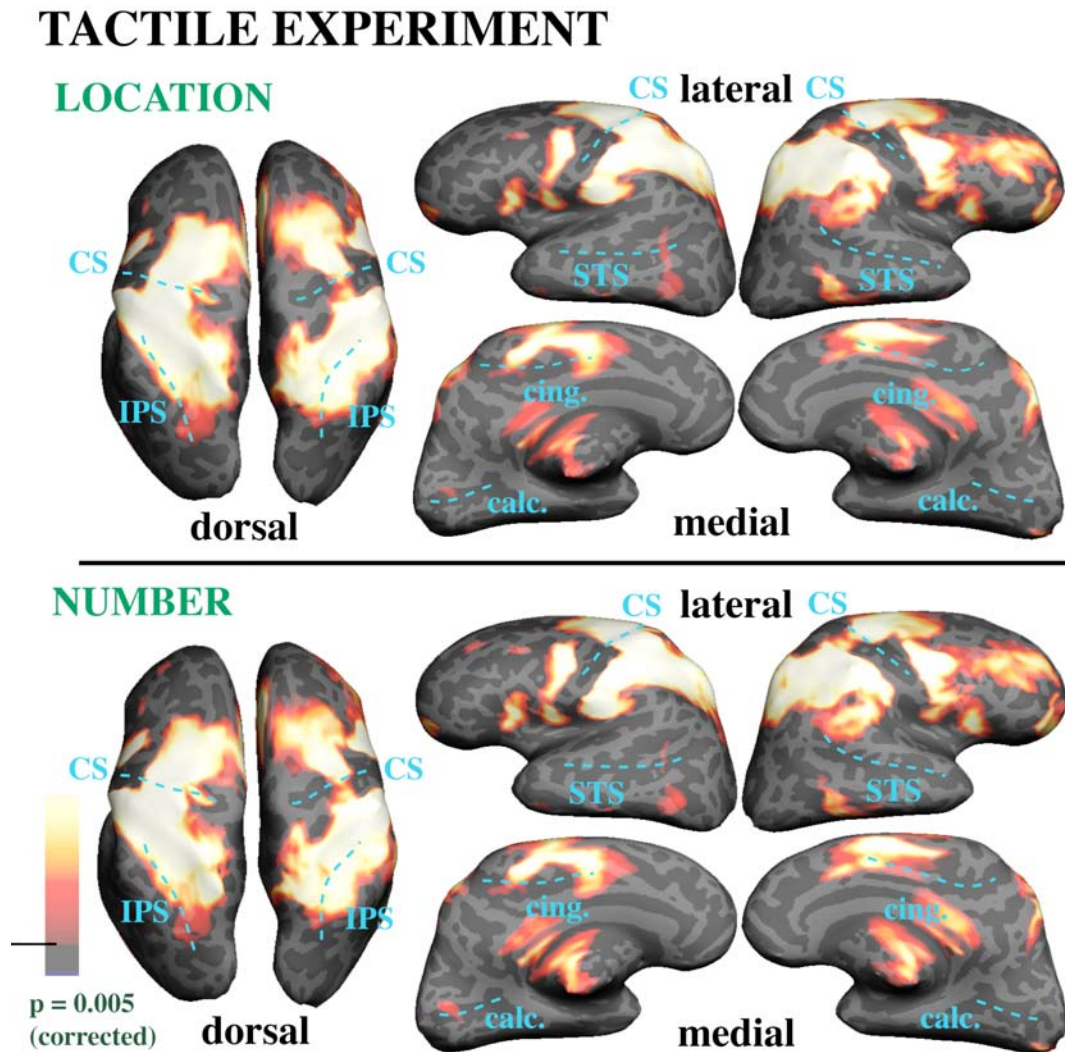
Chapter 4, in part, is being prepared for publication. The dissertation author was the primary investigator and author of this paper. The dissertation author acknowledges the following co-authors as collaborators on this manuscript: Jonathan D. Nelson, Adam T. Tierney, and Martin I. Sereno. Permission from all co-authors has been obtained.



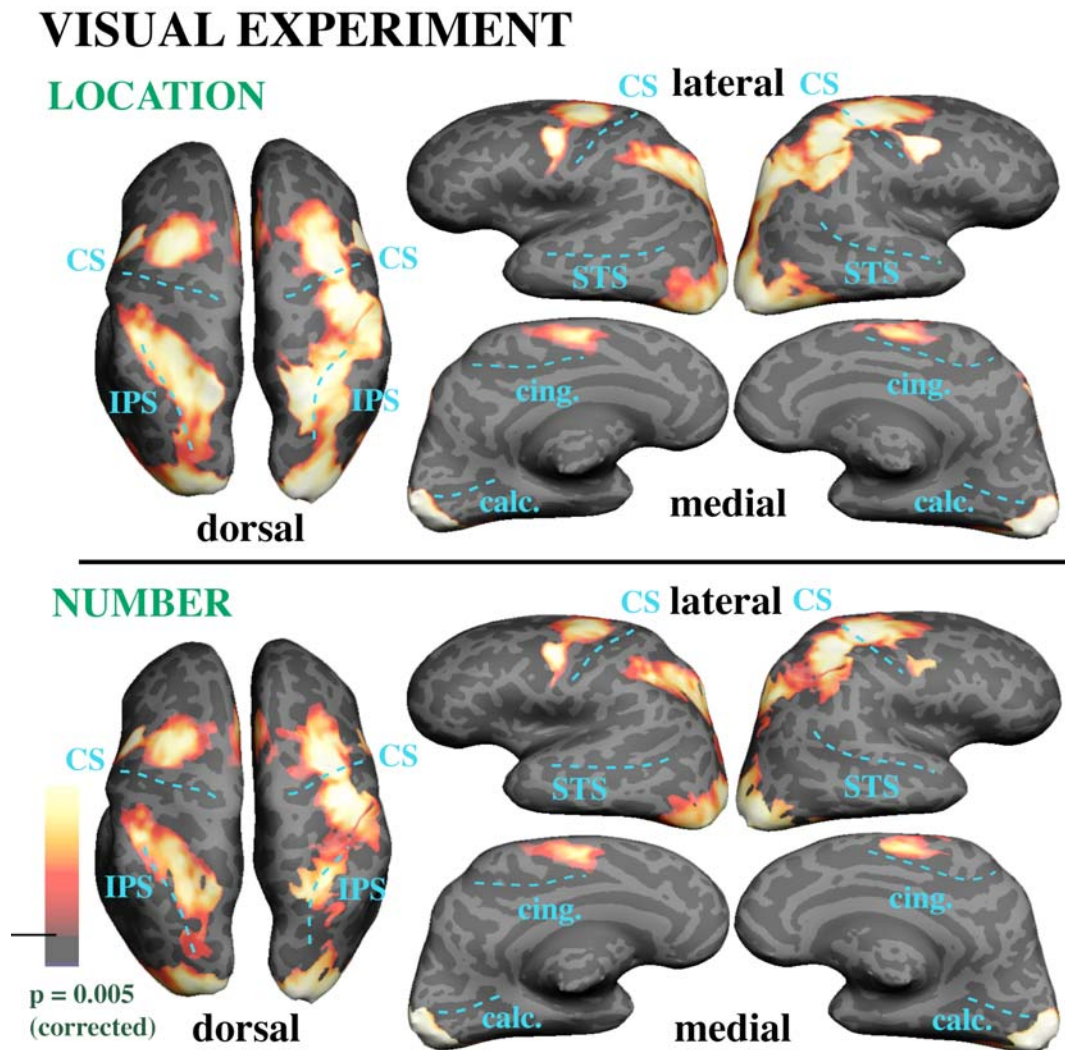
**Fig. 1.** Example stimuli used in the tactile and visual experiments. Lego platforms were presented one at a time either underneath the right hand in the Tactile Experiment or visually on a screen viewed through a mirror in the Visual Experiment. In the Visual Experiment, a red fixation cross was added to the center of each platform. Subjects performed blocks of trials in which they indicated either the Location of the cluster of targets (far left, left of center, right of center, far right) or the Number of targets (1-4), using their left hand.

**Fig. 2. (a)** Average percent correct performance for the Location and Number tasks in the Tactile Experiment ( $n = 12$ ). Subjects' accuracy was very high in both tasks (chance = 25%, indicated with a dashed line). Error bars in all graphs represent the standard deviation. **(b)** Average percent correct for the Location and Number tasks in the Visual Experiment ( $n = 13$ ). **(c)** Average overall accuracy within Tactile and Visual experiments, averaged across Location and Number tasks. Visual performance was significantly more accurate than Tactile performance ( $p < 0.0001$ ). Both Tactile and Visual overall accuracy levels were significantly above chance ( $p < 0.0001$ ).



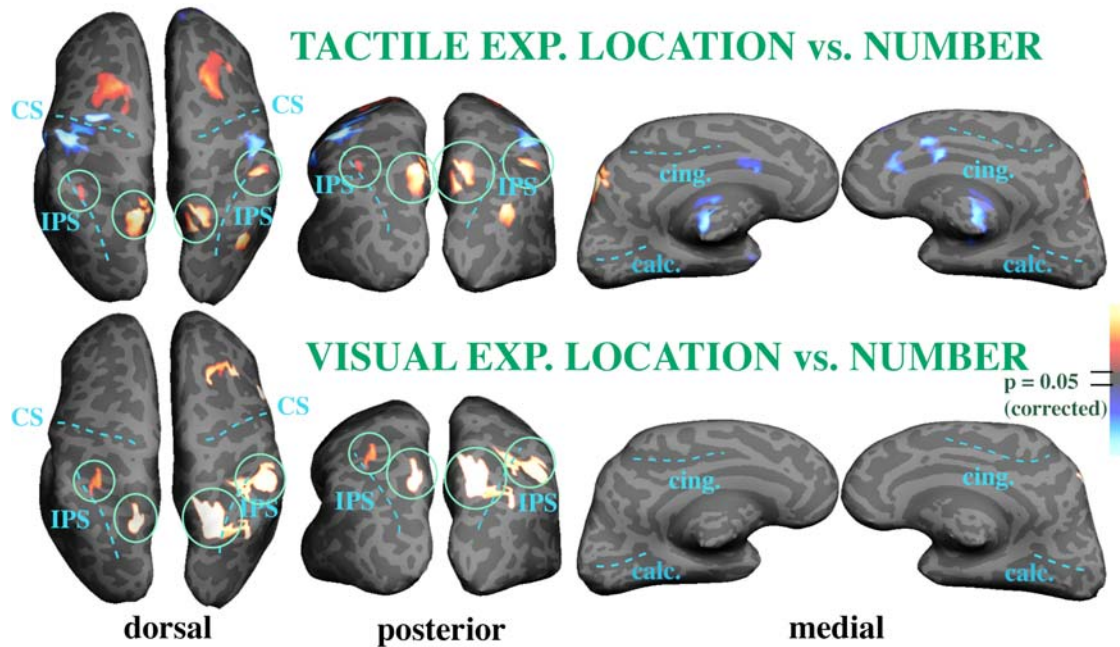


**Fig. 3.** Group cortical surface-averaged activations from 12 subjects for the Location and Number tasks from the Tactile Experiment, versus baseline. Activations are displayed onto inflated cortical surfaces viewed from dorsal, lateral, and medial views. All activations displayed are significant at  $p < 0.005$ , corrected. Location and Number activations were very similar to each other. Both tasks engaged a fronto-parietal network of areas in addition to primary somatosensory and primary motor areas contralateral to the right hand exploring the LEGOs and the left responding hand. Note that subjects were blindfolded during the Tactile Experiment. Sulci are indicated with dashed light-blue lines. CS = central sulcus; IPS = intraparietal sulcus; cing. = cingulate sulcus; calc. = calcarine sulcus; STS = superior temporal sulcus.

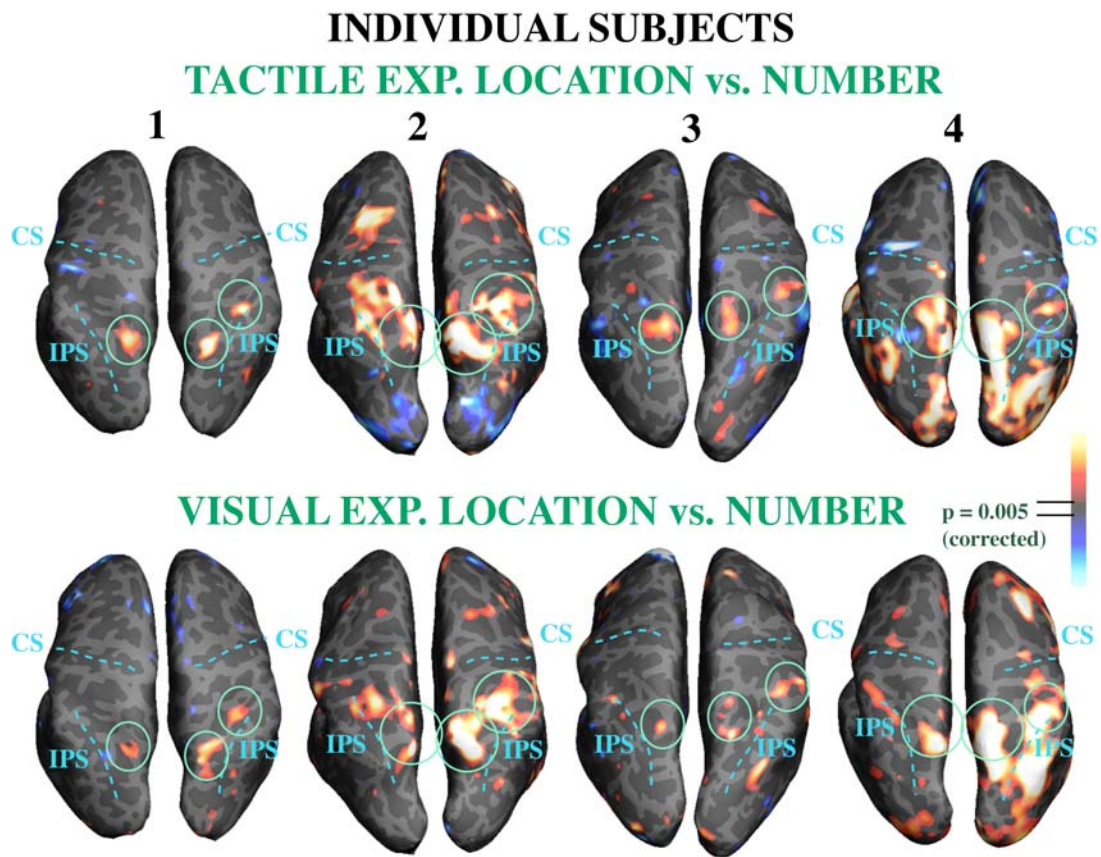


**Fig. 4.** Group cortical surface-averaged activations from 13 subjects for the Location and Number tasks from the Visual Experiment, versus baseline. Activations are displayed onto inflated cortical surfaces viewed from dorsal, lateral, and medial views. All activations displayed are significant at  $p < 0.005$ , corrected. Location and Number activations were very similar to each other and engaged a fronto-parietal network of areas bilaterally. Visual Location activations are stronger in the right hemisphere than the right hemisphere, compared to Visual Number activations. Activations in the right primary somatosensory and motor cortex reflect the left-handed button presses for each trial. Sulci are indicated in dashed light-blue lines as in Fig. 4.3.





**Fig. 5.** Contrast activations for Tactile Location versus Tactile Number (top) and Visual Location versus Visual Number (bottom), from cortical surface-based averages for 12 and 13 subjects, respectively. Note the greater activations for the Location condition compared to Number activations in the superior parietal gyrus (bilaterally), and the right intraparietal sulcus (weaker activations are seen in the left IPS). The parietal regions more strongly activated by Location compared to Number overlapped between the Tactile and Visual Experiments. The lack of difference activations in the occipital lobe for the Visual Experiment at  $p < 0.05$ , corrected, suggests that a similar amount of visual stimulation was present in both the Visual Location and Visual Number condition. The common activation for Tactile Location and Visual Location in the superior parietal lobe and intraparietal sulcus suggest a common substrate for spatial processing independent of sensory input modality. EXP. = Experiment. Red to yellow color-coding reflects greater activation for the Location conditions; Blue to light-blue color coding reflects greater activation for the Number condition.



**Fig. 6.** Contrasts between Tactile Location and Tactile Number (top) and Visual Location and Visual Number (bottom), in 4 subjects who participated in both the Tactile and Visual Experiments. The same parietal regions that were significantly more active in Tactile Location compared to Tactile Number were also significantly more active in Visual Location compared to Visual Number ( $p < 0.005$ , corrected), including the left and right superior parietal gyrus, and the right intraparietal sulcus. Note that not all subjects showed greater Tactile Number activations in the left primary somatosensory and primary motor cortex, with the parietal Location versus Number differences present regardless of those low-level somatomotor differences. EXP. = Experiment.

**TABLE 1.**

Average MNI-space coordinates (mm) for peak activations that differed between Tactile Location and Tactile Number in the Tactile Experiment.

Contrast	ROI	x	y	z	No. of subjects (out of 12)
Location > Number	Right superior parietal gyrus (BA 7)	16	-64	56	11
	Left superior parietal gyrus (BA 7)	-14	-67	55	12
	Right intraparietal sulcus	37	-41	43	11
	Left intraparietal sulcus	-31	-40	45	8
	Right lateral occipital gyrus (BA 19)	36	-69	33	10
	Right superior frontal sulcus	26	-5	55	9
	Left superior frontal sulcus	-20	-3	52	10
Number > Location	Left precentral gyrus (BA 4)	-35	-17	59	7
Location > Number	Left postcentral gyrus (3, 1, 2)	-45	-21	55	7
	Right post-central sulcus	47	-24	48	9
	Right anterior cingulate gyrus (BA 24)	5	24	5	7

All activations were at  $p < 0.005$  (corrected).

**TABLE 2.**

Average MNI-space coordinates (mm) for peak activations that differed between Visual Location and Visual Number in the Visual Experiment.

Contrast	ROI	x	y	z	No. of subjects (out of 13)
Location > Number	Right superior parietal gyrus (BA 7)	18	-69	53	13
	Left superior parietal gyrus (BA 7)	-14	-69	54	13
	Right intraparietal sulcus	41	-38	43	13
	Left intraparietal sulcus	-37	-42	45	12
	Right superior frontal sulcus	23	-2	54	12
	Right lateral occipital gyrus (BA 19)	36	-75	32	13

All activations were at  $p < 0.005$  (corrected).

**TABLE 3.**

Average MNI-space coordinates (mm) for peak activations in ROI overlaps for Visual Location versus Visual Number and Tactile Location versus Tactile Number.

Contrast	ROI	x	y	z	No. of subjects (out of 10)
Location > Number	Right superior parietal gyrus (BA 7)	16	-65	58	9
	Left superior parietal gyrus (BA 7)	-14	-68	54	10
	Right intraparietal sulcus	41	-41	45	8
	Left intraparietal sulcus	-31	-38	45	5
	Right superior frontal sulcus	24	-5	54	6

All activations were at  $p < 0.005$  (corrected).

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