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Human Cortical Control of Hand Movements: Parietofrontal Networks for Reaching, Grasping, and Pointing

Flavia Filimon[1]

Abstract

In primates, control of the limb depends on many cortical areas. Whereas specialized parietofrontal circuits have been proposed for different movements in macaques, functional neuroimaging in humans has revealed widespread, overlapping activations for hand and eye movements and for movements such as reaching and grasping. This review examines the involvement of frontal and parietal areas in hand and arm movements in humans as revealed with functional neuroimaging. The degree of functional specialization, possible homologies with macaque cortical regions, and differences between frontal and posterior parietal areas are discussed, as well as a possible organization of hand movements with respect to different spatial reference frames. The available evidence supports a cortical organization along gradients of sensory (visual to somatosensory) and effector (eye to hand) preferences.

Keywords

hand movement, reaching, grasping, pointing, saccade, posterior parietal cortex (PPC), sensorimotor, premotor cortex, proprioception, parietal reach region (PRR), LIP

Research in both humans and macaques has shown that multiple cortical areas beyond the primary motor cortex (M1) are involved in controlling and guiding movement, including the premotor cortex in the frontal lobe (Picard and Strick 2001; Chouinard and Paus 2006) as well as the posterior parietal cortex (PPC; Fogassi and Luppino 2005; Culham and others 2006). Even simple movements, such as flexing and extending the fingers with eyes closed, activate substantial swaths of frontal and posterior parietal areas in addition to primary sensorimotor areas (Fink and others 1997; Filimon 2008).

This review focuses on the involvement of human parietofrontal cortical networks in hand and arm movements such as reaching, pointing, and grasping, with an emphasis on human functional neuroimaging studies. Several questions shall be considered: 1) What are the functional roles of these different cortical areas in the control of hand movements? In particular, how specialized are these cortical regions for particular kinds of hand movements, for instance, reaching as opposed to grasping, or for particular effectors, for example, hand versus eye, in the human? 2) Are hand movements and their targets represented relative to particular spatial reference frames, and are these reflected in the cortical organization of these brain areas, as revealed with functional magnetic resonance imaging (fMRI)? 3) How do premotor and posterior parietal areas differ in the control of hand movements?

We will begin with a brief overview of the parietofrontal cortical organization underlying hand and eye movements in the macaque.

Parietofrontal Networks Involved in Movement in Macaques

The PPC, located posterior to the postcentral gyrus (primary somatosensory cortex [SI]) and anterior to the occipital cortex, is strongly interconnected with motor areas in the frontal lobe (Matelli and Luppino 2001). It is now well accepted that different regions in the PPC (Fig. 1) have various sensorimotor functions: different neurons respond to different types of sensory input (visual, somatosensory, auditory) as well as during the execution and planning of specific actions (Andersen and Buneo 2002). Similarly, premotor areas, located in front of M1, also participate in specific movements and respond to similar sensory inputs as the parietal areas with which they are connected (Matelli and Luppino 2001).

[1]Max Planck Institute for Human Development, Berlin, Germany

Corresponding Author:
Flavia Filimon, Max Planck Institute for Human Development, Lentzeallee 94, 14195 Berlin, Germany
Email: ffilimon@ucsd.edu
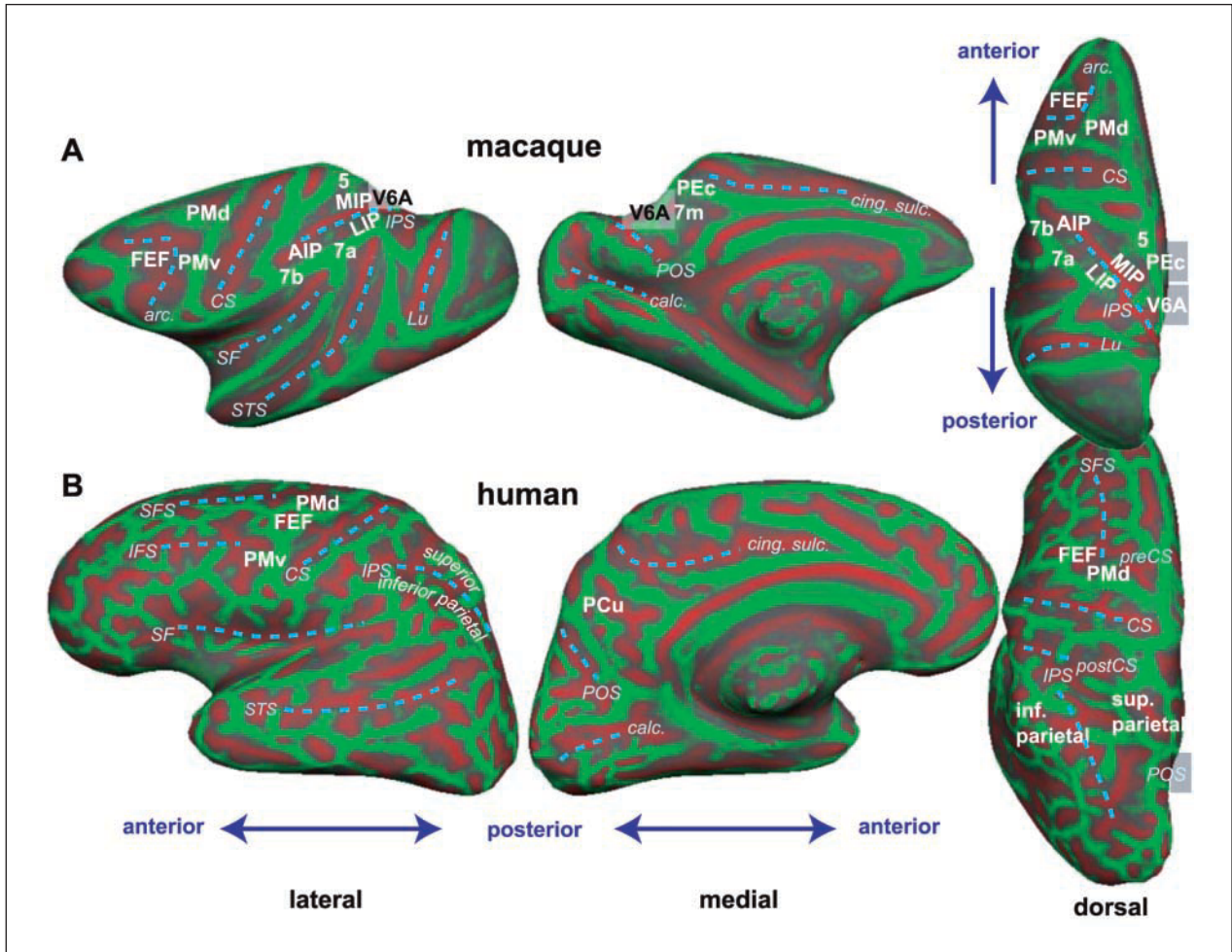
Figure 1. Macaque and human cortical surface anatomy indicating frontal and posterior parietal areas involved in hand and eye movements. Inflated cortical surface of a (A) macaque and (B) human left hemisphere, viewed from lateral, medial, and dorsal aspects. Sulci are indicated in red and gyri in green. Functional areas in the frontal lobes in both the macaque and human are based on information in Picard and Strick (2001). Parietal functional areas in macaque are based on information in Galletti and others (2003), Ferraina and others (1997), and Culham and Kanwisher (2001). As the human homologs of macaque functional posterior parietal areas remain to be established, only anatomical landmarks and divisions are indicated in the human parietal lobe. CS, central sulcus; arc., arcuate sulcus; IPS, intraparietal sulcus; Lu, lunate sulcus; STS, superior temporal sulcus; SF, Sylvian fissure; calc., calcarine sulcus; POS, parieto-occipital sulcus; cing. sulc., cingulate sulcus; PMd, dorsal premotor; PMv, ventral premotor; FEF, frontal eye fields; AIP, anterior intraparietal; LIP, lateral intraparietal; MIP, medial intraparietal; SFS, superior frontal sulcus; IFS, inferior frontal sulcus; preCS, precentral sulcus; postCS, postcentral sulcus; PCu, precuneus.

A dominant view is that different subregions of the macaque PPC and their frontal counterparts are specialized for certain sensorimotor transformations (Andersen and Buneo 2002). In the intraparietal sulcus (IPS) (Matelli and Luppino 2001), for example, neurons located in the caudal part of the medial bank (medial intraparietal area [MIP]) are predominantly involved in arm movement planning and execution. MIP predominantly projects to dorsal premotor cortex (PMd) area F2. MIP neurons additionally respond to visual or to both visual and somatosensory stimuli. The anterior intraparietal sulcus (area AIP) contains bimodal visual and tactile neurons that are involved

in different types of hand prehension (grasping). AIP projects to area F5 in the ventral premotor cortex (PMv), which has similar sensorimotor properties. The lateral intraparietal area (LIP), in contrast, projects to the frontal eye fields (FEF) and is involved in eye movements.

Area V6A, located on the anterior bank of the parieto-occipital sulcus (POS) and on the medial surface of the parietal lobe (the precuneus), also contains neurons responsive during arm movements. Like MIP, V6A also projects predominantly to area F2 in PMd (Matelli and others 1998). Areas MIP and part of V6A are sometimes referred to as the parietal reach region (PRR) (Andersen

and Buneo 2002). In most studies, PRR has mainly referred to MIP, although in some studies, single-cell recordings may have extended into neighboring V6A (Andersen and Cui 2009). The apparent functional specificity of these parietofrontal circuits has led to the view that in the macaque, the MIP/V6A-F2 circuit is specialized for reaching, the LIP-FEF circuit is specialized for saccades, and the AIP-F5 circuit is specialized for grasping (Sakata and Taira 1994; Matelli and Luppino 2001; Andersen and Buneo 2002).

However, it remains unclear how functionally specific and segregated different PPC areas and parietofrontal circuits really are. Reach-related responses have been described in posterior parietal areas outside PRR, such as areas 7a, 7m, PEc (caudal part of superior parietal area PE), and 5 (Sakata and Taira 1994; Ferraina and others 1997; Kalaska and others 1983; Breveglieri and others 2006; Graziano 2001) (Fig. 1). Similarly, area V6A, traditionally thought to be part of the reaching circuit, also contains grasp-selective neurons (Fattori and others 2010; Galletti and others 2003). Finally, both LIP and PRR are not entirely effector specific: LIP neurons respond during the planning of both reaches and saccades, and PRR neurons likewise respond during eye movements; the functional specialization of these areas is thus relative, not absolute (Andersen and Cui 2009). The definition of PRR itself is not entirely clear: in some studies, PRR included MIP, V6A, as well as area 7a (Andersen and Buneo 2002).

Despite the large number of areas containing reach-responsive neurons, there are cytoarchitectonic and functional differences between these areas. For instance, V6A contains neurons responding during both reaching in the dark and reaching in light, with a greater modulation when the arm is seen (Bosco and others 2009). Several V6A cells have visual properties relevant for grasping, such as orientation and size, and for reaching, such as the direction of movement (Galletti and others 2003). Area V6A neurons are modulated by eye position during the execution of reaching movements and by the relative position of the target with respect to the fixation point (Marzocchi and others 2008). In contrast, area PEc, located more anterior in the superior part of the precuneus (Fig. 1), has a large proportion of neurons that respond to passive somatosensory stimulation and joint rotation (Breveglieri and others 2006). These neurons also participate in reaching but may predominantly rely on proprioceptive information from the arm.

Thus, multiple areas participate in multiple types of movements in the macaque, but the particular blend of sensory properties within these PPC areas may vary gradually from area to area. Thus, the relevant question for humans may not be whether a single homologous reach area can be found, for example, but whether there are homologous areas displaying similar mixtures of sensory and motor properties as in the macaque.

Functional Specificity of Human Parietofrontal Areas?

In the quest for human homologs of macaque cortical areas involved in movement, it has been tempting for researchers to isolate single activations out of a network of activations and to, for example, label them as the human PRR or the frontal reach region (FRR). For instance, based on greater activation during planned (delayed) pointing than planned saccades, one fMRI study identified a medial parietal area just anterior to the POS, in the precuneus (Fig. 1), as the putative human equivalent of PRR (Connolly and others 2003). Similar activation differences between delayed pointing versus delayed saccades have been used to identify an FRR in PMd (Tosoni and others 2008).

However, pointing is a much smaller movement than reaching, which typically involves the transport of the forearm (Culham and others 2006). If both pointing and reaching activate these posterior parietal and frontal areas, logically, these areas cannot be reach specific, if reaching is defined as involving arm transport, not just wrist rotations or finger movements. Moreover, as is discussed below, a majority of recent human fMRI studies on both pointing and reaching find extensive cortical activations rather than isolated hand movement–specific areas.

Reaching versus Saccades

In humans, visually guided reaching movements produce large swaths of activations spanning multiple posterior parietal and frontal areas (Filimon and others 2009, 2007; Beurze and others 2009; Blangero and others 2009; Levy and others 2007; Clavagnier and others 2007; Culham and Valyear 2006; Culham and others 2006, 2003; Prado and others 2005; Kertzman and others 1997). Note that *visually guided* reaching could refer either to reaching toward a visual target or to reaching under visual guidance with the hand and arm in sight. The large extent of activations could thus be due not just to the movement itself but also to visual feedback from the hand or to input from the visual target. Several studies have attempted to isolate the influence of each of these sensory inputs.

In one fMRI study, visible and nonvisible reaching movements were compared with saccades to identify reach-selective areas as well as areas that are modulated by visual feedback from the hand (Filimon and others 2009). Multiple areas showed greater activation to either kind of reaching compared with saccades (Fig. 2). In addition, although activations to reaching were stronger than to saccades, saccade activations overlapped with and were part of the network activated by reaching.

Specifically, in the PPC, the IPS, the superior parietal gyrus and precuneus (Brodmann area 7 [BA7]), and the
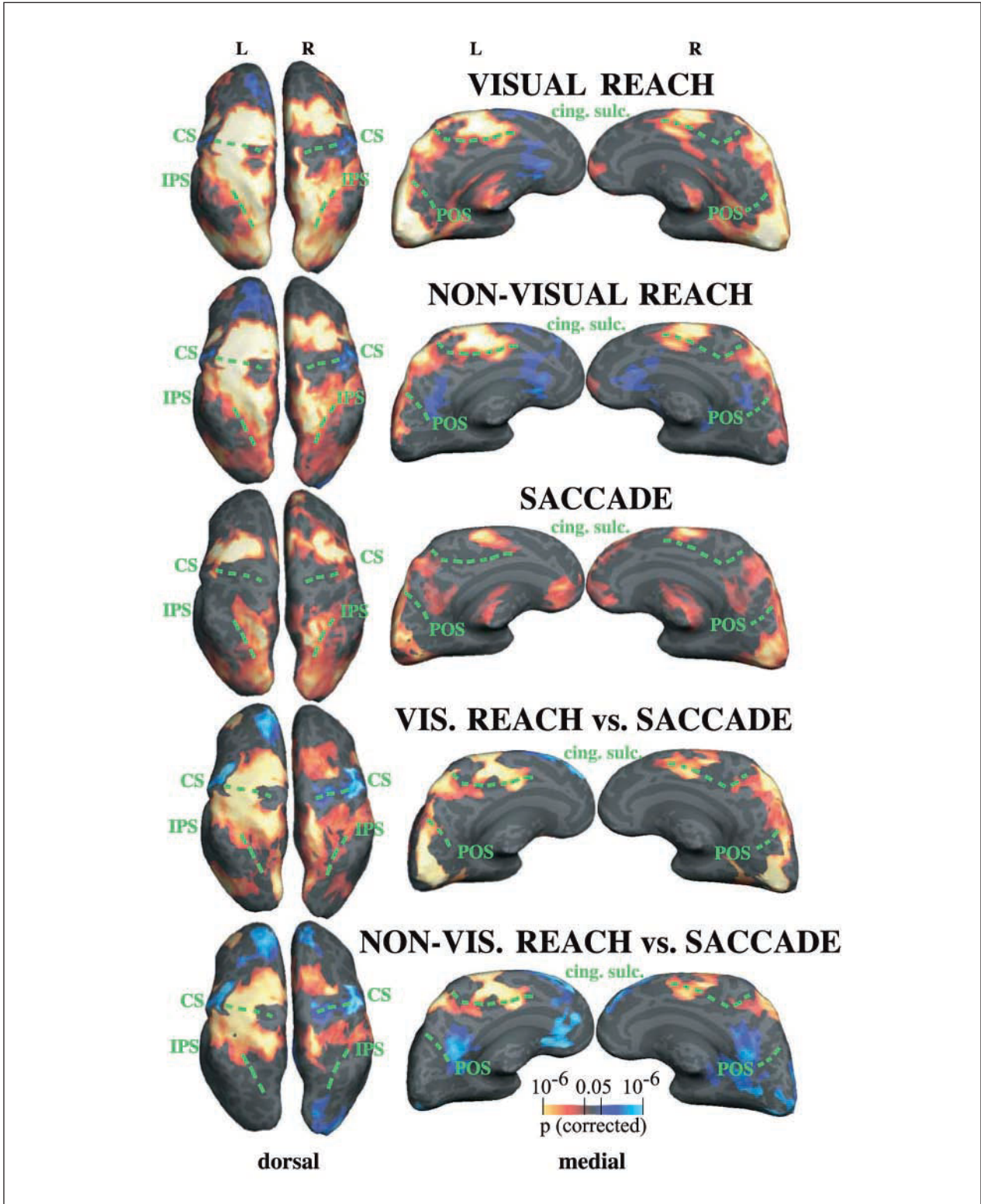
Figure 2. Human fMRI activations to visual (visible) reaches, nonvisual (nonvisible) reaches, and saccades, versus fixation. Reaches were carried out with the right hand in 8 right-handed subjects. Contrasts between visual and nonvisual reaches and saccades are shown at the bottom. Both reaches and saccades yield extended overlapping cortical activations, with stronger reach activations in the frontoparietal cortex. L, left; R, right. Abbreviations of sulci are as in Figure 1. Adapted from Filimon and others (2009) with permission.
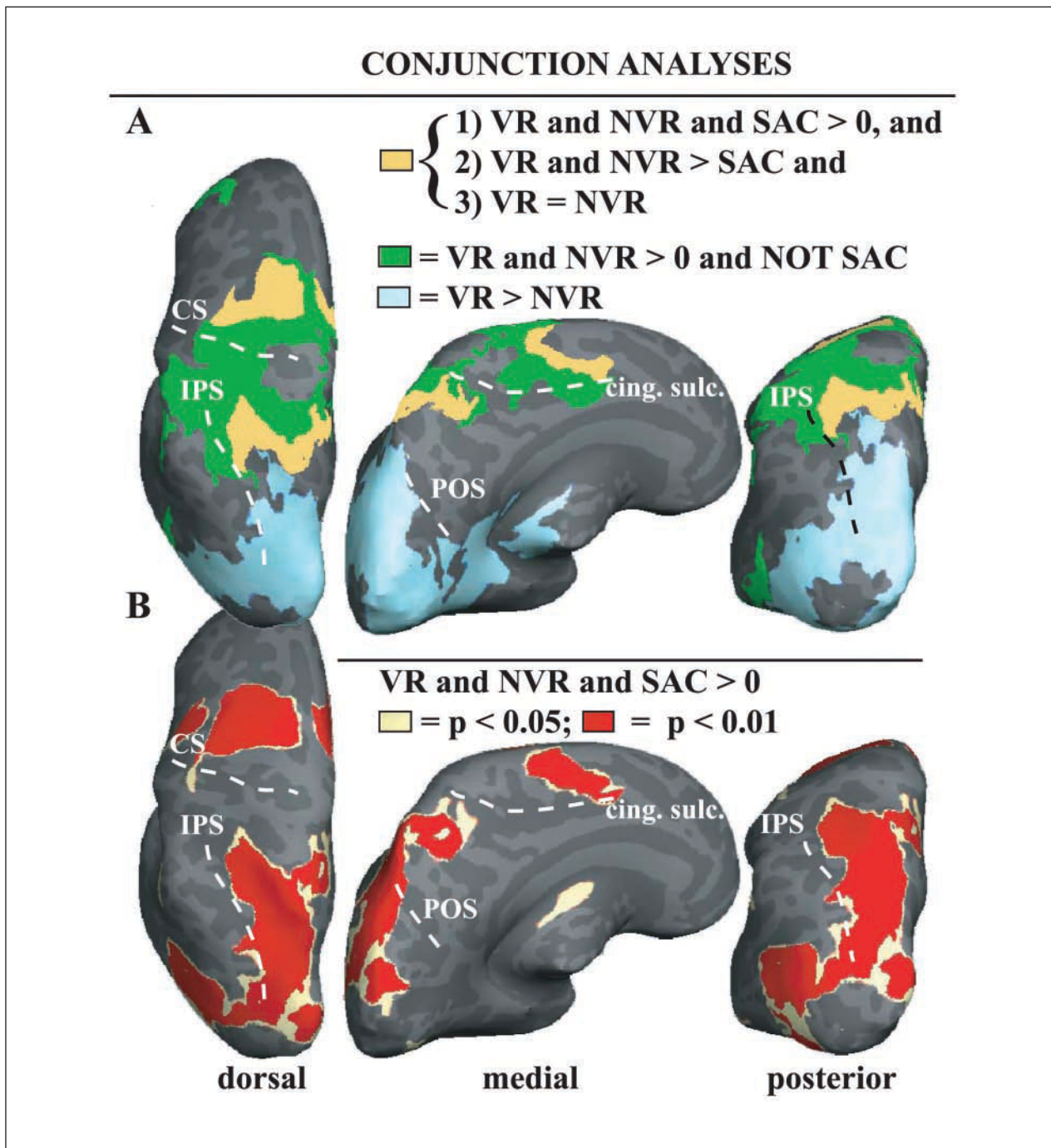
Figure 3. Conjunction analyses of fMRI activations for visible reaches (VR), nonvisible reaches (NVR), and saccades (SAC). (A) Gradient in visual to somatomotor function (blue to green). Yellow: areas activated significantly by all 3 conditions, but more strongly by visible and nonvisible reaches than saccades, and equally by both kinds of reaches. Green: areas activated significantly by both reaches, but not by saccades. Blue: areas activated significantly more strongly by visible reaches than nonvisible reaches. (B) Overlap between visible and nonvisible reaches and saccades at different significance levels. All 3 conditions overlap in the premotor and posterior parietal cortex. Modified from Filimon and others (2009) with permission.

supramarginal gyrus in the inferior parietal lobule (IPL) participate in both visible and nonvisible reaches (Fig. 2). Of these, the medial IPS, superior parietal gyrus, and middle part of the superior precuneus are also activated by saccades, although more weakly than by either kind of reach (Fig. 3). Within caudal IPS and at the superior

aspect of the POS (posterior precuneus), only visible reaches show greater activation than saccades. Thus, within the PPC, a clear visual to somatomotor gradient can be found from posterior to anterior areas (Fig. 3A). The fact that medial IPS and the precuneus show greater, yet overlapping, reach than saccade activity suggests reach *dominance*, rather than exclusive reach *selectivity*, in these areas. In addition, multiple reach-selective regions, rather than a single region, were found in anterior PPC areas: the anterior IPS, the IPL, and the most anterior parts of the superior parietal gyrus and precuneus all responded to both types of reaches but not to saccades. These areas likely receive proprioceptive input from the hand or arm.

Similarly, in the frontal lobe, both types of reaching activate PMd, (including the superior frontal sulcus and gyrus), the FEF, the supplementary and cingulate motor cortices on the medial aspect of the frontal lobe, and a smaller region in PMv. Saccades overlap with both kinds of reaching in the FEF, PMv, the rostral part of PMd, and the presupplementary motor area (pre-SMA), with reach activations dominating in all but PMv.

All of these parietofrontal activations are bilateral, although stronger in the left hemisphere contralateral to the reaching right hand (in right-handed subjects). Primary motor (M1) and somatosensory (S1) activations in the central sulcus are entirely lateralized to the contralateral (left) hemisphere.

Thus, there appears to be a gradient from posterior to anterior in the PPC, with greater visual dominance for saccades or visual reaching in the occipital lobe and posterior parts of the PPC, to mixed saccade and reaching responses in the medial IPS and superior parietal lobule (SPL), and finally to reach-only responses in the anterior IPS and anterior SPL (Fig. 3). In the premotor cortex, an anterior to posterior gradient can be seen, with mixed saccade and reach responses in more rostral parts of PMd and reach- or hand-only responses in caudal parts of PMd. This pattern of overlapping networks argues against separate reach and saccade modules and suggests a visual-to-somatomotor or eye-to-hand preference continuum.

A similar distributed overlapping parietofrontal network for hand and eye movements has been found for planned reaches and saccades (Beurze and others 2009, 2007), planned pointing and saccades (Hagler and others 2007; Connolly and others 2007; Medendorp and others 2005, 2003; Astafiev and others 2003), antisaccades and antipointing (Connolly and others 2000), for pointing or reaching and saccade topography (Hagler and others 2007; Levy and others 2007), as well as actual, nondelayed reaching (Culham and others 2003, 2006). Despite the overlap, the majority of these studies do, however, report stronger activations for hand movement planning and execution than for saccades, especially in areas located

anterior and superior in the PPC, extending medially into the precuneus, and in PMd. These studies confirm that the frontoparietal network for pointing includes the saccade network (Connolly and others 2000; Astafiev and others 2003). Unlike in the macaque, in humans, both FEF and the IPS are more active during planned or executed hand movements than during saccades, although there is evidence that in the macaque, FEF is also involved in reaching (Astafiev and others 2003). One exception can be found in Simon and others (2002), who report a large superior parietal cluster activated by saccades but not pointing. Note that studies on planned movements suggest that these distributed activations are not just due to sensory feedback but also due to motor preparation.

In some studies, pointing does not activate the precuneus more strongly than saccades (Hagler and others 2007). This could be due to the smaller movement of the hand during pointing (often just the index finger) compared to movement of the arm during reaching. Pointing generally also yields weaker and more restricted activations than reaching with the arm. In a study comparing arm movements with finger flexion and extension movements, with closed eyes, arm movements activated areas more medially in the superior parietal cortex (Filimon 2008). This suggests that pointing may not always be sufficient to activate reach-related areas. Also, compared to preparation of button presses, the PPC is more strongly activated by planned saccades (Macaluso and others 2007).

Other fMRI studies also support the idea of a visual-to-somatomotor gradient for hand movements in the PPC (Stark and Zohary 2008). The superior parieto-occipital cortex (SPOC) shows a preference for near viewing of visual targets and responds most strongly to visual objects within reach (Quinlan and Culham 2007; Gallivan and others 2009; Culham and others 2008). In contrast, an area located more anterior in the precuneus is modulated by postural changes of the arm during reaching with closed eyes to targets on the body, such as to the opposite thumb (Pellijeff and others 2006).

Although the network of reach-related cortical areas appears to be rather large, especially in the PPC, this does not preclude additional functional differentiation within the reach network. For instance, peripheral and central reaching involve overlapping but slightly different parietofrontal networks (Prado and others 2005; Clavagnier and others 2007). Reaching in the periphery activates the parieto-occipital junction (POJ) in addition to medial IPS and PMd. In contrast, reaching in central vision activates medial IPS and caudal PMd, but not the POJ. Because the vast majority of fMRI studies have presented reach targets peripherally, it is not clear how the peripheral/central reach organization proposed by Prado and others (2005) relates to the posterior-to-anterior

visual-to-somatomotor organization described above (Filimon and others 2009). The important point, however, is that multiple reach systems appear to exist rather than single reach and saccade modules. Stronger pointing-related compared to saccade-related activations are even found outside posterior parietal and frontal areas: a lateral occipital area, the extrastriate body area, responds more to hand than eye movements with or without visual feedback (Astafiev and others 2004).

It is possible, however, that the apparent discrepancy between human fMRI and macaque neurophysiology regarding the degree of effector specificity is due to differences in technique. An MEG study found direction-selective synchronization in the 70- to 90-Hz gamma band for pointing in a medial parietal area and direction-selective synchronization in the 50- to 60-Hz gamma band for saccades in a more central and posterior part of the PPC (Van Der Werf and others 2010). While spatial localization in MEG depends on source reconstruction and may be difficult to compare directly with fMRI localization, this result does indicate the need to combine multiple techniques to resolve the issue of effector specificity.

Do these functional activations identify homologs of macaque reach-related regions? The pattern of activation at the superior POS is consistent with the visual and motor properties of macaque V6A, which also shows modulation by visual input from the reaching hand and is sensitive to the retinal location of the target (Fattori and others 2001; Marzocchi and others 2008). Anterior areas in the superior precuneus are not modulated by sight of the hand (Filimon and others 2009), suggesting a proprioceptive input consistent with area PEc (Breveglieri and others 2006), although the precuneus region is coactivated with the medial IPS (Fig. 3). The medial IPS area is broadly consistent with macaque MIP. The large hand-selective anterior IPS and IPL responses (Fig. 3), on the other hand, are consistent with previously reported activations for grasping and hence with macaque areas AIP (Culham and others 2003) and 7a. It is possible that this activation is due to somatosensory stimulation from the hand during the transporting of the arm and hand toward a target, even if no grasping occurs.

In the premotor cortex, the anterior dorsal premotor activation to both reaches and saccades (Fig. 3) is consistent with macaque pre-PMd, which receives eye movement signals from parietal areas. The caudal PMd activations to hand movements only are consistent with macaque PMd (Picard and Strick 2001).

Target versus Effector Information

Several fMRI studies have attempted to disentangle cortical activations due to (remembered or present) visual targets and movement-related signals (Beurze and others 2009, 2007; Blangero and others 2009; Fernandez-Ruiz and others 2007; Medendorp and others 2005; Connolly and others 2003, 2000). The general pattern that emerges is again one of a gradient of decreasing importance of the spatial location of the target (left or right visual field) and of increasing importance of the effector (left or right hand, as opposed to the eye) from posterior to anterior in the PPC and from rostral to caudal in the premotor cortex (Fig. 4). In other words, spatial and effector selectivity varies gradually over the parietofrontal cortical network (Beurze and others 2009; Stark and Zohary 2008).

To independently manipulate target and effector information for movement planning, one can first present either the location of the target, and then information about which effector (hand or eye) to move, or vice versa (Beurze and others 2009). When effector information is presented first (instruction to prepare either hand or eye movements), but without target information, parietal areas in the IPS and posterior parts of the SPL as well as dorsal and ventral premotor areas are recruited in an effector-independent manner. As soon as spatial target information is added, effector selectivity (greater hand compared to eye preparatory activity) increases in anterior superior parietal and AIP areas as well as in PMd. An index of effector versus spatial target selectivity (during motor planning after both effector and target information is revealed) shows that caudal IPS (cIPS) represents both target and effector information, while anterior IPS shows stronger effector selectivity (hand dominance) and little target selectivity (Fig. 4). In the premotor cortex, PMv shows strong spatial target (but also some effector) preference, with progressively greater effector selectivity in PMd, to a clear effector dominance in SMA. Note that Beurze and others (2009) found none of these areas to respond exclusively to either effector (hand or eye), which matches the overlapping reach and saccade networks described above. Moreover, the effector dominance developing during motor preparation shows that these activations cannot be interpreted simply as attention-related signals.

A similar result is observed when comparing left- and right-hand movements to left and right targets (Fig. 4). Whereas M1 and S1 show exclusive selectivity for the contralateral hand, as one moves posterior into the PPC and anterior into PMd, left- and right-hand signals are comingled (Medendorp and others 2005; Blangero and others 2009).

Thus, overall, studies on effector and spatial goal representations suggest that effector and target information is represented in a gradient across parietofrontal networks rather than in isolated effector-specific modules. Moreover, effector selectivity is not a fixed property of
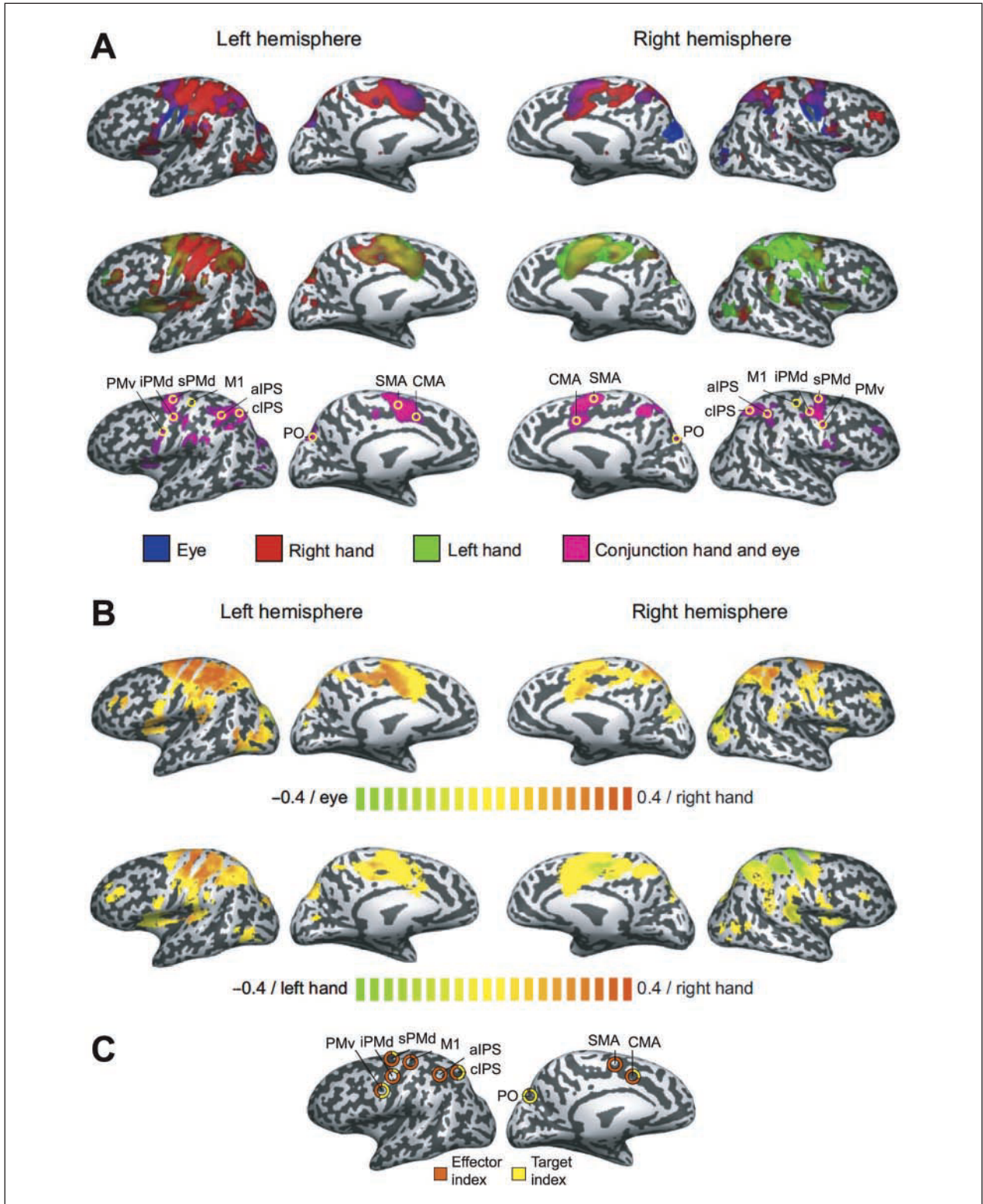
Figure 4. (A) fMRI activations during movement planning with different effectors. Activations for saccade and left- and right-hand movement planning overlap in a parietofrontal network. (B) Index maps of effector preference during movement planning (top: saccades v. right-hand movements; bottom: left-hand v. right-hand movements). (C) Spatial goal location versus effector selectivity. Adapted from Beurze and others (2009) with permission.

sensorimotor areas but develops in the course of the evolving movement plan (Beurze and others 2009).

Reaching versus Grasping

A number of human neuroimaging studies have attempted to identify a human homolog of the AIP-F5 circuit proposed for grasping in monkeys (Hinkley and others 2009; Grol and others 2007; Culham and others 2003; Stark and Zohary 2008; Binkofski and others 1999; Grafton and others 1996; for reviews, see Castiello 2005; Culham and others 2006; Culham and Valyear 2006; Cavina-Pratesi and others, forthcoming). Of particular interest for this review is the degree to which grasping differs from reaching or pointing in the human brain. Several studies have reported activations in the anterior IPS sulcus (aIPS), a likely homolog of AIP, during reaching-to-grasp (Culham and others 2003; Hinkley and others 2009; Frey and others 2005; Grafton and others 1996), haptic object manipulation without a transport component (Hinkley and others 2009; Binkofski and others 1999), during the grip component without a transport phase (Cavina-Pratesi and others, forthcoming), and pantomimed grasping (Simon and others 2002). However, reaching or pointing alone also robustly activates the anterior IPS (Filimon and others 2009; Culham and others 2006; Simon and others 2002). Activations are stronger for grasping than for reaching or reaching-to-point in human AIP (Culham and others 2003; Grafton and others 1996). Nevertheless, the fact that human AIP appears to respond robustly during the transport component (reaching), transport and prehension stages (grasping), and haptic manipulation alone argues against human AIP as an isolated grasping module. Recent work (Cavina-Pratesi and others, forthcoming) shows that aIPS is activated by the grip component even if no transport (reach) is involved. It has been argued that the above-baseline activation of aIPS during reaching might be due not to an involvement in reaching per se but to more general visuomotor control (Cavina-Pratesi and others, forthcoming), although this remains to be established.

In addition, grasping in humans also activates areas in the SPL, which overlap with reach-related activations (Culham and others 2003; Castiello 2005). This suggests that in the human, grasping and reaching are not as distinct as proposed in the macaque, in which a ventral parietofrontal pathway for grasping and a dorsal parietofrontal pathway for reaching have been proposed (Matelli and Luppino 2001). In fact, recent evidence in macaques shows the dorsal pathway is involved in the control of both reaching and grasping (Fattori and others 2009, 2010). Widespread PPC activations for grasping have been found using the ^{14}C-deoxyglucose method in macaques, corroborating human results (Evangeliou and others 2009).

It is, however, possible that grasping recruits multiple PPC regions, while AIP is the most critical site. Transcranial magnetic stimulation (TMS) to aIPS in humans disrupts the grasp but not the transport component, whereas TMS to middle IPS and caudal IPS does not disrupt grasping (Rice and others 2006). Human patients with anterior IPS lesions show impaired grasping (Binkofski and others 1998). This does not necessarily rule out an involvement in grasping in these other PPC areas but instead suggests that aIPS is critically involved in grasping (Cohen and others 2009).

Human homologs of macaque F5 in human PMv have been harder to identify (Castiello 2005). Several early PET studies as well as some fMRI studies did not find ventral premotor activations for reaching-to-grasp movements (Frey and others 2005; Grafton and others 1996; Rizzolatti and others 1996). Other fMRI studies have, however, reported PMv activations during multidigit visually guided grasping (Cavina-Pratesi and others, forthcoming; Grol and others 2007) and object manipulation (Binkofski and others 1999). It is possible that PMv activation depends on the complexity of the grasp (e.g., complex finger configurations) (J. Culham, personal communication). Interestingly, grasping also activates PMd, which is usually activated by reaching (Grol and others 2007; Culham and others 2003; Grafton and others 1996).

Both the dorsolateral circuit (AIP-PMv), traditionally considered to be involved in grasping, and the dorsomedial circuit (SPL-PMd), the putative reaching circuit, are involved in grasping in humans (Grol and others 2007). Effective connectivity between parietofrontal areas in the dorsolateral circuit increases during grasping of small objects, whereas effective connectivity in the dorsomedial circuit increases during grasping of large objects. This is further evidence that the transport and prehension phases are represented by overlapping parietofrontal circuits, suggesting a lack of strict functional segregation between parietofrontal circuits for grasping and reaching in humans.

PMv and PMd could nonetheless play different roles in grasping. For instance, TMS applied to PMv disrupts the grasping phase in a grasp-to-lift task, whereas TMS applied to PMd primarily disrupts the coupling between the grasping and lifting phases by delaying the recruitment of the proximal muscles involved in the lifting phase (Davare and others 2006).

A lack of a strict inferior versus superior, or lateral versus medial, functional division between hand and arm movements also matches current knowledge of M1 functional organization. Whereas earlier views emphasized a homuncular, somatotopic organization of M1, with finger movements represented laterally and arm movements represented medially, current evidence suggests multiple

overlapping representations of distal and proximal movements in M1 (Schieber 2000; Barinaga 1995; Sanes and others 1995). Broad somatotopic gradients in peak activations from finger to arm movements may exist in human M1; however, activity is highly distributed and overlapping (Grafton and others 1993). Unlike the somatosensory or visual systems, which map 2-dimensional surfaces of receptors, the motor system involves muscle activations for movements in 3-dimensional space, making it harder to map muscles onto a 2-dimensional cortical surface (Schieber 2000).

In summary, although human neuroimaging has revealed similarities between human and macaque cortical organization for hand movements (Grefkes and Fink 2005), it appears that in humans, the areas involved in different hand movements are not functionally specialized, isolated cortical regions. Rather, there are highly distributed, overlapping parietofrontal networks with gradients in preference for one movement compared to another. It is also possible that the macaque brain itself is not as modularly organized as has been suggested. It would be useful to compare fMRI or other techniques in both monkeys and humans across a variety of hand movement tasks to identify true differences in cortical organization for hand movements.

Reference Frames for Control of Hand Movements

To initiate a visually guided hand movement toward an external object, the retinal (extrinsic) coordinates of the object must be transformed into joint- and muscle-centered (intrinsic) coordinates that specify the muscle activations required to move the hand to that location (Kalaska 2009; Kalaska and others 2003). The movement can thus be described in terms of kinematics (the spatial displacement, velocity, acceleration of hand motion) and kinetics or dynamics (the muscle forces and joint torques producing the movement) (Soechting and Flanders 1998; Kalaska and others 2003; Kalaska 2009). What level of detail is the movement planned at, what are the intervening coordinate or reference frame transformations, and where are such reference frames represented in the brain?

Although population signals in M1 appear to correlate with directional kinematics of movements, it has been argued that M1 activity can be more parsimoniously explained in low-level muscle control terms, that is, kinetics (Todorov 2000; see Kalaska 2009 for a review). In contrast, parietofrontal regions appear to better correlate with kinematic parameters such as hand position and direction of movement rather than muscle force (Kalaska 2009). Both motor goals and trajectories can be decoded from the PPC (Andersen and others 2010; Mulliken and others 2008; Archambault and others 2009).

Do different parietal and premotor areas encode the reach relative to the eye (gaze position), the body (trunk), or the hand/arm? In an eye-centered reference frame, a neuron's response field shifts with a shift in gaze position, that is, with every eye movement. Thus, an eye-centered neuron responds only to a reaching movement to the same spatial location relative to the eye, wherever the gaze may be fixed. Conversely, body-centered representations for reaching are unaffected by eye movements or by rotations of the head, as long as the reach is happening in the same part of space relative to the trunk, for instance, to the right of the torso. A hand-centered reference frame entails that the neuron's preferred direction of reach is centered on the hand; for example, a neuron might prefer reaches to the left of the hand only, regardless of where the hand is located in space.

Evidence for each of these reference frames has been reported in the macaque. For example, a body-centered reference frame for reaching has been proposed for area 5 of the SPL, an eye-centered reference frame for MIP, and a hand-centered reference frame for the premotor cortex (Graziano 2001).

Other studies have reported mixed eye- and limb-centered coordinate frames for reaching in area 5 and in PMd; that is, cells' response fields shift partially with changes in both eye and limb position (Andersen and Cui 2009; Graziano 2006; Batista and others 2007; Pesaran and others 2006). A hybrid head- and eye-centered reference frame has also been found in both lateral and medial IPS (Mullette-Gillman and others 2009). A mixed eye-centered and space-centered frame for reaching has been proposed for area V6A (Marzocchi and others 2008).

The presence of mixed reference frames and partially shifting receptive fields and mixed reference frames in sensorimotor areas calls into question the one-to-one mapping of one reference frame to one brain area, at least in sensorimotor areas (Pouget and others 2002). Several sensorimotor regions, including the superior colliculus, LIP, and PRR, show partially shifting receptive fields. For instance, when the eyes move, the auditory receptive fields of bimodal visual and auditory neurons in the superior colliculus are only partially shifted to match the new eye position, meaning that the auditory receptive fields are not fully remapped in eye-centered coordinates (Pouget and others 2002).

Different reference frames may be multiplexed depending on the particular hand action to be implemented, such as reaching, withdrawal, or bringing an object to the mouth (Graziano 2006). Coordinate transformations between different reference frames could be achieved through gain field modulations by various position signals. For instance, in area 7a, a neuron's response to a visual stimulus presented at the same retinal location is modulated by the angle of gaze or position of the eyes in
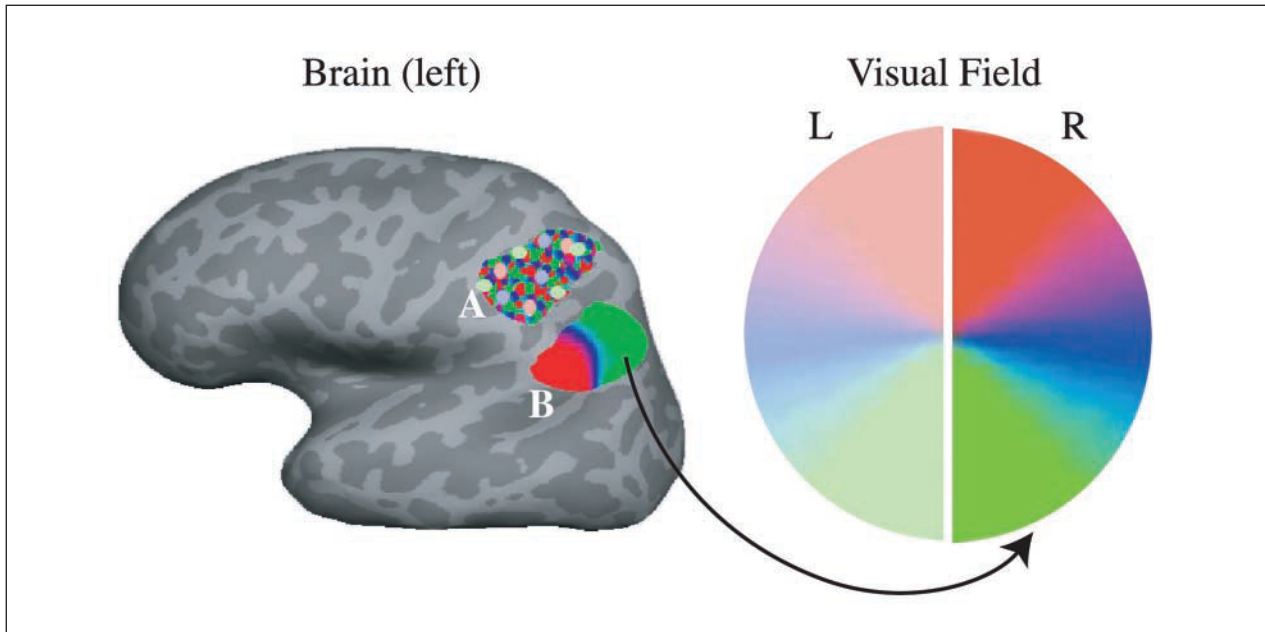
Figure 5. A schematic of two hypothetical brain areas: (A) a hypothetical nontopographic (nonretinotopic) area with receptive fields covering the left and right visual field, and (B) a hypothetical retinotopic map of the right visual field. In the retinotopic area, adjacent eye-centered neurons have adjacent receptive fields in the contralateral visual space (lower, middle, and upper visual field), arranged in an orderly fashion (see arrow and color scheme). The nonretinotopic area also contains eye-centered neurons, but their visual receptive fields cover either the left or right visual field. Adjacent neurons have receptive fields in random parts of the visual field. Colors in smaller circles represent individual eye-centered neurons' receptive field and match different parts of the visual field.

the orbits (Andersen and others 1985). Thus, a neuron will respond differently to retinotopically identical stimulation, depending on whether the eyes are looking left, right, or some other direction. Integrating over area 7a cells that respond most strongly to visual stimuli at different combinations of eye position and retinal location, but the same head-centered location, could thus signal the location of the visual stimulus in head-centered coordinates (Andersen and others 1985).

Such modulation by eye position has been reported in multiple brain areas, including areas involved in hand movements. In humans, fMRI studies have reported gaze-position modulation of pointing activity in rostral IPS (Desouza and others 2000) and of finger-tapping activations in the SPL and several frontal areas (Bédard and others 2008).

Computational models, such as recurrent networks using basis function units, have successfully modeled experimental data on mixed reference frames and partially shifting receptive fields (Pouget and others 2002). Inputs from units representing different reference frames are multiplied in an intermediate layer using basis function units to achieve coordinate transformations. In fact, such models suggest that a motor command (e.g., for reaching) is encoded in all frames of reference available in the network, owing to its recurrent connections between

layers with different frames of reference (Pouget and others 2002).

Note, however, that not all neurons involved in reaching need make use of any reference frame at all. Some neurons in superior parietal area 5 do not code for position of the arm and hand in space per se but for posture or joint angle. For example, some neurons are sensitive to elevation of the shoulder and are hence selective for reaches in the upper part of space, without encoding those reaches in a particular reference frame (Graziano 2001).

In humans, behavioral and functional MRI studies of reference frames for reaching have mostly focused on eye-centered (gaze-centered) representations, partly due to studies suggesting that macaque PRR encodes reaches in eye-centered coordinates (Andersen and Buneo 2002). This has prompted some investigators of human reaching to look for *retinotopic* or *topographic* maps for reaching or pointing movements (Hagler and others 2007; Levy and others 2007; Fernandez-Ruiz and others 2007; Medendorp and others 2003).

However, eye-centered or retino*centric* and retino*topic* are not equivalent terms. As Figure 5 illustrates, individual neurons can use an eye-centered (gaze-centered, or retinocentric) frame of reference, but adjacent neurons may not be organized in an orderly map of the visual field,

that is, may not be retinotopically organized. This would mean that eye-centered neurons could be part of a scrambled, nontopographic, map of visual space.

This in fact appears to be the case in macaque area V6A. The majority of neurons in area V6A have receptive fields anchored to the retina, such that when the eyes move, the receptive fields move too. However, adjacent cells have receptive fields scattered all over the visual field, with receptive fields from adjacent cells even "jumping" from ipsilateral to contralateral or central to peripheral locations in the visual field (Galletti and others 1999). Neuronal tracer injections also failed to find a topographic organization in V6A while revealing a coarse retinotopic organization in area MIP and robust retinotopy in early visual areas V1, V2, V3, and V6 (Galletti and others 2001).

These findings highlight that human pointing- or reaching-related areas need not be organized topographically or retinotopically, even if eye-centered reference frames for reaching may exist. In fact, human fMRI studies looking exclusively for retinotopically organized maps for pointing or reaching as potential homologs of macaque PRR may uncover only subsets of reach-related areas because not all areas involved in reaching are retinotopically organized.

It is, however, also possible that fMRI may uncover an existing retinotopic organization by smoothing and averaging signals from millions of neighboring cells, which single-unit recordings in the macaque cannot measure (Martin I. Sereno, personal communication). Indeed, fMRI studies have revealed overlapping topography for saccades and hand movements in parietal and frontal areas (Hagler and others 2007; Levy and others 2007; Medendorp and others 2003).

Using an intervening saccade task, Medendorp and others (2003) showed that targets for both saccades and pointing movements are remapped (updated) in gaze-centered coordinates in a bilateral posterior parietal area (possibly putative human LIP). In this task, subjects prepared delayed saccades or pointing movements to a visual target. Prior to executing the movement, however, an intervening saccade was carried out, which caused the target to either switch to the contralateral visual field or stay in the ipsilateral visual field. The bilateral parietal region was organized topographically: the left hemisphere mapped targets in the right hemifield, and the right hemisphere mapped targets in the left hemifield. When an intervening saccade caused a target to switch hemifields, the activation in this parietal area shifted to the opposite hemisphere, as would be expected for gaze-centered remapping.

Note, however, that these findings suggest gaze-centered remapping of visual targets for saccades and pointing movements, not necessarily a gaze-centered reference frame for the pointing movement per se. In other words, the pointing movement itself may not be represented in a gaze-centered frame. A target could be located in the right visual field (thus necessitating a rightward saccade) but could require a leftward pointing movement if the hand is to the right of the target. However, the same gaze-centered representation was found in this PPC area, regardless of whether the saccade and pointing movements were in opposite directions: what appears to matter is the location of the visual (or motor) *target* in eye-centered coordinates, not the actual hand *movement* used to get there. This should be distinguished from a gaze-centered representation of the actual hand movement. It could be that this PPC area represents targets topographically, while the pointing movement could be represented elsewhere, in a nontopographic area. The same issue applies to studies of antimovements (in which the movement is directed to an imaginary target 180° away from the visual cue), because the visual target of the movement is simply remapped, and target versus movement direction still need to be controlled independently. The hand movement path to an antitarget can still vary depending on initial hand position.

The issue of whether parietal areas represent the visual (or motor) goal as opposed to the movement direction relative to gaze was addressed in an fMRI study that reversed the visual input with prisms (Fernandez-Ruiz and others 2007). By using left/right reversing prisms, rightward pointing targets and movements were now seen as leftward and vice versa. A region at the POJ in the precuneus represented the visual goal of the movement during movement planning but not the actual movement direction. The topography of activations (left-hemispheric activation for intended rightward pointing and right-hemispheric activation for intended leftward pointing) was reversed to match the new, reversed goal (left-hemispheric activation for leftward movements). Moreover, the activity remained reversed not only during planning but also during execution of the pointing movement. The authors therefore concluded that it is the visual movement goal, not the movement direction, that is encoded topographically in gaze-centered coordinates in the PPC. The same reversal was observed in (putative) human LIP and BA7 but not in the angular gyrus.

This raises the possibility that the topographical areas for reaching or pointing movements reported by other fMRI studies are actually topographical (specifically, retinotopic) maps for *visual goals* of hand movements, not hand movement directions. It thus remains to be established whether any regions actually encode hand movement direction in eye-centered coordinates in humans.

This finding may also help explain why fMRI studies have reported highly overlapping retinotopic maps for

saccades and hand movements in the IPS, SPL, and superior frontal cortex, despite the difference in effectors used (Levy and others 2007; Hagler and others 2007). These topographical maps may represent the target and not the movement. This is consistent with the sensorimotor nature of these areas: they represent not only movements but also visual targets. The maps may thus reflect the visual organization of these areas but not necessarily their motor organization.

The idea of a single reference frame for both effector and target arises from the need to compute a difference vector between target and hand location. Because the target is already represented in eye-centered coordinates, it is conceivable that the hand location could be transformed into eye-centered coordinates for a direct comparison (Medendorp and others 2008). Behavioral studies of reference frames in humans show that reach errors depend on the location of the target in both eye and hand coordinates, but not in body coordinates, with or without vision of the hand (Medendorp and others 2008; Beurze and others 2006). In other words, two movements have similar end-point errors if the target is the same in eye and hand coordinates. However, as cautioned by Medendorp and others (2008), this could be interpreted either as target and hand position being coded in eye-centered coordinates, or target and gaze position being coded in hand-centered coordinates, or both gaze and hand position being coded in target coordinates. Other behavioral studies have instead suggested that the reference frame for reaching is centered on the body (Flanders and others 1992). It thus remains to be seen if hand movements are coded with respect to a single reference frame in any brain area in humans.

Parietal versus Frontal Involvement in Hand Movement Control

How do parietal and frontal areas differ in their involvement in motor control? Whereas the caudal part of PMd and the SMA (but not rostral PMd or pre-SMA) have direct projections to M1 and the spinal cord (Picard and Strick 2001; Chouinard and Paus 2006), posterior parietal areas do not have a direct connection to the spinal cord. However, the PPC clearly has motor functions (Fogassi and Luppino 2005). Microstimulation of different parts of the anterior PPC in anesthetized galagos evokes different types of movements (e.g., forelimb defensive, face defensive, reaching, or eye movements) (Stepniewska and others 2005). Similarly, electrical stimulation of the IPL in human patients triggers the intention to move the contralateral limb (Desmurget and others 2009). Anatomical tracer studies in nonhuman primates have shown that the PPC receives input from motor

nuclei in the thalamus and shares overlapping thalamo-cortical connections with the frontal cortex (Gharbawie and others 2008). In humans, damage to the PPC leads to misreaching (optic ataxia) and misgrasping deficits that cannot be attributed to a basic sensory or basic motor deficit (Jackson and others 2009; Wolpert and others 1998). Even if a direct connection to the spinal cord is not present, interconnections with premotor areas and coactivation with frontal areas during execution and planning of movements suggest a PPC role in movement control.

Current theories of motor control suggest the motor system is organized as multiple nested feedback loops coupled to feed-forward signals (Kalaska and others 2003). When a motor command is generated, the current state of the system (e.g., limb) is provided by sensory feedback systems and is continuously compared to the desired goal state (Kalaska and others 2003). The difference between the current state and goal state is used to update the motor command. However, sensory feedback can be slow due to conduction delays: it takes visual and somatosensory feedback 90 ms and 30 ms, respectively, to reach the sensorimotor cortex (Andersen and others 2010). Because of this, the current state estimate cannot rely on sensory feedback alone but must use a forward state estimate (prediction of current state) based on efference copies of motor commands (Kalaska and others 2003). Current models suggest that the PPC combines sensory feedback and efference copies of motor commands issued by frontal motor areas to construct a forward model that predicts the current state of a moving limb as well as the sensory consequences of movement (Andersen and others 2010; Andersen and Cui 2009). This model predicts that activity reflecting motor commands should start in frontal areas and arrive later in the PPC as efference copies. Evidence from M1 versus PPC areas supports such a model: neurons in areas 5 and V6A respond just before and during movement but discharge on average 60 ms after M1 cells (Graziano 2001). However, evidence on the timing of premotor areas compared to posterior parietal areas is less clear.

In humans, fMRI studies typically show coactivation of reciprocally connected parietal and frontal areas during sensorimotor tasks such as reaching. Given the low temporal resolution of fMRI, it has proven difficult to differentiate the roles of posterior parietal versus premotor cortical areas in movement control, at least with respect to timing.

In macaques, multiple patterns of timing differences have emerged. Simultaneous recordings from PRR and PMd during reaching have shown that PRR and PMd spike latencies do not differ in simple center-out tasks (reaching to a peripheral target) (Pesaran and others 2008). In contrast, PMd spike responses precede PRR spike responses

by about 30 ms in free choice tasks, when the monkey needs to decide what sequence of reaches to execute between multiple targets, as well as in instructed search tasks, when the monkey moves the arm in a particular sequence. In addition, the spike–local field potential (LFP) coherence between PMd and PRR is greater during free choice compared to instructed arm movements and precedes PRR-PMd spike-field coherence by 30 ms (Pesaran and others 2008). This suggests that the flow of information depends on the task: in some cases, information may flow from the premotor cortex to the PPC (and possibly back to the premotor cortex), whereas in other tasks, both regions are active simultaneously.

Another approach to studying the relative timing of PMd and PRR activity during reaching involves dissociating cue-related and motor goal–related responses using an antireach task, in which monkeys reach away from the spatial location of the cue (Westendorff and others 2010). Using a partial precueing paradigm, the monkey can be first told either the rule cue (proreach or antireach), or the spatial cue (spatial location, but not yet prodirection or antidirection), or can be informed of both at the same time, followed by an instructed delay. In a separate condition, monkeys receive no precue, and monkeys move immediately to a rule-based or spatial go-target. This allows for dissociation between visual cue-related and motor goal–related signals. Also, motor goal response latencies can be separately examined at the beginning of an instructed delay, when no motor command has yet been issued, and after the go-cue just before motor execution. In other words, this attempts to dissociate motor goal signals and motor execution signals. Westendorff and others (2010) found that when spatial remapping of the motor goal was required, such as during antireaches, PMd neurons were tuned earlier for the motor goal than neurons in PRR, even before the motor command (go signal) was issued. When no spatial remapping was necessary, motor goal tuning latencies were similar in PMd and PRR. The authors interpret this finding as evidence for dynamic reorganization of network activity in the PRR, contingent on input from PMd. This suggests that forward estimates are generated not only following actual motor commands (i.e., not only based on corollary discharges) but also during the motor planning process (Westendorff and others 2010). Similar preparatory motor activity inconsistent with a strict efference copy signal has also been reported in a subset of V6A neurons (Fattori and others 2005; Galletti and others 2003, 1997).

Interestingly, simultaneous recordings from LIP and FEF suggest a very different picture. Lawrence and Snyder (2006) compared FEF and LIP responses to cue-delay-target trials. In these trials, an effector cue (eye or hand)

is presented first, instructing the monkey to prepare for either a saccade or reach trial. Following a variable delay, the spatial target for the movement is presented. By using this paradigm, effector-specific (or effector-dominant) signals can be measured independent of a spatial target. Both FEF and LIP showed a preference for saccade trials compared to reach trials (i.e., effector preference or dominance). Surprisingly, the onset of effector-specific modulation occurred about 400 ms later in FEF than LIP. During the delay, the magnitude of effector preference was significantly smaller in FEF than in LIP and PRR. Moreover, effector specificity (preference) in FEF was largely due to FEF neurons predicting the spatial location where the target would appear (namely, inside the receptive field). LIP neurons, in contrast, continued to show effector preference whether the target subsequently appeared inside or outside the receptive field. FEF and LIP neurons had similar visual response latencies to the onset of the targets, thus arguing against a sluggish sample of FEF neurons. Lawrence and Snyder (2006) thus suggest that effector-dominant signals in LIP cannot be the result of a top-down influence from FEF, although they may originate from other frontal areas, such as the supplementary eye fields (SEF). These results suggest that the interplay between frontal and parietal areas depends not only on the task but also on the specific parietofrontal circuit.

In addition to latency differences, single-unit recordings have also shown other functional differences between premotor and parietal areas. When monkeys are instructed to move a central handle to peripheral locations, neurons in PMd and in area 5 behave differently following GO and NOGO cues (Kalaska and Crammond 1995). Following the appearance of a GO or NOGO cue that tells the monkey whether or not to move to a later-appearing target, PMd neurons clearly signal the decision not to move, towards the end of the delay. In contrast, area 5 neurons continue to fire during the delay following both GO and NOGO cues. This suggests different representations of potential motor responses in the parietal and premotor cortex, with the premotor cortex playing a greater role in response selection (Kalaska and Crammond 1995).

Similar results have been reported with fMRI in humans (Thoenissen and others 2002). Intraparietal and superior parietal regions responded during a delayed finger-flexing task regardless of the probability of later executing the movement, whereas precentral areas only responded when the cue predicted a GO trial. This suggests frontal areas might be closer to movement execution than parietal areas (Thoenissen and others 2002).

Human fMRI studies have also made use of the promovement and antimovement task to elucidate different contributions from frontal and parietal areas, although

the timing and direction of information flow are harder to assess due to the lower temporal resolution of fMRI. Both frontal and posterior parietal areas are activated during prosaccades and antisaccades as well as propointing and antipointing (Curtis and Connolly 2008; Connolly and others 2000). Both the IPS and FEF show sustained delay activity even if only the proinstruction or anti-instruction cue is known, before the spatial location of the target is revealed (Curtis and Connolly 2008). This contradicts an earlier fMRI study in which only FEF was found to show delay activity following the proinstruction or anti-instruction, before knowledge of the spatial target location (Connolly and others 2002), although this discrepancy could be due to differences in task design. However, compared to the IPS, FEF shows a greater bias for movements in the opposite visual field (contraversive saccades) (Curtis and Connolly 2008).

In summary, the differential roles of premotor and parietal areas in movement control remain unclear in both humans and macaques. Although premotor activity appears to precede posterior parietal activity in some instances, this timing difference is dependent on the task, parietofrontal circuit, and effector used. Not all PPC motor-related activity may be due to efference-copy signals. This is compatible with the functional heterogeneity of different posterior parietal and premotor areas. It is of course possible that other frontal areas, such as the dorsolateral prefrontal cortex, exert top-down control on both premotor regions such as PMd and parietal regions such as the PRR. Multiunit recordings in several brain regions might be able to address this possibility in the future.

Conclusions and Future Research Directions

Neuroimaging evidence in humans predominantly suggests that the cortical representations for different movements, specifically the parietofrontal circuits for different limb or eye movements, are highly distributed and overlapping. Nonetheless, there are gradients of functional preference or effector dominance across the PPC and premotor cortex. Thus, while there do not appear to be specific modules for reaching or saccades, or entirely separate reach circuits versus grasp circuits, there are gradients in effector preference or sensory gradients from visual to somatosensory information. Although there are broad homologies between movement-related areas in human and nonhuman primates, human parietofrontal networks for movements appear less specialized than those in the macaque.

However, it is possible that differences in techniques used in the two species could account for this discrepancy. Compared to invasive recordings, fMRI has much

lower spatial and temporal resolution. It is possible that highly specialized populations of neurons may exist in the human parietofrontal network too, but that they might be too small or intermingled. Whenever a specialized population of intermingled neurons is active, the entire region will appear to be activated, due to local blurring of signals in fMRI, thus giving the impression of a lack of functional specificity. On the other hand, single-unit neurophysiology also has its shortcomings. Only a few hundred cells are typically recorded from, whereas fMRI can give an overview of activity in the entire brain. Selection bias toward neurons with certain functional properties (Kriegeskorte and others 2009) can give the impression of greater functional specificity than warranted. Also, there is evidence that the macaque brain itself is not as modularly organized as sometimes suggested (Fattori and others 2010).

Even if different parietofrontal networks are highly distributed and overlapping, future research could attempt to capture the distributed nature of such functional networks using multivoxel pattern analysis (MVPA) of fMRI data. MVPA is especially useful for uncovering subtle differences in overlapping activations distributed across multiple voxels, which traditional univariate fMRI analyses fail to capture (Raizada and Kriegeskorte 2010). A similar approach has proven fruitful in decoding different object categories from overlapping ventral visual activations (Norman and others 2006). MVPA applied to the dorsal parietofrontal stream could help dissociate distributed overlapping networks for different actions.

By investigating the finer-grained functional networks associated with different sensorimotor tasks, future experiments could potentially address the problem of intermingled populations of neurons. The patterns of voxel activations could be investigated in progressively smaller regions of interest, to identify which area(s) carry the most discriminating signals for different sensorimotor functions. Note that this goes beyond identifying maxima in BOLD activations because signals could be distributed and overlapping yet show distinct patterns of activation within the same area (Raizada and Kriegeskorte 2010). For instance, can saccades be distinguished from reaching or pointing based on distributed activations in both the precuneus and MIP? Can they still be distinguished based on the pattern of voxel activations within MIP or the precuneus alone? Can distributed activations be better decoded from parietal or frontal areas? In macaques, intended movements can be decoded via microelectrode arrays implanted in the PPC alone (Andersen and others 2010; Andersen and Cui 2009). Also, because it appears likely that several macaque areas contain multiple populations of neurons with different mixtures of reference frames, perhaps an MVPA approach could also reveal brain networks underlying different reference frames.

Figure 6. Functional and structural subdivisions of the human precuneus based on 3 different techniques: (A) functional activations from standard task-related BOLD fMRI, (B) functional differentiations based on resting-state functional connectivity, and (C) anatomical subdivisions based on postmortem brain cytoarchitectonics. All 3 techniques show very similar subdivisions in the human precuneus. A adapted from Filimon and others (2009) with permission; B adapted from Margulies and others (2009) with permission; and C adapted from Scheperjans and others (2008) with permission.

In addition, other brain techniques could be combined with task-based fMRI or MEG experiments to uncover functional networks or boundaries between different areas. For instance, resting-state functional connectivity analysis has revealed functional subdivisions in the precuneus based on patterns of connectivity during rest (Margulies and others 2009) (Fig. 6). Interestingly, those subdivisions map very well onto cytoarchitectonic boundaries identified in postmortem human brains (Scheperjans and others 2008), as well as onto functional differences between regions identified with traditional BOLD fMRI experiments (Fig. 6). Combining techniques that investigate function, structure, and intrinsic connectivity between brain areas could paint a more accurate picture of functional networks, thus going beyond the idea of separate isolated modules for different sensorimotor functions. Together with techniques with higher temporal resolution than fMRI (e.g., MEG), such a multilevel approach

can provide novel insights into the functional specificity of parietofrontal networks in both human and nonhuman species.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

References

Andersen RA, Buneo CA. 2002. Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189–220.

Andersen RA, Cui H. 2009. Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63(5):568–83.

Andersen RA, Essick GK, Siegel RM. 1985. Encoding of spatial location by posterior parietal neurons. Science 230(4724):456–8.

Andersen RA, Hwang EJ, Mulliken GH. 2010. Cognitive neural prosthetics. Annu Rev Psychol 61:169–90, C1–3.

Archambault PS, Caminiti R, Battaglia-Mayer A. 2009. Cortical mechanisms for online control of hand movement trajectory: the role of the posterior parietal cortex. Cereb Cortex 19(12):2848–64.

Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van Essen DC, Corbetta M. 2003. Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. J Neurosci 23(11):4689–99.

Astafiev SV, Stanley CM, Shulman GL, Corbetta M. 2004. Extrastriate body area in human occipital cortex responds to the performance of motor actions. Nat Neurosci 7(5):542–8.

Barinaga M. 1995. Remapping the motor cortex. Science 268(5218):1696–8.

Batista AP, Santhanam G, Yu BM, Ryu SI, Afshar A, Shenoy KV. (2007). Reference frames for reach planning in macaque dorsal premotor cortex. J Neurophysiol 98(2):966–83.

Bédard P, Thangavel A, Sanes JN. 2008. Gaze influences finger movement-related and visual-related activation across the human brain. Exp Brain Res 188(1):63–75.

Beurze SM, de Lange FP, Toni I, Medendorp WP. 2007. Integration of target and effector information in the human brain during reach planning. J Neurophysiol 97(1):188–99.

Beurze SM, de Lange FP, Toni I, Medendorp WP. 2009. Spatial and effector processing in the human parietofrontal network for reaches and saccades. J Neurophysiol 101(6):3053–62.

Beurze SM, Van Pelt S, Medendorp WP. 2006. Behavioral reference frames for planning human reaching movements. J Neurophysiol 96(1):352–62.

Binkofski F, Dohle C, Posse S, Stephan KM, Hefter H, Seitz RJ, Freund H-J. 1998. Human anterior intraparietal area subserves prehension: a combined lesion and functional MRI activation study. Neurology 50:1253–9.

Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H. 1999. A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. Eur J Neurosci 11(9):3276–86.

Blangero A, Menz MM, McNamara A, Binkofski F. 2009. Parietal modules for reaching. Neuropsychologia 47(6):1500–7.

Bosco A, Breveglieri R, Chinellato E, Galletti C, Fattori P. 2009. Influence of visual feedback on reaching activity in parietal area V6A. Abstr Soc Neurosci 355.20.

Breveglieri R, Galletti C, Gamberini M, Passarelli L, Fattori P. 2006. Somatosensory cells in area PEc of macaque posterior parietal cortex. J Neurosci 26(14):3679–84.

Castiello U. 2005. The neuroscience of grasping. Nat Rev Neurosci 6(9):726–36.

Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam T, Quinlan D, and others. Forthcoming. fMRI reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions. J Neurosci.

Chouinard PA, Paus T. 2006. The primary motor and premotor areas of the human cerebral cortex. Neuroscientist 12(2):143–52.

Clavagnier S, Prado J, Kennedy H, Perenin M-T. 2007. How humans reach: distinct cortical systems for central and peripheral vision. Neuroscientist 13(1):22–7.

Cohen NR, Cross ES, Tunik E, Grafton ST, Culham JC. 2009. Ventral and dorsal stream contributions to the online control of immediate and delayed grasping: a TMS approach. Neuropsychologia 47(6):1553–62.

Connolly JD, Andersen RA, Goodale MA. 2003. FMRI evidence for a 'parietal reach region' in the human brain. Exp Brain Res 153(2):140–5.

Connolly JD, Goodale MA, Cant JS, Munoz DP. 2007. Effector-specific fields for motor preparation in the human frontal cortex. NeuroImage 34(3):1209–19.

Connolly JD, Goodale MA, Desouza JF, Menon RS, Vilis T. 2000. A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. J Neurophysiol 84(3):1645–55.

Connolly JD, Goodale MA, Menon RS, Munoz DP. 2002. Human fMRI evidence for the neural correlates of preparatory set. Nat Neurosci 5(12):1345–52.

Culham JC, Cavina-Pratesi C, Singhal A. 2006. The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia 44(13):2668–84.

Culham JC, Danckert SL, DeSouza JFX, Gati JS, Menon RS, Goodale MA. 2003. Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Exp Brain Res 153(2):180–9.

Culham JC, Kanwisher NG. 2001. Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol 11(2):157–63.

Culham JC, Gallivan J, Cavina-Pratesi C, Quinlan DJ. 2008. fMRI investigations of reaching in ego space in human superior parieto-occipital cortex. In: Klatzky R, McWhinney B, Berhmann M, editors. Embodiment, ego-space, and action. Mahwah (NJ): Erlbaum. p 247–74.

Culham JC, Valyear KF. 2006. Human parietal cortex in action. Curr Opin Neurobiol 16(2):205–12.

Curtis CE, Connolly JD. 2008. Saccade preparation signals in the human frontal and parietal cortices. J Neurophysiol 99(1):133–45.

Davare M, Andres M, Cosnard G, Thonnard J-L, Olivier E. 2006. Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci 26(8):2260–8.

Desmurget M, Reilly KT, Richard N, Szathmari A, Mottolese C, Sirigu A. 2009. Movement intention after parietal cortex stimulation in humans. Science 324(5928):811–3.

Desouza JF, Dukelow SP, Gati JS, Menon RS, Andersen RA, Vilis T. 2000. Eye position signal modulates a human parietal pointing region during memory-guided movements. J Neurosci 20(15):5835–40.

Evangeliou MN, Raos V, Galletti C, Savaki HE. 2009. Functional imaging of the parietal cortex during action execution and observation. Cereb Cortex 19(3):624–39.

Fattori P, Breveglieri R, Marzocchi N, Filippini D, Bosco A, Galletti C. 2009. Hand orientation during reach-to-grasp movements modulates neuronal activity in the medial posterior parietal area V6A. J Neurosci 29(6):1928–36.

Fattori P, Gamberini M, Kutz DF, Galletti C. 2001. 'Arm-reaching' neurons in the parietal area V6A of the macaque monkey. Eur J Neurosci 13(12):2309–13.

Fattori P, Kutz DF, Breveglieri R, Marzocchi N, Galletti C. 2005. Spatial tuning of reaching activity in the medial parieto-occipital cortex (area V6A) of macaque monkey. Eur J Neurosci 22(4):956-72.

Fattori P, Raos V, Breveglieri R, Bosco A, Marzocchi N, Galletti C. 2010. The dorsomedial pathway is not just for reaching: grasping neurons in the medial parieto-occipital cortex of the macaque monkey. J Neurosci 30(1):342–9.

Fernandez-Ruiz J, Goltz HC, DeSouza JFX, Vilis T, Crawford JD. 2007. Human parietal "reach region" primarily encodes intrinsic visual direction, not extrinsic movement direction, in a visual motor dissociation task. Cereb Cortex 17(10):2283–92.

Ferraina S, Johnson PB, Garasto MR, Battaglia-Mayer A, Ercolani L, Bianchi L, and others. 1997. Combination of hand and gaze signals during reaching: activity in parietal area 7 m of the monkey. J Neurophysiol 77(2):1034–8.

Filimon F, Nelson JD, Hagler DJ, Sereno MI. 2007. Human cortical representations for reaching: mirror neurons for execution, observation, and imagery. NeuroImage 37(4): 1315–28.

Filimon F, Nelson JD, Huang R-S, Sereno MI. 2009. Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. J Neurosci 29(9):2961–71.

Filimon F. 2008. Non-spatial posterior parietal activations for finger, hand, and arm movements in humans. Abstr Soc Neurosci 854.16.

Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE. 1997. Multiple nonprimary motor areas in the human cortex. J Neurophysiol 77(4):2164–74.

Flanders M, Tillery SIH, Soechting JF. 1992. Early stages in a sensorimotor transformation. Behav Brain Sci 15: 309–62.

Fogassi L, Luppino G. 2005. Motor functions of the parietal lobe. Curr Opin Neurobiol 15(6):626–31.

Frey SH, Vinton D, Norlund R, Grafton ST. 2005. Cortical topography of human anterior intraparietal cortex active during visually guided grasping. Brain Res Cogn Brain Res 23(2–3):397–405.

Galletti C, Fattori P, Kutz DF, Battaglini PP. 1997. Arm movement-related neurons in the visual area V6A of the macaque superior parietal lobule. Eur J Neurosci 9(2):410-3.

Galletti C, Fattori P, Kutz DF, Gamberini M. 1999. Brain location and visual topography of cortical area V6A in the macaque monkey. Eur J Neurosci 11(2):575–82.

Galletti C, Gamberini M, Kutz DF, Fattori P, Luppino G, Matelli M. 2001. The cortical connections of area V6: an occipito-parietal network processing visual information. Eur J Neurosci 13(8):1572–88.

Galletti C, Kutz DF, Gamberini M, Breveglieri R, Fattori P. 2003. Role of the medial parieto-occipital cortex in the control of reaching and grasping movements. Exp Brain Res 153(2):158–70.

Gallivan JP, Cavina-Pratesi C, Culham JC. 2009. Is that within reach? fMRI reveals that the human superior parieto-occipital cortex encodes objects reachable by the hand. J Neurosci 29(14):4381–91.

Gharbawie OA, Stepniewska I, Burish MJ, Kaas JH. 2008. Comparison of thalamocortical connections of frontal and posterior parietal cortex in New World primates. Abstr Soc Neurosci 78.5.

Grafton ST, Fagg AH, Woods RP, Arbib MA. 1996. Functional anatomy of pointing and grasping in humans. Cereb Cortex 6(2):226–37.

Grafton ST, Woods RP, Mazziotta JC. 1993. Within-arm somatotopy in human motor areas determined by positron emission tomography imaging of cerebral blood flow. Exp Brain Res 95(1):172–6.

Graziano MS. 2001. Is reaching eye-centered, body-centered, hand-centered, or a combination? Rev Neurosci 12(2): 175–85.

Graziano MSA. 2006. Progress in understanding spatial coordinate systems in the primate brain. Neuron 51(1):7–9.

Grefkes C, Fink GR. 2005. The functional organization of the intraparietal sulcus in humans and monkeys. J Anat 207(1):3–17.

Grol MJ, Majdandzić J, Stephan KE, Verhagen L, Dijkerman HC, Bekkering H, and others. 2007. Parieto-frontal connectivity during visually guided grasping. J Neurosci 27(44):11877–87.

Hagler DJ, Riecke L, Sereno MI. 2007. Parietal and superior frontal visuospatial maps activated by pointing and saccades. NeuroImage 35(4):1562–77.

Hinkley LBN, Krubitzer LA, Padberg J, Disbrow EA. 2009. Visual-manual exploration and posterior parietal cortex in humans. J Neurophysiol 102(6):3433–46.

Jackson SR, Newport R, Husain M, Fowlie JE, O'Donoghue M, Bajaj N. 2009. There may be more to reaching than meets the eye: re-thinking optic ataxia. Neuropsychologia 47(6): 1397–408.

Kalaska JF. 2009. From intention to action: motor cortex and the control of reaching movements. Adv Exp Med Biol 629: 139–78.

Kalaska JF, Caminiti R, Georgopoulos AP. 1983. Cortical mechanisms related to the direction of two-dimensional arm movements: relations in parietal area 5 and comparison with motor cortex. Exp Brain Res 51(2):247–60.

Kalaska JF, Cisek P, Gosselin-Kessiby N. 2003. Mechanisms of selection and guidance of reaching movements in the parietal lobe. Adv Neurol 93:97–119.

Kalaska JF, Crammond DJ. 1995. Deciding not to GO: neuronal correlates of response selection in a GO/NOGO task in primate premotor and parietal cortex. Cereb Cortex 5(5): 410–28.

Kertzman C, Schwarz U, Zeffiro TA, Hallett M. 1997. The role of posterior parietal cortex in visually guided reaching movements in humans. Exp Brain Res 114(1): 170-83.

Kriegeskorte N, Simmons WK, Bellgowan PSF, Baker CI. 2009. Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 12(5):535–40.

Lawrence BM, Snyder LH. 2006. Comparison of effector-specific signals in frontal and parietal cortices. J Neurophysiol 96(3):1393–400.

Levy I, Schluppeck D, Heeger DJ, Glimcher PW. 2007. Specificity of human cortical areas for reaches and saccades. J Neurosci 27(17):4687–96.

Macaluso E, Frith CD, Driver J. 2007. Delay activity and sensory-motor translation during planned eye or hand movements to visual or tactile targets. J Neurophysiol 98(5): 3081–94.

Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, and others. 2009. Precuneus shares intrinsic functional architecture in humans and monkeys. Proc Natl Acad Sci USA 106(47):20069–74.

Marzocchi N, Breveglieri R, Galletti C, Fattori P. 2008. Reaching activity in parietal area V6A of macaque: eye influence on arm activity or retinocentric coding of reaching movements? Eur J Neurosci 27(3):775–89.

Matelli M, Govoni P, Galletti C, Kutz DF, Luppino G. 1998. Superior area 6 afferents from the superior parietal lobule in the macaque monkey. J Comp Neurol 402(3): 327-52.

Matelli M, Luppino G. 2001. Parietofrontal circuits for action and space perception in the macaque monkey. NeuroImage 14(1 Pt 2):S27–32.

Medendorp WP, Beurze SM, Van Pelt S, Van Der Werf J. 2008. Behavioral and cortical mechanisms for spatial coding and action planning. Cortex 44(5):587–97.

Medendorp WP, Goltz HC, Crawford JD, Vilis T. 2005. Integration of target and effector information in human posterior parietal cortex for the planning of action. J Neurophysiol 93(2):954–62.

Medendorp WP, Goltz HC, Vilis T, Crawford JD. 2003. Gaze-centered updating of visual space in human parietal cortex. J Neurosci 23(15):6209–14.

Mullette-Gillman ODA, Cohen YE, Groh JM. 2009. Motor-related signals in the intraparietal cortex encode locations in a hybrid, rather than eye-centered reference frame. Cereb Cortex 19(8):1761–75.

Mulliken GH, Musallam S, Andersen RA. 2008. Decoding trajectories from posterior parietal cortex ensembles. J Neurosci 28(48):12913–26.

Norman KA, Polyn SM, Detre GJ, Haxby JV. 2006. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cogn Sci (Regul Ed) 10(9):424–30.

Pellijeff A, Bonilha L, Morgan PS, McKenzie K, Jackson SR. 2006. Parietal updating of limb posture: an event-related fMRI study. Neuropsychologia 44(13):2685–90.

Pesaran B, Nelson MJ, Andersen RA. 2006. Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. Neuron 51(1):125–34.

Pesaran B, Nelson MJ, Andersen RA. 2008. Free choice activates a decision circuit between frontal and parietal cortex. Nature 453(7193):406–9.

Picard N, Strick PL. 2001. Imaging the premotor areas. Curr Opin Neurobiol 11(6):663–72.

Pouget A, Deneve S, Duhamel J-R. 2002. A computational perspective on the neural basis of multisensory spatial representations. Nat Rev Neurosci 3(9):741–7.

Prado J, Clavagnier S, Otzenberger H, Scheiber C, Kennedy H, Perenin M-T. 2005. Two cortical systems for reaching in central and peripheral vision. Neuron 48(5):849–58.

Quinlan DJ, Culham JC. 2007. fMRI reveals a preference for near viewing in the human parieto-occipital cortex. NeuroImage 36(1):167–87.

Raizada RDS, Kriegeskorte N. 2010. Pattern-information fMRI: new questions which it opens up and challenges which face it. Int J Imaging Syst Technol 20(1):31–41.

Rice NJ, Tunik E, Grafton ST. 2006. The anterior intraparietal sulcus mediates grasp execution, independent of requirement to update: new insights from transcranial magnetic stimulation. J Neurosci 26(31):8176–82.

Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D, Fazio F. 1996. Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp Brain Res 111(2):246-52.

Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D, Fazio F. 1996. Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp Brain Res 111(2):246-52.

Sakata H, Taira M. 1994. Parietal control of hand action. Curr Opin Neurobiol 4(6):847–56.

Sanes JN, Donoghue JP, Thangaraj V, Edelman RR, Warach S. 1995. Shared neural substrates controlling hand movements in human motor cortex. Science 268(5218):1775–7.

Scheperjans F, Eickhoff SB, Homke L, Mohlberg H, Hermann K, Amunts K, and others. 2008. Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. Cereb Cortex 18(9): 2141–57.

Schieber M. 2000. New views of the primary motor cortex. Neuroscientist 6(5):380–9.

Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron 33(3):475–87.

Soechting JF, Flanders M. 1998. Movement planning: kinematics, dynamics, both or neither? In: Harris L, Jenkin M, editors. Vision and action. New York: Cambridge University Press. p 352–71.

Stark A, Zohary E. 2008. Parietal mapping of visuomotor transformations during human tool grasping. Cereb Cortex 18(10):2358–68.

Stepniewska I, Fang P-C, Kaas JH. 2005. Microstimulation reveals specialized subregions for different complex movements in posterior parietal cortex of prosimian galagos. Proc Natl Acad Sci USA 102(13):4878–83.

Thoenissen D, Zilles K, Toni I. 2002. Differential involvement of parietal and precentral regions in movement preparation and motor intention. J Neurosci 22(20):9024–34.

Todorov E. 2000. Direct cortical control of muscle activation in voluntary arm movements: a model. Nat Neurosci 3(4): 391–8.

Tosoni A, Galati G, Romani GL, Corbetta M. 2008. Sensory-motor mechanisms in human parietal cortex underlie arbitrary visual decisions. Nat Neurosci 11(12):1446–53.

Van Der Werf J, Jensen O, Fries P, Medendorp WP. 2010. Neuronal synchronization in human posterior parietal cortex during reach planning. J Neurosci 30(4):1402–12.

Westendorff S, Klaes C, Gail A. 2010. The cortical timeline for deciding on reach motor goals. J Neurosci 30(15): 5426–36.

Wolpert DM, Goodbody SJ, Husain M. 1998. Maintaining internal representations: the role of the human superior parietal lobe. Nat Neurosci 1(6):529–33.