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Decoding motor intentions from human brain activity

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Graduate Program in Neuroscience
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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DECODING MOTOR INTENTIONS FROM HUMAN BRAIN ACTIVITY

(Spine title: Decoding motor intentions from human brain activity)

by

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SCHOOL OF GRADUATE AND POSTDOCTORAL STUDIES

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Abstract

"You read my mind." Although this simple everyday expression implies 'knowledge or understanding' of another's thinking, true '*mind-reading'* capabilities implicitly seem constrained to the domains of Hollywood and science-fiction. In the field of sensorimotor neuroscience, however, significant progress in this area has come from mapping characteristic changes in brain activity that occur prior to an action being initiated. For instance, invasive neural recordings in non-human primates have significantly increased our understanding of how highly cognitive and abstract processes like intentions and decisions are represented in the brain by showing that it is possible to decode or 'predict' upcoming sensorimotor behaviors (e.g., movements of the arm/eyes) based on preceding changes in the neuronal output of parieto-frontal cortex, a network of areas critical for motor planning. In the human brain, however, a successful counterpart for this predictive ability and a similar detailed understanding of intention-related signals in parieto-frontal cortex have remained largely unattainable due to the limitations of non-invasive brain mapping techniques like functional magnetic resonance imaging (fMRI). Knowing how and where in the human brain intentions or plans for action are coded is not only important for understanding the neuroanatomical organization and cortical mechanisms that govern goal-directed behaviours like reaching, grasping and looking – movements critical to our interactions with the world – but also for understanding homologies between human and non-human primate brain areas, allowing the transfer of neural findings between species.

In the current thesis, I employed multi-voxel pattern analysis (MVPA), a new fMRI technique that has made it possible to examine the coding of neural information at a more fine-grained level than that previously available. I used fMRI MVPA to examine how and where movement intentions are coded in human parieto-frontal cortex and specifically asked the question: What types of predictive information about a subject's upcoming movement can be decoded from preceding changes in neural activity?

Project 1 first used fMRI MVPA to determine, largely as a proof-of-concept, whether or not specific object-directed hand actions (grasps and reaches) could be predicted from intention-related brain activity patterns. Next, Project 2 examined whether effector-specific (arm vs. eye) movement plans along with their intended directions (left vs. right) could also be decoded prior to movement. Lastly, Project 3 examined exactly where in the human brain higher-level movement goals were represented independently from how those goals were to be implemented. To this aim, Project 3 had subjects *either* grasp or reach toward an object (two different motor goals) using *either* their hand or a novel tool (with kinematics opposite to those of the hand). In this way, the goal of the action (grasping vs. reaching) could be maintained across actions, but the way in which those actions were kinematically achieved changed in accordance with the effector (hand or tool). All three projects employed a similar event-related delayed-movement fMRI paradigm that separated in time planning and execution neural responses, allowing us to isolate the preparatory patterns of brain activity that form prior to movement.

Project 1 found that the plan-related activity patterns in several parieto-frontal brain regions were predictive of different upcoming hand movements (grasps vs. reaches). Moreover, we found that several parieto-frontal brain regions, similar to that only previously demonstrated in non-human primates, could actually be characterized according to the types of movements they can decode. Project 2 found a variety of functional subdivisions: some parieto-frontal areas discriminated movement plans for the different reach directions, some for the different eye movement directions, and a few areas accurately predicted upcoming directional movements for both the hand and eye. This latter finding demonstrates -- similar to that shown previously in non-human primates -- that some brain areas code for the end motor goal (i.e., target location) independent of effector used. Project 3 identified regions that decoded upcoming hand actions only, upcoming tool actions only, and rather interestingly, areas that predicted actions with both effectors (hand and tool). Notably, some of these latter areas were found to represent the higher-level goals of the movement (grasping vs. reaching) instead of the specific lower-level kinematics (hand vs. tool) necessary to implement those goals.

Taken together, these findings offer substantial new insights into the types of intention-related signals contained in human brain activity patterns and specify a hierarchical neural architecture spanning parieto-frontal cortex that guides the construction of complex object-directed behaviors.

Keywords: fMRI, action planning, intention, motor control, grasping, reaching, saccades, tool-use, parietal cortex, premotor cortex, pattern classification, pattern analysis

Co-Authorship

All contents of the current thesis were carried out in collaboration with my advisor, Dr. Jody C. Culham. The research and writing were supervised by Dr. Culham, who contributed to experimental design, interpretation, and manuscript editing. Projects 1, 2 and 3 (Chapters 3, 4 and 5) were in additional collaboration with Adam McLean, who assisted with experimental design, data collection, analysis, and provided feedback on the written manuscripts. Adam McLean also helped with programming stimuli for presentation in the MR unit and operated the scanner. Kenneth Valyear assisted with the experiment design of Project 1 and provided feedback on the written manuscript. In addition, Charles Pettypiece assisted with the data collection of Project 1 and also provided feedback on the written manuscript. Fraser Smith assisted with data analysis, interpretation and provided feedback on the written manuscript for Project 2. The written material in this thesis is my own work, which was edited by my advisor, Dr. Culham.

Acknowledgments

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I would like to give a special acknowledgment to Dr. Melvyn Goodale. He has been particularly influential to my development as a scientist and has often provided me with an encyclopaedic source of knowledge, wisdom and insight. He has been remarkably generous to me with his time, despite his busy schedule, serving for my entire graduate career on my Advisory Committee and also as a supervisor for my Comprehensive exams. Furthermore, Mel has also generously agreed to serve as an Examiner for my thesis. His door has always been open to me and he has been continuously supportive of my research efforts. I am enormously appreciative to him for sharing his brilliance, guidance and encouragement throughout the years.

The remaining two members of my Advisory Committe, Drs. Daniel Ansari and Paul Gribble, also deserve special thanks. I have gotten to know Daniel quite well during my PhD, having collaborated with him on several side projects, and he never fails to astound me with his his ideas and insights. He has served as an inspiration for me in several aspects of my work and I am truly thankful for all his input and guidance over our collaborations. Paul has been a continuous source of advice over the years; an expert in all things statistical and mathematical and someone with an exceptional grasp of motor control. He also served as a supervisor for my Comprehensive exams, an experience that has guided much of my current thinking and approach in research. Without fail, Paul always asks the tough questions, and in doing so he has made me a more critical, thoughtful scientist and has prepared me well for a future in research. I also thank both Daniel and Paul for their comments and feedback on an earlier draft of this thesis.

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life in such a short period of time, and I greatly appreciate both of these indivduals for making that a possibility by sharing their brilliance and insights with me.

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List of Abbreviations

3D: three dimensional
AC-PC: anterior commissure-posterior commissure
AIP: anterior intraparietal area
aIPS: anterior intraparietal sulcus
BMI: brain machine interface
BOLD: blood oxygenation level dependent
EPI: echo-planar image
FA: flip angle
fMRI: functional magnetic resonance imaging
GABA: gamma-aminobutyric acid
GLM: general linear model
IPS: intraparietal sulcus
ITI: intertrial interval
LED: light-emitting diode
LIP: lateral intraparietal area
LOC: lateral occipital complex
M1: primary motor area
MIP: medial intraparietal area
midIPS: middle intraparietal sulcus
MRI: magnetic resonance imaging
MVPA: multi-voxel pattern analysis
pIPS: posterior intraparietal sulcus
PMd: dorsal premotor area
PMv: ventral premotor area
POS: parieto-occipital sulcus
Post. aIPS: posterior anterior intraparietal sulcus
PPC: posterior parietal cortex
Pre-SMA: presupplementary motor area
RFX: random effects analysis
ROI: region of interest
s: seconds
SEM: standard error of the mean
SMA: supplementary motor area
SMG: supramarginal gyrus
SPOC: superior pareito-occipital sulcus
SS cortex: somatosensory cortex
SVM: support vector machine
T1: anatomical magnetic resonance image
T2*: functional magnetic resonance image
TE: time to echo
TMS: transcranial magnetic stimulation
V1: primary visual area
V2: secondary visual area
V3: tertiary visual area

V6: visual area 6, within parieto-occipital cortex
V6A: visual area dorsal and anterior to V6

Chapter 1

1. General Introduction

1.1 Movement and the Brain

How does the human brain plan movements of the body? Understanding the intimate links between the processes of the brain and body has been a problem that has captivated philosophers, economists, psychologists, physiologists, neuroscientists, medical doctors, and robotics researchers alike for decades, and in some cases, centuries. The importance of understanding this relationship is by no means trivial: Movement of the body is the only meaningful way we have of interacting with our surrounding environment. Action provides us with the ability to communicate ideas with others (e.g., speech, hand gestures), to change and adapt our surroundings through the manipulation of objects (e.g., relocating items of interest), and to travel from point A to point B (e.g., walking, running, driving). It also gives us -- in the hands of the most skilled speakers, artists, writers, and musicians -- the ability to captivate imagination, stir emotions, unite and divide peoples, and fascinate much of the world. To be sure, the significance of being able to control movement in our everyday lives becomes all too clear in the many cases of individuals suffering from neurological disease, injury or limb loss. Thus, understanding the tight linkage between the brain and body and more specifically, the cortical basis of movement planning and control, is not just an abstract exercise but an important endeavor if we are to understand the many cases of sensorimotor dysfunction and provide rehabilitative programs and recovery-of-function options for individuals and patients.

A basic premise embedded in the question posed at the beginning of this thesis is of course, that it is in fact the *brain* that is responsible for controlling actions of the body. Based on a rather considerable and august literature, we know this fact to be only partially true. For instance, at the lowest-levels of motor control, movements of the body are in effect initiated by spinal motor neurons, whose activity then leads to the contraction or relaxation of different muscle groups, which themselves subsequently cause movements of the skeletal components to which they are attached (Kandel et al., 2000, pp 653-867). In fact, simple movements of the arms and legs need not actually require descending inputs from the brain at all: Limb movement can be initiated by electrical stimulation of the spinal cord alone, as well demonstrated in decereberated animals (e.g., Kandel et al., 2000, pp 714-736; Giszter et al., 2007). Suffice it to say, movement control is a rather sophisticated, dynamic, and hierarchical process, requiring the coordination of individual spinal motor neurons and muscle fibres in order to drive large systematic changes that can be observed at the behavioral level (e.g., moving a limb or finger). The focus of the present thesis, however, is not concerned with understanding motor control at these lower kinematic and mechanical levels (already well described in detail elsewhere) but rather at elucidating the higher-level cognitive processes in the brain that lead to voluntary movement.

In nature, goal-directed purposeful movements in primates largely result as a consequence of a complex interplay between several specialized subregions within the brain (Wise, 1985; Schall and Thompson, 1999; Kandel et al., 2000, pp 653-867; Rizzolatti and Luppino, 2001; Andersen and Buneo, 2002; Cisek and Kalaska, 2010; Filimon, 2010) that together, through their coordination, instruct the spinal cord on which specific movements to implement. The specific aim of the current work was to understand both how and where in the human brain high-level goal-directed action plans for movement are coded. In particular, the first objective of these projects was to determine whether we could actually 'decode' the content of a subject's movement decision from the preparatory brain activity patterns that form prior to movement onset, and thus in doing so, accurately predict their upcoming actions and behavior – as I will outline in the pages below, this feat of 'mind-reading' or 'decoding' motor intentions was in itself a significant technical hurdle. The second and more overarching goal of these projects was to determine whether different regions of the human brain could be characterized and differentiated based on the types of movements they can predict. This second goal relates to the notion that the primate brain contains several specialized subpopulations of neurons and signals that reflect different motor intentions of the individual (e.g., to move the eyes vs. arm, to move to the left vs. right) and has served as a recurring theme in non-human primate neural recording studies (Andersen et al., 1997; Andersen and Buneo, 2002; Fecteau and Munoz, 2003; Cisek and Kalaska, 2010). To date, however, a similar understanding of the human brain signals and neural organization that guide high-level processes like action planning has remained elusive. By using these two main experimental objectives to focus the types of questions asked in the current research projects, I hypothesized that some of our findings might provide critical insights into the underlying neural mechanisms that govern the planning of human hand and eye movements and perhaps also, based on previous observations of intention-related activity in the monkey, inform inferences about potential homologies between human and monkey brain areas.

In brief, the goal of Project 1 was to determine whether or not, as a general proof-of-concept, human preparatory fMRI activity patterns could be used to decode the motor intentions of the individual, and in effect, predict upcoming behaviors. Project 2 then sought to map-out the planning-related cortical processes that govern eye and hand movements in humans and in doing so, offer more substantive comparisons with the same types of neural processes well characterized in monkeys. In the third and final project we asked whether the planning of different tool-related movements could be decoded from human brain activity and if so, how these intention-related activity patterns compared to the activity patterns elicited when the same types of movements were planned with the hand alone. In many ways, it was actually in this last project that we were able to address largely new types of experimental questions related to action planning that had not already been previously answered within the domain of non-human primate neurophysiology.

Rather than overwhelming the reader with an exhaustive and historical review of the previous motor control and action-related literature – which is quite substantial (Andersen et al., 1997; Wise et al., 1997; Andersen and Buneo, 2002; Goodale and Milner, 2004; Castiello, 2005; Castiello and Begliomini, 2008) -- the goal of this introduction will be instead to provide a more concise and focused overview of the current state of the field, with a level of detail appropriate for understanding the overall scope and aims of the proposed research. As such, I intend to delineate the boundaries of our current understanding of movement planning processes in primates and, as a useful springboard for the experiments provided here, highlight in a few cases what remains largely uncharted territory in humans.

1.2 Human and Monkey Brain areas important for the control of action

Nearly all aspects of normal, everyday visually-guided object-directed behavior (e.g., reaching out to pick up an object) first begins with a simple retinal representation of the target object to be acted upon. Visual processing of this retinal information is then carried out by a successive chain of early visual cortical areas (e.g., V1, V2, V3, etc.) with each extracting increasingly complex features of the target stimulus (e.g., lines, orientation, colour, etc.)(Livingstone and Hubel, 1988). Following some more intermediary stages of processing, visual information then diverges along two largely separate but interacting streams (see Figure 1.1). One processing pathway for this visual information extends into ventral-temporal cortex, where the further extraction of higher-order visual perceptual features (e.g., shape, texture, material, etc.) takes place, ultimately leading to high-level cognitive attributes like object recognition (see Goodale and Milner, 2004 for a detailed review). The other visual pathway ascends along posterior parietal cortex (PPC) and into various premotor areas located in frontal cortex, where instead of playing a role perceptual processing, the visual features directly relevant for movement planning (e.g., location, distance, etc.) are extracted and processed (Andersen and Buneo, 2002; Goodale and Milner, 2004). It is here, in these highly interconnected parieto-frontal brain regions, that higher-level cognitive aspects of movement like intention and decision are coded (Andersen and Buneo, 2002; Gold and Shadlen, 2007; Andersen and Cui, 2009; Andersen et al., 2010; Cisek and Kalaska, 2010) and where the sensorimotor transformations required to convert visual attributes about an object into the motor commands required to act upon that object take place (Andersen et al., 1997).

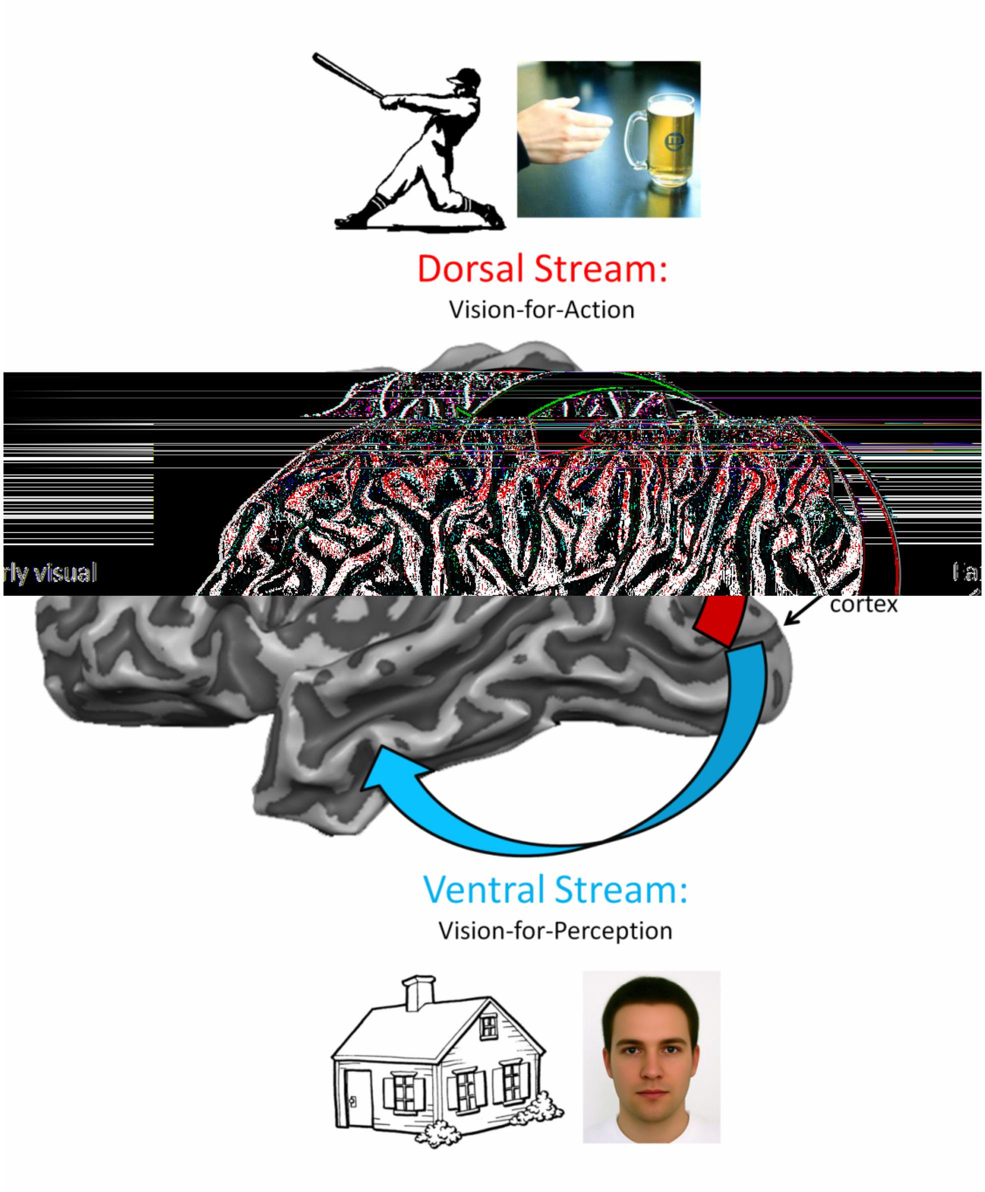
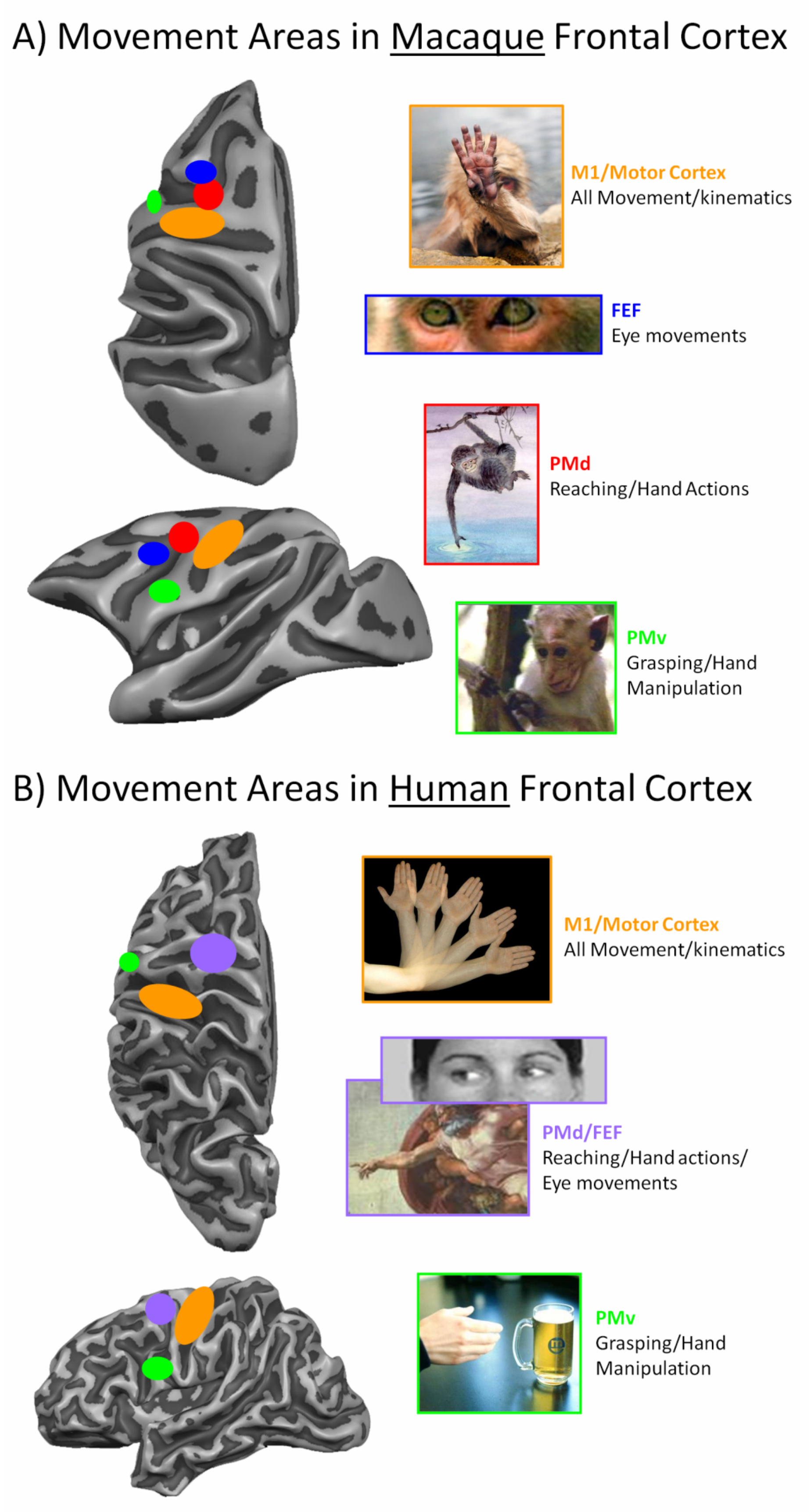


Figure 1.1: Dual visual streams hypothesis (Goodale and Milner, 1992). Vision is first processed in early visual cortex (V1) and then projects into two separate but interacting streams. The dorsal stream, shown with the red arrow, ascends from occipital to posterior parietal cortex (PPC) and extracts visual features relevant for the control of action (like the spatial location of a baseball for hitting or the orientation of a cup for grasping). The ventral stream, shown in the blue arrow, projects from occipital to ventral-temporal cortex and extracts visual features relevant for perception and object recognition (like whether the individual is looking at a house or face).

1.2.1 Movement-related areas in premotor cortex

The critical role that several frontal cortical areas play in movement generation has been well documented for more than a century (Fritsch and Hitzig, 1870; Ferrier, 1876, 1890; Sherrington, 1906; Penfield and Boldrey, 1937; Graziano, 2009 for a detailed review). Perhaps the best described of these frontal action-related areas is primary motor cortex (M1), which provides the primary source of descending motor commands to the spinal cord (Murray and Coulter, 1981; Toyoshima and Sakai, 1982; Porter and Lemon, 1993; Dum and Strick, 2002; Chouinard and Paus, 2006). Consistent with these outputs, much of the neural activity in M1 can be described in lower-level muscle control terms like force, direction, and speed (Evarts and Thach, 1969; Schwartz, 1994; Todorov, 2000; Kalaska, 2009, although see Graziano, 2006). In addition to these intrinsic factors, some lines of evidence also point to M1 as playing a role in coding for extrinsic factors, like movement direction or limb trajectory (Georgopoulos et al., 1986; Georgopoulos et al., 1988; although see Scott et al., 2001). Lesions to the area produce several movement-related deficits like inappropriate force scaling for objects and an impairment in individual finger movements (e.g., Porter and Lemon, 1993; Schieber and Poliakov, 1998; Fogassi et al., 2001; Murata et al., 2008). Regions anterior to M1 in the frontal lobe appear to be involved in higher-level aspects of action planning and decision-related processes (Wise, 1985; Miller and Cohen, 2001; Rizzolatti and Luppino, 2001). These anterior premotor areas have far fewer direct spinal connections but are highly interconnected with each other and M1 (Murray and Coulter, 1981; Toyoshima and Sakai, 1982; Dum and Strick, 1991, 2002; Chouinard and Paus, 2006; Boudrias et al., 2009) and several of these areas can be subdivided based on their activation preferences. For instance, the activity in some premotor areas appears to be linked to the effector to be used in an upcoming movement (arm vs. eyes) and/or the type of hand movement to be performed (reach vs. grasp actions). Although premotor cortex can be functionally subdivided into many distinct neuroanatomical regions, for the purposes of this Introduction, I will focus on only a few of these regions.


A) Movement Areas in Macaque Frontal Cortex

B) Movement Areas in Human Frontal Cortex

Figure 1.2: Action-related areas of frontal cortex shown on the cortical surface of a macaque monkey (A) and human (B) brain. The cortical surfaces were defined at the gray-white matter boundary and have been partially inflated to reveal regions within the sulci while preserving a sense of curvature. Brain areas are color-coded according to the current consensus on the ascribed function of each area based on neurophysiological recordings in monkeys (A) and fMRI in humans (B). Areas coded with similar color suggest possible functional homologies between humans and monkeys. PMd = premotor dorsal cortex, PMv = premotor ventral cortex. FEF = frontal eye fields. PMd and FEF are similarly color-coded in the human due to the difficulty in separating their activations with fMRI. Modified with permissions from Culham and Valyear (2006).

One area that appears integral to reach planning is dorsal premotor (PMd) cortex, an area located near the junction of the arcuate and principal sulci and lying on the posterior bank of the arcuate sulcus in monkeys (Rizzolatti and Luppino, 2001) and at the junction of the precentral and superior frontal sulci in humans (Chouinard and Paus, 2006, see Figure 1.2). PMd contains neurons responsive to arm movements (Weinrich and Wise, 1982; Weinrich et al., 1984; Caminiti et al., 1990; Beurze et al., 2007), shows activity specific for reach direction (Pesaran et al., 2006; Batista et al., 2007; Andersen and Cui, 2009) and encodes the target and arm to be used in an upcoming reach in both humans and monkeys (Boussaoud and Wise, 1993; Hoshi and Tanji, 2006; Beurze et al., 2010). Congruent with these observations, microstimulation of PMd in monkeys also induces a complex array of ecologically-relevant movements like reaching and grasping (Graziano et al., 2002; Graziano, 2006; Graziano and Aflalo, 2007). Beyond this critical role in hand movement planning, however, it remains to be determined what other functions PMd might play in goal-directed behavior.

Another important action-related region in premotor cortex is the frontal eye fields (FEF), located on the anterior bank of the arcuate sulcus near the junction of the arcuate and principal sulci in monkeys (Schall and Thompson, 1999; Rizzolatti and Luppino, 2001, see Figure 1.2A). As its name implies, the area is predominantly involved in the planning and execution of eye movements and is the main oculomotor control center in frontal cortex (Bruce and Goldberg, 1985; Bruce et al., 1985; Schlag and Schlag-Rey, 1987; Goldberg and Bruce, 1990; Schall and Thompson, 1999; Fecteau and Munoz, 2003). Commensurate with this, FEF neurons send prominent projections to the superior colliculus located in the midbrain, one of the final command centers for initiating eye movements. In the human, however, given the close anatomical proximity of both FEF and PMd combined with the comparatively poorer spatial resolution of fMRI (see Figure 1.2A), their activations substantially overlap, making it difficult to dissociate their processes (e.g., Connolly et al., 2007; Filimon, 2010, this is meant to be reflected in Figure 1.2B).

A frontal brain region thought to be necessary for hand grasping and object manipulation is ventral premotor (PMv) cortex. In monkeys it is located posteriorly along the inferior bank of the arcuate sulcus (Rizzolatti and Luppino, 2001) and in humans it lies posterior and inferior to the junction of the precentral gyrus and inferior frontal sulcus (Tomassini et al., 2007, see Figure 1.2). Microstimulation of PMv leads to a variety of hand movements (Rizzolatti et al., 1998) and converging neural evidence indicates that it encodes the sensorimotor transformations required for hand shaping (Rizzolatti and Luppino, 2001). For instance, PMv contains neurons that in addition to coding for certain types of hand actions -- like whole-hand prehension, precision grasping and individuated finger movements (Rizzolatti et al., 1998; Raos et al., 2006) – show selectivity for certain object properties like size, shape and orientation (Murata et al., 2000; Fluet et al., 2010). These neurons can be activated by the mere visual presentation of a graspable object and are thought to play an facilitatory role in the visual-motor transformations necessary for object grasping (Rizzolatti and Luppino, 2001) -- a suggestion reinforced by the observation that the visual specificity of a neuron closely matches its motor specificity (Murata et al., 2000; Fluet et al., 2010). Furthermore, muscimol (GABA-agonist) inactivation of PMv markedly impairs both hand preshaping and posture for object-directed grasping (Fogassi et al., 2001). Several of these findings in monkeys have been confirmed in humans. Transcranial magnetic stimulation (TMS) applied to human PMv, which interferes with the neural processing within a region, will disrupt the grasping phase of grasp-to-lift task (Davare et al., 2006) and fMRI activity in PMv is readily observed during any grasping task (e.g., Cavina-Pratesi et al., 2010). In addition, human PMv also encodes 3D object properties in the context of object grasping (e.g., Joly et al., 2009), commensurate with an integral role in computing the sensorimotor transformations for grasping in humans as well.

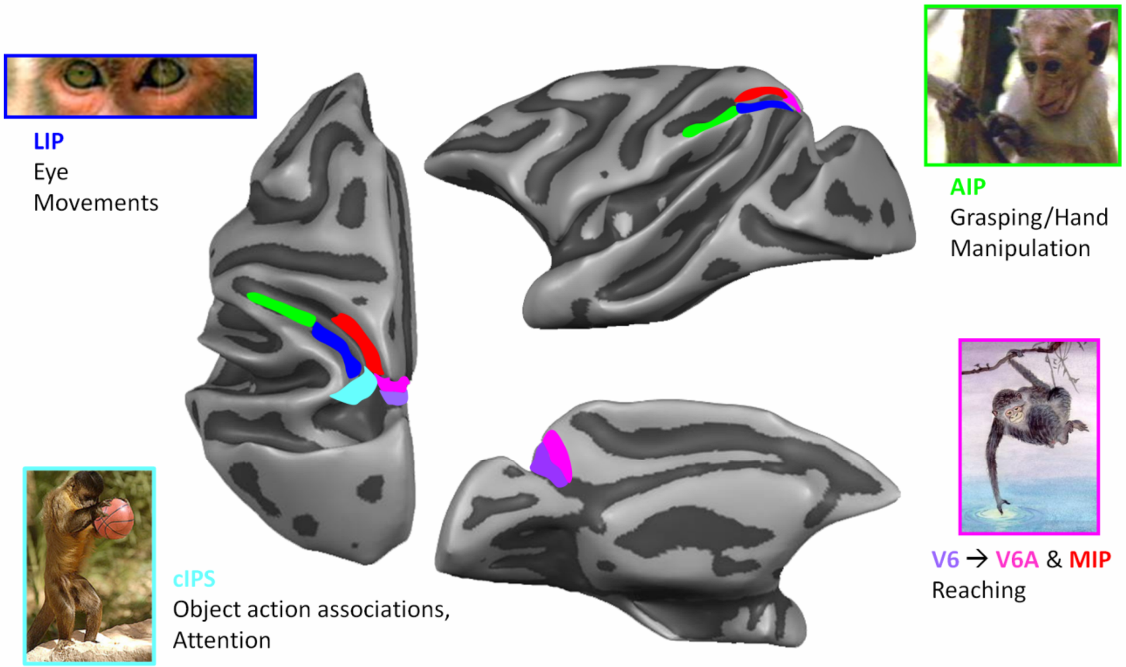
It is important at this point to note that the aforementioned specialized subdivisions of premotor cortex do not appear to be simply organized at random. Rather, these specializations seemingly reflect their distinct patterns of interconnectivity with similarly specialized subregions in PPC (Johnson et al., 1996; Matelli and Luppino, 2000; Andersen and Buneo, 2002; Tanne-Gariepy et al., 2002). In fact, beyond premotor regions sending projections to M1 and their immediate interconnections with each other, a predominant source of its incoming signals and a main recipient of its outgoing signals is the PPC (Matelli and Luppino, 2000; Tanne-Gariepy et al., 2002). This of course, raises the question, what then is being coded in the PPC? I will now briefly turn to describe some of its important functional properties.

1.2.2 Movement-related areas in PPC

The significant role that the PPC plays in movement generation, as compared to that of frontal cortex, has gained prominence only recently (Mountcastle et al., 1975). This is in part due to the historical assessment of the PPC as a sensory ‘association’ area – a designation that is perhaps not surprising given that it is anatomically situated at the junction between the primary visual, auditory and somatosensory cortical areas. Correspondingly, the anterior section of parietal cortex responds to somatosensory stimulation (Mountcastle, 1957) whereas the posterior aspect shows a variety of neural properties related to spatial attention and awareness (Critchley, 1953; Ungerleider and Mishkin, 1982; Colby and Goldberg, 1999). Perhaps, most notably, damage to the PPC and surrounding structures can often cause a lack of awareness or 'neglect' to the contralesional side of space (Critchley, 1953; Goodale and Milner, 2004; Husain and Nachev, 2007). More recently, however, there has been an explosion of neural findings that also implicate the PPC in cognitive processes related to movement planning (Mountcastle et al., 1975; Andersen et al., 1997; Snyder et al., 1997; Andersen and Buneo, 2002; Cisek and Kalaska, 2010) – a fact that again is perhaps not surprising, given that its anatomical position would allow it to serve as an useful interface between sensory and motor systems. Consistent with a role in sensorimotor transformations and intention- and decision-related processes, neural recording studies in monkeys and fMRI studies in humans have found a diverse range of sensory, cognitive and motor-related properties in the PPC (Culham and Valyear, 2006; Gold and Shadlen, 2007; Cisek and Kalaska, 2010). Commensurate with this prominent sensorimotor role, patients with PPC lesions can also suffer from a variety of deficits related to movement - deficits that are neither exclusively motor nor sensory in nature. For instance, damage to the PPC can cause optic ataxia -- a disorder characterized by the patient having difficulty in localizing periperhal target locations for reaches (Perenin and Vighetto, 1988) -- and/or one of the apraxias -- disorders most often characterized by a difficulty in planning goal-directed movements (Haaland et al., 1999, 2000). As an aside, it should be noted that this fairly inclusive description of the PPC as a sensorimotor interface might also be overly simplistic: The PPC has been implicated in subserving a dizzying array of high-level sensorimotor and cognitive functions, including action planning and coordinate transformations (Andersen and Buneo, 2002), decision-making and value-estimation (Gold and Shadlen, 2007), forward state estimation and prediction (Wolpert et al., 1998; Shadmehr and Wise, 2005), goal encoding (Musallam et al., 2004; Andersen et al., 2010), cognitive set (Stoet and Snyder, 2004), categorization (Freedman and Assad, 2006), shape recognition (Sereno and Maunsell, 1998), timing (Walsh, 2003), attention (Colby and Goldberg, 1999; Bisley and Goldberg, 2003), learning (Clower et al., 1996; Rossetti et al., 1998; Linden et al., 1999), number and magnitude processing (Walsh, 2003; Hubbard et al., 2005; Ansari, 2008; Nieder and Dehaene, 2009), and working memory (Xu and Chun, 2006, 2009), just to name a few. It is important to note, however, that the common thread underlying all of these diverse PPC functional properties is a general involvement in the specification and selection of goal-directed behaviors.

Similar to the organization found in frontal cortex, the PPC also contains a mosaic of specialized subregions used for controlling the movement of different body parts (e.g., arm, hand, eyes) and producing desired motor acts and goals (Blatt et al., 1990; Andersen and Buneo, 2002; Culham et al., 2006, see Figure 1.3). Consistent with these subdivisions, microstimulation of different parts of monkey PPC evokes a vast array of complex movements and behaviors (e.g., reaching, grasping, eye movements, defense actions)(Stepniewska et al., 2005) and electrical stimulation of the inferior parietal lobe in human patients initiates the desire to move different effectors (Desmurget et al., 2009). Importantly, in contrast to regions in the frontal lobe, the PPC has considerably less direct anatomical projections to the spinal cord (approximately less than 1/5th the number of connections, (Murray and Coulter, 1981; Toyoshima and Sakai, 1982)). As such, given the PPC's prominent projections to frontal cortex, parietal areas are much more likely to indirectly influence the activity M1 neurons (and thus the spinal cord) through their interactions with interconnected premotor areas. This neuroanatomical organization suggests that the PPC is likely to be involved in the earlier stages of movement planning and more abstractly removed from the precise kinematics that need to be coded by M1 in order to achieve desired actions.

A) Movement Areas in Macaque Parietal Cortex



B) Movement Areas in Human Parietal Cortex

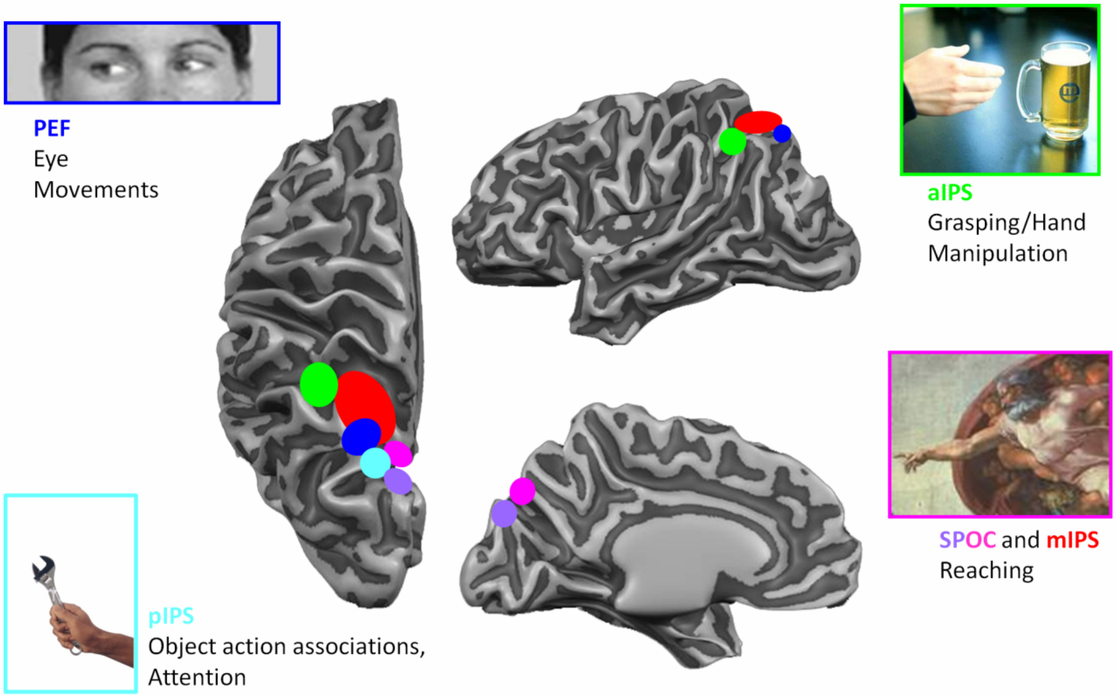


Figure 1.3: Action-related areas of parietal cortex shown on the cortical surface of a macaque monkey (A) and human (B) brain. The cortical surfaces were defined at the gray-white matter boundary and have been partially inflated to reveal regions within the sulci while preserving a sense of curvature. Brain areas are color-coded according to the current consensus on the ascribed function of each area based on neurophysiological recordings in monkeys (A) and fMRI in humans (B). Areas coded with similar color suggest possible functional homologies between humans and monkeys. Monkey areas: V6 = visual area 6, V6A = visual area 6A, MIP = medial intraparietal area, cIPS = caudal intraparietal sulcus, LIP = lateral intraprietal area, AIP = anterior intraparietal area. Human areas: SPOC = superior parieto-occipital cortex, mIPS = middle IPS, pIPS = posterior intraparietal sulcus, PEF = parietal eye field, aIPS = anterior intraparietal sulcus. Modified with permissions from Culham and Valyear (2006).

An important brain area involved in reaching in human PPC is the superior parieto-occipital cortex (SPOC), a putative human homologue of area V6A in the monkey (Pitzalis et al., 2006, see Figure 1.3), located slightly anterior to the parieto-occipital sulcus. Neurons in monkey V6A show sensitivity to reach direction and encode targets for reaching (Galletti et al., 1997; Galletti et al., 2003) and damage to the area leads to misreaching errors (Battaglini et al., 2002). In humans, TMS disruption (Vesia et al., 2010) or cortical damage (Karnath and Perenin, 2005) to SPOC can produce errant reach trajectories and fMRI evidence points to its direct involvement in reach execution (Prado et al., 2005; Bernier and Grafton, 2010; Cavina-Pratesi et al., 2010) but to date, its precise role in reach planning has yet to be well demonstrated. Just anterior to SPOC is the Precuneus, an area also implicated in reaching actions (Filimon et al., 2009; Bernier and Grafton, 2010). In addition, this region shows selectivity for pointing actions (Connolly et al., 2003; Fernandez-Ruiz et al., 2007) as well as for both observed and imagined reaching (Filimon et al., 2007). Although SPOC and the Precuneus are often co-activated in a variety of reach tasks, they may in fact be functionally distinct (e.g., Filimon et al., 2009; Bernier and Grafton, 2010) -- a notion supported by differences in the underlying cytoarchitecture (Scheperjans et al., 2008b; Scheperjans et al., 2008a). Nevertheless, both of these areas appear functionally interconnected with a more anterior region in the middle IPS (midIPS, Matelli and Luppino, 2000) -- also heavily implicated in reach planning and execution (e.g., Snyder et al., 1997) – and with the reach-related PMd located in frontal cortex.

While exact functional homologies between midIPS in the human and monkey remain unclear, the general anatomical region in monkeys codes for both eye and arm movements. For instance, the lateral intraparietal (LIP) area, located on the lateral bank of the middle IPS in monkeys (Figure 1.3) contains neurons more selective for eye movements than reaching movements (Snyder et al., 1997; Cui and Andersen, 2007) and it is anatomically interconnected with FEF in frontal cortex (Andersen et al., 1985a; Andersen et al., 1990; Anderson et al., 2011). Consistent with this, LIP activity represents upcoming decisions related to eye movements (Gold and Shadlen, 2007) and electrical stimulation of LIP produces fixed-vector saccades (Thier and Andersen, 1996, 1998; Constantin et al., 2007). In contrast, the medial intraparietal (MIP) area, located on the medial bank of the middle IPS in monkeys (Figure 1.3), contains neurons that are selective for reach movements rather than eye movements (Snyder et al., 1997; Calton et al., 2002; Cui and Andersen, 2007), encodes the sensorimotor transformations required for arm movements (Batista et al., 1999) and sends prominent projections to PMd in frontal cortex (Tanne-Gariepy et al., 2002).

In contrast to the monkey, it has been much more difficult to isolate and dissociate arm and eye movement-related activity from human midIPS. This difficulty may be due to several different non-mutually exclusive factors: 1) The neuroanatomical locations of LIP and MIP lie directly adjacent to eachother in the monkey brain and in comparison to single neuron recordings, fMRI has far poorer spatial resolution to allow for similar levels of detection, 2) there may actually be less effector-specificity in human compared to monkey cortex (Heed et al., 2011), 3) despite similarities in neuroanatomical position, human midIPS may not house the functional homologues of LIP and MIP in the monkey and 4) the signals being measured by fMRI do not reflect a one-to-one relationship with the action potentials recorded from neural electrodes in monkeys (Logothetis et al., 2001)(many of these important issues will receive further discussion in the pages that follow). What we do know for certain is that the degree of fMRI activation overlap for reaching and saccades in the IPS is generally quite high and varies across studies (Astafiev et al., 2003; Connolly et al., 2003; Culham et al., 2006; Beurze et al., 2007; Hagler et al., 2007; Levy et al., 2007; Filimon, 2010), and this issue is unquestionably further compounded by the fact that neurons showing arm-specificity can be found on both the lateral and medial banks of the midIPS (Snyder et al., 1997; Calton et al., 2002; Chang and Snyder, 2010). No doubt this dense intermingling and multiplexed organization of arm- and eye-related neurons in the IPS facilitates the coupling of both effectors and their coordination (Andersen and Buneo, 2002; Andersen and Cui, 2009), as is likely the case for PMd and FEF in premotor cortex. Nevertheless, for significant advances to be made in our understanding of these same neural populations in humans an fMRI technique able to differentiate these highly distributed and overlapping neural activations would seem critical.

Caudal to the midIPS is another functional subdivision, the posterior IPS (pIPS), implicated in a wide assortment of cognitive- and visual-motor-related functions in humans (Figure 1.3). For instance, human pIPS is activated in experimental tasks requiring visual selection and attention (Wojciulik and Kanwisher, 1999; Szczepanski et al., 2010) and it encodes both target- and effector-related information for movement (Beurze et al., 2007, 2009). Neural evidence from monkeys also suggests that the caudal IPS also encodes 3D object features relevant for movement (Sakata et al., 1998). Beyond these rather vague descriptions of the pIPS, however, very little is known about the types of action-related processes that are computed within the area.

In the monkey, the most anterior section of the IPS (aIPS; Figure 1.3) contains neurons selectively involved in hand preshaping and grasping (Taira et al., 1990; Sakata et al., 1997; Murata et al., 2000; Baumann et al., 2009). Consistent with this, muscimol (GABA-agonist) injections into aIPS disrupts object-directed hand grasping (Gallese et al., 1994). Consistent with a similar functional organization, aIPS in the human also shows selectivity for grasp execution with fMRI (Culham et al., 2003; Frey et al., 2005; Begliomini et al., 2007; Gallivan et al., 2009) and TMS to the region interferes with the grasp component of a reach-to-grasp action (Tunik et al., 2005; Rice et al., 2006). As might be anticipated with these grasp-related functional properties, aIPS sends prominent projections to PMv in frontal cortex (Tanne-Gariepy et al., 2002; Borra et al., 2008).

1.2.3 Parallel parieto-frontal pathways for reaching and grasping

As already alluded to above, the neuroanatomical organization of specialized regions for reaching, grasping and looking emerge from the distinct patterns of interconnectivity between parietal and frontal cortex. Based on these and other observations, it has been argued that the parieto-frontal network contains two distinct parallel networks for prehension: a dorso-lateral circuit involving interconnections between pIPS, AIP and PMv, thought to be specialized for grasping, and a dorso-medial circuit involving interconnections between SPOC/precuneus, midIPS and PMd, thought to be specialized for reaching (Jeannerod, 1988; Sakata and Taira, 1994; Matelli and Luppino, 2000; Andersen and Buneo, 2002; Johnson and Grafton, 2003; Rizzolatti and Matelli, 2003; Grafton, 2010, see Figure 1.4). While this view has proved to be a useful heuristic and generated several testable predictions and experimental investigations, it has faced increasing criticism as it fails to account for a number of findings. First, grasp-selective neurons have recently been reported in area V6A of the monkey, an area thought to be exclusively involved in reach movements (Fattori et al., 2009; Fattori et al., 2010). Second, it has been shown using dynamic causal modeling with fMRI that the degress of finger precision required by grasping movements alone can elicit the differential engagement of the dorso-medial and dorso-lateral circuits (Grol et al., 2007) -- a finding incompatible with the strict grasping vs. reaching divisions of the parallel-pathway view. Third, reach-related neural responses can be found in several areas outside of the dorso-medial circuit (Graziano, 2001; Breveglieri et al., 2006). Fourth, the view importantly ignores the close interconnections throughout parietal cortex (Gamberini et al., 2009), and in particular, between the dorso-medial and –lateral circuits (Gardner et al., 2007a; Gardner et al., 2007b), making the quantification of any dissociative processes quite difficult. Part of the aim of the present work was to help resolve some of these discrepancies and examine whether a specialized module for certain types of actions (grasping, reaching and saccades) is actually representative of underlying human brain function and cognitive organization.

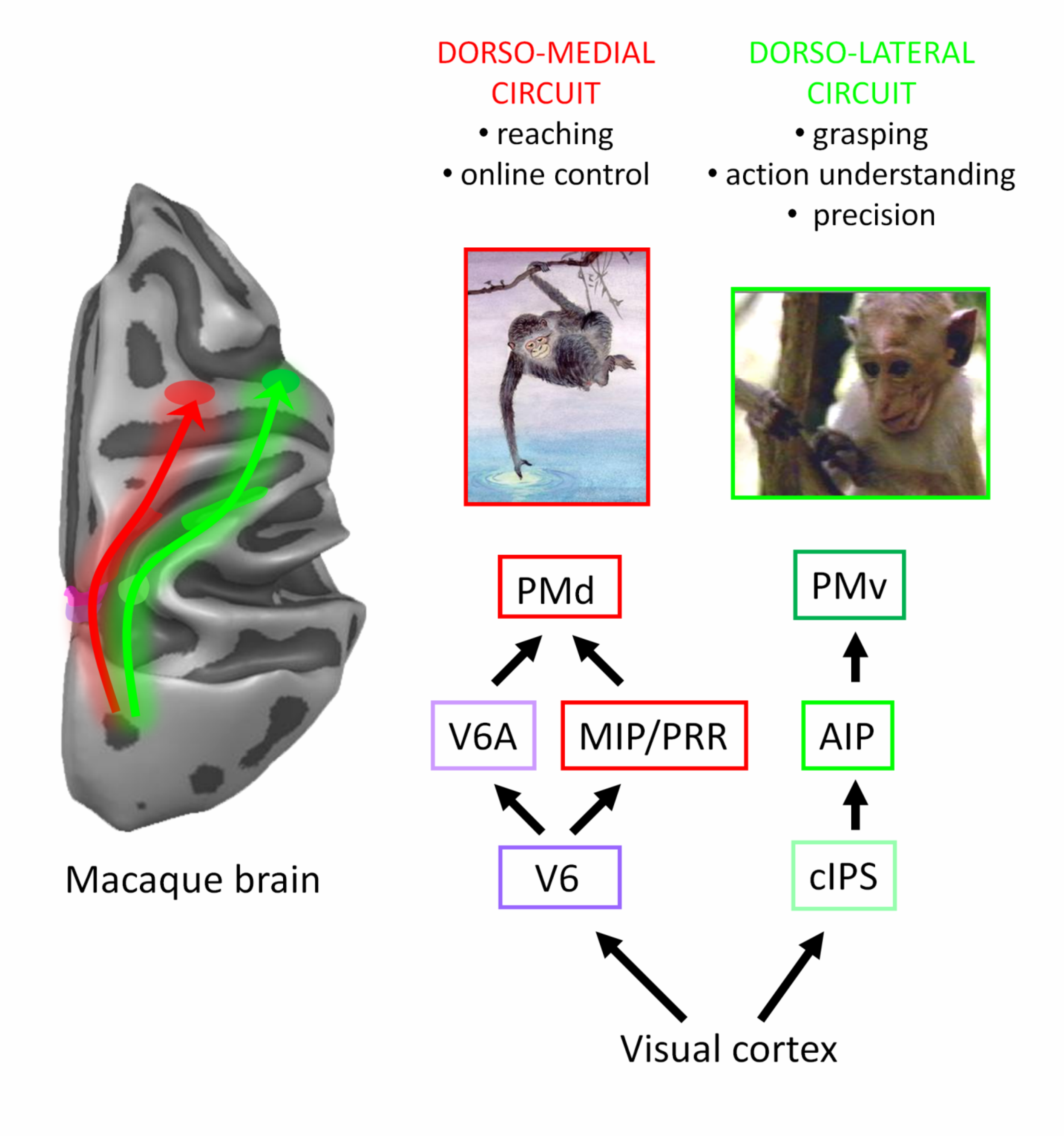

DORSO-MEDIAL CIRCUIT
• reaching
• online control
DORSO-LATERAL CIRCUIT
• grasping
• action understanding
• precision
Macaque brain
PMd
PMv
V6A
MIP/PRR
AIP
V6
cIPS
Visual cortex

Figure 1.4: Suggested parallel visual-motor pathways for reaching and grasping in the macaque monkey. (Left) The cortical surface of a macaque monkey brain was defined at the gray-white matter boundary and has been partially inflated to reveal regions within the sulci while preserving a sense of curvature. Colored arrows denote the parallel processing of reach-related information in a dorso-medial circuit (in red) and grasp-related information in a dorso-lateral circuit (in green). Both parallel pathways begin with object-related visual processing in early visual cortex (V1) and then undergo sensorimotor transformations for movement in parietal and premotor cortex. (Right) Schematic representation of the brain areas involved in each pathway, with arrows denoting the direction of information processing. At the end stages of movement preparation, it is thought that both PMd and PMv then inform M1 of the desired motor acts. V6 = visual area 6, V6A = visual area 6A, MIP = medial intraparietal area, PRR = parietal reach region, PMd = premotor dorsal cortex, cIPS = caudal intraparietal sulcus, AIP = anterior intraparietal area, PMv = premotor ventral cortex.

1.2.4 Decoding intentions in the monkey brain

Let us stop at this point and briefly recount the significant insights gained with monkey neurophysiology into how cognitive processes like decisions and intentions are represented in the primate brain. First and foremost, neural recording studies have provided remarkably detailed descriptions as to specifically *where* different motor intentions are coded. This has most notably been accomplished through the demonstration that certain brain regions can be well characterized based on the types of preparatory and predictive signals they contain. For instance, as recently reviewed, regions within both parietal and premotor cortex can be functionally subdivided according to whether the resident preparatory neural signals relate to upcoming saccades, reaches or grasping movements (Taira et al., 1990; Snyder et al., 1997; Andersen and Buneo, 2002). In conjunction with these descriptions, monkey studies have also specifically shown *how* motor intentions are coded. For example, some neurons seem to represent the upcoming spatial location of the target to be acted upon, others how the target will be interacted with, while many may represent both critical pieces of information (Calton et al., 2002; Dickinson et al., 2003; Cui and Andersen, 2007; Andersen and Cui, 2009). It has also been shown that prior to a monkey being instructed as to which target to act upon, populations of neurons in different parieto-frontal regions will simultaneously represent movements to multiple potential targets and their corresponding spatial locations (Platt and Glimcher, 1997; Snyder et al., 1997; Cisek and Kalaska, 2005; for review see Cisek and Kalaska, 2010). This simultaneous specification of multiple possible movements occurs even when only a single object is being viewed; the potential movements in this case reflecting different grasping actions (Baumann et al., 2009). In addition, with repect to the neurons that show spatial tuning for target direction, many studies revealed that this spatial representation is directly linked to a particular frame of reference (e.g., anchored to the eye, Andersen et al., 1985b; Batista et al., 1999; Andersen and Buneo, 2002) and that postural signals related to the position of various effectors (eyes or hands) can scale the levels of activity in these spatially-tuned neurons (called gain-field scaling). These gain-fields can have important implications. For instance, the work of Zipser and Andersen (1988) first demonstrated that the postural signal of the eye's orbital position could be used to convert eye-centred neural responses into head-centred responses. While this originally served as proof-of-principle model for how gain signals could be combined to produce distributed spatial representations, it is now well accepted that gain-fields have a prominent role to play in coding the sensorimotor transformations for action (Snyder et al., 1998; Chang et al., 2009). Lastly, monkey studies have also provided critical insights into exactly *when* intentions for action are formed. On this front, an examination of the neural activity that forms prior to a monkey executing a decision has been particularly revealing. In these types of choice-related experiments the monkey is generally trained to perform some kind of discrimination task (e.g., determine to what side of space a group of dots are moving) or autonomously to make a target selection and indicate its final decision through some measurable behaviour (e.g., by moving their limb or their eye). A ubiquitous observation found in these tasks is that the cognitive signals conveying the monkey's decision processes will evolve in the same brain regions involved in initiating the final movement (Gold and Shadlen, 2007; Kable and Glimcher, 2009; Cisek and Kalaska, 2010). For instance, if the response task requires an eye movement, signals expressing the monkey's upcoming decision will accumulate in eye movement-related areas (Platt and Glimcher, 1999; Cui and Andersen, 2007; Gold and Shadlen, 2007) whereas if the decision task requires a reaching movement, corresponding activity changes leading up to the action can be observed in reach-related brain areas (Cisek and Kalaska, 2005; Cui and Andersen, 2007; Pesaran et al., 2008). In effect, such tasks allow neurophysiologists to view the unfolding of a monkey's decision over time, permitting them to pinpoint with high reliability -- moments before action initiation -- which decision has been reached and thus which action will be performed.

1.3 From the monkey to the human

A critical point worth re-emphasizing here is that nearly everything we currently know about the neuroanatomical organization and cortical mechanisms that guide the *planning* of goal-directed actions in the *human* (e.g., sensorimotor transformations involved in movement generation, temporal unfolding of action decisions, coding of higher-level movement goals, etc.) is founded on neurophysiological investigations in *monkeys* (for example, see Figure 1.5). This is by no means coincidental: Any sort of direct investigation of human planning-related processes with behavioral measures or non-invasive neuroimaging methods has been met with varying degrees of success and/or has been limited in the types of conclusions that can be drawn. Indeed, from a behavioral perspective, the tricky thing about measuring and quantifying high-level cognitive processes like intentions or decisions is that these processes need not actually manifest themselves behaviorally. For instance, I can either intend to lift my arm or not, but without me actually lifting my arm, you would never know for certain that I ever really contemplated the decision[1]. As such, at the precise moment of their instantiation, these more abstract brain processes can remain covert or 'hidden' from any detailed examination of behavior. Thus, in order to directly examine these types of hidden brain processes (intention- and decision-related signals) in the human we also need a non-invasive neuroimaging method that allows us a 'window' through which to view their evolution prior to the initiation of any behavioral response.

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[1] I should acknowledge that this intention-related information (i.e., to lift arm) might also be expressed at the level of subthreshold muscle activity and thus resolvable with electromyography (EMG) recordings. However, for the purposes of this example, I presume that any high-level intention- or decision-related coding is abstractly removed from any muscle-related specification of the movement (i.e., observable at the level of EMG) and constrained to the level of brain activity patterns.

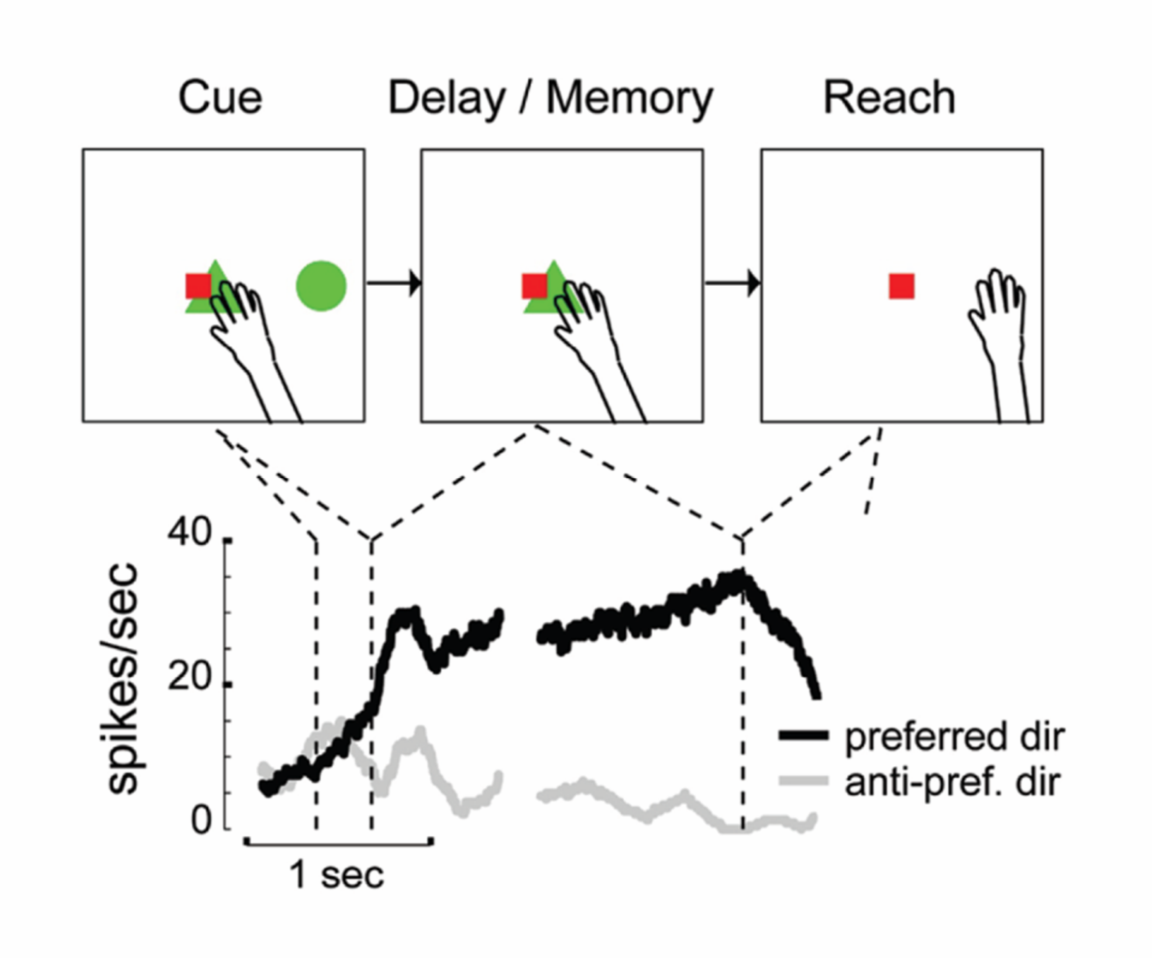

Figure 1.5: Intention-related activity in parietal cortex reflects a monkey's upcoming reach movement direction. Neural activity is recorded from the parietal reach region (PRR) while a monkey performs a delayed-movement task. In this task (Top), the monkey fixates centrally (on red square) and places their hand at the starting point (green triangle). A peripheral reach target is briefly flashed (green circle) and the monkey then plans a reach to the cued location but importantly does not move until the green triangle is extinguished. (Bottom) The spiking-related activity of a single PRR neuron during the delayed movement task. When the cued reach target location coincides with the preferred direction of the PRR neuron, there is an increased rate of spiking during the delay period (black trace; compared to a non-preferred direction, gray trace). It is critical to note, that the elevated and persistent rate of neuron firing during the delay period is related to the monkey's *intention* to make an arm movement, as no sensory stimulus or movement is initiated during that time phase. Reprinted with permission from Andersen et al., (2010).

To date, the best available and most recognized technique for examining and mapping cortical neural activity in humans is fMRI[2], but it is certainly not without its limitations. For starters, fMRI has far poorer spatial and temporal resolution compared to that of neural recordings, and it therefore makes it difficult to not only *reveal* but then also *relate* (providing homologies) the same types of neural processes in both species. For instance, instead of actually measuring the spiking activity of individual neurons, the fMRI Blood-Oxygenation-Level-Dependent (BOLD) signal relies on measuring changes in the concentration of deoxyhemoglobin, which directly reflects underlying changes in the oxygen consumption of neural populations (i.e., increased neural activity → increased metabolic costs → increased oxygen consumption → decreased blood oxygen levels → increased blood flow → decreased concentration of paramagnetic deoxyhemoglobin → increased BOLD signal). As such, BOLD activity is indirectly related to neural events through complex neuro-vascular coupling mechanisms and thus, from a spatial resolution perspective, it reveals a neurophysiological process observed at a much coarser spatial scale than that of a single neuron (typically each functional voxel, which is the smallest unit of fMRI activity, is on the order of 3 mm x 3 mm x 3 mm and encompasses approximately 1.35 – 1.62 million neurons; (given estimates that each cubmic millimetre (mm3) of human cortex contains between 50,000-60,000 neurons (Pakkenberg and Gundersen, 1997; Koch, 2004). Also, from a temporal resolution perspective, whereas neural investigations of intention-related signals in monkeys will typically examine the activity within the 1-2 seconds prior to the monkey initiating an action, fMRI -- due to the sluggishness of the BOLD response (which typically lags 4-6 seconds after a neural event (Huettel et al., 2004)) -- often requires the planning phases for movement to be considerably lengthened (e.g., approximately 10 seconds) so that an adequate sampling of the BOLD signal is acquired.

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[2] Please note that the non-invasive decoding of intention-related signals in humans can also be accomplished with electroencepholgrams (EEGs). To date, EEG signals have been successfully used to accurately decode planned hand movements (e.g., intent to open the hand) on the order of milliseconds before the action is initiated in normal healthy subjects (Allison et al., 2010) as well as in individuals suffering from a variety of neurological diseases and paralysis (Muralidharan et al., 2010; Wolpaw et al., 2007; Birbaumer and Cohen, 2007). Although EEG offers superior temporal resolution to fMRI (see above), it also provides far poorer spatial resolution, unable to pinpoint the source of decodable signals beyond the gross anatomical level. Moreover, the ability of EEG to detect subtle differences in the intentions of an individual (i.e., outside of simple hand opening vs. hand closing), is quite limited.

With these substantive methodological issues aside, the study of real motor actions in the fMRI scanner environment also presents several significant challenges. Head motion, even on the order of millimetres, can lead to spurious activations and render the data unusable – an issue that is particularly problematic when a motor task requires subjects make arm and hand movements which can inadvertently shift the position of the head. In addition, arm movements on their own can introduce artifacts in the data, as any mass moving through the magnetic field of the scanner may lead to MR-signal perturbations (Barry et al., 2010). A further constraint is the small size of the MR bore (~60 cm) which necessarily limits the space that subjects have to perform movements. Our lab, however has overcome several of these technical issues by developing the apparatus (e.g., platforms for object presentation), paradigms (e.g., slow-event related fMRI designs which uncouple the motion artifact from the BOLD response), accessories (e.g., specialized radio frequency coils and careful head restraint) and preprocessing algorithms to optimize data quality.

In addition to these many challenges, there is also the problem of how fMRI data is typically analyzed. The common approach taken in nearly all fMRI studies to date is to examine each voxel independently (i.e., voxel-wise analyses) and typically smooth or average across adjacent voxels (see Figure 1.7, left panel), and in many cases across different subjects. This is of course done for practical reasons: First, from a statistical standpoint, running statistics or any functional contrast of interest (e.g., Condition A vs. B) at each individual voxel in the brain provides a highly tractable approach to detecting and localizing activation differences across several thousands of the voxels. Second, from a physiological standpoint, the populations of neural activity from which the BOLD signal is being measured will often traverse more than one functional voxel (Huettel et al., 2004) and thus spatial smoothing or averaging the activity across a subset of voxels seems sensible. Third, from a pragmatic standpoint, it allows the investigator to maximize their fMRI signal/noise ratio within an individual brain region, facilitating the detection of differences in the signal amplitude of a BOLD response corresponding to the condition(s)-of-interest. With respect to this last point, smoothing and averaging the activity across adjacent voxels (and subjects) is also particularly beneficial for group analyses, where individual subject differences in anatomical variability necessarily limit the functional overlap of different regions-of-interest (ROIs). Note that this approach of detecting differences in the signal amplitude of neural responses in order to ascribe function to a particular brain region directly borrows from the rationale and approach taken with single-unit neuron recording (see Figure

1.5), with the exception that with fMRI, this is done over a much larger expanse of brain (~50-200 voxels).

This voxel-wise approach has been quite successful in many respects, revealing a range of neural structures and functional subdivisions involved in the execution of several effector-specific movements. For instance, work from our lab and others have been able to pinpoint activity within the human aIPS as being related to grasping (Culham et al., 2003; Frey et al., 2005) by typically contrasting the activity evoked by a grasp vs. reach movement. Similarly, our lab has also been able to localize reach-selective activity in human SPOC, by contrasting the activity evoked during grasping actions that involved arm transport vs. those that did not (Cavina-Pratesi et al., 2010).

As previously alluded to, however, fMRI has not been able to shed much light on how early plans for movement (i.e., prior to an action being executed) are coded and organized in the human brain. Indeed, previous attempts to characterize and examine intention-related signals with human fMRI have revealed largely overlapping and indistinguishable signal amplitudes for different planned movements (see Figure 1.6B for real example fMRI data). This might be because the neural responses representing planned movements are more subtle or it possibly relates to the highly intermingled and distributed neural organization of parieto-frontal cortex (Andersen and Buneo, 2002; Andersen and Cui, 2009; Chang and Snyder, 2010); nevertheless both cases provide an impediment to detection with conventional fMRI methods. For both these reasons, a brain region -- when measured at the coarse scale of fMRI -- may exhibit no overall signal amplitude differences despite the fact that at the neural level, there exists highly specialized and intermingled populations of neurons which represent various effectors (e.g. eye vs. hand) or their parameters (e.g. movement left vs. right). A common interpretation for this null finding with fMRI (again, see overlapping response amplitudes in Figure 1.6B) may be that the brain area is equally involved in, or alternatively, makes use of a similar encoding scheme or reference frame for the planning processes being compared (e.g., Culham et al., 2006; Filimon, 2010). Indeed, these types of ambiguities necessarily make precise experimental questions about the coding of intention-related signals in the human, as they have been examined in the monkey (Andersen and Buneo, 2002; Andersen and Cui, 2009), quite challenging to answer. As such, our predominant and current understanding of how the human brain plans movement requires certain inferences to be made based on the well documented functional organization of the monkey brain.

It is at this point that we can fully appreciate and encapsulate a central paradox in the field of sensorimotor neuroscience: Our current understanding of how the human brain plans movements of the body necessarily relies on several proposed brain homologies with the monkey and yet these proposed homologies are nearly impossible to verify given that we have no way of examining and mapping the same types of intention-related brain signals in the human.

So, it would seem in several respects that we have come full circle and can return to the basic question that began this thesis at the outset: *How does the human brain plan movements of the body?* Certainly, it appears that in moving forward we will be unable to answer this question using traditional fMRI voxel-wise analysis techniques and that it will require a new way of conceptualizing fMRI data -- one that is far more sensitive to the subtle and distributed changes in brain activity which accompany changes in one's thoughts, decisions, and intentions.

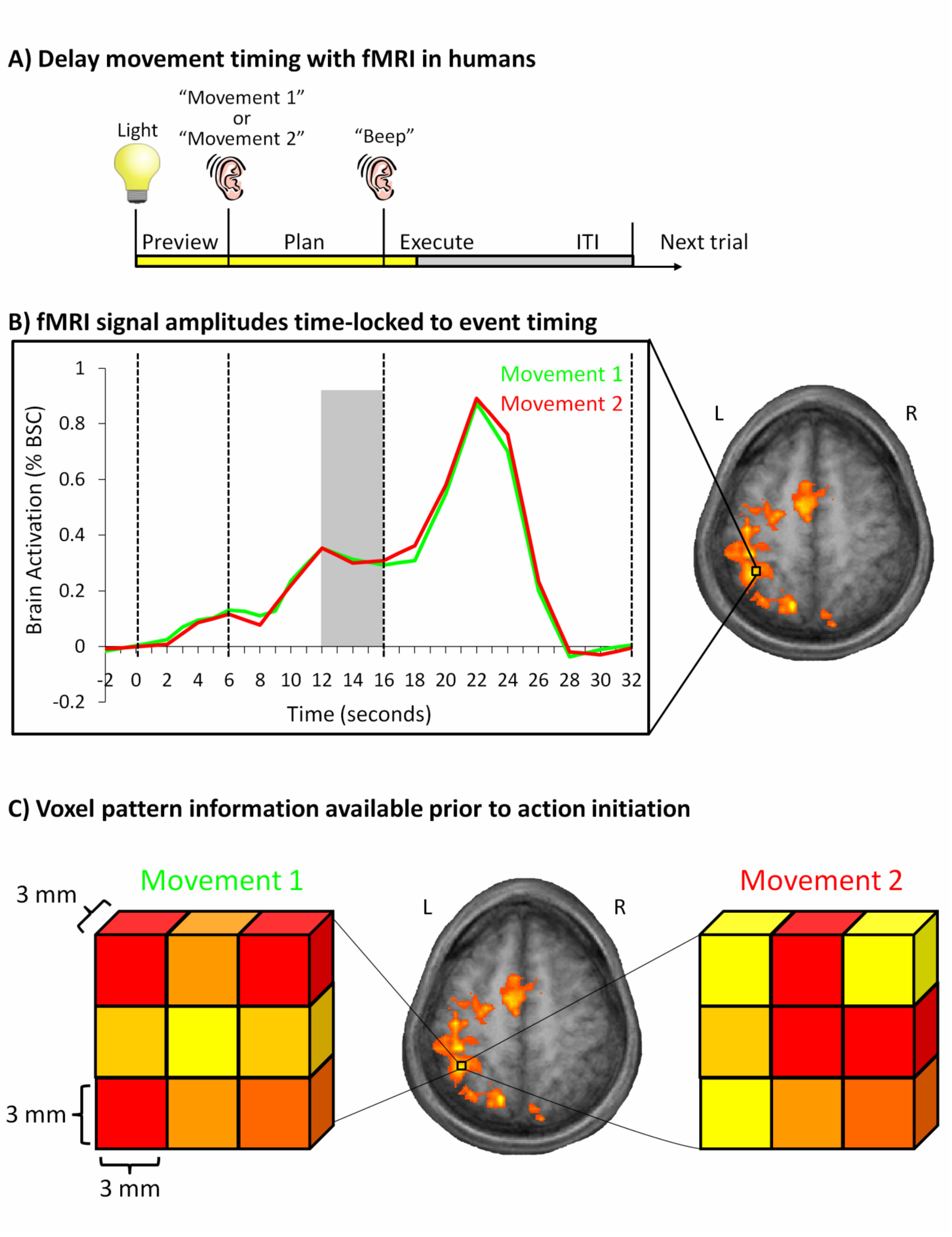

Figure 1.6: The difficulty of examining intention-related brain activity in humans with standard fMRI analyses and a possible solution that side-steps this problem. Similar to the approach taken in macaque monkeys, in order to effectively examine movement planning

processes in humans, intention-related activity needs to be isolated from the sensory and motor events of the task. This is also accomplished with a variant of the delayed-movement paradigm. In such a task (A), a target object is first visually presented to a participant (Preview phase). Moments later, the subject is then instructed via headphones on how to act upon that target object -- in the example here, “Movement 1” or “Movement 2” (this audio cue initiates the beginning of the Plan phase). It is important to note that no visual information changes between object presentation and movement instruction. Following a delay period, the subject is then given the Go cue (“Beep”) and then performs the cued action upon the target object. Following the completion of this movement, vision of the object is extinguished. When fMRI activation is extracted from a particular movement-related region-of-interest (ROI; in the case here, parietal cortex) corresponding to the task (B), we typically find a distinct and highly-reproducible time-course profile (note that the activity in B is time-locked to the timing of events in A). In response to visual target object presentation during the Preview phase (i.e., a sensory event), the activity in the ROI will correspondingly increase slightly and transiently (time 2s – 6s). Next, during the Plan phase, when subjects have the required information available to plan the upcoming movement (via audio cue), the activity will rise to a new higher level (time 8s – 12s), and importantly be maintained at this elevated level prior to movement onset (time 12s – 16s). Following movement initiation at the onset of the Execute phase (time 16s - 18s), however, there is another robust change in the signal amplitude of the neural responses (time 18s – 26s; note that while the fMRI activity shown is largely for illustrative purposes, the activation time-courses are in fact from real data in Project 1, and generally indicative of the type of activation profiles found throughout parietal and premotor cortex). It is critical to note, that despite the two planned movements being different, we find no corresponding differences in fMRI signal amplitude throughout the entire length of the trial (red and green curves overlap completely) – this is specifically the case in the last few seconds leading up to the movement (gray shaded bar). These indistinguishable fMRI activation profiles contrast markedly with the planning-related activity found in monkeys with neural recordings, where the intention of an upcoming movement (e.g., Movement 1 vs. Movement 2) can be accurately decoded moments prior to the monkey acting (see Figure 1.5). For these types of fine-grained investigations (i.e., examining intention-related activity) brute force fMRI signal amplitude comparisons between conditions (the conventional and standard approach taken in fMRI analyses) may not be ideal. In these conventional analyses, each voxel is examined separately and the activation is often smoothed or spatially averaged across adjacent voxels (facilitating the detection of fMRI signal amplitude differences). Alternatively, the ability to differentiate the fine-grained spatial voxel patterns of activity within a given area may provide sensitivity to largely distributed or overlapping neural representations related to different movement intentions. Depicted in C, is a zoomed-in view of the spatial voxel patterns from the same ROI (each voxel has 3 mm x 3 mm x 3 mm dimensions) for the last few seconds of the Plan phase (from the gray shaded bar in B; patterns shown here are not real and are only for illustrative purposes). Figure C is meant to illustrate that although the average fMRI signal amplitudes may overlap between different movement plans (in B), it may in fact be possible to decode and predict the upcoming movements to be performed from the fine-grained voxel activity patterns evoked by the task.

1.4 Decoding intentions from fMRI spatial activity patterns

It is becoming increasingly clear in the field of neuroimaging, that the conventional fMRI approach of comparing BOLD signal response amplitudes may lack the sensitivity to detect certain types of neural information (Haxby et al., 2001; Kamitani and Tong, 2005). A recent fMRI tool that has been gaining increasing prominence is multi-voxel pattern analysis (MVPA), a multivariate technique that has made it possible to probe the cognitive contents of the human mind with a level of sensitivity previously unavailable. In brief, MVPA uses pattern classification algorithms to differentiate the fine-grained spatial voxel patterns of activity within a given area – in effect, revealing distributed and overlapping neural representations largely ignored by conventional analysis approaches (Kriegeskorte et al., 2006; Mur et al., 2009; Pereira et al., 2009; Pereira and Botvinick, 2011)(see also Figures 1.6, 1.7, and 1.8). MVPA has most notably been applied to the domain of visual-perceptual research, and shows how visual and auditory stimuli being presented can be decoded from spatial voxel patterns of activity in visual (Haxby et al., 2001; Haynes and Rees, 2005; Kamitani and Tong, 2005; Haynes and Rees, 2006; Williams et al., 2008) and auditory cortex (Formisano et al., 2008; Meyer et al., 2010), respectively. Although MVPA has increased, and in several cases substantially altered our understanding of the organization and neural mechanisms employed in visual-perceptual brain areas, few MVPA experiments to date have examined the neural bases underlying the planning of complex goal-directed movements. Indeed, whereas previous fMRI studies have predominantly used MVPA for decoding the neural responses which accompany (and *follow from*) the presentation of sensory stimuli, a central question here was whether we could also use MVPA to decode motor actions moments prior to them actually being performed. That is, could the *intention* to carry out a particular goal-directed movement be decoded from preparatory fMRI brain activity? And if so, could we then also use MVPA to characterize different brain regions according to the types of goal-directed movements they can predict? To date, mapping the characteristic changes in brain activity which occur prior to an action being initiated has been constrained solely within the domain of invasive neurophysiological recordings in monkeys (e.g., Andersen and Buneo, 2002; Gold and Shadlen, 2007) and the aims of the present research was to provide key insights into the underlying neuroanatomical organization and cortical mechanisms that govern the *planning* of goal-directed behaviors in humans.

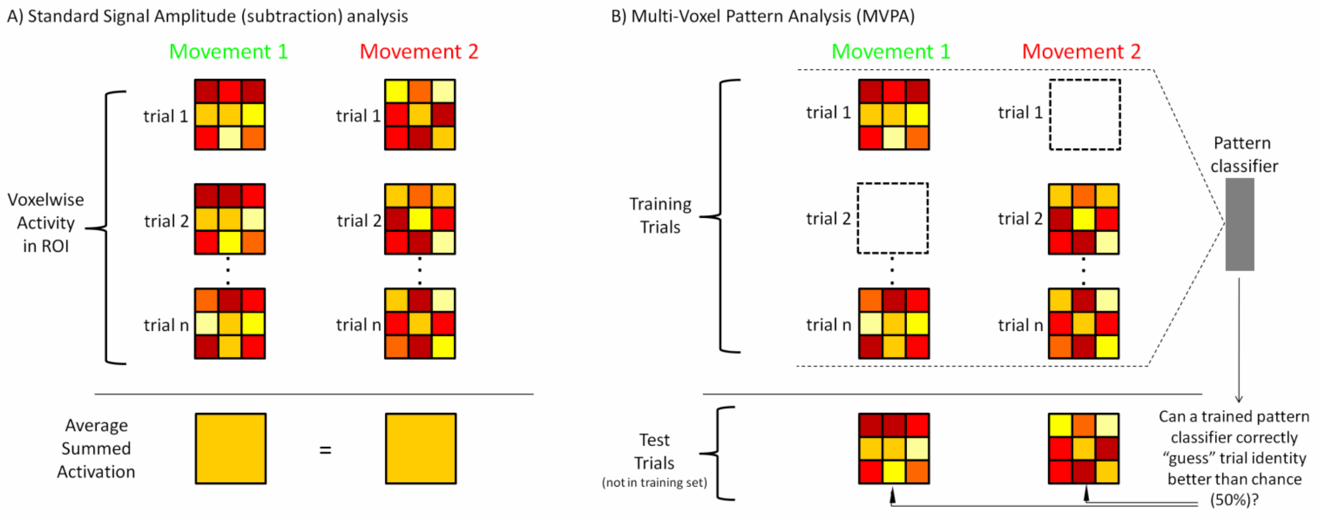

Figure 1.7: Schematic comparison of Conventional/Standard Signal Amplitude analysis vs. Multi-Voxel Pattern Analysis (MVPA) techniques in fMRI. A) Overview of how conventional voxel-wise fMRI analyses are typically performed. In this approach, individual fMRI trials within an ROI (depicted here as spatial activity patterns, as done in Figure 1.6C) are averaged together to produce average signal amplitude responses (this can be done both with raw % signal change activation or beta weights, with the latter based on how well the height of the % signal change activation fits a pre-described hemodynamic response model). The average beta weights for different conditions can then be statistically compared within each voxel across the whole brain (e.g., by subtracting the response of Movement 2 from that of Movement 1) and we can then use these fMRI activation differences to localize brain areas specifying a particular effect (i.e., directed-search or voxel-wise analyses). In the example shown here, although there may be general voxel pattern differences between conditions, when we average across voxels and trials (at bottom), these activity differences are no longer detectable (the average summed activations shown in yellow are meant to reflect the overlapping response amplitudes shown in Figure 1.6B). B) Overview of how MVPA is performed. This analysis technique uses the reverse approach: instead of using a model (e.g., beta weights within a general linear model) to specify differences in brain activity (i.e., voxel-wise analyses), we use differences in brain activity patterns in order to specify a model. In brief, MVPA works by training a pattern classifier (the model) to learn a response mapping between a condition-of-interest (in our case, a specific action plan for Movement 1 or Movement 2)) and the spatial voxel activity patterns evoked by that specific condition (this process is denoted by the training trials). The accuracy of this trained model is then tested on fMRI trials not yet seen by the classifier (these test trials are actually fMRI trials removed from the training set prior to classifier training, as denoted by empty boxes). If the classifier can successfully predict or 'decode' the identity of the independent test trial(s) in question, then the voxel patterns must contain meaningful information regarding the conditions-of-interest.

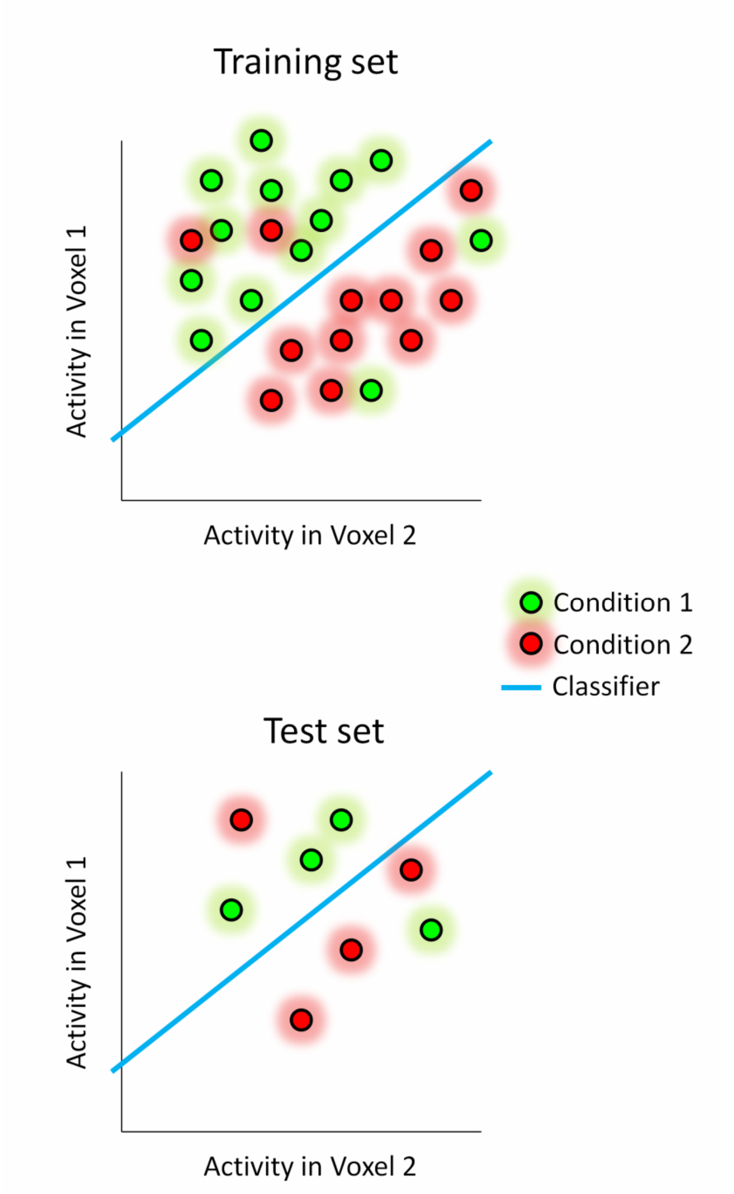

Figure 1.8: How spatial voxel patterns are compared and classified using Support Vector Machines (SVMs). In short, MVPA with an SVM classifier requires a model to be ‘trained’ with a subset of the data (top plot), and then ‘tested’ with an independent subset (bottom plot). Conceptually, the training of a SVM classifier requires the Train set to be plotted in voxel space such that the projection of any point (trial) onto the Nth dimensional axis is the response amplitude for that trial in voxel N. The simplest of these cases is depicted here, with a two voxel spatial pattern (understandably, it is impossible to visually represent this multidimensional voxel space beyond 3 voxels). Since the multidimensional voxel landscape contains two sets of trials (for instance, conditions 1 and 2), the goal of the classifier, knowing both trial identities, is to define a hyperplane that best separates these sets into two classes. For example, if a trial falls on one side of the hyperplane then it belongs to Class A and if it falls on the other side of the hyperplane then it belongs to Class B. A successful classifier is one that can correctly separate, or ‘decode’, the remaining trials (test set, bottom plot) according to their actual class, with an accuracy above chance (in this one example, the classifier would perform with 75% accuracy (6/8 trials correct)). Being able to train a single successful classifier, however, does not mean

that the set of trials can be generalized into two separate classes. As such, an iterative cross-validation procedure is used to confirm the separability of the sets of trials. For each iteration of the cross-validation procedure, different subsets of trials are used to train/test the classifier. The correct separability of the sets of trials into classes is then assessed by comparing the average accuracy of the classifier over N-iterations to the chance level (Duda et al., 2001).

The broader impact of this line of research is to also provide a more updated view of functional homologies between monkey and human brain areas and in doing so, also assist in the future development of brain machine interfaces (BMIs). BMIs hope to provide human movement-impaired patient populations (e.g. individuals with neurologic disease, injury, or limb loss) some recovery-of-function options by allowing them to control external robotic devices from intention-related brain signals reflecting movement goals. Despite the increasingly successful implementation of BMIs in monkeys (Musallam et al., 2004; Schwartz, 2004; Andersen et al., 2010), when applied in humans, many simple manual tasks still remain highly problematic and challenging (e.g., grasping or lifting an object). These shortcomings, however, relate not to insufficiencies in the electronics or robotics required to operate such devices, but instead point to an inadequate understanding of the human intention-related signals and brain organization which governs action planning. In fact, a central question in this field -- even in the case of monkeys -- is where in the brain to position neural recording arrays so to best capture the goals and intentions of the individual (Andersen et al., 2010). Thus, one indirect aim the current research is to pinpoint several possible candidate brain regions that can be further explored in both humans and monkeys to aid the development and efficacy of these devices.

1.5 Current projects

The goals of the present work was to use fMRI MVPA to determine whether an examination of distributed spatial patterns of activity could reveal substantial new insights into the neural organization and intention-related signals in the human brain that guide high-level movement planning processes (grasping, reaching and looking). Each of the current projects was guided by the central experimental question: What types of predictive information about a subject's upcoming movement can be decoded from preceding changes in neural activity? Again, it is worth noting that to date, the ability to address this question has been reliant on invasive neural recording techniques in non-human primates. A major theme developed through the current series of projects is that several brain areas within human parieto-frontal cortex can actually be characterized -- similar to that shown in the monkey -- according to the specific types of intention-related signals they contain.

Project 1 (Chapter 3) used fMRI to first determine, largely as a proof-of-concept, whether MVPA could actually be used to predict specific object-directed hand actions from intention-related brain activity patterns. Given that conventional fMRI analyses in humans have revealed widespread, overlapping, and largely undifferentiated activations for different planned movements (Culham et al., 2006; Filimon, 2010), we expected that the fine-grained sensitivity of MVPA might provide additional insights into how different brain regions contribute to the planning of object-directed hand actions. Using MVPA we hypothesized that we might be able to predict upcoming reach movements with the hand from the intention-related activity patterns located in interconnected reach-related brain areas like SPOC, midIPS, and PMd. Similarly, we hypothesized that we might predict upcoming grasp movements and perhaps also the object size to be grasped from the preparatory activity patterns in interconnected grasp-related areas like pIPS, aIPS and PMv. To test these hypotheses we had human subjects perform an event-related delayed movement task towards a single centrally located object (consisting of a small cube attached atop a larger cube). For each trial, following visual presentation of the object, one of three hand movements was instructed: grasp the top cube, grasp the bottom cube, or reach to touch the side of the object (without preshaping the hand). We found that despite an absence of fMRI signal amplitude differences between the planned movements, the spatial activity patterns in multiple parietal and premotor brain areas accurately predicted upcoming grasp and reach movements. Furthermore, the patterns of activity in a subset of these areas additionally predicted the object size to be grasped. It is critical to note that different activation patterns resulted from differences in the *motor intentions* of the subject rather than differences in kinematics, sensory feedback or motion-related artifacts. Importantly, consistent with our hypotheses, we found that we could also categorize different parieto-frontal brain regions according to the types of upcoming movements they could decode.

Project 2 (Chapter 4) followed up on the novel findings of Project 1 and asked whether we could also then use fMRI MVPA to decode effector-specific movement plans (reaches vs. eye movements) in many of the same parieto-frontal regions, a feat only previously demonstrated with invasive neural recordings in the monkey. This second study had subjects plan (and then execute) either reach or eye movements to different target locations in space and used a similar delay-movement paradigm as in Project 1. In this second project we found an interesting mixture of different decoding profiles across parieto-frontal regions: some areas discriminated movement plans for the different reach directions, some for the different eye movement directions, and a few areas accurately decoded planned movements for both the hand and eye. This latter finding is particularly noteworthy as it shows that some human brain regions represent the target location (end goal of the movement) largely independent of the effector (eye vs. hand) chosen to perform the movement. In addition, in many of the areas examined, we also found a representation of the effector to be used independent of the spatial location to be acted upon. In contrast to the largely graded effector- and direction-related planning responses found with conventional fMRI analysis methods, these results reveal considerable consensus with the parieto-frontal network organization suggested from primate neurophysiology and bolster arguments for several brain homologies between monkeys and humans. Moreover, these findings specifically show how both spatial- and effector-specific predictive movement information coexists within single human parieto-frontal areas.

Project 3 (Chapter 5), in light of the findings provided from Project 2, specifically investigated using fMRI MVPA how and where in the human brain the higher-level goals of an action are encoded separately from how those goals are accomplished. In order to examine this research question we took advantage of a common everyday behavioral implement that routinely achieves higher-level movement goals largely independent of the lower-level motor kinematics required: a hand-manipulative tool. Using a similar plan-related task as in Projects 1 and 2, we had participants *either* grasp or reach (i.e., two different motor goals) a centrally-located object using *either* their hand or a reverse tool (with kinematics opposite to those of the hand). In this way, we could hold constant the general goals of an action across movements while at the same time, uncoupling the precise hand mechanics used to operate each effector (hand vs. tool). We identified areas within the parieto-frontal network that decoded upcoming hand actions only, upcoming tool actions only, and rather interestingly, areas that decoded upcoming grasp vs. reach actions with both effectors. Further investigation of the signals in these latter areas showed that in anterior parietal and motor cortex, voxel patterns decoding movement plans for the hand and tool remained distinct whereas in contrast, in posterior parietal and premotor cortex these predictive activity patterns were shared across effectors. As such, these latter areas appeared to abstractly represent the goals of the movement (grasping vs. reaching) instead of the specific kinematics necessary to implement the desired goals. Using the everyday example of tool-use, these findings show that different levels of a goal-directed motor hierarchy (low-level kinematics vs. high-level goals) can be functionally localized to specific regions with parieto-frontal cortex.

1.6 References

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annual Review of Neuroscience 25:189-220.

Andersen RA, Cui H (2009) Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63:568-583.

Andersen RA, Asanuma C, Cowan WM (1985a) Callosal and prefrontal associational projecting cell populations in area 7A of the macaque monkey: a study using retrogradely transported fluorescent dyes. J Comp Neurol 232:443-455.

Andersen RA, Essick GK, Siegel RM (1985b) Encoding of spatial location by posterior parietal neurons. Science 230:456-458.

Andersen RA, Hwang EJ, Mulliken GH (2010) Cognitive neural prosthetics. Annu Rev Psychol 61:169-190, C161-163.

Andersen RA, Asanuma C, Essick G, Siegel RM (1990) Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. J Comp Neurol 296:65-113.

Andersen RA, Snyder LH, Bradley DC, Xing J (1997) Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annual Review of Neuroscience 20:303-330.

Anderson JC, Kennedy H, Martin KA (2011) Pathways of attention: synaptic relationships of frontal eye field to v4, lateral intraparietal cortex, and area 46 in macaque monkey. J Neurosci 31:10872-10881.

Ansari D (2008) Effects of development and enculturation on number representation in the brain. Nat Rev Neurosci 9:278-291.

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 23:4689-4699.

Barry RL, Williams JM, Klassen LM, Gallivan JP, Culham JC, Menon RS (2010) Evaluation of preprocessing steps to compensate for magnetic field distortions due to body movements in BOLD fMRI. Magn Reson Imaging 28:235-244.

Batista AP, Buneo CA, Snyder LH, Andersen RA (1999) Reach plans in eye-centered coordinates. Science 285:257-260.

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 98:966-983.

Battaglini PP, Muzur A, Galletti C, Skrap M, Brovelli A, Fattori P (2002) Effects of lesions to area V6A in monkeys. Exp Brain Res 144:419-422.

Baumann MA, Fluet MC, Scherberger H (2009) Context-specific Grasp Movement Representation in the Macaque Anterior Intraparietal Area. J Neurosci 29:6436-6448.

Begliomini C, Wall MB, Smith AT, Castiello U (2007) Differential cortical activity for precision and whole-hand visually guided grasping in humans. Eur J Neurosci 25:1245-1252.

Bernier PM, Grafton ST (2010) Human posterior parietal cortex flexibly determines reference frames for reaching based on sensory context. Neuron 68:776-788.

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 97:188-199.

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 101:3053-3062.

Beurze SM, Toni I, Pisella L, Medendorp WP (2010) Reference frames for reach planning in human parietofrontal cortex. J Neurophysiol 104:1736-1745.

Bisley JW, Goldberg ME (2003) Neuronal activity in the lateral intraparietal area and spatial attention. Science 299:81-86.

Blatt GJ, Andersen RA, Stoner GR (1990) Visual receptive field organization and cortico-cortical connections of the lateral intraparietal area (area LIP) in the macaque. J Comp Neurol 299:421-445.

Borra E, Belmalih A, Calzavara R, Gerbella M, Murata A, Rozzi S, Luppino G (2008) Cortical connections of the macaque anterior intraparietal (AIP) area. Cereb Cortex 18:1094-1111.

Boudrias MH, McPherson RL, Frost SB, Cheney PD (2009) Output properties and organization of the forelimb representation of motor areas on the lateral aspect of the hemisphere in rhesus macaques. Cereb Cortex 20:169-186.

Boussaoud D, Wise SP (1993) Primate frontal cortex: effects of stimulus and movement. Exp Brain Res 95:28-40.

Breveglieri R, Galletti C, Gamberini M, Passarelli L, Fattori P (2006) Somatosensory cells in area PEc of macaque posterior parietal cortex. J Neurosci 26:3679-3684.

Bruce CJ, Goldberg ME (1985) Primate frontal eye fields. I. Single neurons discharging before saccades. J Neurophysiol 53:603-635.

Bruce CJ, Goldberg ME, Bushnell MC, Stanton GB (1985) Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. J Neurophysiol 54:714-734.

Calton JL, Dickinson AR, Snyder LH (2002) Non-spatial, motor-specific activation in posterior parietal cortex. Nat Neurosci 5:580-588.

Caminiti R, Johnson PB, Burnod Y, Galli C, Ferraina S (1990) Shift of preferred directions of premotor cortical cells with arm movements performed across the workspace. Exp Brain Res 83:228-232.

Castiello U (2005) The neuroscience of grasping. Nat Rev Neurosci 6:726-736.

Castiello U, Begliomini C (2008) The cortical control of visually guided grasping. Neuroscientist 14:157-170.

Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam TD, Quinlan DJ, Goodale MA, Culham JC (2010) Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. J Neurosci 30:10306-10323.

Chang SW, Snyder LH (2010) Idiosyncratic and systematic aspects of spatial representations in the macaque parietal cortex. Proc Natl Acad Sci U S A 107:7951-7956.

Chang SW, Papadimitriou C, Snyder LH (2009) Using a compound gain field to compute a reach plan. Neuron 64:744-755.

Chouinard PA, Paus T (2006) The primary motor and premotor areas of the human cerebral cortex. Neuroscientist 12:143-152.

Cisek P, Kalaska JF (2005) Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. Neuron 3:801-814.

Cisek P, Kalaska JF (2010) Neural Mechanisms for Interacting with a World Full of Action Choices. Annu Rev Neurosci.

Clower DM, Hoffman JM, Votaw JR, Faber TL, Woods RP, Alexander GE (1996) Role of posterior parietal cortex in the recalibration of visually guided reaching. Nature 383:618-621.

Colby CL, Goldberg ME (1999) Space and attention in parietal cortex. Annu Rev Neurosci 22:319-349.

Connolly JD, Andersen RA, Goodale MA (2003) FMRI evidence for a 'parietal reach region' in the human brain. Exp Brain Res 153:140-145.

Connolly JD, Goodale MA, Cant JS, Munoz DP (2007) Effector-specific fields for motor preparation in the human frontal cortex. Neuroimage 34:1209-1219.

Constantin AG, Wang H, Martinez-Trujillo JC, Crawford JD (2007) Frames of reference for gaze saccades evoked during stimulation of lateral intraparietal cortex. J Neurophysiol 98:696-709.

Critchley M (1953) The Parietal Lobes. London: Arnold.

Cui H, Andersen RA (2007) Posterior parietal cortex encodes autonomously selected motor plans. Neuron 56:552-559.

Culham JC, Valyear KF (2006) Human parietal cortex in action. Curr Opin Neurobiol 16:205-212.

Culham JC, Cavina-Pratesi C, Singhal A (2006) The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia 44:2668-2684.

Culham JC, Danckert SL, DeSouza JF, Gati JS, Menon RS, Goodale MA (2003) Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Exp Brain Res 153:180-189.

Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E (2006) Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci 26:2260-2268.

Desmurget M, Reilly KT, Richard N, Szathmari A, Mottolese C, Sirigu A (2009) Movement intention after parietal cortex stimulation in humans. Science 324:811-813.

Dickinson AR, Calton JL, Snyder LH (2003) Nonspatial saccade-specific activation in area LIP of monkey parietal cortex. J Neurophysiol 90:2460-2464.

Duda RO, Hart PE, Stork DG (2001) Pattern Classification, Second Edition Edition. New York: John Wiley & Sons, Inc.

Dum RP, Strick PL (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci 11:667-689.

Dum RP, Strick PL (2002) Motor areas in the frontal lobe of the primate. Physiol Behav 77:677-682.

Evarts EV, Thach WT (1969) Motor mechanisms of the CNS: cerebro-cerebellar interrelations. Annu Rev Physiol 31:451-498.

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 29:1928-1936.

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 30:342-349.

Fecteau JH, Munoz DP (2003) Exploring the consequences of the previous trial. Nat Rev Neurosci 4:435-443.

Fernandez-Ruiz J, Goltz HC, DeSouza JF, 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 17:2283-2292.

Ferrier D (1876) Functions of the Brain. London: Smith, Elder and Co.

Ferrier D (1890) Cerebral Localisation. London: Smith, Elder and Co.

Filimon F (2010) Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. Neuroscientist 16:388-407.

Filimon F, Nelson JD, Hagler DJ, Sereno MI (2007) Human cortical representations for reaching: mirron neurons for execution, observation, and imagery. Neuroimage 37:1315-1328.

Filimon F, Nelson JD, Huang RS, Sereno MI (2009) Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. J Neurosci 29:2961-2971.

Fluet MC, Baumann MA, Scherberger H (2010) Context-specific grasp movement representation in macaque ventral premotor cortex. J Neurosci 30:15175-15184.

Fogassi L, Gallese V, Buccino G, Craighero L, Fadiga L, Rizzolatti G (2001) Cortical mechanism for the visual guidance of hand grasping movements in the monkey: A reversible inactivation study. Brain 124:571-586.

Formisano E, De Martino F, Bonte M, Goebel R (2008) "Who" is saying "what"? Brain-based decoding of human voice and speech. Science 322:970-973.

Freedman DJ, Assad JA (2006) Experience-dependent representation of visual categories in parietal cortex. Nature 443:85-88.

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 23:397-405.

Fritsch GT, Hitzig E (1870) On the electircal excitability of the cerebrum. Springfield, IL: Charles C. Thomas.

Gallese V, Murata A, Kaseda M, Niki N, Sakata H (1994) Deficit of hand preshaping after muscimol injection in monkey parietal cortex. Neuroreport 5:1525-1529.

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 9:410-413.

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 153:158-170.

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 29:4381-4391.

Gamberini M, Passarelli L, Fattori P, Zucchelli M, Bakola S, Luppino G, Galletti C (2009) Cortical connections of the visuomotor parietooccipital area V6Ad of the macaque monkey. J Comp Neurol 513:622-642.

Gardner EP, Babu KS, Ghosh S, Sherwood A, Chen J (2007a) Neurophysiology of prehension. III. Representation of object features in posterior parietal cortex of the macaque monkey. J Neurophysiol 98:3708-3730.

Gardner EP, Babu KS, Reitzen SD, Ghosh S, Brown AS, Chen J, Hall AL, Herzlinger MD, Kohlenstein JB, Ro JY (2007b) Neurophysiology of prehension. I. Posterior parietal cortex and object-oriented hand behaviors. J Neurophysiol 97:387-406.

Georgopoulos AP, Schwartz AB, Kettner RE (1986) Neuronal population coding of movement direction. Science 233:1416-1419.

Georgopoulos AP, Kettner RE, Schwartz AB (1988) Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of the direction of movement by a neuronal population. J Neurosci 8:2928-2937.

Giszter S, Patil V, Hart C (2007) Primitives, premotor drives, and pattern generation: a combined computational and neuroethological perspective. Prog Brain Res 165:323-346.

Gold JI, Shadlen MN (2007) The neural basis of decision making. Annu Rev Neurosci 30:535-574.

Goldberg ME, Bruce CJ (1990) Primate frontal eye fields. III. Maintenance of a spatially accurate saccade signal. J Neurophysiol 64:489-508.

Goodale MA, Milner AD (1992) Separate visual pathways for perception and action. Trends Neurosci 15:20-25.

Goodale MA, Milner AD (2004) Sight unseen : an exploration of conscious and unconscious vision. Oxford ; New York: Oxford University Press.

Grafton ST (2010) The cognitive neuroscience of prehension: recent developments. Exp Brain Res 204:475-491.

Graziano M (2006) The Organization of Behavioral Repertoire in Motor Cortex. Annu Rev Neurosci.

Graziano MS (2001) Is reaching eye-centered, body-centered, hand-centered, or a combination? Rev Neurosci 12:175-185.

Graziano MS (2009) The intelligent movement machine: an ethological perspective on the primate motor system. New York: Oxford University Press, Inc.

Graziano MS, Aflalo TN (2007) Mapping behavioral repertoire onto the cortex. Neuron 56:239-251.

Graziano MS, Taylor CS, Moore T (2002) Complex movements evoked by microstimulation of precentral cortex. Neuron 34:841-851.

Grol MJ, Majdandzic J, Stephan KE, Verhagen L, Dijkerman C, Bekkering H, Verstraten F, Toni I (2007) Parieto-frontal connectivity during visually guided grasping. J Neurosci 27:11877-11887.

Haaland KY, Harrington DL, Knight RT (1999) Spatial deficits in ideomotor limb apraxia. A kinematic analysis of aiming movements. Brain 122 (Pt 6):1169-1182.

Haaland KY, Harrington DL, Knight RT (2000) Neural representations of skilled movement. Brain 123 (Pt 11):2306-2313.

Hagler DJ, Jr., Riecke L, Sereno MI (2007) Parietal and superior frontal visuospatial maps activated by pointing and saccades. Neuroimage 35:1562-1577.

Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293:2425-2430.

Haynes JD, Rees G (2005) Predicting the orientation of invisible stimuli from activity in human primary visual cortex. Nat Neurosci 8:686-691.

Haynes JD, Rees G (2006) Decoding mental states from brain activity in humans. Nat Rev Neurosci 7:523-534.

Heed T, Beurze SM, Toni I, Roder B, Medendorp WP (2011) Functional rather than effector-specific organization of human posterior parietal cortex. J Neurosci 31:3066-3076.

Hoshi E, Tanji J (2006) Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. J Neurophysiol 95:3596-3616.

Hubbard EM, Piazza M, Pinel P, Dehaene S (2005) Interactions between number and space in parietal cortex. Nat Rev Neurosci 6:435-448.

Huettel SA, Song AW, McCarthy G (2004) Functional magnetic resonance imaging. Sunderland, Mass.: Sinauer Associates.

Husain M, Nachev P (2007) Space and the parietal cortex. Trends Cogn Sci 11:30-36.

Jeannerod M (1988) The Neural and Behavioral Organization of Goal-Directed Movements. Oxford U.K.: Oxford University Press.

Johnson PB, Ferraina S, Bianchi L, Caminiti R (1996) Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. Cereb Cortex 6:102-119.

Johnson SH, Grafton ST (2003) From 'acting on' to 'acting with': the functional anatomy of object-oriented action schemata. Prog Brain Res 142:127-139.

Joly O, Vanduffel W, Orban GA (2009) The monkey ventral premotor cortex processes 3D shape from disparity. Neuroimage 47:262-272.

Kable JW, Glimcher PW (2009) The neurobiology of decision: consensus and controversy. Neuron 63:733-745.

Kalaska JF (2009) From intention to action: motor cortex and the control of reaching movements. Adv Exp Med Biol 629:139-178.

Kamitani Y, Tong F (2005) Decoding the visual and subjective contents of the human brain. Nat Neurosci 8:679-685.

Kandel ER, Schwartz JH, Jessell TM (2000) Principles of Neural Science. New York: McGraw-Hill.

Karnath HO, Perenin MT (2005) Cortical control of visually guided reaching: evidence from patients with optic ataxia. Cereb Cortex 15:1561-1569.

Koch C (2004) The quest for consciousness: a neurobiological approach: Roberts & Company Publishers.

Kriegeskorte N, Goebel R, Bandettini P (2006) Information-based functional brain mapping. Proc Natl Acad Sci U S A 103:3863-3868.

Levy I, Schluppeck D, Heeger DJ, Glimcher PW (2007) Specificity of human cortical areas for reaches and saccades. J Neurosci 27:4687-4696.

Linden JF, Grunewald A, Andersen RA (1999) Responses to auditory stimuli in macaque lateral intraparietal area. II. Behavioral modulation. J Neurophysiol 82:343-358.

Livingstone M, Hubel D (1988) Segregation of form, color, movement, and depth: Anatomy, physiology, and perception. Science 240:740-749.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150-157.

Matelli M, Luppino G (2000) Parietofrontal circuits: parallel channels for sensory-motor integrations. Advances in Neurology 84:51-61.

Meyer K, Kaplan JT, Essex R, Webber C, Damasio H, Damasio A (2010) Predicting visual stimuli on the basis of activity in auditory cortices. Nat Neurosci 13:667-668.

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167-202.

Mountcastle VB (1957) Modaility and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 20:408-434.

Mountcastle VB, Lynch JC, Georgopoulos A, Sakata H, Acuna C (1975) Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. J Neurophysiol 38:871-908.

Mur M, Bandettini PA, Kriegeskorte N (2009) Revealing representational content with pattern-information fMRI--an introductory guide. Soc Cogn Affect Neurosci 4:101-109.

Murata A, Gallese V, Luppino G, Kaseda M, Sakata H (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. J Neurophysiol 83:2580-2601.

Murata Y, Higo N, Oishi T, Yamashita A, Matsuda K, Hayashi M, Yamane S (2008) Effects of motor training on the recovery of manual dexterity after primary motor cortex lesion in macaque monkeys. J Neurophysiol 99:773-786.

Murray EA, Coulter JD (1981) Organization of corticospinal neurons in the monkey. J Comp Neurol 195:339-365.

Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA (2004) Cognitive control signals for neural prosthetics. Science 305:258-262.

Nieder A, Dehaene S (2009) Representation of number in the brain. Annu Rev Neurosci 32:185-208.

Pakkenberg B, Gundersen HJ (1997) Neocortical neuron number in humans: effect of sex and age. J Comp Neurol 384.

Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389-443.

Pereira F, Botvinick M (2011) Information mapping with pattern classifiers: A comparative study. Neuroimage.

Pereira F, Mitchell T, Botvinick M (2009) Machine learning classifiers and fMRI: a tutorial overview. Neuroimage 45:S199-209.

Perenin MT, Vighetto A (1988) Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. Brain 111:643-674.

Pesaran B, Nelson MJ, Andersen RA (2006) Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. Neuron 51:125-134.

Pesaran B, Nelson MJ, Andersen RA (2008) Free choice activates a decision circuit between frontal and parietal cortex. Nature 453:406-409.

Pitzalis S, Sereno M, Committeri G, Galati G, Fattori P, Galletti C (2006) A possible human homologue of the macaque V6A. Journal of Vision 6:536a.

Platt ML, Glimcher PW (1997) Responses of intraparietal neurons to saccadic targets and visual distractors. J Neurophysiol 78:1574-1589.

Platt ML, Glimcher PW (1999) Neural correlates of decision variables in parietal cortex Nature 400:233-238.

Porter R, Lemon RN (1993) Corticospinal function and voluntary movement. Oxford, UK: Clarendon Press.

Prado J, Clavagnier S, Otzenberger H, Scheiber C, Kennedy H, Perenin MT (2005) Two cortical systems for reaching in central and peripheral vision. Neuron 48:849-858.

Raos V, Umilta MA, Murata A, Fogassi L, Gallese V (2006) Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. J Neurophysiol 95:709-729.

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 26:8176-8182

Rizzolatti G, Luppino G (2001) The cortical motor system. Neuron 31:889-901.

Rizzolatti G, Matelli M (2003) Two different streams form the dorsal visual system: anatomy and functions. Exp Brain Res 153:146-157.

Rizzolatti G, Luppino G, Matelli M (1998) The organization of the cortical motor system: new concepts. Electroencephalogr Clin Neurophysiol 106:283-296.

Rossetti Y, Rode G, Pisella L, Farne A, Li L, Boisson D, Perenin MT (1998) Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 395:166-169.

Sakata H, Taira M (1994) Parietal control of hand action. Curr Opin Neurobiol 4:847-856.

Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y (1997) The TINS Lecture. The parietal association cortex in depth perception and visual control of hand action. Trends Neurosci 20:350-357.

Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y, Tsutsui K (1998) Neural coding of 3D features of objects for hand action in the parietal cortex of the monkey. Philos Trans R Soc Lond B Biol Sci 353:1363-1373.

Schall JD, Thompson KG (1999) Neural selection and control of visually guided eye movements. Annu Rev Neurosci 22:241-259.

Scheperjans F, Hermann K, Eickhoff SB, Amunts K, Schleicher A, Zilles K (2008a) Observer-independent cytoarchitectonic mapping of the human superior parietal cortex. Cereb Cortex 18:846-867.

Scheperjans F, Eickhoff SB, Homke L, Mohlberg H, Hermann K, Amunts K, Zilles K (2008b) Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. Cereb Cortex 18:2141-2157.

Schieber MH, Poliakov AV (1998) Partial inactivation of the primary motor cortex hand area: effects on individuated finger movements. J Neurosci 18:9038-9054.

Schlag J, Schlag-Rey M (1987) Does microstimulation evoke fixed-vector saccades by generating their vector or by specifying their goal? Exp Brain Res 68:442-444.

Schwartz AB (1994) Direct cortical representation of drawing. Science 265:540-542.

Schwartz AB (2004) Cortical neural prosthetics. Annu Rev Neurosci 27:487-507.

Scott SH, Gribble PL, Graham KM, Cabel DW (2001) Dissociation between hand motion and population vectors from neural activity in motor cortex. Nature 413:161-165.

Sereno AB, Maunsell JH (1998) Shape selectivity in primate lateral intraparietal cortex. Nature 395:500-503.

Shadmehr R, Wise SP, eds (2005) The Computation Neurobiology of Reaching and Pointing. Cambridge, MA: MIT Press.

Sherrington CS (1906) The integrative action of the nervous system. New Haven, CT: Yale University Press.

Snyder LH, Batista AP, Andersen RA (1997) Coding of intention in the posterior parietal cortex. Nature 386:167-123.

Snyder LH, Grieve KL, Brotchie P, Andersen RA (1998) Separate body- and world-referenced representations of visual space in parietal cortex. Nature 394:887-891.

Stepniewska I, Fang PC, Kaas JH (2005) Microstimulation reveals specialized subregions for different complex movements in posterior parietal cortex of prosimian galagos. Proc Natl Acad Sci U S A 102:4878-4883.

Stoet G, Snyder LH (2004) Single neurons in posterior parietal cortex of monkeys encode cognitive set. Neuron 42:1003-1012.

Szczepanski SM, Konen CS, Kastner S (2010) Mechanisms of spatial attention control in frontal and parietal cortex. J Neurosci 30:148-160.

Taira M, Mine S, Georgopoulos AP, Murata A, Sakata H (1990) Parietal cortex neurons of the monkey related to the visual guidance of hand movement. Exp Brain Res 83:29-36.

Tanne-Gariepy J, Rouiller EM, Boussaoud D (2002) Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp Brain Res 145:91-103.

Thier P, Andersen RA (1996) Electrical microstimulation suggests two different forms of representation of head-centered space in the intraparietal sulcus of rhesus monkeys. Proc Natl Acad Sci U S A 93:4962-4967.

Thier P, Andersen RA (1998) Electrical microstimulation distinguishes distinct saccade-related areas in the posterior parietal cortex. J Neurophysiol 80:1713-1735.

Todorov E (2000) Direct cortical control of muscle activation in voluntary arm movements: a model. Nat Neurosci 3:391-398.

Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H (2007) Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J Neurosci 27:10259-10269.

Toyoshima K, Sakai H (1982) Exact cortical extent of the origin of the corticospinal tract (CST) and the quantitative contribution to the CST in different cytoarchitectonic areas. A study with horseradish peroxidase in the monkey. J Hirnforsch 23:257-269.

Tunik E, Frey SH, Grafton ST (2005) Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. Nat Neurosci 8:505-511.

Ungerleider LG, Mishkin M (1982) Two cortical visual systems. In: Analysis of Visual Behavior (Ingle DJ, Goodale MA, Mansfield RJW, eds), pp 549-586. Cambridge, MA: MIT Press.

Vesia M, Prime SL, Yan X, Sergio LE, Crawford JD (2010) Specificity of human parietal saccade and reach regions during transcranial magnetic stimulation. J Neurosci 30:13053-13065.

Walsh V (2003) A theory of magnitude: common cortical metrics of time, space and quantity. Trends Cogn Sci 7:483-488.

Weinrich M, Wise SP (1982) The premotor cortex of the monkey. J Neurosci 2:1329-1345.

Weinrich M, Wise SP, Mauritz KH (1984) A neurophysiological study of the premotor cortex in the rhesus monkey. Brain 107 (Pt 2):385-414.

Williams MA, Baker CI, Op de Beeck HP, Shim WM, Dang S, Triantafyllou C, Kanwisher N (2008) Feedback of visual object information to foveal retinotopic cortex. Nat Neurosci 11:1439-1445.

Wise SP (1985) The primate premotor cortex: past, present, and preparatory. Annu Rev Neurosci 8:1-19.

Wise SP, Boussaoud D, Johnson PB, Caminiti R (1997) Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. Annual Review of Neuroscience 20:25-42.

Wojciulik E, Kanwisher N (1999) The generality of parietal involvement in visual attention. Neuron 23:747-764.

Wolpert DM, Goodbody SJ, Husain M (1998) Maintaining internal representations: The role of the human superior parietal lobe. Nature neuroscience 1:529-533.

Xu Y, Chun MM (2006) Dissociable neural mechanisms supporting visual short-term memory for objects. Nature 440:91-95.

Xu Y, Chun MM (2009) Selecting and perceiving multiple visual objects. Trends Cogn Sci 13:167-174.

Zipser D, Andersen RA (1988) A back-propagation programmed network that simulates response properties of a subset of posterior parietal neurons. Nature 331:679-684.

Chapter 2

2. General Materials and Methods for the three projects

2.1 Preamble

Given that each of the three projects in the current thesis used very similar, and in many cases, the exact same methodologies (experimental setups, timing, MRI acquisition and preprocessing parameters, analysis approaches) coupled with the fact that each project largely followed from the last, in order to facilitate readability and reduce large amounts of methodological redundancy between projects a general methods section is provided in full detail here. A more truncated methods section containing project-specific details will be provided with each corresponding project chapter.

2.2 Subjects

All subjects were recruited from the University of Western Ontario (London, Ontario, Canada). Informed consent was obtained in accordance with procedures approved by the University's Health Sciences Research Ethics Board. Subjects were naïve with respect to hypothesis testing.

2.3 Setup and Apparatus

Each subject's workspace within the fMRI scanner consisted of a black platform placed over the waist and tilted away from the horizontal at an angle (~15 degrees) to maximize comfort and target visibility. To facilitate direct viewing of the workspace, we also tilted the head coil and used foam cushions to give an approximate overall head tilt of 30 deg from supine (see Figure 2.1). Participants performed individual movements according to the experimenter's instructions specific to each project. To minimize limb-related artifacts, participants had the right upper arm braced, limiting movement to the elbow, creating an arc of reachability (see Figure 2.1). The target object(s) was specific to each individual project and was secured to the workspace along arc of reachability for the participant's right arm. The exact placement of the target object(s) was adjusted to match each participant's arm length such that all required movements were comfortable.

During the experiment, the target object(s) was illuminated from the front by a bright white Light Emitting Diode (LED) attached to a flexible plastic stalk (Loc-Line, Lockwood Products, Lake Oswego OR). Each trial was preceded by a period in which participants were in complete darkness. During participant setup, the illuminator LED was positioned to illuminate the target object(s) well. Experimental timing and lighting were controlled with in-house software created with MATLAB (The Mathworks). To control for eye movements, a small green fixation LED was placed above and at a further depth location than the target object(s) and subjects were required to always foveate the fixation LED during functional scans (unless otherwise instructed, see Project 2). Eye fixation and arm movements were examined off-line from videos recorded using an MR-compatible infrared-sensitive camera (MRC Systems GmbH) positioned underneath the fixation LED and directed toward the subject's eyes and hand.

For each trial, subjects were required to perform a single action dependent on the project-specific instruction given to the subject (as specified in the Methods sections of upcoming chapters). Other than the execution phase of each action, throughout the other phases of the trial (Preview phase, Plan phase and intertrial interval, ITI) the hand was to remain still and in a relaxed 'home' position. For each participant and study the home/starting position was marked with a small elevation of black tape and subjects were required to always return to this same position following execution of the instructed movement.

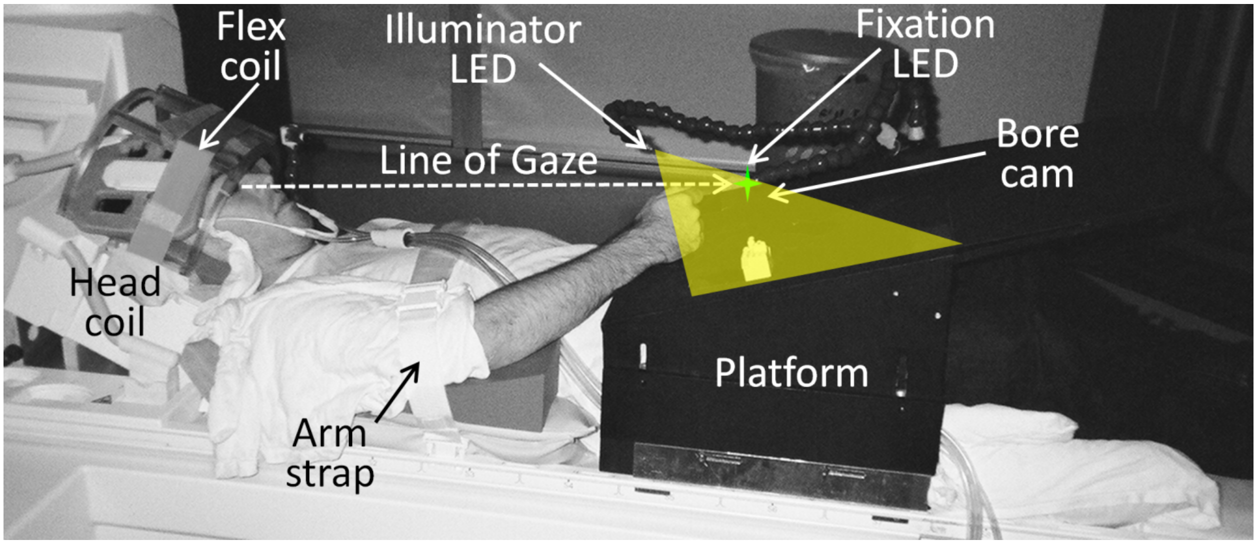

Figure 2.1. Picture of subject setup from side view (taken with the subject on the scanner bed outside of the magnet bore). The subject's head is tilted to permit a direct viewing of objects placed on the platform in front of them (i.e., without the need of a mirror, which would require additional visual-motor transformations and processing). The subject's right arm is braced (see arm strap) to limit arm movement-related artifacts in the fMRI signal. Data was collected with a combination of imaging coils; the suspended 4-channel flex coil captured signal from the anterior part of the head and the back half of the 12-channel head coil (6-channels) captured signal from the posterior part of the head.

2.4 Experiment Design and Timing

To extract the visual-motor planning response from the simple visual and motor execution responses, we used a slow event-related planning paradigm with 32-34 s trials, each consisting of three distinct phases: ‘Preview’, ‘Plan’ and ‘Execute’ (see Figure 2.2 for example of timing; Project 1 used 32 s trials and Projects 2 and 3 used 34 s trials). We adapted this paradigm from previous work with eye- and arm-movements that have successfully isolated delay activity from the transient responses following the onset of visual input and movement execution (Curtis et al., 2004; Beurze et al., 2007, 2009; Pertzov et al., 2010).

In our tasks, each trial was preceded by a period where participants were in complete darkness except for the fixation LED upon which they maintained their gaze. Each trial began with the Preview phase, during which the subject’s workspace was illuminated revealing the target object(s). After 6 s of the Preview phase, subjects were given an auditory cue (0.5 s) through headphones providing instructions regarding the upcoming movement that would be required (see each project methods for details); this cue marked the onset of the Plan phase. Although there were no visual differences between the Preview and Plan phase portions of the trial (i.e. the target object(s) was always visually present), only in the Plan phase did the subjects have the necessary motor information in order to prepare the upcoming movement. After 10-12 s of the Plan phase (depending on whether it was Project 1 or Projects 2 and 3, respectively), a 0.5 s auditory ‘beep’ cued participants to immediately execute the planned action (for a duration of approximately 2 s), initiating the Execute phase of the trial. Two seconds following the beginning of this Go cue, the illuminator was turned off, cueing the subjects to return the effector (hand or, in some trials of Project 2, eye) to its starting position. After the illuminator was extinguished, subjects then waited in the dark while maintaining fixation for 14 s, allowing the BOLD response to return to baseline prior to the next trial (ITI phase). All trial types were randomized and balanced across all runs so that each trial type was preceded and followed equally often by every other trial type across the entire experiment.

Separate practice sessions were carried out before the actual experiment to familiarize participants with the required actions and delay paradigm. These sessions were carried out before the subjects entered the scanner as well as during the anatomical scan (collected at the beginning of every experiment). A testing session for each participant included set-up time (~45 minutes), generally eight functional runs and one anatomical scan, and lasted approximately 3 hours. A more rigorous tracking of the eyes was not performed because our eye-tracking software does not work while the head is tilted due to a partial occlusion from the eyelids.

2.5 MRI acquisition and preprocessing

Subjects were scanned using a 3-Tesla Siemens TIM MAGNETOM Trio MRI scanner. The T1-weighted anatomical image was collected using an ADNI MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, field of view = 192 mm x 240 mm x 256 mm, matrix size = 192 x 240 x 256, flip angle = 9°, 1 mm isotropic voxels). Functional MRI volumes were collected using a T2*-weighted single-shot gradient-echo echo-planar imaging (EPI) acquisition sequence (time to repetition (TR) = 2000 ms, slice thickness = 3 mm, in-plane resolution = 3 mm x 3 mm, time to echo (TE) = 30 ms , field of view = 240 mm x 240 mm, matrix size = 80 x 80, flip angle = 90°, and acceleration factor (integrated parallel acquisition technologies, iPAT) = 2 with generalized auto-calibrating partially parallel acquisitions (GRAPPA) reconstruction). Each volume comprised 34 contiguous (no gap) oblique slices acquired at a ~30° caudal tilt with respect to the plane of the anterior and posterior commissure (AC-PC), providing near whole brain coverage. We used a combination of imaging coils to achieve a good signal:noise ratio and to enable direct viewing without mirrors or occlusion. Specifically, we tilted (~20° degrees) the posterior half of the 12-channel receive-only head coil (6-channels) and suspended a 4-channel receive-only flex coil over the anterior-superior part of the head. We reconstructed the cortical surface from one subject from a high-resolution anatomical image, a procedure that included segmenting the gray and white matter and inflating the surface at the boundary between them. This inflated cortical surface was used to overlay group activation for figure presentation. All preprocessing and univariate analyses were performed using Brain Voyager QX version 2.12 (Brain Innovation, Maastricht, Netherlands).

Following slice scan-time correction, 3D motion correction (such that each volume was aligned to the volume of the functional scan closest to the anatomical scan), high-pass temporal filtering and functional-to-anatomical co-registration, functional and anatomical images were rotated such that the axial plane passed through the anterior and posterior commissures (AC-PC space) and then transformed into Talairach space. Other than the sinc interpolation inherent in all transformations, no additional spatial smoothing was performed. Talairach data was used only for group voxelwise Random-Effects (RFX) analyses in order to display the pre-defined action-related regions of interest (ROIs). For MVPA, these areas were defined anatomically within each subject's AC-PC data. Given that MVPA discriminates spatial patterns across voxels, we have found it beneficial to select ROIs at the single subject level and use AC-PC data in lieu of the Talairach data (thus avoiding further voxel smoothing due to Talairach interpolation).

For each participant, functional data from each session were screened for motion and/or magnet artifacts by examining the time-course movies and the motion plots created with the motion correction algorithms. Error trials – trials where the participant fumbled with the object, performed the incorrect instruction, or contaminated the plan phase data by slightly moving their limb or eyes or by performing the action before the 'Go' cue -- were identified off-line from the videos recorded during the session; see project-specific Materials and Methods for the number of trials removed.

2.6 Regions of Interest (ROI)

To localize the specific *a priori* action-related areas in individual subjects in which to implement MVPA, we used a general linear model (GLM) with predictors created from boxcar functions convolved with the Boynton haemodynamic response function (Boynton et al., 1996). For each trial, a boxcar function was aligned to the onset of each phase, with a height dependent upon duration of each phase: i) 3 volumes for the Preview phase, ii) 5-6 volumes for the Plan phase (depending on whether it was Project 1 or Projects 2 and 3, respectively), and iii) 1 volume for the execute phase. The ITI was excluded from the model; therefore all regression coeffcients (betas) were defined relative to the baseline activity during the ITI. In addition, the time-course for each voxel was converted to percent signal change before applying the RFX-GLM.

To specify our pre-defined ROIs and select voxels to submit for MVPA from each subject we searched for brain areas involved in movement generation and contrasted activity for movement planning and execution vs. the simple visual response to object presentation prior to instruction: (Plan & Execute > Preview; note that in Project 1 only the Plan > Preview contrast was used). The resulting statistical map of all positively active voxels in each subject ($t(7) = 3$, $p<0.003$, each subject's activation map was cluster threshold corrected (corrected, $p<0.05$) so that only voxels passing a minimum cluster size were selected; for details see *ROI selection* for each project) was then used to define different parieto-frontal ROIs (see project-specific Materials and Methods information for a listing of these ROIs). All of these ROIs were selected based on their well-documented involvement in movement planning/generation. The voxels included in for each ROI were easily defined based on all significant activity within a 3375 mm^3 cube (15 mm cubes) centered on a pre-defined anatomical landmarks that corresponded with functional activity (see *ROI selection* for each project). These ROI sizes were chosen not only for the inclusion of numerous functional voxels for pattern classification (an important consideration), but also to ensure that adjacent ROIs did not overlap (for the average number of functional voxels selected across each project see Tables 3.1, 4.1, 5.1). Critically, given the orthogonal contrast employed to select our ROIs (i.e. Plan & Execute > Preview), their activity is not biased to show any preview-, plan- or execute-related pattern differences *between* any of the experimental conditions. All univariate statistical tests are Greenhouse-Geisser corrected and for post-hoc tests (two-tailed paired t-tests), we applied a threshold of $p<0.05$. Only significant results are reported. For ROI selection details see project-specific methods sections.

To provide a Type I-error control, we also tested the performance of our classifiers in ROIs outside of our action-related network where no statistically significant classification would be expected. To select these ROIs, we further reduced our statistical threshold (after specifying the [Plan & Execute > Preview] network within each subject) to $t=0$, $p=1$ and selected all positive activation within 3375 mm^3 centered on a consistent point 1) within each subject's right ventricle or 2) at a location situated just outside the skull of the right hemisphere, in the AC-PC plane and near right visual cortex (Projects 1 and 2) or directly in line with the posterior commissure (Project 3).

2.7 Multi-voxel pattern analysis (MVPA)

Whereas conventional univariate fMRI analyses examine each voxel separately -- typically smoothing and averaging activity across multiple adjacent voxels in order to detect differences in signal amplitude -- MVPA instead uses classification algorithms to differentiate the fine-grained spatial voxel patterns elicited by different classes of stimuli. In effect, voxel pattern classification is able to reveal distributed neural representations contained in spatial activity patterns that might be ignored or missed by traditional analysis approaches (Mur et al., 2009; Pereira et al., 2009; Raizada and Kriegeskorte, 2010). The additional benefit of the MVPA technique is that it allowed us to investigate the underlying nature and mechanisms of the predictive neural representations. For this, we used cross-trial-type classification to directly examine whether decoding would generalize across experimental manipulations. For example, in Project 2, we tested whether discriminations between targets on the left and right would generalize across the effector used, hand or eye, which would indicate and effector-invariant representation of space (see *cross-trial-type decoding* below for further details).

2.7.1 Support Vector Machine Classifiers

MVPA was performed with a combination of in-house software (using Matlab) and the Princeton MVPA Toolbox for Matlab (http://code.google.com/p/princeton-mvpa-toolbox/) using a Support Vector Machines (SVM) binary classifier (libSVM, http://www.csie.ntu.edu.tw/~cjlin/libsvm/). The SVM model used a linear kernel function and a constant cost parameter, C=1, (congruent with many other fMRI studies, LaConte et al., 2003; Mitchell et al., 2003; Mourao-Miranda et al., 2005; Haynes et al., 2007; Pessoa and Padmala, 2007) to compute a hyperplane that best separated the trial responses.

In brief, MVPA with linear Support Vector Machine (SVM) classifiers (Kamitani and Tong, 2005; Harrison and Tong, 2009; Chen et al., 2010; Meyer et al., 2010) requires a model to be 'trained' with a subset of the data, and then 'tested' with an independent set (a more detailed explanation can be found elsewhere, e.g.(Pereira et al., 2009)). To verify the generalizability of the set of trials into two separate stimulus classes an iterative cross-validation procedure, where several independent subsets of trials are used to train and test the classifier, is employed. The separability of the sets of trials into the correct classes is then assessed by comparing the average accuracy of the classifier over N-iterations to the chance level (Duda et al., 2001).

2.7.2 Voxel Pattern Preparation

To prepare the data for spatial pattern classification, the percent signal change was computed from the time-course at a time point(s) of interest with respect to the time-course at a common baseline, for all voxels in the ROI. This was done using two approaches. The first approach involved extracting the percent signal change values for a windowed-average at three different epochs over the course of the trial (Preview, Plan and Execute phases of the trial; called epoch-related decoding) – this approach was implemented in all three projects. The second approach involved extracting percent signal change values for each time point in the trial (time-resolved decoding) – this approach was implemented in the third project only. For both approaches, the baseline window was defined as volume -1, a time point prior to initiation of the current trial (volume 0) and avoiding contamination from the previous trial. In the trial epoch approach, for the Preview phase time points, we extracted the mean of volumes 3-4 (4-8s); time points corresponding to the peak of the visual transient response (see Figure 2.2 for example). For the Execute phase time points, we extracted the average of volumes 12-13 (22-26s) although volumes 11-12 (20-24s) in Project 1), time points corresponding to the peak of the transient movement-related response, following the subject's action (see Figure 2.2 for example). Lastly, for the Plan phase – the time points of critical interest in order to examine whether we could predict upcoming movements -- we extracted the average of volumes 8-9 (14-18s) the final two volumes of the Plan phase; although this was volumes 7-8 in Project 1 (12-16s)), corresponding to the sustained activity of a planning response (see Figure 2.2 for example).

Our reasoning for using the average of the final two volumes of the Plan phase for pattern classification is obvious: Planning is not a transient but a sustained process. Whereas simple visual or motor execution responses typically show transient neural activity (Andersen et al., 1997; Andersen and Buneo, 2002) -- in which the hemodynamic response function peaks approximately at 6 s after the event and then falls -- planning responses generally remain high for the duration of the intended movement (Curtis and D'Esposito, 2003; Curtis et al., 2004; Chapman et al., in press). With this rationale, we reasoned if pattern differences were to arise during movement planning, they would more likely occur during the sustained planning response after the hemodynamic response had reached its peak. For these reasons, we selected the final two volumes of the Plan phase to serve as our data points of interest -- a critical 2-volume window where the hemodynamic response had already plateaued, any non-plan related transient responses associated with the auditory cue would be diminishing, and most importantly, a time point prior to the subject initiating any movement.

Following the extraction of each trial's percent signal change, these values were either z-scored (Projects 1 and 2) or rescaled (Project 3; between -1 and +1) across all trials for each individual voxel within an ROI. Importantly, with this time-dependent decoding approach, in addition to revealing which types of movements could be decoded, we could also examine specifically when predictive information pertaining to specific actions arose (i.e., with the first approach, either within the Preview, Plan or Execute phase and with the second approach (implemented only in Project 3), within which specific imaging volume).

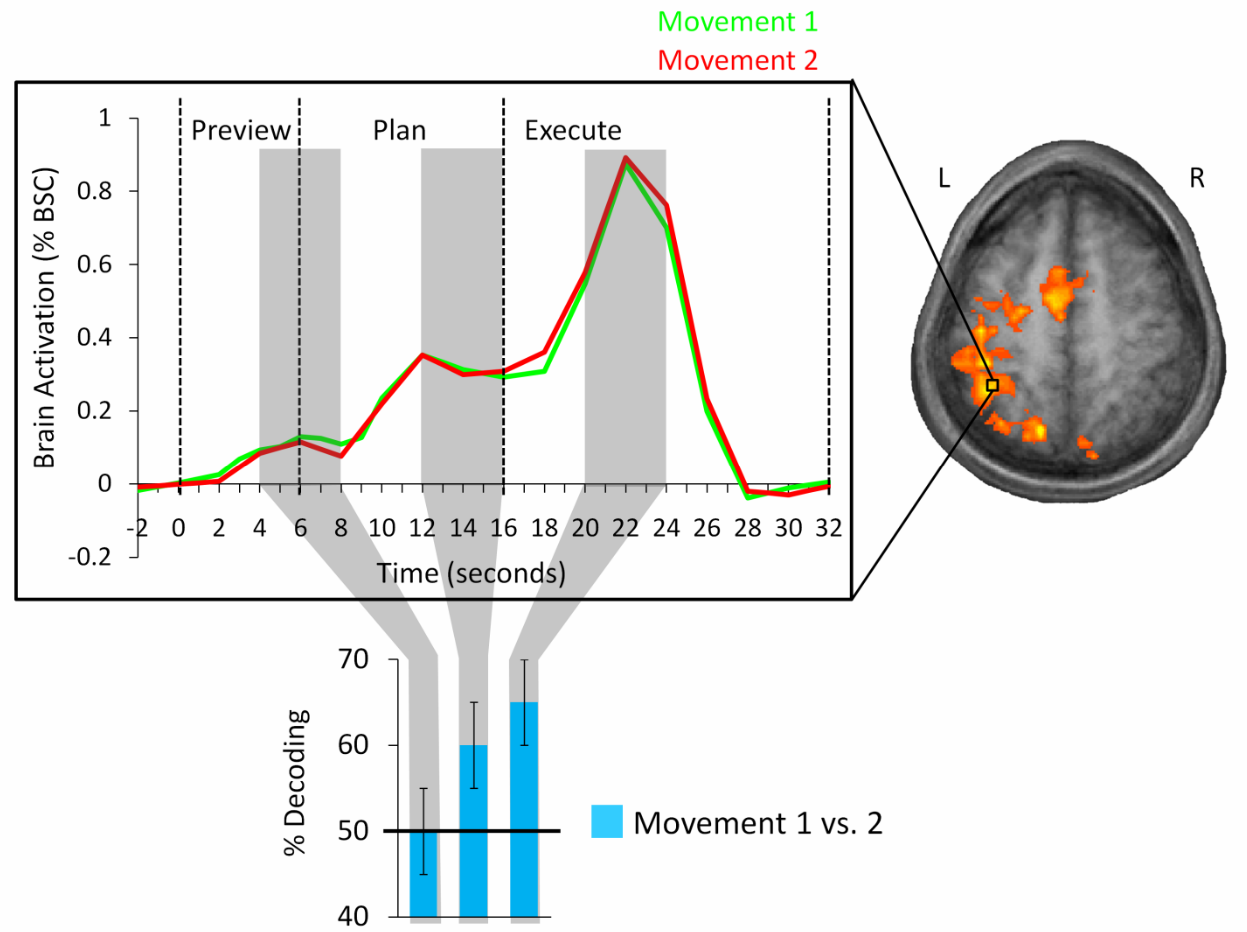

Figure 2.2: Time-dependent decoding approach used in the three experiments. To examine how action decoding evolved across the length of a trial, MVPA was performed on single fMRI trials and based on the windowed average of the % signal change corresponding to the three different time-points denoted by each of the gray shaded bars (top plot). Each averaged time point corresponded to the activity elicited from a distinct phase of the trial: Preview, Plan and Execute (from left to right). We reasoned that if we would be able to predict a subject's upcoming movement from brain activity, then these intention-related signals should be present in the few seconds prior to the subject performing an action (Plan phase gray bar). Decoding during the Preview phase was used as a type I error control, given the rather obvious fact that as a proof-of-principle, we should not be able to decode the intentions of an action prior to the subject being instructed of which movement to perform. Decoding during the Execute phase allowed us to characterize the actual motor-related activity within a given area. (Bottom plot) Decoding accuracies are plotted according to trial phase (left to right) and pair-wise comparison (e.g., Movement 1 vs. 2; hypothesized decoding accuracies shown).

2.7.3 Pair-wise Discriminations

SVMs are designed for classifying differences between two stimuli. LibSVM (the SVM package implemented here) uses the so-called "one-against-one method" for each pair-wise discrimination; in other words, it discriminates between two and only two conditions Although it is often the case that multiple pair-wise results are combined to produce multiclass discriminations (Hsu and Lin, 2002) (i.e., to distinguish among more than two stimuli), for the purposes of this particular set of projects (i.e., to characterize brain regions according to the types of upcoming movements they could predict: grasps vs. reaches, eye vs. hand, left vs. right actions), we found it imperative to examine the individual pair-wise discriminations separately (e.g., decoding accuracies for a hand action to the left vs. a hand action to the right). For instance, a brain region that could predict hand movement directions (i.e., left vs. right), but not eye movement direction – a potentially interesting theoretical finding – would not be readily apparent with a traditional multiclass discrimination approach.

2.7.4 Single-Trial classification

For each subject, each action-related ROI, and each timepoint of interest, separate binary support vector machine (SVM) classifiers were estimated for MVPA. We used a "leave-N-trials-out" cross-validation to test the accuracy of the binary SVM classifiers. That is, N trials from each of the conditions being compared were reserved for testing the classifier and the remaining trials were used for classifier training (see project-specific Materials and Methods for the exact number of trials left out of classifier training). Single trials in the independent test data set were either classified with the trained classifier (Project 1) or, prior to classifier testing, averaged according to condition (i.e., creating an averaged spatial pattern of activity for each condition), improving voxel pattern signal-to-noise in the test data set (see also Smith and Muckli, 2010). Project 1 used leave-8-trials-out SVM classification, Project 2 a leave-5-trials-out classification, and Project 3 a leave-4-trials-out classification approach. However, because a full cross validation is not entirely reasonable with a "leave-4-trials-out" design (due to the $\sim 10^{>4}$ possible iterations (and more so the case with $\sim 10^{>8}$ and $\sim 10^{>5}$ possible interations), to provide a highly reliable estimate of decoding accuracies we performed a minimum of 1000 train-and-test iterations for each pair-wise discrimination.

To ensure unbiased classification results with single-trial classification analysis, it is necessary that each individual trial and condition type, in addition to being randomly selected for each iteration, be equally represented across the total number of iterations for classifier training and testing. We achieved this by running a minimum of 1000 iterations in each subject (see project-specific Materials and Methods details for the exact number of iterations ran). This large number of train-and-test iterations produces a highly representative sample and precise estimate of true classification accuracies. For instance, this approach provided a test-retest reliability within +/- 0.5% based on multiple simulations of 1000 iterations conducted in two subjects (in Projects 1 and 2).

Decoding accuracies were computed separately for each subject, as an average across iterations. The average across subjects for each ROI is plotted in each decoding figure. To access the statistical significance of decoding accuracies, we performed one-sample t-tests across subjects in each of the ROIs to test whether the decoding accuracy for each pair-wise discrimination was significantly higher than 50% chance (2-tailed tests)(Chen et al., 2010).

2.7.5 Permutation Tests

In addition to the t-test, for each of the three projects we separately assessed statistical significance with non-parametric randomization tests (Golland and Fischl, 2003; Etzel et al., 2008; Chen et al., 2010; Smith and Muckli, 2010). In brief, this involved permuting the correspondance between the activity patterns and condition labels mutliple times so that any resultant pattern classification on this mislabelled data would reflect a distribution of decoding accuracies due to chance. We then defined the percentiles of statistical significance for this random distribution (i.e., $p<0.05$, $p<0.01$, $p<0.005$, $p<0.001$) allowing us to empirically determine the significance of our true decoding accuracies (correctly labelled activity patterns) and thus, whether they were likely to have arisen due to chance.

For each subject, ROI, and pair-wise comparison, following classifier training (and testing) with the true trial identities, we permuted the correspondence between the Test trial identities and data one hundred different times before testing the classifier, and then computed classifier performance the same as before (minimum average of 1000 train-and-test iterations) for each individual permutation of the Test labels. This produced one hundred mean accuracies (the one ‘true’ mean accuracy containing the correct test labeling was appended to this permuted distribution). We then generated a randomized population of 1000 mean accuracies, based on 1000 combinations of randomly drawn accuracies from each subject’s permuted distribution (of 101 accuracies), and then found the ‘true’ group mean accuracy’s empirical probability based on its place in a rank-ordering of this randomized distribution. The peak percentiles of significance (p<0.001) are limited by the number of samples producing the randomized probability distribution at the group level. The findings from this non-parametric randomization test produced significant results with much higher significance than those found with a standard parametric t-test (a finding also noted by Chen et al., 2010; Smith and Muckli, 2010). For instance decoding accuracies showing statistical significance at p<0.05 with the standard t-test showed significance at p<0.001 with the permutation tests. This indicates that the t-test group analysis provides a highly conservative estimate of the statistical significance of the decoding accuracies. The important finding highlighted from these permutation tests is that the brain areas showing significant decoding with the one sample parametric t-tests (vs. 50%) *also* show significant decoding (albeit higher) with the empirical non-parametric permutation tests. For all parametric tests, we additionally verified that the mean accuracies across subjects were in accordance with an underlying normal distribution by performing Lilliefors tests.

2.7.6 Within-Trial tests (only applied in Project 1)

We also performed a within-trial test for the significance of our decoding accuracies by examining whether classification accuracies found during the Plan and Execute phases of the trial were significantly higher than the decoding accuracies found during the preceding Preview phase. In other words, we wanted to assess whether significant pattern classifications observed in the Plan and Execute phases could unequivocally be attributed to movement intentions (and executions) rather than simple visual pattern differences that begin to arise during object presentation when subjects had no prior knowledge which action they would be performing (Preview Phase). To do this, we ran paired t-tests in each ROI to determine whether the decoding accuracies discriminating between trial types during the Plan and Execute phase were significantly higher than the Preview phase decoding accuracies occurring earlier within the same trials (2-tailed tests; see red asterisks in Figure 3.4).

2.7.7 Cross-trial-type decoding (only applied in Projects 2 and 3)

In order to test whether a SVM pattern classifier trained to discriminate between two types of trials (e.g., *train set*: left vs. right arm movement trial types in Project 2) could then be used to accurately decode pattern differences when tested on a different set of trials (e.g., *test set*: left vs. right eye movement trial types), we also used the “leave-N-trials-out” cross-validation analysis (where the trials in the independent test set were averaged within condition to create a mean spatial pattern). The exception is that in this case, the N trials of each movement reserved for testing the pattern classifier belonged to the different set of trials than that used for training.

Cross-trial-type decoding accuracies for each subject were computed by averaging together the two mean accuracies generated by using each pair of trial types for classifier training and testing (e.g., Arm trials were used to train the classifier in one analysis when Eye trials were used for testing, and then they were used to test the classifier in the other analysis when the Eye trials were used for classifier training). The means across subjects of this cross-trial-type decoding approach are reported in cross-decoding figures for Projects 2 and 3. We statistically assessed decoding significance with a two-tailed t-test vs. 50% chance decoding.

2.8 References

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annual Review of Neuroscience 25:189-220.

Andersen RA, Snyder LH, Bradley DC, Xing J (1997) Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annual Review of Neuroscience 20:303-330.

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 97:188-199.

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 101:3053-3062.

Boynton GM, Engel SA, Glover GH, Heeger DJ (1996) Linear systems analysis of functional magnetic resonance imaging in human V1. J Neurosci 16:4207-4221.

Chapman CS, Gallivan JP, Culham JC, Goodale MA (in press) Mental Blocks: fMRI reveals top-down modulation of early visual cortex when planning a grasp movement that is interfered with by an obstacle. Neuropsychologia.

Chen Y, Namburi P, Elliott LT, Heinzle J, Soon CS, Chee MW, Haynes JD (2010) Cortical surface-based searchlight decoding. Neuroimage.

Curtis CE, D'Esposito M (2003) Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci 7:415-423.

Curtis CE, Rao VY, D'Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 24:3944-3952.

Duda RO, Hart PE, Stork DG (2001) Pattern Classification, Second Edition Edition. New York: John Wiley & Sons, Inc.

Etzel JA, Gazzola V, Keysers C (2008) Testing simulation theory with cross-modal multivariate classification of fMRI data. PLoS One 3:e3690.

Golland P, Fischl B (2003) Permutation tests for classification: towards statistical significance in image-based studies. Inf Process Med Imaging 18:330-341.

Harrison SA, Tong F (2009) Decoding reveals the contents of visual working memory in early visual areas. Nature 458:632-635.

Haynes JD, Sakai K, Rees G, Gilbert S, Frith C, Passingham RE (2007) Reading hidden intentions in the human brain. Curr Biol 17:323-328.

Hsu CW, Lin CJ (2002) A comparison of methods for multi-class support vector machiens. IEEE Transactions on Neural Networks 13:415-425.

Kamitani Y, Tong F (2005) Decoding the visual and subjective contents of the human brain. Nat Neurosci 8:679-685.

LaConte S, Anderson J, Muley S, Ashe J, Frutiger S, Rehm K, Hansen LK, Yacoub E, Hu X, Rottenberg D, Strother S (2003) The evaluation of preprocessing choices in single-subject BOLD fMRI using NPAIRS performance metrics. Neuroimage 18:10-27.

Meyer K, Kaplan JT, Essex R, Webber C, Damasio H, Damasio A (2010) Predicting visual stimuli on the basis of activity in auditory cortices. Nat Neurosci 13:667-668.

Mitchell TM, Hutchinson R, Just MA, Niculescu RS, Pereira F, Wang X (2003) Classifying instantaneous cognitive states from FMRI data. AMIA Annu Symp Proc:465-469.

Mourao-Miranda J, Bokde AL, Born C, Hampel H, Stetter M (2005) Classifying brain states and determining the discriminating activation patterns: Support Vector Machine on functional MRI data. Neuroimage 28:980-995.

Mur M, Bandettini PA, Kriegeskorte N (2009) Revealing representational content with pattern-information fMRI--an introductory guide. Soc Cogn Affect Neurosci 4:101-109.

Pereira F, Mitchell T, Botvinick M (2009) Machine learning classifiers and fMRI: a tutorial overview. Neuroimage 45:S199-209.

Pertzov Y, Avidan G, Zohary E (2010) Multiple reference frames for saccadic planning in the human parietal cortex. J Neurosci 31:1059-1068.

Pessoa L, Padmala S (2007) Decoding near-threshold perception of fear from distributed single-trial brain activation. Cereb Cortex 17:691-701.

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

Smith FW, Muckli L (2010) Non-stimulated early visual areas carry information about surrounding context. Proc Natl Acad Sci U S A.

Chapter 3

3. Decoding action intentions from preparatory brain activity in human parieto-frontal networks[3]

3.1 Introduction

Significant developments in understanding the neural underpinnings of highly cognitive and abstract processes like intentions and decision-making have predominantly come from neurophysiological investigations in non-human primates. Principal among these has been the ability to predict or decode upcoming sensorimotor behaviours (such as movements of the arm or eyes) based on changes in parieto-frontal neural activity that precede movement onset (Andersen and Buneo, 2002; Gold and Shadlen, 2007; Andersen and Cui, 2009; Cisek and Kalaska, 2010). To date, the ability to predict goal-directed movements based on intention-related cortical signals has almost entirely been constrained to invasive neural recordings in non-human primates. Recently, however, advances in neuroimaging using pattern classification, a multivariate statistical technique used to discriminate classes of stimuli by assessing differences in the elicited spatial patterns of functional magnetic resonance imaging (fMRI) signals, have made it possible to probe the cognitive contents of the human mind with a level of sensitivity previously unavailable. Indeed, pattern classification has provided a wealth of knowledge within the domain of sensory-perceptual processing, showing that visual stimuli being viewed (Haxby et al., 2001; Kamitani and Tong, 2005), imagined (Stokes et al., 2009), or remembered (Harrison and Tong, 2009) and that categories of presented auditory stimuli (Formisano et al., 2008) can be accurately decoded from the spatial pattern of signals in visual and auditory cortex, respectively.

Few pattern classification experiments to date, however, have examined the primary purpose of perceptual processing: the planning of complex object-directed actions. Given the rather poor understanding of the human sensorimotor planning processes which guide target-directed behaviour, the goals of this experiment were two-fold. The first goal was to examine whether object-directed grasp and reach actions with the hand can be decoded from intention-related activity, recorded prior to movement execution, as has only previously been shown with neural recording studies in monkeys (Andersen and Buneo, 2002). The second goal, pending success of

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[3] A version of this chapter has recently been published. Gallivan, J.P., McLean, D.A., Valyear, K.F., Pettypiece, C., & Culham, J.C. (2011). Decoding action intentions from preparatory brain activity in human parieto-frontal networks. *Journal of Neuroscience* 31 (26): 9599-9610.

the first, was to determine whether different parieto-frontal brain areas can be characterized according to the types of planned movements they can decode. For instance, we questioned whether plan-related activity in interconnected reach-related areas like superior parietal cortex, middle intraparietal sulcus (IPS), and premotor dorsal (PMd) cortex (Andersen and Cui, 2009) can predict an upcoming reach movement. Similarly, we questioned whether preparatory signals in interconnected hand-related areas like posterior and anterior IPS and premotor ventral (PMv) cortex (Rizzolatti and Matelli, 2003; Grafton, 2010) can predict upcoming grasp movements, and moreover even discriminate different precision grasps. More revealingly, we wondered whether the increased sensitivity of decoding approaches would enable us to predict an upcoming movement from brain regions not previously implicated in particular hand actions. Given that conventional fMRI analyses in humans have shown widespread, highly overlapping, and largely undifferentiated activations for different movements (e.g. Culham et al., 2006) combined with mounting evidence that standard fMRI methods may ignore the neural information contained in distributed activity patterns (Harrison and Tong, 2009), we expected that our pattern classification approach might offer a new understanding of how various parieto-frontal brain regions contribute to the planning of goal-directed hand actions.

3.2 Materials and Methods:

To address these two main questions, we measured activity across the whole brain using fMRI while human subjects performed a delayed object-directed movement task. The task required three different hand actions to be carried out upon a target object comprised of a small block attached atop a larger block (see Figure 3.1). These actions were: grasping the top (GT), grasping the bottom (GB) or touching the side (Touch) (see Figure 3.1B). This delayed movement task allowed us to separate, in time, the transient neural activity associated with visual responses (Preview phase) and movement execution (Execute phase) responses from the more sustained plan-related responses that evolve prior to the movement (Plan Phase)(Andersen and Buneo, 2002; Beurze et al., 2007) (see Figure 3.1 C,D). This experimental design permits a direct investigation of whether pattern classifiers implemented during the planning phase of an action in a given brain area can decode: 1) upcoming grasp vs. touch actions [(GT vs. Touch) AND (GB vs. Touch)], two general types of hand movements requiring slight differences in wrist orientation and hand preshaping and 2) upcoming grasp movements from each other (GT vs. GB), performed on different blocks, requiring far more subtle differences in size and location. Emphasis on decoding during the planning phase of actions has the added advantage of utilizing activity patterns uncontaminated by the subject's limb movement. Importantly, given this task design, where all actions are performed on a centrally-located object that never changes position from trial-to-trial, any movement decoding during planning would be independent of simple retinotopic and general attention-related differences across trial types.

First, in order to localize the common brain areas among individuals in which to perform pattern analyses, we searched for regions at the group level preferentially involved in movement planning. To do this, we contrasted activity elicited by the planning of a hand action (i.e. following movement instruction) vs. the transient activity elicited by visual presentation of the object prior to the instruction (Plan>Preview). We reasoned that in comparison to the activity elicited when the object was illuminated and the subject was unaware of the action to be carried out (Preview phase), areas involved in movement planning should show heightened responses once movement instruction information has been given (Plan phase), even though the object was visible in both phases. This rationale provides a logical extension of recent studies that examined areas involved in planning to temporally spaced instructions about target location and effector in fMRI movement tasks (Beurze et al., 2007; Chapman et al., in press).This group contrast allowed us to define 14 well-documented action-related regions-of-interest (ROIs) as well as three sensory-related ROIs which could then be reliably identified in single subjects with the same contrast. In each subject we then iteratively trained and tested pattern classifiers in each pre-defined ROI in order to determine whether, prior to movement, its preparatory spatial activity patterns were predictive of the hand movement to be performed.

3.2.1 Subjects

Nine right-handed volunteers participated in this study (5 males, mean age: 26.2 years). One subject was excluded due to head motion beyond 1 mm translation and 1 deg rotation in their experimental runs (see *MRI acquisition and preprocessing* below).

3.2.2 Setup and Apparatus

The target object was made up of a smaller cube atop a larger cube (bottom block: 5 cm x 5 cm x 5 cm, top block: 2.5 cm x 2.5 cm x 1.5 cm) and was secured to the workspace at a location along the arc of reachability for the right hand, at the point corresponding to the participant's sagittal midline.

For each trial, the subjects were required to perform one of three actions on the object with their right hand: Grasp the top cube (GT; using a precision grip with the thumb and index finger placed on opposing surfaces of the cube), Grasp the bottom cube (GB) using the same grip, or manually touch the side of the object with the knuckles (transport the hand to the object without hand preshaping). Importantly, for each trial, the graspable object never changed its centrally-located position.

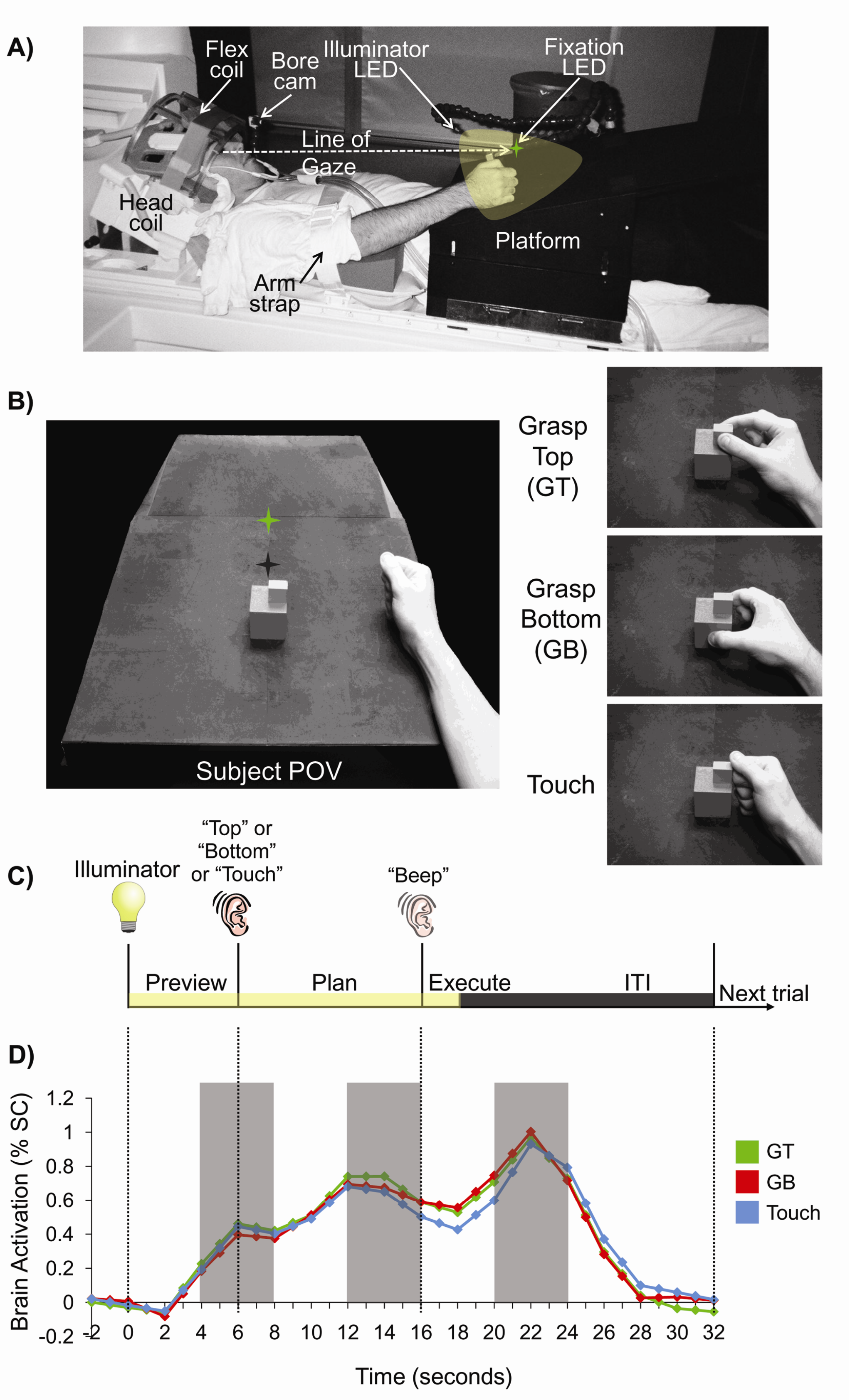
A)
Flex coil
Bore cam
Illuminator LED
Fixation LED
Line of Gaze
Head coil
Arm strap
Platform
B)
Subject POV
Grasp Top (GT)
Grasp Bottom (GB)
Touch
C)
Illuminator
"Top" or "Bottom" or "Touch"
"Beep"
Preview
Plan
Execute
ITI
Next trial
D)
Brain Activation (% SC)
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-2
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
Time (seconds)
🟩 GT
🟥 GB
🟦 Touch

Figure 3.1: Experiment setup, conditions, timing and trial-related brain activity. A) Setup from side view. The participant's head is tilted to permit direct viewing of objects on the platform. **B)** Experimental apparatus and graspable object shown from the participant's point of view. The same object (consisting of a smaller cube attached atop a larger cube) was always presented at the same location on the platform for every trial. Green star with dark shadow represents the fixation LED and its location in depth. Hand is positioned at its starting location. (Right) The three different hand movements. **C)** Timing of one event-related trial. Trials began with the 3D graspable object being illuminated while the subject maintained fixation (Preview phase; 6 s). Subjects were then instructed via headphones to perform one of three hand actions: Grasp the top cube ("Top"), Grasp the bottom cube ("Bottom"), or touch both cubes with their knuckles ("Touch"). This cue initiated the Plan phase portion of the trial, where, in addition to having visual information from the object, subjects also knew which hand action they were to perform. Following a delay interval (10 s), subjects were cued (via an auditory beep) to perform the instructed hand movement (Execute phase). Two seconds after the movement, vision of the object was extinguished and participants waited for commencement of the following trial (14 s, ITI). **D)** Example event-related BOLD activity from parietal cortex (posterior IPS) over the length of a trial. Events in **D** are time-locked to correspond to events in **C**. Pattern classification analysis was performed on single trials based on the windowed average of the % signal change corresponding to the three different time-points denoted by each of the gray shaded bars (each corresponding to activity elicited from the three distinct trial phases Preview, Plan and Execute).

3.2.3 Experiment Design and Timing

We used a slow event-related planning paradigm with 32 s trials, each consisting of three distinct phases: ‘Preview’, ‘Plan’ and ‘Execute’ (see Figure 3.1C). The trial began with the Preview phase and illumination of the workspace and centrally located object. After 6 s of the Preview phase, a voice auditory cue (0.5 s; one of “Grasp-Top”, “Grasp-Bottom” or “Touch”) was given to the subject and instructed the corresponding upcoming movement, marking the onset of the Plan phase. After 10 s of the Plan phase, a 0.5 s auditory beep cue instructed participants to immediately execute the planned action (for a duration of approximately 2 s), initiating the Execute phase of the trial. Two seconds following the beginning of this Go cue, the illuminator was extinguished providing 14 s of darkness/fixation which allowed the BOLD response to return to baseline prior to the next trial (ITI phase). The three trial types, with six repetitions per condition (18 trials total per run) were pseudo-randomized within a run and balanced across all runs so that each trial type was preceded and followed equally often by every other trial type across the entire experiment.

3.2.4 MRI acquisition and preprocessing

No task-related errors were observed, likely because, by the time they actually performed the required movements in the scanner, subjects were well trained in the delay task.

3.2.5 Regions of Interest (ROI)

Using the GLM, we contrasted activity for movement planning vs. the simple visual response to object presentation [Plan > Preview: (GT-Plan + GB-Plan + Touch-Plan) vs. (GT-Preview + GB-Preview + Touch-Preview)]. We reasoned that in comparison to the activity elicited when the object was illuminated and the subject was unaware of the action to be carried out (Preview phase), areas involved in movement planning should show heightened responses once movement instruction information has been given (Plan phase), even though the object was visible in both phases. This rationale provides a logical extension of recent studies that examined areas involved in planning to temporally spaced instructions about target location and effector (e.g. eye vs. hand) in fMRI movement tasks (Beurze et al., 2007, 2009).

The Plan>Preview statistical map of all positively active voxels (RFX, $t(7) = 3.5$, $p<0.01$) was then used to define 17 ROIs (foci of activity selected within a 15 mm cube centered on a particular anatomical landmark; only clusters of voxels larger than 297 mm^3 were used (minimum cluster size estimated by 1000 Monte Carlo simulations of $p<0.05$ corrected, implemented in the cluster threshold plug-in for BVQX)) which could then be localized in single subjects. Fourteen of these ROIs (across parietal, motor, and premotor cortex) were selected based on their well documented and highly-reliable co-activations across several movement-related tasks and paradigms (Andersen and Buneo, 2002; Chouinard and Paus, 2006; Culham et al., 2006; Filimon et al., 2009; Cisek and Kalaska, 2010; Filimon, 2010; Grafton, 2010) and the other three ROIs (somatosensory cortex, and left and right Heschl's gyrus) were selected as regions known to respond to transient stimuli (i.e. sensory and auditory events) and often activated in experimental contexts, but not expected to necessarily participate in sustained movement planning or intentional-related processes (i.e. to serve as sensory control regions). Importantly, all these ROIs are easily defined according to anatomical landmarks (sulci and gyri) and functional activations in each individual subject's AC-PC data (see paragraph and *ROI selection* below). Critically, given the contrast employed to select these 17 areas (i.e. Plan>Preview), their activity is not directionally biased to show any plan-related pattern differences between any of the experimental conditions (for confirmation of this fact, see the univariate analyses in Figure 3.5).

Voxels submitted for pattern classification analysis were selected from the Plan>Preview GLM contrast on single subject AC-PC data and based on all activity within a (15 mm)^3 cube centered on defined anatomical landmarks for each of the 17 ROIs (for details see *ROI selection*, below). These ROIs were selected at a threshold of $t=3$, $p<0.003$, from an overlay of each subject's activation map (cluster threshold corrected, $p<0.05$, so that only voxels passing a minimum cluster size were selected; average minimum cluster size across subjects: 110 mm^3).

3.2.6 ROI selection

Left- and Right-Superior parieto-occipital cortex (SPOC)

- defined by selecting voxels located medially and directly anterior to the Parieto-occipital sulcus (POS) on the left and right (Gallivan et al., 2009).

Left anterior Precuneus (L-aPCu)

- defined by selecting voxels further anterior and superior to the L-SPOC ROI, near the Transverse parietal sulcus (in most subjects this activity was located medially, within the same sagittal plane as SPOC, however, in a few subjects this activity was located slightly more laterally)(Filimon et al., 2009).

Left posterior IPS (L-pIPS)

- defined by selecting activity at the caudal end of the IPS (Beurze et al., 2009).

Left middle IPS (L-midIPS)

- defined by selecting voxels approximately half-way up the length of the IPS, on the medial bank (Calton et al., 2002), near a characteristic ‘knob’ landmark that we observed consistently within each subject.

Left region located posterior to L-aIPS (L-post aIPS)

- defined by selecting voxels just posterior to the junction of the IPS and Post-central sulcus (PCS), on the medial bank of the IPS (Culham, 2004).

Left aIPS (L-aIPS)

- defined by selecting voxels directly at the junction of the IPS and PCS (Culham et al., 2003).

Left Supramarginal gyrus (L-SMG)

- defined by selecting voxels on the supramarginal gyrus, lateral to the anterior segment of the IPS (Lewis, 2006).

Left Motor cortex

- defined by selecting voxels around the left ‘hand knob’ landmark in the Central sulcus (CS)(Yousry et al., 1997).

Left Premotor dorsal (L-PMd)

- defined by selecting voxels at the junction of the Precentral sulcus (PreCS) and Superior frontal sulcus (SFS)(Picard and Strick, 2001).

Left Precentral gyrus

- defined by selecting voxels lateral to the junction of the PreCS and SFS, encompassing the Precentral gyrus and posterior edge of the PreCS.

Left Premotor ventral (L-PMv)

- defined by selecting voxels slightly inferior and posterior to the junction of the Inferior frontal sulcus (IFS) and PreCS (Tomassini et al., 2007).

Left Pre-Supplementary motor area (L-PreSMA)

- defined by selecting bilateral voxels (although mostly left-lateralized) superior to the middle/anterior segment of the cingulate sulcus, anterior to the plane of the anterior commissure, and more anterior and inferior than those selected for L-SMA (Picard and Strick, 2001).

Left supplementary motor area (L-SMA)

- defined by selecting voxels bilaterally (although mostly left-lateralized) adjacent and anterior to the medial end of the CS, and posterior to the plane of the anterior commissure (Picard and Strick, 2001).

Left somatosensory cortex (L-SS cortex)

- defined by selecting voxels medial and anterior to the aIPS, encompassing the Post-central gyrus and PCS.

Left- and Right-Heschl's gyri (HG)

- defined by selecting voxels half-way up along the Superior temporal sulcus (STS), on the superior temporal gyrus (between the insular cortex and outer-lateral edge of the superior temporal gyrus)(Meyer et al., 2010).

See Table 3.1 for details about ROI coordinates and sizes, and Figure 3.2 for anatomical locations on one representative subject's brain.

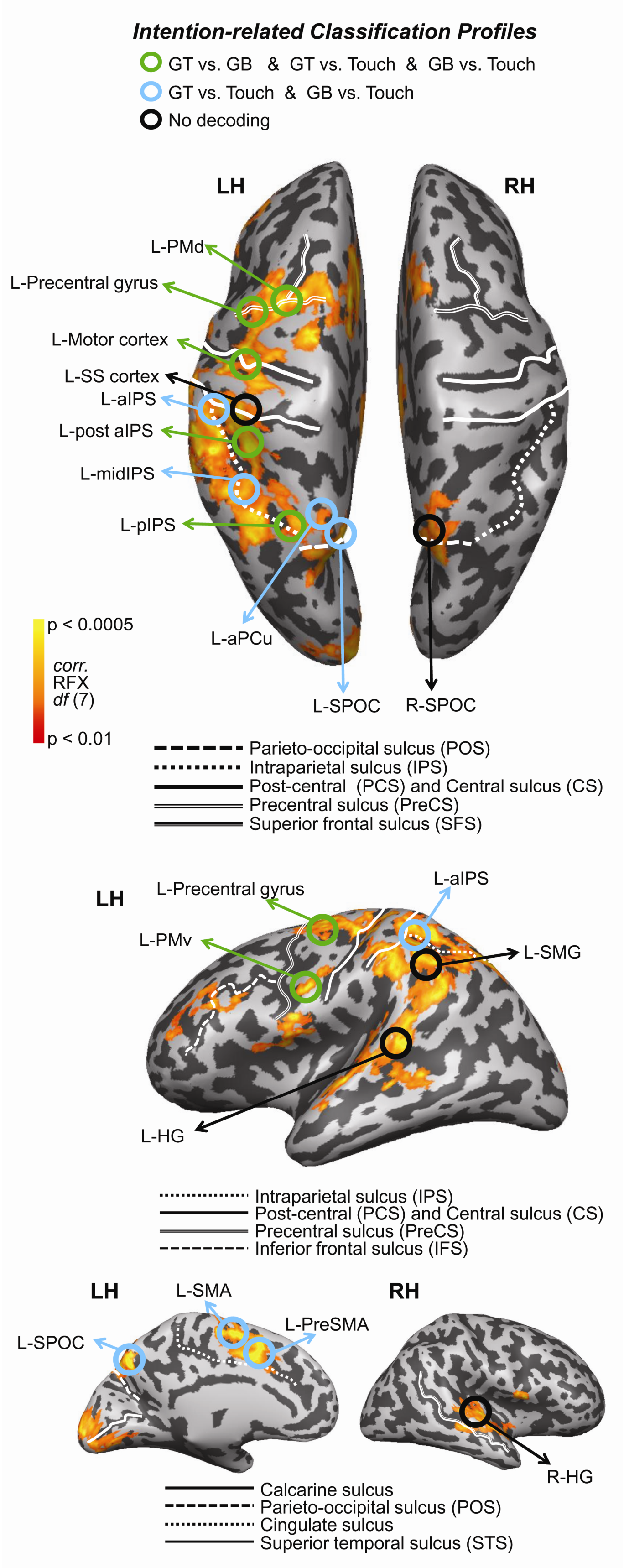
Intention-related Classification Profiles
○ GT vs. GB & GT vs. Touch & GB vs. Touch
○ GT vs. Touch & GB vs. Touch
○ No decoding
LH
RH
L-PMd
L-Precentral gyrus
L-Motor cortex
L-SS cortex
L-aIPS
L-post aIPS
L-midIPS
L-pIPS
L-aPCu
L-SPOC
R-SPOC
p < 0.0005
corr.
RFX
df (7)
p < 0.01
Parieto-occipital sulcus (POS)
Intraparietal sulcus (IPS)
Post-central (PCS) and Central sulcus (CS)
Precentral sulcus (PreCS)
Superior frontal sulcus (SFS)
LH
L-Precentral gyrus
L-aIPS
L-PMv
L-SMG
L-HG
Intraparietal sulcus (IPS)
Post-central (PCS) and Central sulcus (CS)
Precentral sulcus (PreCS)
Inferior frontal sulcus (IFS)
LH
L-SMA
L-PreSMA
L-SPOC
RH
R-HG
Calcarine sulcus
Parieto-occipital sulcus (POS)
Cingulate sulcus
Superior temporal sulcus (STS)

Figure 3.2: Decoding of object-directed movement intentions across the parieto-frontal network. Cortical areas that exhibited larger responses during movement planning than the preceding visual phase (Plan > Preview) are shown in orange/yellow activation. Results calculated across all subjects (Random Effects GLM) are displayed on one representative subject's inflated hemispheres. The general locations of the selected ROIs are outlined in circles (actual ROIs were anatomically defined separately in each subject). Each ROI is colour-coded according to the pair-wise discriminations they can decode during the Plan phase (found in Figure 3.4); see colour legend at top for classification profiles. Colours denote significant decoding accuracies for upcoming actions with respect to 50% chance. L = Left, R = Right, SPOC = superior parieto-occipital cortex, aPCu = anterior precuneus, pIPS = posterior intraparietal sulcus, midIPS = middle IPS, post aIPS = posterior anterior IPS, SS cortex = somatosensory cortex, PMd = premotor dorsal, PMv = premotor ventral, SMA = supplementary motor area, HG = Heschl's gyrus. Sulcal landmarks are denoted by white lines (stylized according to the corresponding legends below each brain). LH = Left-hemisphere, RH = Right-hemisphere.

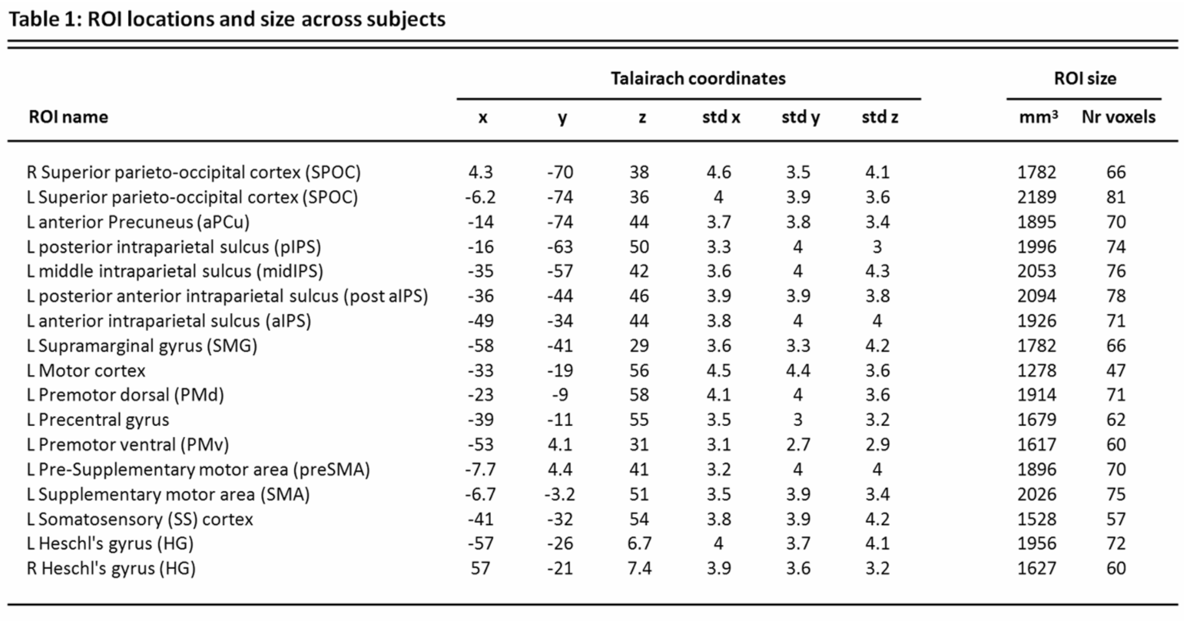

Table 1: ROI locations and size across subjects

	Talairach coordinates						ROI size	
ROI name	**x**	**y**	**z**	**std x**	**std y**	**std z**	**mm³**	**Nr voxels**
R Superior parieto-occipital cortex (SPOC)	4.3	-70	38	4.6	3.5	4.1	1782	66
L Superior parieto-occipital cortex (SPOC)	-6.2	-74	36	4	3.9	3.6	2189	81
L anterior Precuneus (aPCu)	-14	-74	44	3.7	3.8	3.4	1895	70
L posterior intraparietal sulcus (pIPS)	-16	-63	50	3.3	4	3	1996	74
L middle intraparietal sulcus (midIPS)	-35	-57	42	3.6	4	4.3	2053	76
L posterior anterior intraparietal sulcus (post aIPS)	-36	-44	46	3.9	3.9	3.8	2094	78
L anterior intraparietal sulcus (aIPS)	-49	-34	44	3.8	4	4	1926	71
L Supramarginal gyrus (SMG)	-58	-41	29	3.6	3.3	4.2	1782	66
L Motor cortex	-33	-19	56	4.5	4.4	3.6	1278	47
L Premotor dorsal (PMd)	-23	-9	58	4.1	4	3.6	1914	71
L Precentral gyrus	-39	-11	55	3.5	3	3.2	1679	62
L Premotor ventral (PMv)	-53	4.1	31	3.1	2.7	2.9	1617	60
L Pre-Supplementary motor area (preSMA)	-7.7	4.4	41	3.2	4	4	1896	70
L Supplementary motor area (SMA)	-6.7	-3.2	51	3.5	3.9	3.4	2026	75
L Somatosensory (SS) cortex	-41	-32	54	3.8	3.9	4.2	1528	57
L Heschl's gyrus (HG)	-57	-26	6.7	4	3.7	4.1	1956	72
R Heschl's gyrus (HG)	57	-21	7.4	3.9	3.6	3.2	1627	60

Table 3.1: ROIs with corresponding Talairach coordinates (mean x, y, and z centre of mass and std). Mean ROI sizes across subjects from AC-PC data (in mm^3 and functional voxels).

3.2.7 Multivariate pattern classification analysis (MVPA)

3.2.7.1 Voxel pattern preparation

For each region and each trial, we extracted the average percent signal change (% SC) activation corresponding to the 4-s time-windows specified by each of the gray shaded bars in Figure 3.1D and Figure 3.3 (i.e. the activity elicited by each distinct phase of the trial: Plan, Preview and Execute) and entered these as data points for pattern classification (see Methods in Chapter 2 for more details).

3.2.7.2 Single-Trial classification

For each subject and for each of the 17 plan-related ROIs, nine different binary support vector machine (SVM) classifiers were estimated for MVPA (i.e. for each of the *Preview*, *Plan* and *Execute* phases and each pair-wise comparison, GT vs. GB, GT vs. Touch, and GB vs. Touch). We used "leave eight trials out" cross-validation to test the accuracy of the binary SVM classifiers, meaning that eight trials from each condition (i.e. 16 trials total) were reserved for testing the classifier and the remaining trials were used to train the classifier (i.e. 40 or 46 remaining trials per condition, depending on whether the subject participated in eight or nine experimental runs, respectively). While a full cross validation is not feasible with a "leave eight trials out" design due to the ~10^8 possible iterations, a minimum of 1002 iterations of test/train were performed for each classification. For subjects with 8 runs, 1002 iterations were used (each trial was used exactly 167 times to train the classifier. For subjects with 9 runs, a perfect solution was not achievable. For these subjects, the number of iterations was increased to 1026 to ensure that each trial was used 152 +/- 1 times to train the classifier. Given the noise inherent in single-trials and the fact that each trial for training could be randomly selected from any point throughout the experiment, single-trial classification provides a highly conservative but robust measure of decoding accuracies. Moreover, much of the motivation of this present work is to determine the feasibility of predicting specific motor intentions from single fMRI trials, which could be then be applied to human movement-impaired patient populations.

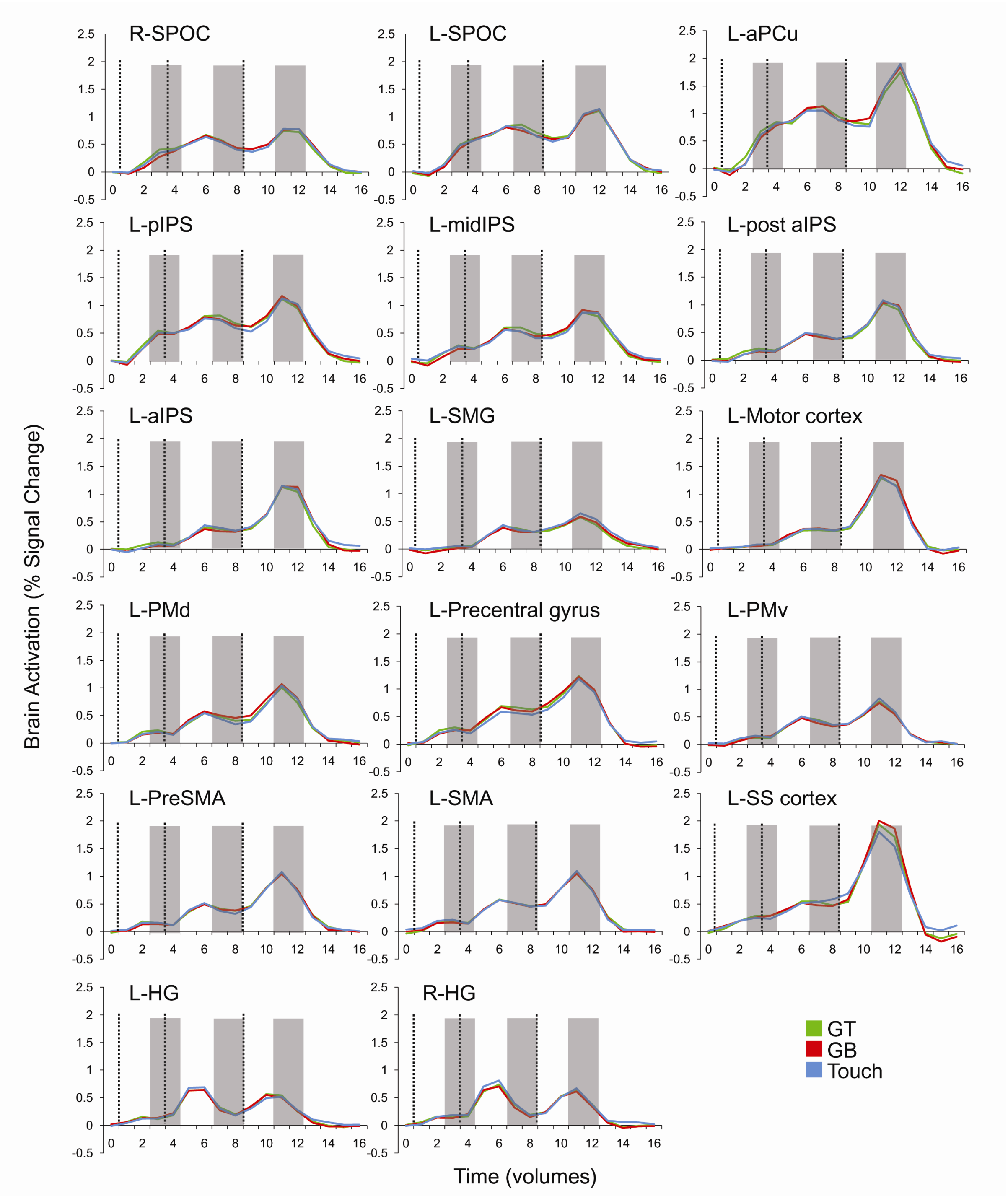

Figure 3.3: Trial-related percent signal change fMRI activations from each of the 14 plan-network ROIs and 3 sensory control ROIs. Activity in each plot is averaged across voxels within each ROI and across subjects. Plots show the profiles of typical preparatory activity found throughout parieto-frontal network areas. Vertical dashed lines correspond to the onset of the Preview, Plan and Execute phases of each trial (from left to right). Shaded gray bars highlight the

2-volume (4 s) windows that were averaged and extracted for pattern classification analysis. Note that time corresponds to imaging volumes (TR=2), and not seconds.

3.3 Results

3.3.1 Decoding Analyses

The voxel patterns within several of the plan-related ROIs enabled the accurate decoding of grasp vs. touch comparisons [(GT vs. Touch) *AND* (GB vs. Touch)] and in some cases, all three comparisons (*also* GT vs. GB) with respect to 50% chance (See Figure 3.4 for the corresponding plan-related decoding accuracies). For instance, pattern classification in all of the following ROIs successfully decoded movement plans for the grasp vs. touch conditions (GT vs. Touch *AND* GB vs. Touch): L-SPOC, L-aPCu, L-midIPS, L-aIPS, L-SMA, and L-PreSMA. Given that we found overlapping and indistinguishable response amplitudes for the three different movements types in all of these areas for each of the different time phases (Preview, Plan and Execute; see Figure 3.3), this decoding result suggests that each of these regions differentially contribute to both grasp and reach planning (instead of coding one action vs. the other) but importantly, not towards the planning of the two different grasp movements. Instead, the decoding of movement plans for precision grasps upon the different sized objects (as well as differentiation of grasp vs. touch actions; GT vs. GB *AND* GT vs. Touch *AND* GB vs. Touch) were constrained to a different set of ROIs: L-pIPS, L-post aIPS, L-Motor cortex, L-Precentral gyrus, L-PMd, and L-PMv (see Figure 3.4). This pattern of results across these parieto-frontal areas suggest that regions can be functionally classified according to whether the resident preparatory signals are predictive of upcoming grasp vs. reach movements or, in addition, different precision grasps (for instance, see Figure 3.2 for a color-coding of the ROIs depending on the types of movements they can predict). Note that decoding accuracies were based on single-trial classifications, and as such, demonstrate that the spatial voxel patterns generated during movement planning (and used for classifier training) were robust and consistent enough across the full experiment (all 8-9 experimental runs) to allow for successful prediction.

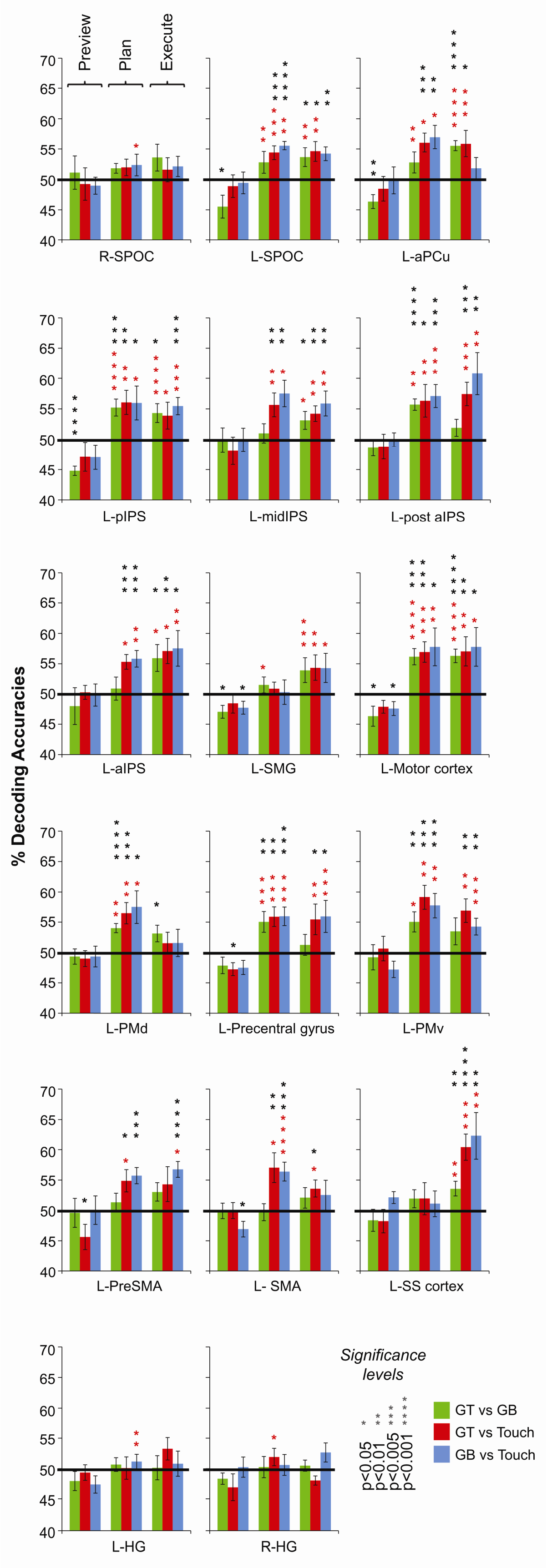
Preview
Plan
Execute
% Decoding Accuracies
70
65
60
55
50
45
40
R-SPOC
L-SPOC
L-aPCu
L-pIPS
L-midIPS
L-post aIPS
L-aIPS
L-SMG
L-Motor cortex
L-PMd
L-Precentral gyrus
L-PMv
L-PreSMA
L- SMA
L-SS cortex
L-HG
R-HG
Significance levels
* p<0.05
** p<0.01
*** p<0.005
**** p<0.001
GT vs GB
GT vs Touch
GB vs Touch

Figure 3.4: Classifier decoding accuracies for each ROI for the three trial phases (Preview, Plan and Execute; the middle three bars correspond to accuracies elicited during the Plan Phase). Errors bars represent SEM across subjects. Solid black lines are chance accuracy level (50%). Black asterisks assess statistical significance with 2-tailed t-tests across subjects with respect to 50%. Note that no above chance decoding is shown during the Preview phase, when subjects were unaware which movement they were going to perform. Red asterisks denote statistical significance with paired 2-tailed t-tests for decoding accuracies across subjects for Plan and Execute phases with respect to within-trial decoding accuracies found during the preceding Preview phase (i.e. assessing where accuracies are higher than that for simple object visual presentation, when subjects were unaware which action they would be performing). Importantly, any areas showing significant decoding during the Plan phase with respect to 50% also show significant decoding with respect to the permutation tests (see materials and methods) and Preview phase. Note that accurate classification can only be attributed to the spatial response patterns of different planned movement types, and not the overall signal amplitudes within each ROI (see Figure 3.5). GT = Grasp Top, GB = Grasp Bottom. Also note that decoding accuracies are colour-coded according to pair-wise discriminations and not trial types.

As anticipated, the three sensory control areas (L-SS cortex, L- and R-HG) showed no significant decoding during planning, highlighting the fact that predictive information can be specifically localized to particular nodes of the parieto-frontal network. This is largely intuitive for our sensory control areas: somatosensory cortex should not be expected to decode anything until the mechanoreceptors of the hand are stimulated at movement onset (see Figure 3.4). Likewise, L- and R-Heschl's gyri are primary auditory structures, and thus are not expected to carry sustained plan-related predictive information. Null results should always be interpreted with caution in pattern classification (as they may reflect limitations in the classification algorithms rather than the data (see Pereira and Botvinick, in press); nevertheless, the absence of decoding during planning in these areas is certainly consistent with expectations.

Importantly, our results also show that plan-related decoding can only be attributed to the *intention* to perform a specific movement, as we find no significant decoding above 50% chance in the preceding Preview phase (i.e. when movement-planning information was unavailable). Moreover, when we additionally tested whether above chance decoding during planning was also significantly higher than the within-trial decoding found during the preceding Preview phase, we found this to be the case in every region (denoted by red asterisks in Figure 3.4). Critically, accurate classification only reflects the spatial response pattern profiles of different planned movement types, and not the overall fMRI signal amplitudes within each ROI. When we averaged the trial responses across all voxels and subjects in each ROI (as done in conventional fMRI ROI analyses) we found no significant differences for the three different hand movements, in any phase of the trial (Preview, Plan or Execute; see trial time courses in Figure 3.3 and an univariate analysis of signal amplitudes for the same time windows as those extracted for MVPA in Figure 3.5, for confirmation of this fact). As an additional Type I error control for our classification accuracies, we ran the same pattern discrimination analysis on two non-cortical ROIs outside of our plan-related network where classification should not be possible: the right ventricle and outside the brain. As expected, pattern classification revealed no significant decoding in these two areas for any phase of the trial (Figure 3.6).

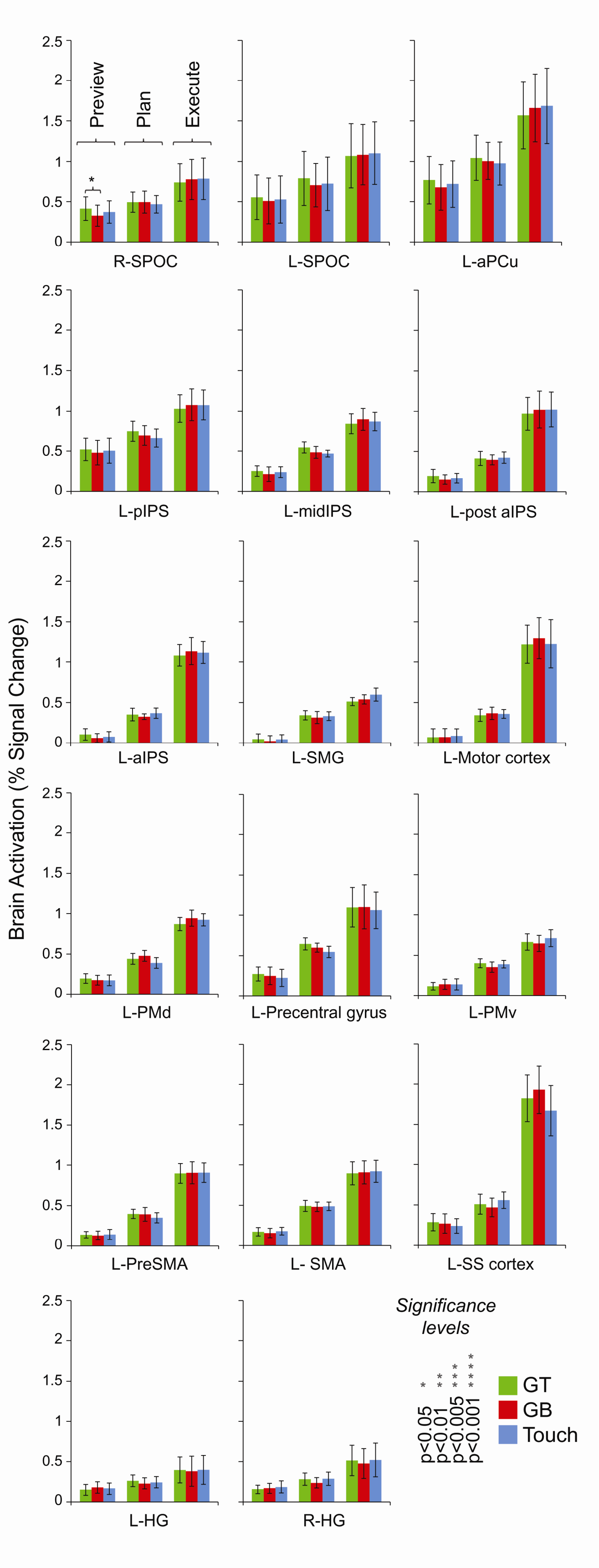
Brain Activation (% Signal Change)
2.5
2
1.5
1
0.5
0
Preview
Plan
Execute
*
R-SPOC
L-SPOC
L-aPCu
L-pIPS
L-midIPS
L-post aIPS
L-aIPS
L-SMG
L-Motor cortex
L-PMd
L-Precentral gyrus
L-PMv
L-PreSMA
L- SMA
L-SS cortex
L-HG
R-HG
Significance levels
p<0.05 *
p<0.01 **
p<0.005 ***
p<0.001 ****
GT
GB
Touch

Figure 3.5: No fMRI signal amplitude differences found within the parieto-frontal regions used for pattern classification. Responses are averaged across voxels within each ROI and across subjects (2-volume averaged windows corresponding to Preview, Plan and Execute phases). Note that only one significant univariate difference is observed in R-SPOC, a non-decoding region. Errors bars represent SEM across subjects.

In addition to using the spatial voxel activity patterns in order to predict upcoming hand movements, we performed a voxel weight analysis for each ROI (for example, see Kamitani and Tong, 2005) in order to directly determine whether any structured spatial relationship of voxel activity according to the action being planned could be found (data not shown). In order to do this, for each iteration of the cross-validation (1002 or 1026 iterations, depending on the number of runs per subject) a different SVM discriminant function was refined based on the subset of trials included for training. We calculated the voxel weights for each function and then averaged across all iterations to produce a set of mean voxel weights; this procedure was repeated for each pair-wise comparison, ROI and subject (note that the weight of each voxel provides a measure of its relationship with the class label as learned by the classifier; in this case, GT, GB, or Touch planned actions)(for details, see Pereira and Botvinick, in press). Both across and within subjects for each ROI and pair-wise comparison, we found little structured relationship of voxel weights according to the action being planned. For instance, no correspondence was found between the GT vs. Touch and GB vs. Touch spatial arrangement of voxel weights in each ROI, despite the two grasp actions being highly similar and the two touch actions being exactly the same. We did, however, notice that within individual ROIs, despite the inconsistency of voxel weight patterns across subjects and across pair-wise comparisons, voxels that discriminated one planned movement vs. another tended to cluster. That is, voxels coding for one particular movement (reflected by the positive or negative direction of the weight) tended to lie adjacent to one another within the ROI, even though these sub-ROI clusters were not necessarily consistent between comparisons. While caution should be applied to interpreting the magnitude of the voxel weights assigned by any classifier (Pereira and Botvinick, in press), this general result is to be expected based on the structure of the surrounding vasculature and spatial resolution of the BOLD response (Logothetis and Wandell, 2004), further reinforcing the notion that spatial voxel patterns directly reflect underlying physiological changes. Furthermore, and more generally, the findings from this voxel weight analysis are highly consistent with expectations from monkey neurophysiology. The neural organization of macaque parieto-frontal cortex is highly distributed and multiplexed, with neurons containing different sensorimotor frames of reference and separate response properties (e.g., for effector or location) residing in close anatomical proximity (Snyder et al., 1997; Andersen and Buneo, 2002; Calton et al., 2002; Andersen and Cui, 2009; Chang and Snyder, 2010). As such, combined with the fact that we are able to accurately predict upcoming hand actions from the trained pattern classifiers, the largely unstructured arrangement of voxel weights appears to have a well-documented anatomical basis.

3.3.2 Additional Univariate Analyses

Although not shown, we also performed a univariate contrast of [(GT-Execute + GB-Execute) vs. 2*(Touch-Execute)] in order to define left aIPS, a brain area frequently reported in studies from our lab, consistently shown to be preferentially involved in grasping actions (Culham et al., 2003; Gallivan et al., 2009; Cavina-Pratesi et al., 2010). We localized this region in six of eight subjects ($t=2.4$, $p<0.05$, in four subjects these clusters did not survive cluster threshold correction) allowing a direct comparison of its general anatomical location with the left aIPS regions we defined in single subjects for pattern analyses according to the contrast of Plan>Preview (which instead shows no univariate differences between Grasp vs. Touch trials during the Execute phase; see Figure 3.5). We found a good degree of overlap between the (Plan>Preview)-defined left aIPS and the left aIPS defined by a contrast of [(GT-Execute + GB-Execute) vs. 2*(Touch-Execute)], with the latter aIPS being much smaller in size. For instance, in the 6 subjects who showed activity in aIPS with the [(GT-Execute + GB-Execute) vs. 2*(Touch-Execute)] contrast, we found that this area shared the following percentage of its total voxels with the larger aIPS area defined by the Plan>Preview contrast: Subject 1 (13.7%; size of Grasps vs. Touch defined aIPS: 66 voxels; size of Plan>Preview defined aIPS: 100 voxels), Subject 2 (25%; size of Grasps vs. Touch defined aIPS: 4 voxels; size of Plan>Preview defined aIPS: 97 voxels), Subject 3 (75%; size of Grasps vs. Touch defined aIPS: 4 voxels; size of Plan>Preview defined aIPS: 62 voxels), Subject 4 (33.3%; size of Grasps vs. Touch defined aIPS: 6 voxels; size of Plan>Preview defined aIPS: 59 voxels), Subject 5 (33.3%; size of Grasps vs. Touch defined aIPS: 3 voxels; size of Plan>Preview defined aIPS: 92 voxels) and Subject 6 (75%; size of Grasps vs. Touch defined aIPS: 4 voxels; size of Plan>Preview defined aIPS: 84 voxels). The discrepancy in the size and signal amplitude differences between these two regions can be easily explained as a difference of contrasts: specifying a directed search for Grasps > Touches reveals a much smaller subset of aIPS voxels, with each individual voxel showing the specified effect. In comparison, the anatomically defined aIPS for the more general contrast of Plan > Preview (used for pattern analyses here) additionally selects for voxels outside the range of this smaller voxel subset and thus when averaging the response amplitudes across this larger cluster size (as shown in Figures 3 and 5), we effectively diminish the influence of each individual voxel's contribution on the overall ROI signal. It is worth mentioning that in addition to finding small left aIPS activations in six subjects with the univariate contrast of [(GT-Execute + GB-Execute) vs. 2*(Touch-Execute)], small clusters of voxels in three other areas (left pIPS, left motor cortex and left PMd) were also reliably co-activated; areas revealed here to decode all three planned movements with pattern classification analyses. Apart from distinguishing univariate and multivariate approaches (for further explanations and examples see (Mur et al., 2009; Pereira et al., 2009; Raizada and Kriegeskorte, 2010)) these findings, more than anything, highlight the additional plan-related information contained in voxel spatial patterns.

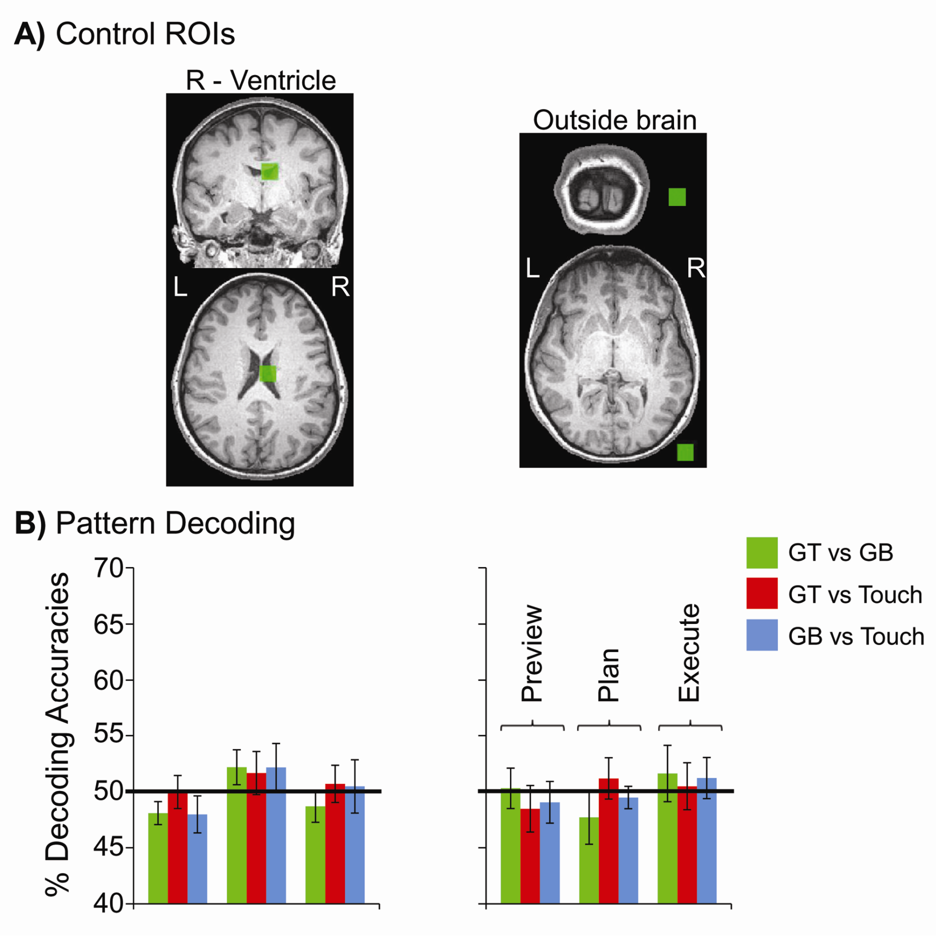

Figure 3.6: Classifier decoding accuracies in non-brain control regions. A) Non-brain control ROIs defined in each subject (denoted in green; example subject shown). **B)** Classifier accuracies for the 3 trial phases for the right ventricle (left) and outside the brain ROI (right). Error bars represent SEM across subjects. Solid lines show chance classification accuracy (50%). Importantly, no significant differences were found with t-tests across subjects with respect to 50% chance.

3.4 Discussion

For the first time, fMRI signal decoding is used to unravel predictive neural signals underlying the planning and implementation of real object-directed hand actions in humans. We show that this predictive information is not revealed in preparatory response amplitudes but in the spatial pattern profiles of voxels. This finding may explain why previous characterizations of plan-related activity in parieto-frontal networks from traditional fMRI subtraction methods have been largely met with mixed degrees of success. From a theoretical perspective, these results provide new insights into the different roles played by various regions within the human parieto-frontal network -- results that add to our previous understanding of the predictive movement information contained in parietal preparatory responses (Andersen and Buneo, 2002; Cisek and Kalaska, 2010) and advance previous notions of motor and premotor contributions to movement planning (Tanne-Gariepy et al., 2002; Filimon, 2010).

3.4.1 Decoding in Parietal cortex

A particularly notable finding from this study is that preparatory activity along the dorso-medial circuit (L-SPOC, L-aPCu, and L-midIPS) decodes planned grasp vs. touch movements. Although these areas are well known to be involved in the planning and execution of reaching movements in both humans and monkeys (e.g. Andersen and Buneo, 2002; Culham et al., 2006; Beurze et al., 2007), there has been remarkably little evidence to suggest their particular involvement during grasp planning. To our knowledge, the only evidence to date in support of this notion comes from neural recordings in monkeys showing that parieto-occipital neurons, in addition to being sensitive for reach direction, are also sensitive to grip/wrist orientation and grip type (Fattori et al., 2009; Fattori et al., 2010). Based on our similar findings in SPOC, it now seems clear that fMRI pattern analysis in humans can provide a new tool for capturing neural representations only previously detected with invasive electrode recordings in monkeys. Moreover, our present results advance these previous findings by showing for the first time that motor plans requiring hand preshaping or precise object-directed interactions extend further anteriorly into both the precuneus and midIPS.

The posterior IPS (pIPS) in the human and macaque monkey appears to serve a variety of visual-motor and attention related functions: it is involved in the orienting of visual selection and attention (Szczepanski et al., 2010), encodes the 3D visual features of objects for hand actions (Sakata et al., 1998), and integrates both target and effector-specific information for movements (Beurze et al., 2009). pIPS preparatory activity in our task may largely reflect the combined coding of all these properties given that differences in finger precision, hand orientation, and attention to 3D object shape is required across the three hand movements. Since attention is often directed towards a target location prior to movement, these particular findings might provide additional evidence for the integration of visual-motor and attention-related processes within common brain areas during movement planning (Moore and Fallah, 2001; Baldauf and Deubel, 2010).

Area aIPS in both the human and monkey shows selective activity for the execution of grasping movements (e.g. Murata et al., 2000; Culham et al., 2003). Here we show that both aIPS and an immediately posterior division, post-aIPS, are selective for the *planning* of grasp vs. reach movements. Moreover, aIPS decodes between similar grasps upon objects of different sizes during execution while post-aIPS performs such discriminations during planning. These results are consistent with object size-tuning expected from macaque AIP (Murata et al., 2000) and provide additional support for a homology between AIP and human aIPS. Importantly, the distinction here between the two human divisions of aIPS provides evidence for a gradient of grasp-related function, with an anterior division perhaps more related to somatosensory feedback (Culham, 2004) and the online control of grip force (Ehrsson et al., 2003) and a posterior division more related to visual object features (Culham, 2004; Durand et al., 2007) and object-action associations (Valyear et al., 2007). In fact, these functionally distinct regions may correspond to anatomically distinct regions defined by cytoarchitechtonics (Choi et al., 2006).

3.4.2 Decoding in Motor and Premotor cortex

Although motor cortex, traditionally speaking, is predominantly engaged near the moment of movement execution and presumed -- at least in comparison to the higher-level cognitive processing observed in parietal and premotor cortex -- to be a relatively lower-level motor output structure (i.e. given its direct connections with corticospinal neurons (Chouinard and Paus, 2006) and that much of its activity can be explained in simple muscle control terms (Todorov, 2000)), such descriptions likely only partially capture some of its complexity. For instance, microstimulation of motor cortex structures can produce a complex array of ecologically relevant movements (e.g. grasping, feeding etc.(Graziano, 2006) and recent evidence also suggests that its outputs reflect whether an action goal is present or not (Cattaneo et al., 2009). The fact that we can decode each particular hand movement from the preparatory responses in motor cortex several moments prior to action execution might additionally speak to a more prominent role in movement planning processes. Alternatively, it might reflect the fact that higher-level signals from other regions must often pass through motor cortex before going to spinal cord.

In addition to motor cortex, areas in premotor cortex have direct anatomical connections (albeit weaker) to spinal cord (Chouinard and Paus, 2006), but importantly, are also highly interconnected with frontal, parietal and motor cortical regions (Andersen and Cui, 2009), making them ideally situated to receive, influence, and communicate high-level cognitive movement-related information. Beyond forming a critical node in the visual-motor planning network, recent evidence proposes that different premotor areas (e.g. PMd and PMv) may have dissociable processes. For instance, experiments in both humans and monkeys appear to suggest that PMv is more involved in hand preshaping and grip-specific responses (distal components) whereas PMd is more involved in power-grip or reach-related hand movements (proximal components)(e.g. Tanne-Gariepy et al., 2002; Davare et al., 2006). These findings are consistent with the suggestion that PMv and PMd form the anterior components of dissociable parieto-frontal networks involved in visual-motor control, with the dorso-lateral circuit (DLC) -- involving connections from pIPS to AIP and then to PMv -- thought to be specialized for grasping, and the dorso-medial circuit (DMC) -- involving connections between V6A/aPCu to midIPS and then to PMd -- thought to be specialized for reaching (for reviews see Rizzolatti and Matelli, 2003; Grafton, 2010). Given that most of these previous distinctions are based on characterizations of activity evoked during the movement itself, the accurate decoding of different *planned* hand movements shown here provides a significant additional dimension to such descriptions. Indeed, while our finding that PMv can discriminate different upcoming movements with the hand (grasps and reaches) may be congruent with this parallel-pathway view, the same finding in PMd (more traditionally implicated in reach planning) seems largely incompatible. There are several reasons, however, to suspect that PMd, as shown here, may also be involved in grasp-related movement planning. For instance, both PMd and PMv contain distinct hand digit representations (Dum and Strick, 2005), PMd activity is modulated during object grasping (Raos et al., 2004), by grasp-relevant object properties (Grol et al., 2007; Verhagen et al., 2008) and the grip force scaling required (Hendrix et al., 2009), and multiunit responses in PMd (as well as PMv) are highly predictive of the current reach and grasp movement (Stark and Abeles, 2007). Furthermore, previous work from our lab has found differences in PMd between grasping and reaching during the execution phase of the movement

(Culham et al., 2003; Cavina-Pratesi et al., 2010). Our current findings with fMRI in humans add to an emerging view that simple grasp (distal) vs. reach (proximal) descriptions cannot directly account for the preparatory responses in PMd and PMv and that significant coordination between the two regions may be a requirement for complex object-directed behaviour.

3.4.3 Implications

Here we have demonstrated that MVPA can decode surprisingly subtle distinctions between actions across a larger network of areas than would be expected from past human neuroimaging research. Based on non-human primate neurophysiology, one might expect decoding of more pronounced differences between trials (such as the effector used or the target location acted upon). Here, however, effector and object location remained constant, yet we found decoding of slight differences in the *planning* of actions: in several areas we were able to discriminate upcoming grasp vs. reach hand movements, and in a subset of these areas -- even more surprisingly -- we could additionally discriminate upcoming precision grasps upon objects of subtlely different sizes. These findings suggest that neural implants within several of the reported predictive regions may eventually enable the reconstruction of highly specific planned actions in movement-impaired human patient populations. A critical consideration for cognitive neural prosthetics is the optimal positioning of electrode arrays in order to capture the appropriate intention-related signals (Andersen et al., 2010). Here, we highlight a number of promising candidate regions that can be further explored in non-human primates to not only further assist their development but also expand our understanding of intention-related signals related to complex sensorimotor behaviours.

3.5 References

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annual Review of Neuroscience 25:189-220.

Andersen RA, Cui H (2009) Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63:568-583.

Andersen RA, Hwang EJ, Mulliken GH (2010) Cognitive neural prosthetics. Annu Rev Psychol 61:169-190, C161-163.

Baldauf D, Deubel H (2010) Attentional landscapes in reaching and grasping. Vision Res 50:999-1013.

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 97:188-199.

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 101:3053-3062.

Calton JL, Dickinson AR, Snyder LH (2002) Non-spatial, motor-specific activation in posterior parietal cortex. Nat Neurosci 5:580-588.

Cattaneo L, Caruana F, Jezzini A, Rizzolatti G (2009) Representation of goal and movements without overt motor behavior in the human motor cortex: a transcranial magnetic stimulation study. J Neurosci 29:11134-11138.

Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam TD, Quinlan DJ, Goodale MA, Culham JC (2010) Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. J Neurosci 30:10306-10323.

Chang SW, Snyder LH (2010) Idiosyncratic and systematic aspects of spatial representations in the macaque parietal cortex. Proc Natl Acad Sci U S A 107:7951-7956.

Chapman CS, Gallivan JP, Culham JC, Goodale MA (in press) Mental Blocks: fMRI reveals top-down modulation of early visual cortex when planning a grasp movement that is interfered with by an obstacle. Neuropsychologia.

Choi HJ, Zilles K, Mohlberg H, Schleicher A, Fink GR, Armstrong E, Amunts K (2006) Cytoarchitectonic identification and probabilistic mapping of two distinct areas within the anterior ventral bank of the human intraparietal sulcus. J Comp Neurol 495:53-69.

Chouinard PA, Paus T (2006) The primary motor and premotor areas of the human cerebral cortex. Neuroscientist 12:143-152.

Cisek P, Kalaska JF (2010) Neural Mechanisms for Interacting with a World Full of Action Choices. Annu Rev Neurosci.

Culham JC (2004) Human brain imaging reveals a parietal area specialized for grasping. In: Attention and Performance XX: Functional Brain Imaging of Human Cognition (Kanwisher N, Duncan J, eds). Oxford, U.K.: Oxford University Press.

Culham JC, Cavina-Pratesi C, Singhal A (2006) The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia 44:2668-2684.

Culham JC, Danckert SL, DeSouza JF, Gati JS, Menon RS, Goodale MA (2003) Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Exp Brain Res 153:180-189.

Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E (2006) Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci 26:2260-2268.

Dum RP, Strick PL (2005) Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. J Neurosci 25:1375-1386.

Durand JB, Nelissen K, Joly O, Wardak C, Todd JT, Norman JF, Janssen P, Vanduffel W, Orban GA (2007) Anterior regions of monkey parietal cortex process visual 3D shape. Neuron 55:493-505.

Ehrsson HH, Fagergren A, Johansson RS, Forssberg H (2003) Evidence for the involvement of the posterior parietal cortex in coordination of fingertip forces for grasp stability in manipulation. J Neurophysiol 90:2978-2986.

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 29:1928-1936.

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 30:342-349.

Filimon F (2010) Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. Neuroscientist 16:388-407.

Filimon F, Nelson JD, Huang RS, Sereno MI (2009) Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. J Neurosci 29:2961-2971.

Formisano E, De Martino F, Bonte M, Goebel R (2008) "Who" is saying "what"? Brain-based decoding of human voice and speech. Science 322:970-973.

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 29:4381-4391.

Gold JI, Shadlen MN (2007) The neural basis of decision making. Annu Rev Neurosci 30:535-574.

Grafton ST (2010) The cognitive neuroscience of prehension: recent developments. Exp Brain Res 204:475-491.

Graziano M (2006) The Organization of Behavioral Repertoire in Motor Cortex. Annu Rev Neurosci.

Grol MJ, Majdandzic J, Stephan KE, Verhagen L, Dijkerman C, Bekkering H, Verstraten F, Toni I (2007) Parieto-frontal connectivity during visually guided grasping. J Neurosci 27:11877-11887.

Harrison SA, Tong F (2009) Decoding reveals the contents of visual working memory in early visual areas. Nature 458:632-635.

Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293:2425-2430.

Hendrix CM, Mason CR, Ebner TJ (2009) Signaling of grasp dimension and grasp force in dorsal premotor cortex and primary motor cortex neurons during reach to grasp in the monkey. J Neurophysiol 102:132-145.

Kamitani Y, Tong F (2005) Decoding the visual and subjective contents of the human brain. Nat Neurosci 8:679-685.

Lewis JW (2006) Cortical networks related to human use of tools. Neuroscientist 12:211-231.

Logothetis NK, Wandell BA (2004) Interpreting the BOLD signal. Annual Review of Physiology 66:735-769.

Meyer K, Kaplan JT, Essex R, Webber C, Damasio H, Damasio A (2010) Predicting visual stimuli on the basis of activity in auditory cortices. Nat Neurosci 13:667-668.

Moore T, Fallah M (2001) Control of eye movements and spatial attention. Proc Natl Acad Sci U S A 98:1273-1276.

Mur M, Bandettini PA, Kriegeskorte N (2009) Revealing representational content with pattern-information fMRI--an introductory guide. Soc Cogn Affect Neurosci 4:101-109.

Murata A, Gallese V, Luppino G, Kaseda M, Sakata H (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. J Neurophysiol 83:2580-2601.

Pereira F, Botvinick M (in press) Information mapping with pattern classifiers: A comparative study. Neuroimage.

Pereira F, Mitchell T, Botvinick M (2009) Machine learning classifiers and fMRI: a tutorial overview. Neuroimage 45:S199-209.

Picard N, Strick PL (2001) Imaging the premotor areas. Curr Opin Neurobiol 11:663-672.

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

Raos V, Umilta MA, Gallese V, Fogassi L (2004) Functional properties of grasping-related neurons in the dorsal premotor area F2 of the macaque monkey. J Neurophysiol 92:1990-2002.

Rizzolatti G, Matelli M (2003) Two different streams form the dorsal visual system: anatomy and functions. Exp Brain Res 153:146-157.

Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y, Tsutsui K (1998) Neural coding of 3D features of objects for hand action in the parietal cortex of the monkey. Philos Trans R Soc Lond B Biol Sci 353:1363-1373.

Snyder LH, Batista AP, Andersen RA (1997) Coding of intention in the posterior parietal cortex. Nature 386:167-123.

Stark E, Abeles M (2007) Predicting movement from multiunit activity. J Neurosci 27:8387-8394.

Stokes M, Thompson R, Cusack R, Duncan J (2009) Top-down activation of shape-specific population codes in visual cortex during mental imagery. J Neurosci 29:1565-1572.

Szczepanski SM, Konen CS, Kastner S (2010) Mechanisms of spatial attention control in frontal and parietal cortex. J Neurosci 30:148-160.

Tanne-Gariepy J, Rouiller EM, Boussaoud D (2002) Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp Brain Res 145:91-103.

Todorov E (2000) Direct cortical control of muscle activation in voluntary arm movements: a model. Nat Neurosci 3:391-398.

Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H (2007) Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J Neurosci 27:10259-10269.

Valyear KF, Cavina-Pratesi C, Stiglick AJ, Culham JC (2007) Does tool-related fMRI activity within the intraparietal sulcus reflect the plan to grasp? Neuroimage 36 Suppl 2:T94-T108.

Verhagen L, Dijkerman C, Grol MJ, Toni I (2008) Perceptuo-motor interactions during prehension movements. J Neurosci 28:4726-4735.

Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P (1997) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 120:141-157.

Chapter 4

4. Decoding effector-dependent and effector-independent movement intentions from human parieto-frontal brain activity[4]

4.1 Introduction:

How the human brain plans and effortlessly orchestrates movements of different body effectors (e.g. hands and eyes) remains a poorly understood problem in visual-motor neuroscience. An influential view, based on neural recording studies in monkeys, proposes that movement intentions are organized into effector-specific subregions (e.g. eyes vs. hand), with each region predominantly involved in the visual-motor planning and control of its own effector (e.g. saccades vs. reaches (Snyder et al., 1997)). For instance, interconnected regions like the medial intraparietal area (MIP), V6A, and dorsal premotor cortex (PMd), are preferentially engaged when reach movements are being planned, whereas interconnected areas like the lateral intraparietal area (LIP) and frontal eye-fields (FEF) are preferentially engaged in eye movement planning (Andersen and Buneo, 2002; Andersen and Cui, 2009), even when in both cases, the spatial target of the movement remains unknown (Hoshi and Tanji, 2000; Calton et al., 2002; Dickinson et al., 2003). Furthermore, planning processes in these areas, while still intimately linked to the preferred effector, abstractly reflect the spatial goals/intentions of an action rather than the specific muscle activations required. For example, neural recordings from MIP show that reach targets are predominantly encoded in gaze-centred coordinates, as is the case in LIP (Andersen et al., 1985; Batista et al., 1999). This use of a common reference frame can facilitate the first stages of the coordinate transformations required to convert sensory inputs (e.g. visual) into motor (e.g. limb) outputs and additionally assist coordination between the hand and eye (Andersen and Buneo, 2002). But how do these neural findings in monkeys compare and translate to our current understanding of how movement intentions are coded in the human brain?

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[4] A version of this chapter is currently under revision for resubmission. Gallivan, J.P., McLean, D.A., Smith, F.W. & Culham, J.C. (in revision) Decoding effector-dependent and effector-independent movement intentions from human parieto-frontal brain activity. *Journal of Neuroscience.*

The poorer spatial sensitivity inherent in non-invasive methodologies like functional magnetic resonance imaging (fMRI) presents clear difficulties in comparing brain activity between species (Kagan et al., 2010). For instance, even if there were a region with highly specialized and intermingled populations of neurons that separately encode various effectors (e.g. eye vs. hand) or their parameters (e.g. movement left vs. right), the coarse spatial resolution of fMRI may fail to reveal overall signal amplitude differences. Despite these challenges, multiple efforts have been made to compare and topographically describe these attributes of visual-motor integration. To date, the emerging viewpoint, in contrast to findings in the monkey, suggests that effector-selectivity and spatial planning processes are poorly localized, varying only gradually across the human parieto-frontal network (for review, see Culham et al., 2006; Filimon, 2010). It is becoming increasingly clear, however, that this conventional fMRI approach of comparing signal response amplitudes (and examining the activity within each voxel independently) may lack the sensitivity to detect certain types of neural information (Haxby et al., 2001; Kamitani and Tong, 2005).

Here we implemented multi-voxel pattern analyses (MVPA), an fMRI technique that discriminates between conditions based on the evoked spatial voxel activity patterns, in order to re-examine the effector-specific and spatially specific nature of intention-related signals in the human brain. Using a delayed eye and hand movement task we found, in contrast to the largely undifferentiated human parieto-frontal activations observed with conventional fMRI subtraction analyses, that during planning we can predict distinctly effector-specific and spatially specific movements across several parieto-frontal brain areas.

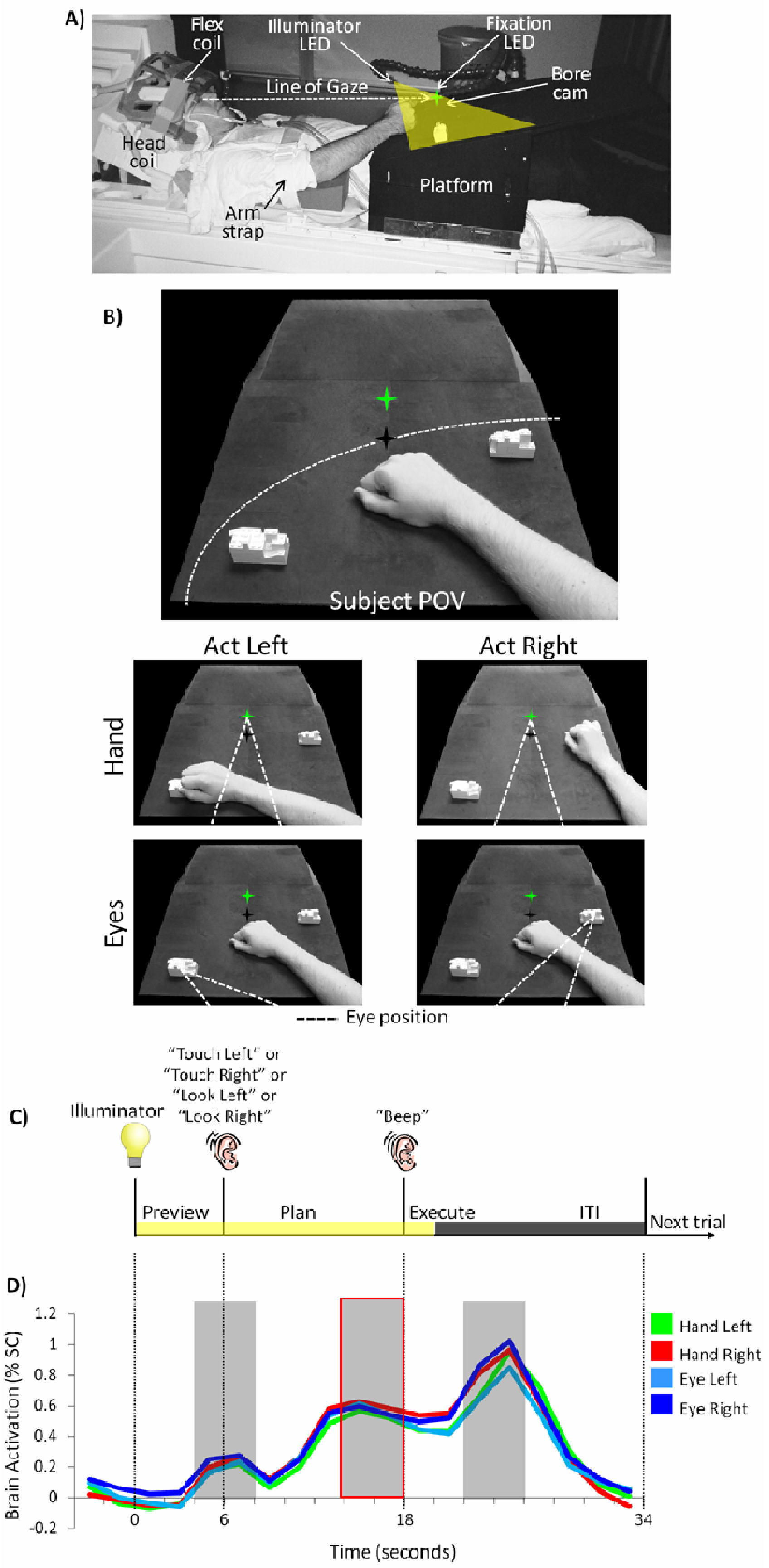

A)
Flex coil
Illuminator LED
Fixation LED
Line of Gaze
Bore cam
Head coil
Platform
Arm strap
B)
Subject POV
Act Left
Act Right
Hand
Eyes
---- Eye position
C)
Illuminator
"Touch Left" or "Touch Right" or "Look Left" or "Look Right"
"Beep"
Preview
Plan
Execute
ITI
Next trial
D)
Brain Activation (% SC)
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
0
6
18
34
Time (seconds)
Hand Left
Hand Right
Eye Left
Eye Right

Figure 4.1: Experimental methods and example brain activity. A) Subject setup from side view. **B)** (Top) Experimental apparatus and objects shown from the subject's point of view. The objects (white blocks) never changed position from trial-to-trial. Green star with dark shadow represents the fixation LED and its location in depth. Dashed line represents the arc of reachability with respect to the participant. The hand is positioned at its starting location. (Below) Executed saccade and reach movements. Dashed lines represent eye position. **C)** Timing of one event-related trial. Trials began with the 3D objects being simultaneously illuminated while the subject maintained fixation (Preview phase; 6 s). Subjects were then instructed via headphones to perform one of four movements: Touch the left object ("Touch Left"), Touch the right object ("Touch Right"), Saccade to the left object ("Look Left") or Saccade to the right object ("Look Right"). This cue initiated the Plan phase portion of the trial. Following a fixed delay interval (12 s), subjects were cued ('beep') to perform the instructed hand movement (initiating the Execute phase). Two seconds after the Go cue, vision of the workspace was extinguished and participants waited for the following trial to begin (14 s, ITI). **D)** Averaged neural activity from left posterior IPS over the length of a single trial. Events in **D** are time-locked to correspond to events in **C**. MVPA was performed on single trials based on the windowed average of the % signal change corresponding to the three different time-points denoted by each of the gray shaded bars (each corresponding to activity elicited from the three distinct trial phases Preview, Plan and Execute). The time points corresponding to the Plan phase (bordered in red) were of critical interest, and provide the focus of our analyses.

4.2 Materials and Methods:

In brief, our task required subjects to perform either a reach or saccade movement towards a target in one of two different locations on each trial; subjects were first cued to the action to be carried out then, following a delay period, performed the action (see Figure 4.1 B,C). On all trials, both objects were presented throughout the sequence, such that the visual presentation remained constant and only the instructions differed. This delayed-timing paradigm allowed us to isolate the sustained plan-related neural activity that evolves prior to movement from the transient visual response (Preview phase) and movement execution responses (Execute phase) (Figure 4.1D).

The focus of this study was to examine whether MVPA implemented in specific regions-of-interest (ROIs) during movement planning (Plan Phase) could predict 1) upcoming reaches vs. saccades and 2) upcoming leftward vs. rightward movements. In the former case, we examined the dependence of effector decoding on the spatial location of the object to be acted upon, Effector-within-space. This included two decoding tests: (1) Hand-Left (HandL) vs. Eye-Left (EyeL); and (2) Hand-Right (HandR) vs. Eye-Right (EyeR). In the latter case, we examined the dependence of spatial decoding on the effector to be used, Space-within-effector. This included two decoding tests: (1) HandL vs. HandR; and (2) EyeL vs. EyeR.

Furthermore, we also examined whether the intention-related signals in an area were governed by *shared* or *separate* sensorimotor mechanisms (e.g. Dinstein et al., 2008). To do this, we performed cross-trial-type MVPA by using one set of trials to train the pattern classifier and a different set of trials to test the classifier. For instance, to test Space-across-effector, we trained the classifier to discriminate location for one effector (e.g. EyeL vs. EyeR trials) and tested it on the other (e.g. HandL vs. HandR). By similar logic, we tested Effector-across-space by training the classifier to discriminate effector for one location (EyeL vs. HandL) and testing it on the other (EyeR vs. HandR). In sum, this additional analysis allows us to test whether the patterns of activity discriminating two movements are the *same as* or *different than* the patterns of activity discriminating a different set of movements. For instance, although classifiers accurately discriminating both HandL vs. EyeL *and* HandR vs. EyeR pair-wise comparisons indicate that actions are being planned with respect to an effector, accurate cross-trial-type decoding would furthermore show that the effector-specificity is represented independent of target location. Likewise, in terms of spatial-specificity, by crossing classifier training-and-testing for EyeL vs. EyeR and HandL vs. HandR trials, we can assess whether eye and arm movements are being prepared in a common spatial reference frame, independent of the effector to be used (as reported in the monkey (Andersen and Buneo, 2002; Buneo et al., 2002)). Critically, similar to many natural environmental interactions -- where the spatial locations of targets remain constant and it is only our *planned* interactions that change – in our task the positions of the two target objects never changed from trial-to-trial.

To localize a set of common ROIs that could then be selected in each individual subject for use in the MVPA analysis, we performed a whole-brain group-level voxel-wise search to find areas where the activity during movement generation (i.e. movement planning (Plan) and execution (Execute)) was higher than the activity during simple visual object presentation (Preview; when subjects had vision of both targets yet were unaware of which action to perform). This [Plan & Execute > Preview] contrast revealed activity throughout a well-documented parieto-frontal network of areas (Figure 4.2, see Table 2.1 for coordinates). Within this network, we focused MVPA on six commonly described human and monkey anatomical ROIs in both the left and right hemispheres, each previously implicated in visual-motor processing: 1) superior parieto-occipital cortex (SPOC), an area involved in reach preparation and execution (Galletti et al., 1997; Prado et al., 2005; Cavina-Pratesi et al., 2010) 2) posterior intraparietal sulcus (pIPS), an area involved in attention and eye and hand movement-related processes (Calton et al., 2002; Beurze et al., 2009; Chang and Snyder, 2010; Szczepanski et al., 2010) 3) middle IPS (midIPS), an area often implicated in both eye and reach movement planning (Andersen et al., 1985; Snyder et al., 1997; Batista et al., 1999; Culham et al., 2006) 4) premotor dorsal (PMd), a region primarily involved in reach-related processes (Caminiti et al., 1990b; Caminiti et al., 1990a; Pesaran et al., 2006; Cavina-Pratesi et al., 2010) 5) precentral gyrus, an area often implicated in general eye and hand motor-related processes (Beurze et al., 2009; Filimon, 2010) and 6) premotor ventral (PMv), an ROI most often implicated in hand-related actions (Graziano et al., 1994; Cavina-Pratesi et al., 2010; Filimon, 2010). One additional area, left somatosensory (SS cortex), was selected as a sensory control region, not expected to accurately decode movements until stimulation of the hand's mechanoreceptors at movement onset (i.e. at Execute phase). The question of interest here was whether we would be able to predict upcoming reaches and/or saccades and their movement directions from preparatory activity in each of these pre-specified areas.

4.2.1 Subjects

Eight right-handed volunteers participated in this study (4 females; mean age: 24.3 years).

4.2.2 Setup and Apparatus

Participants performed individual movements with the eyes or the right hand towards one of two object locations when required. The target objects were made of LEGO pieces (length: 7 cm x depth: 3 cm x height: 3 cm) and were secured to the workspace at a location along the arc of reachability for the right hand. The target stimuli were painted white to increase their contrast with the black background of the platform. The left target object was placed on the left side of the platform within reach by the participant's right hand and the right target object was placed on the right side of the platform, equidistant with respect to the subject's sagittal plane, at a further distance nearing the maximal extent of the participant's reach. Once specified, the target objects were secured to the platform at these locations (see Figure 4.1B). During the experiment, the two objects were illuminated simultaneously from the front by a bright white Light Emitting Diode (LED). During participant setup, the illuminator LED was positioned so as to equally illuminate the objects in both locations. To control for eye movements, a small green fixation LED was placed above and immediately between the two target objects and subjects were required to always foveate the fixation LED, unless a saccade was executed.

For each trial, the subjects were required to perform one of four actions upon the target objects, following a delay period: 1) manually touch the top of the left object with the knuckles ("Touch Left" auditory command; HandL trial) which required transporting the hand to the object without hand pre-shaping, 2) touch the right object ("Touch Right" auditory command; HandR trial) which required the exact same hand posture, 3) saccade to the left object ("Look Left" auditory command; EyeL trial) or 4) saccade to the right object ("Look Right" auditory command, EyeR trial). For both of the eye movement conditions, in order to specifically control for the amplitude of the saccades and allow equivalency across trials, small black dot stickers were placed on the centers of the target stimuli (on the object surface which faced the subject), and when cued, participants were required to saccade to these specific locations. Importantly, for each trial, the target objects never changed their peripherally-located positions, thus eliminating retinal differences across the experiment. Critically, from trial to trial, it was only the subject's movement intentions that changed.

4.2.3 Experiment Design and Timing

We used a slow event-related planning paradigm with 34 s trials, each consisting of three distinct phases: 'Preview', 'Plan' and 'Execute' (see Figure 4.1C). Each trial began with the Preview phase, where the subject's workspace was illuminated revealing the two peripherally-located target objects. After 6 s of the Preview phase, subjects were given an auditory cue (0.5 s), either "Touch Left", "Touch Right", "Look Left" or "Look Right", informing them of the upcoming movement required; this cue marked the onset of the Plan phase. After 12 s of the Plan phase, a 0.5 s auditory beep cued participants to immediately execute the planned action (for a duration of approximately 2 s), initiating the Execute phase of the trial. Two seconds following the beginning of this Go cue, the illuminator was turned off. For reach movements, subjects were instructed to touch the top of the target object and return the hand to its central starting position when the illuminator was extinguished. For eye movements, subjects were instructed to saccade to the target object (and foveate the black dot) and then return the eyes to the fixation LED when the illuminator was extinguished. After the illuminator was turned off, subjects then waited in the dark while maintaining fixation for 14 s, allowing the BOLD response to return to baseline prior to the next trial (ITI phase). The four trial types, with five repetitions per condition (20 trials total) were randomized within a run and balanced across all runs so that each trial type was preceded and followed equally often by every other trial type across the entire experiment.

4.2.4 MRI acquisition and preprocessing

Error trials – trials where the participant fumbled with the object, performed the incorrect instruction, or contaminated the plan phase data by slightly moving their limb or eyes or by performing the action before the 'Go' cue -- were identified off-line from the videos recorded during the session; only two trials from two subjects (four trials total) contained such movement errors.

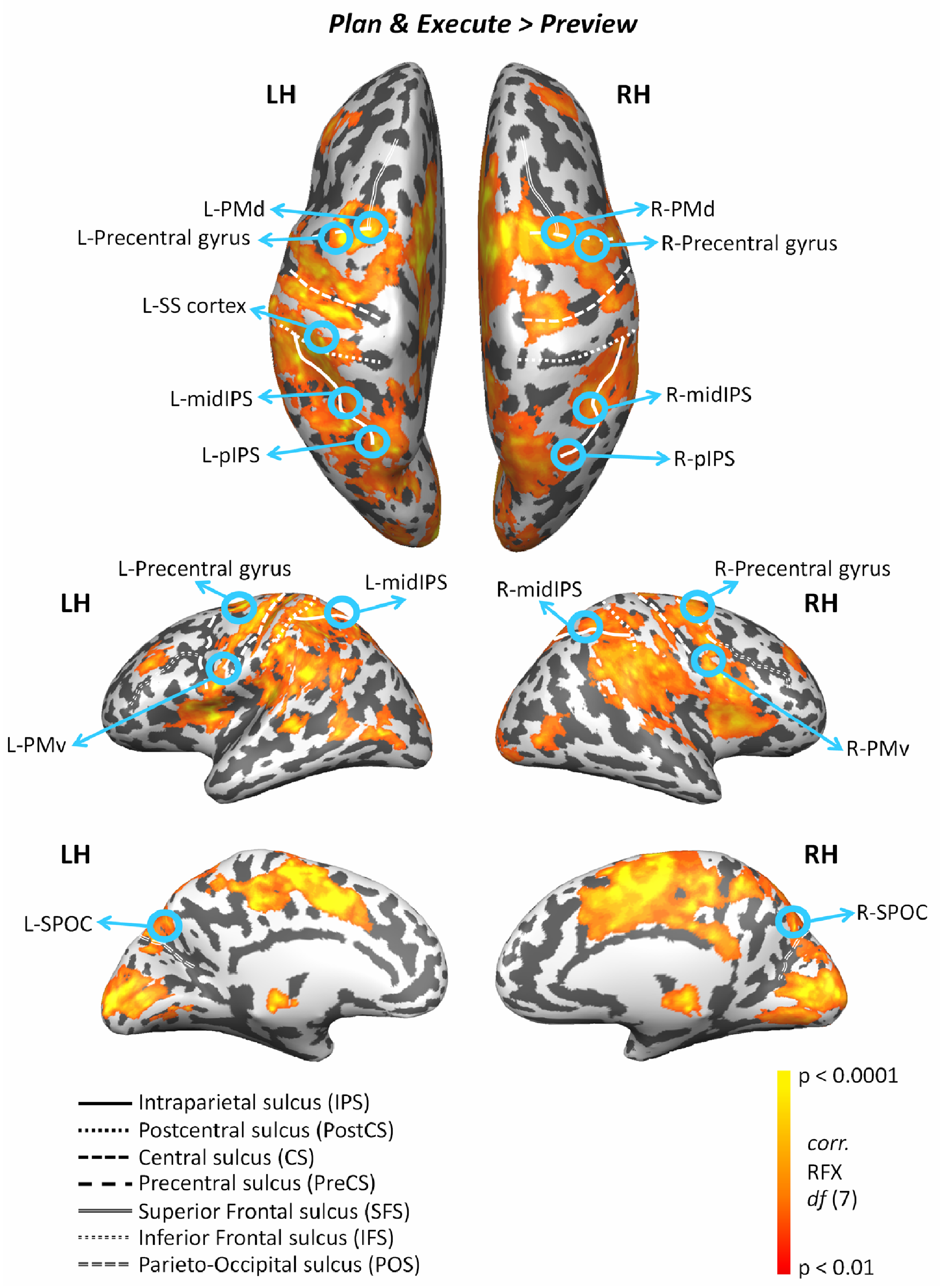

Plan & Execute > Preview
LH
RH
L-PMd
L-Precentral gyrus
L-SS cortex
L-midIPS
L-pIPS
R-PMd
R-Precentral gyrus
R-midIPS
R-pIPS
L-Precentral gyrus
L-midIPS
LH
L-PMv
R-midIPS
R-Precentral gyrus
RH
R-PMv
LH
L-SPOC
RH
R-SPOC
Intraparietal sulcus (IPS)
Postcentral sulcus (PostCS)
Central sulcus (CS)
Precentral sulcus (PreCS)
Superior Frontal sulcus (SFS)
Inferior Frontal sulcus (IFS)
Parieto-Occipital sulcus (POS)
p < 0.0001
corr.
RFX
df (7)
p < 0.01

Figure 4.2: Parieto-frontal brain areas selected for MVPA. Cortical areas that exhibited larger responses during movement generation than the preceding visual phase [(Plan + Execute) > 2*(Preview)] are shown in orange/yellow activation. Results calculated across all subjects (Random Effects GLM) are displayed on one representative subject's inflated hemispheres. The general locations of the selected ROIs are outlined in circles (actual ROIs were anatomically defined separately in each subject). L = Left, R = Right (ROI acronyms are spelled out in main text). Sulcal landmarks are denoted by white lines (stylized according to the corresponding legend). LH = Left-hemisphere, RH = Right-hemisphere.

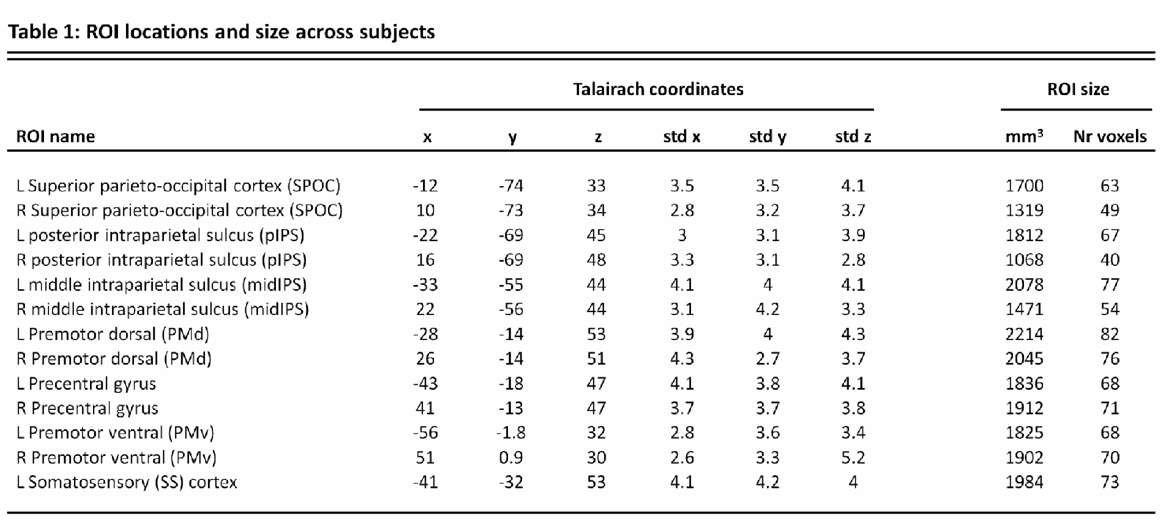


Table 1: ROI locations and size across subjects

	Talairach coordinates						ROI size	
ROI name	**x**	**y**	**z**	**std x**	**std y**	**std z**	**mm^3**	**Nr voxels**
L Superior parieto-occipital cortex (SPOC)	-12	-74	33	3.5	3.5	4.1	1700	63
R Superior parieto-occipital cortex (SPOC)	10	-73	34	2.8	3.2	3.7	1319	49
L posterior intraparietal sulcus (pIPS)	-22	-69	45	3	3.1	3.9	1812	67
R posterior intraparietal sulcus (pIPS)	16	-69	48	3.3	3.1	2.8	1068	40
L middle intraparietal sulcus (midIPS)	-33	-55	44	4.1	4	4.1	2078	77
R middle intraparietal sulcus (midIPS)	22	-56	44	3.1	4.2	3.3	1471	54
L Premotor dorsal (PMd)	-28	-14	53	3.9	4	4.3	2214	82
R Premotor dorsal (PMd)	26	-14	51	4.3	2.7	3.7	2045	76
L Precentral gyrus	-43	-18	47	4.1	3.8	4.1	1836	68
R Precentral gyrus	41	-13	47	3.7	3.7	3.8	1912	71
L Premotor ventral (PMv)	-56	-1.8	32	2.8	3.6	3.4	1825	68
R Premotor ventral (PMv)	51	0.9	30	2.6	3.3	5.2	1902	70
L Somatosensory (SS) cortex	-41	-32	53	4.1	4.2	4	1984	73

Table 4.1: ROIs with corresponding Talairach coordinates (mean x, y, and z centre of mass and std). Mean ROI sizes across subjects from AC-PC data (in mm^3 and functional voxels).

4.2.5 Regions of Interest (ROI)

To specify our ROIs at the group level (allowing further investigation of common ROIs at the single-subject level), we searched for brain areas involved in movement generation and contrasted activity for movement planning and execution (collapsed over effector and spatial target location) vs. the simple visual response to object presentation prior to instruction: [Plan(EyeL + EyeR + HandL + HandR) + Execute(EyeL + EyeR + HandL + HandR) > 2*Preview(EyeL + EyeR + HandL + HandR)]. The resulting statistical map of all positively active voxels (RFX, $t(7) = 3$, $p<0.01$, cluster threshold corrected: 278mm^3) was then used to define 13 different ROIs (6 ROIs on both the left and right, and one ROI, somatosensory cortex, on the left; for activity from this contrast see Figure 4.2). Six of these ROIs (across parietal and premotor cortex) were selected based on their well-documented involvement in movement planning/execution and the final ROI, left somatosensory cortex, was selected as a sensory control region (i.e. known to respond to transient stimuli (i.e. sensory events), but not expected to participate in sustained movement planning/intention-related processes). Importantly, each of these ROIs could then be easily anatomically localized in each individual's AC-PC-aligned data (see *ROI selection* below).

The specific voxels submitted for MVPA were then selected from the (Plan & Execute > Preview) GLM contrast on single subject AC-PC-aligned data and based on all significant activity within a 3375 mm^3 cube centered on the pre-defined anatomical landmarks for each of the 13 ROIs ($t=3$, $p<0.003$, each subject's activation map was cluster threshold corrected (corrected, $p<0.05$) so that only voxels passing a minimum cluster size were selected; average minimum cluster size across subjects was 112.5 mm^3; for details see *ROI selection*, below).

4.2.6 ROI selection:

Left and Right Superior parieto-occipital cortex (SPOC)

- defined by selecting voxels located medially and directly anterior to the Parieto-occipital sulcus (POS)(Gallivan et al., 2009)

Left and Right posterior IPS (pIPS)

- defined by selecting activity at the caudal end of the IPS (Sakata et al., 1998; Beurze et al., 2009).

Left and Right middle IPS (midIPS)

- defined by selecting voxels half-way up the length of the IPS, centred on the medial bank (Calton et al., 2002; Chang et al., 2009), near a characteristic ‘knob’ landmark observed consistently within each subject.

Left and Right Premotor dorsal (PMd)

- defined by selecting voxels at the junction of the Precentral sulcus (PreCS) and Superior frontal sulcus (SFS)(Picard and Strick, 2001).

Left and Right Precentral gyrus

- defined by selecting voxels lateral to the junction of the PreCS and SFS, encompassing the Precentral gyrus and posterior edge of the PreCS.

Left and Right Premotor ventral (PMv)

- defined by selecting voxels slightly inferior and posterior to the junction of the Inferior frontal sulcus (IFS) and PreCS (Tomassini et al., 2007).

Left somatosensory cortex (L-SS cortex)

- defined by selecting voxels encompassing the Post-central gyrus and Post-central sulcus (PCS), medial and anterior to the anterior IPS.

See Table 4.1 for details about ROI coordinates and sizes, and Figure 4.2 for representative anatomical locations on one subject’s brain.

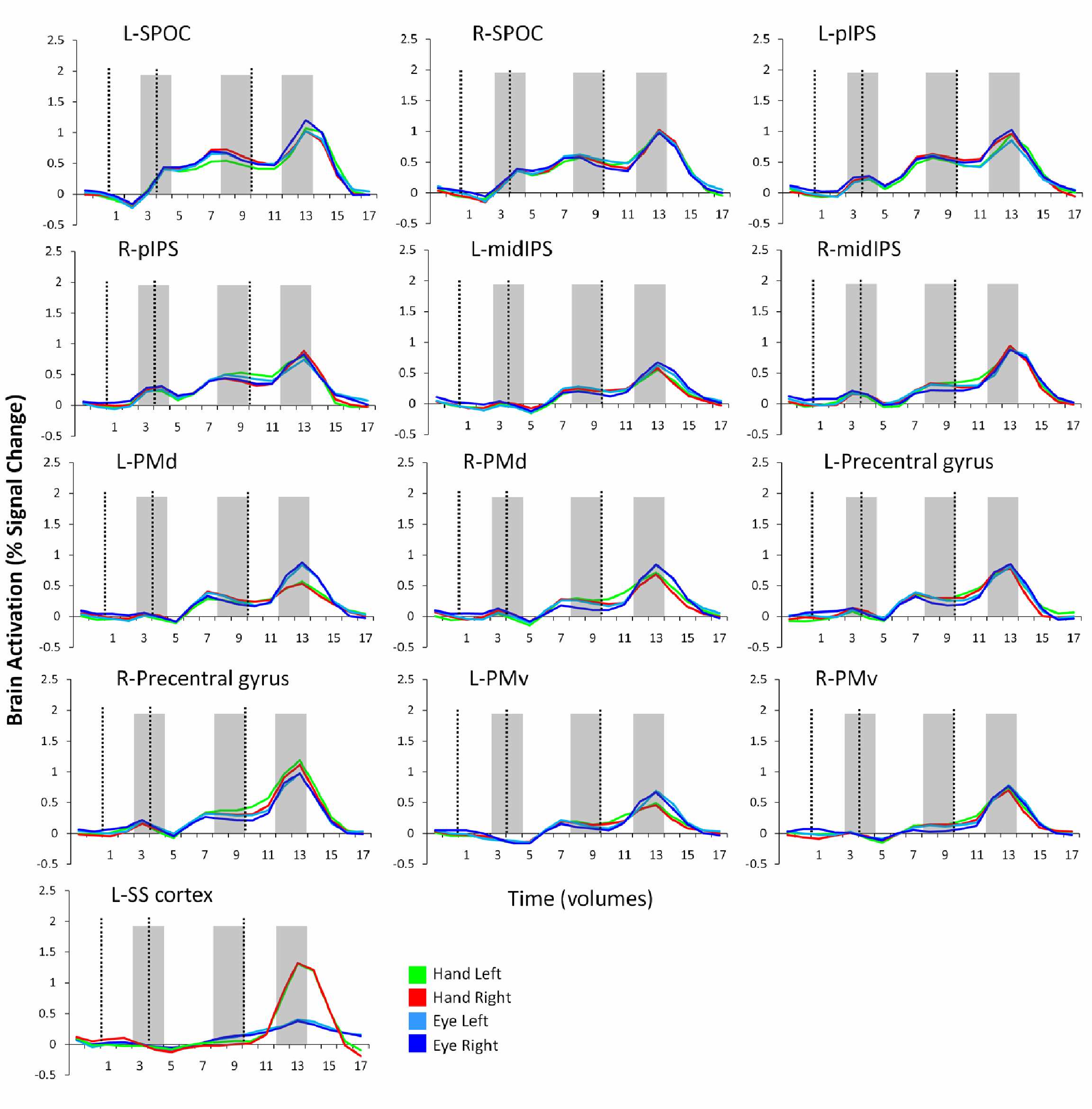


Figure 4.3: Trial-related percent signal change neural activity in the parieto-frontal regions used for MVPA. Activity in each plot is averaged across voxels within each ROI and across subjects. Vertical dashed lines correspond to the onset of the Preview, Plan and Execute phases of each trial (from left to right). Shaded gray bars highlight the 2-volume (4 s) windows that were averaged and extracted for MVPA (a conventional univariate analysis of signal amplitude differences within these same time-windows is provided in Figure 4.6). Note that time corresponds to imaging volumes (TR=2), and not seconds.

4.2.7 Multi-voxel pattern analysis (MVPA)

4.2.7.1 Voxel Pattern Preparation

To prepare the data for spatial pattern classification, the percent signal change was computed from a windowed-average of the time-course at a time point of interest (e.g. Preview, Plan or Execute) with respect to a windowed average of the time-course at a common baseline, for all voxels in the ROI (see Methods in Chapter 2 for more details).

4.2.7.2 Single-Trial classification

For each subject and for each of the 13 action-related ROIs, 12 separate binary support vector machine (SVM) classifiers were estimated for MVPA (i.e. for each of the *Preview*, *Plan* and *Execute* phases and each pair-wise comparison, HandL vs. EyeL, HandR vs. EyeR, HandL vs. HandR, and EyeL vs. EyeR). We used a “leave-five-trials-out” cross-validation to test the accuracy of the binary SVM classifiers, meaning that five trials from each of the conditions being compared (i.e. 10 trials total) were reserved for testing the classifier and the remaining trials were used for classifier training (i.e. 35 or 40 remaining trials per condition, depending on whether the subject participated in eight or nine experimental runs, respectively). Single trials in the independent test data set (ten total), prior to classifier testing, were averaged according to condition (i.e. creating two averaged data points to be separated in multidimensional voxel space), improving voxel pattern signal-to-noise in the test data set (see also Smith and Muckli, 2010). Because a full cross validation is not entirely reasonable with a “leave-five-trials-out” design due to the $\sim 10^5$ possible iterations, to provide a highly reliable estimate of decoding accuracies we performed 1008 train-and-test iterations for each pair-wise discrimination . For subjects with eight runs, each trial was used exactly 126 times to train the classifier and in subjects with nine runs, each trial was used exactly 112 times to train the classifier.

4.3 Results

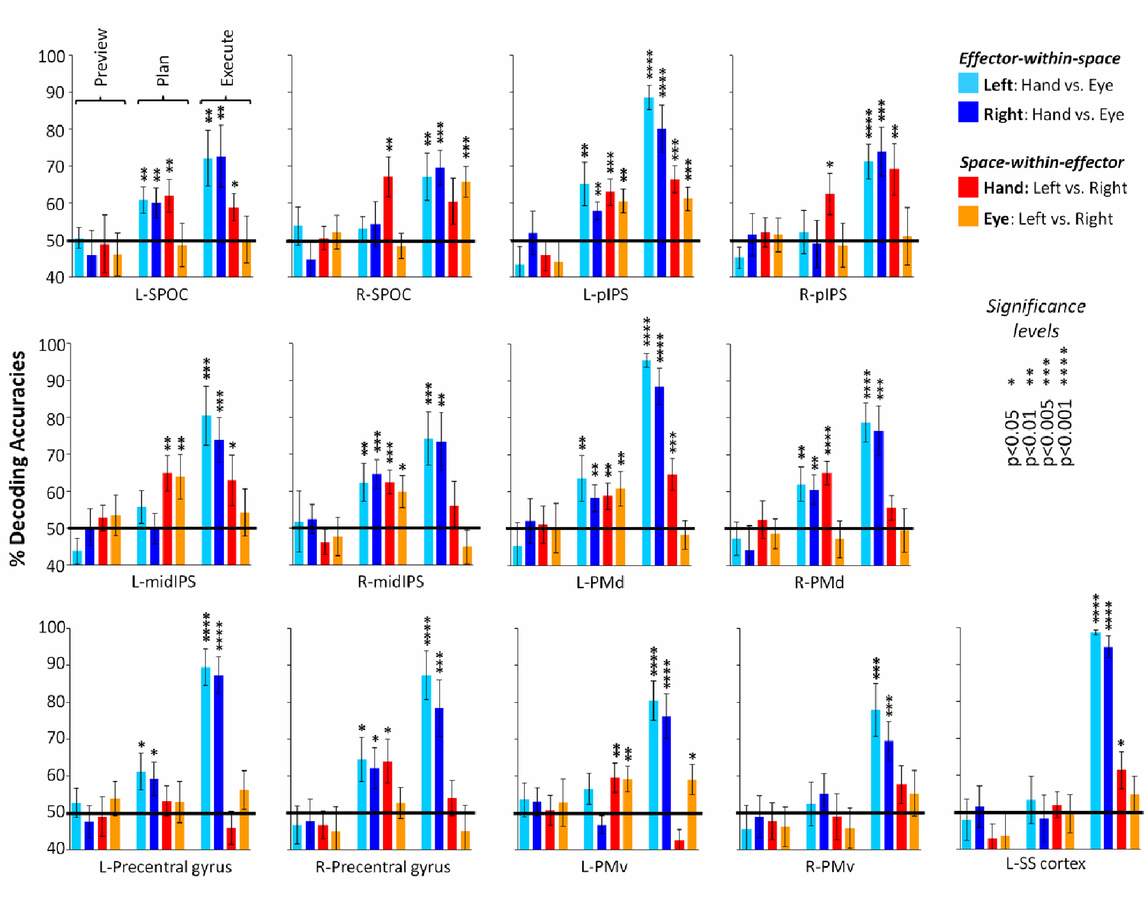


Figure 4.4: Decoding movement intentions across the parieto-frontal network. Decoding accuracies are shown for each time phase (Preview, Plan, and Execute) in each ROI. Classifier training was done on single trials and tested on the average activity patterns of the single trials for each condition in the independent test data set. Importantly, accurate classification can only be attributed to the spatial response patterns of different planned movement types, and not the overall signal amplitudes within each ROI (see Figure 4.6). Note that decoding accuracies are colour-coded according to pair-wise discriminations and not trial types. Error bars represent standard error of the mean (SEM) across subjects. Solid black lines are chance accuracy level (50%). Asterisks assess statistical significance with t-tests across subjects with respect to 50%.

During movement planning we found a wide range of decoding profiles across the network of specified parieto-frontal brain regions: activity patterns in several of the areas predicted the effector to be used (eye vs. hand) or the target location to be acted upon (left vs. right), and in several regions, we could accurately predict both types of movement information (Figure 4.4). For instance, in parietal cortex, L- and R-SPOC -- a region often implicated in reaching (Galletti et al., 1997; Prado et al., 2005; Fattori et al., 2009; Gallivan et al., 2009; Cavina-Pratesi et al., 2010) -- not only showed effector-specific preparatory responses but also predicted the direction of an upcoming reach (but not the direction of an impending eye movement). In both L-pIPS and R-midIPS, areas implicated in eye and hand movement processes (Snyder et al., 1997; Chang et al., 2008; Beurze et al., 2009; Chang and Snyder, 2010), a combined effector-specific and spatially specific planning response was observed: both areas predicted all conjunctions of the effector to be used (hand vs. eye) and the location to be acted upon (left vs. right). Interestingly, this contrasts with the decoding profile found in L-midIPS, which instead showed only effector-independent movement intentions: the spatial location to be acted upon was encoded regardless of the effector required to perform the movement. In premotor cortex we found a similar array of decoding profiles, with 1) the reach-related L-PMd (Caminiti et al., 1990b; Caminiti et al., 1990a; Pesaran et al., 2006; Andersen and Cui, 2009) predicting all conjunctions of spatial and effector movements, 2) the hand-related L-PMv (Graziano et al., 1994; Cavina-Pratesi et al., 2010) encoding effector-independent (spatially specific) movement intentions, and 3) the R-PMd and L- and R-precentral gyrus regions encoding mostly reach-specific movement plans (i.e. decoding the effector to be used and reach direction). Importantly, consistent with expectations, our control region L-SS cortex, failed to decode planned movements (and only the executed actions, see Figure 4.4), reinforcing the notion that predictive movement information is constrained within plan-related parieto-frontal areas. As an additional control of our decoding accuracies, we ran the same classification analyses in two non-brain ROIs where decoding is unlikely: the right ventricle and outside the brain. Indeed, MVPA in these two areas showed no accurate decoding for any trial phase (see Figure 4.7).

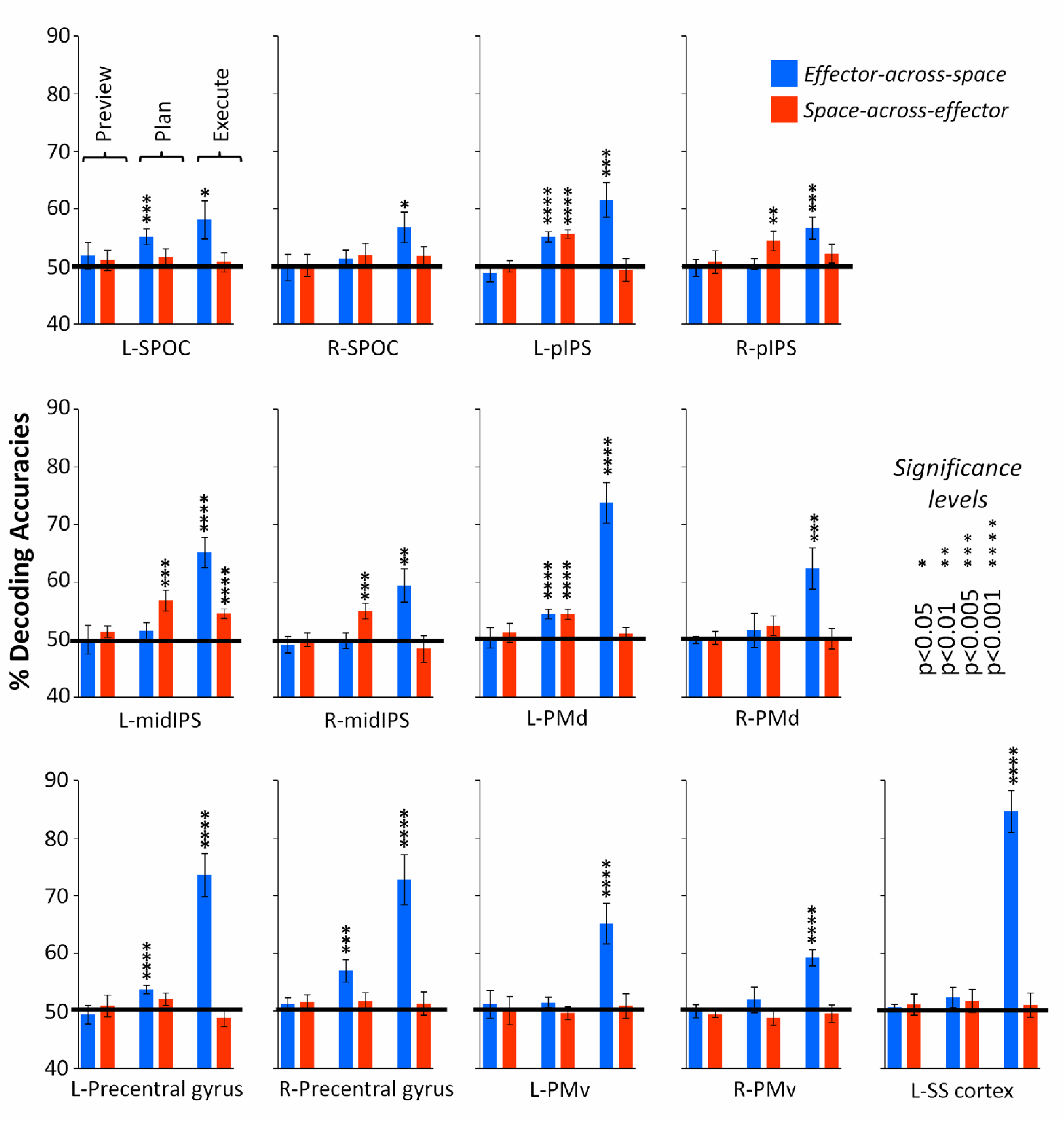


Figure 4.5: Cross-trial-type decoding accuracies examining the degree of effector-specificity and spatial-specificity of the intended movements. Decoding accuracies are shown for each time phase (Preview, Plan, and Execute) in each ROI. Effector-across-space accuracies were computed from training classifiers on HandL vs. EyeL trials and testing on HandR vs. EyeR trials and then averaging these values with the opposite train-and-test ordering, within each subject. Space-across-effector accuracies were computed from training classifiers on EyeL vs. EyeR trials and testing on HandL vs. HandR trials (again, averaging these values with the opposite train-and-test ordering, within each subject). Error bars represent SEM across subjects. Solid black lines are chance accuracy level (50%). Asterisks assess statistical significance with t-tests across subjects with respect to 50%.

Expanding on the within-trial MVPA analysis, we also examined whether movement intentions were coded by *shared* or *separate* distributed neural mechanisms using cross-trial-type MVPA (see Dinstein et al., 2008; Formisano et al., 2008; Harrison and Tong, 2009). To test whether the spatially selective coding of planned reach and saccade movements found in several of the parieto-frontal areas relied on a common spatial reference frame, we trained pattern classifiers using EyeL and EyeR trials and tested the accuracy of the classifiers using HandL and HandR trials (the opposite train-and-test process -- train set: HandL vs. HandR, test set: EyeL and EyeR -- was also performed and we averaged the accuracies from both approaches). This *Space-across-effector* decoding approach was statistically significant in L-pIPS, R-pIPS, L-midIPS, R-midIPS, and L-PMd (Figure 4.5, red bars). Significant cross-trial-type decoding seems sensible in many of the areas where the within-trial activity patterns are already able to accurately discriminate both reach and saccade direction (i.e. HandL vs. Hand R & EyeL vs. EyeR trials) like in L-pIPS or L-midIPS (see Figure 4.4), and further suggests that the spatial-specificity of the response in these areas is reliant on a shared coordinate frame for the hand and eye (given that the spatial locations of the targets are constant across the planning of reaches and saccades). In fact, even *non-significant* cross-trial-type decoding can be informative in areas able to individually discriminate reach and saccade direction (e.g. L-PMv) as it suggests that the spatial frames of reference underlying eye and hand movements may be different. There is difficulty, however, in interpreting the Space-across-effector results from the plan-related activity in R-pIPS and the execute-related activity in L-midIPS, as both these regions fail to show accurate decoding for EyeL vs. EyeR trials in the respective trial phases when we used within-trial MVPA (see Figure 4.4).

We next examined whether the effector-specificity of the planned movements in several parieto-frontal areas could be further discriminated from resident spatial processes in the area by training classifiers using HandL and EyeL trials and testing the classifiers using HandR and EyeR trials (again, the opposite train-and-test process was also performed and the accuracies were averaged). This *Effector-across-space* decoding analysis was statistically significant during planning in several regions: L-SPOC, L-pIPS, L-PMd, and L- and R-Precentral gyrus (Figure 4.5, blue bars), indicating that the neural coding for the effector to be used was not dependent on the spatial location to be acted upon. Rather interestingly, several of these same areas also showed spatial tuning with respect to the planned target location from within-trial MVPA (Figure 4.4). We comment further on this finding in the discussion below.

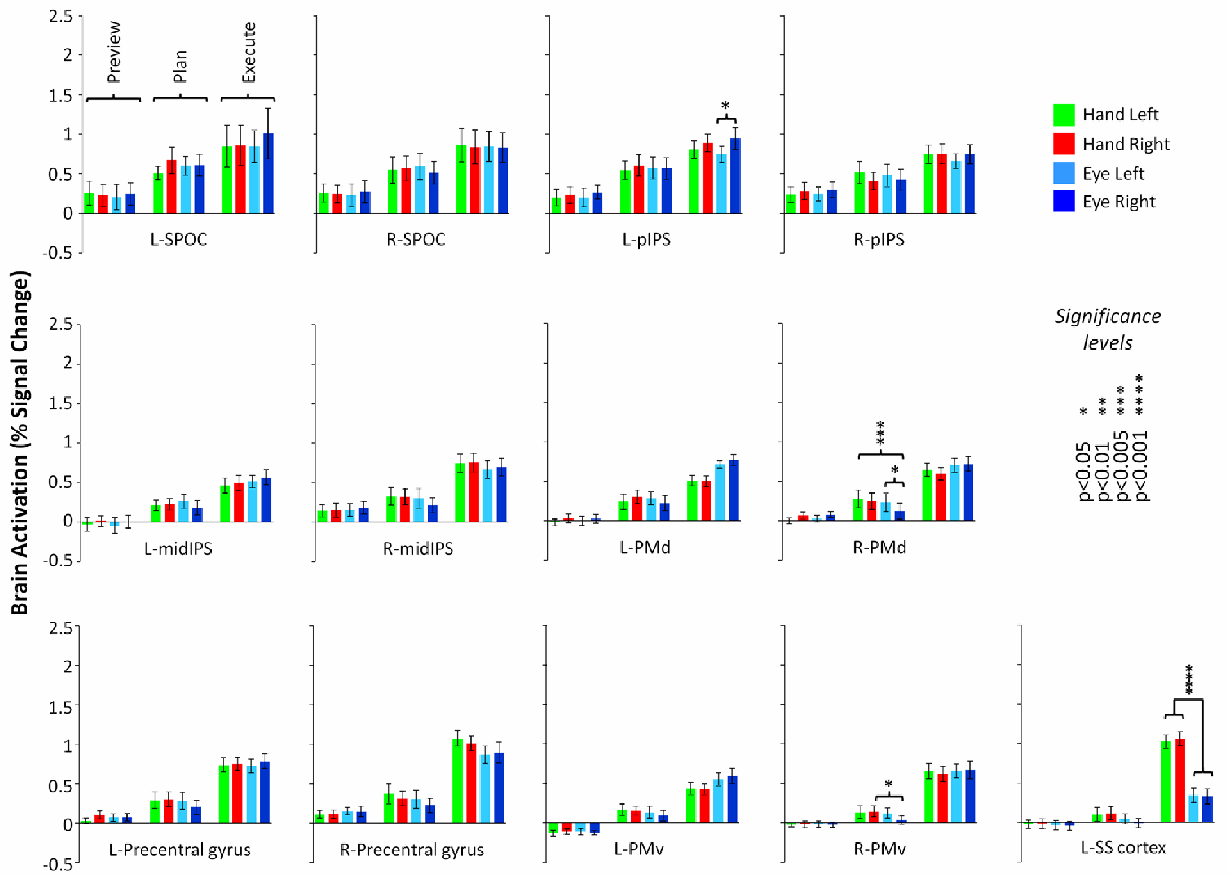
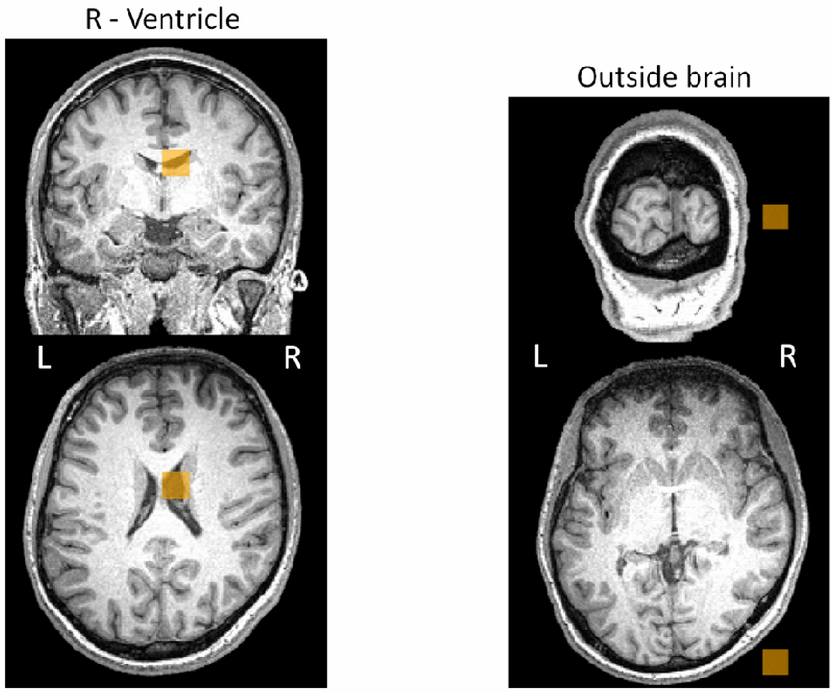


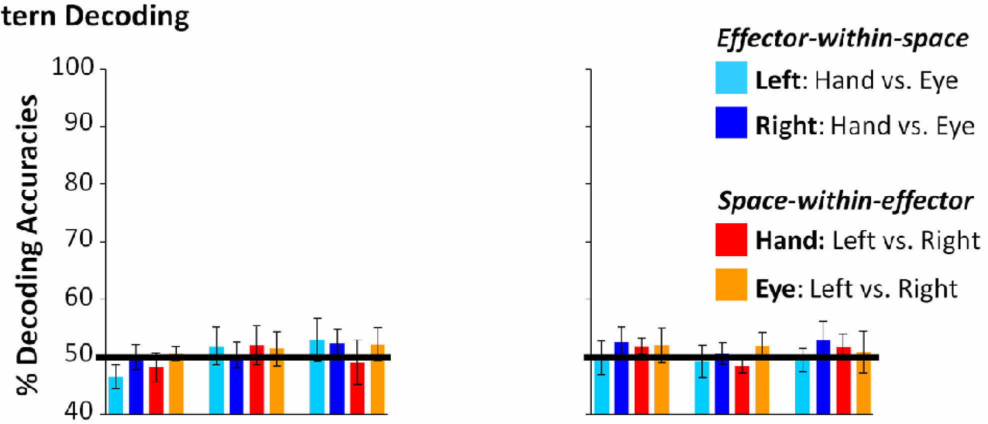
Figure 4.6: Few signal amplitude differences found within the parieto-frontal regions and time-windows used for MVPA. Responses are averaged across voxels within each ROI and across subjects for the 2-volume averaged windows corresponding to Preview, Plan and Execute phases. Note that very few statistically significant univariate differences are found throughout the parieto-frontal network. Errors bars represent SEM across subjects.

Critically, our results show that decoding revealed during the Plan phase can only be attributed to the *intention* to perform a specific movement, given the absence of decoding observed during the preceding Preview phase, when movement-planning information was unavailable (Figures 4.4 and 4.5). Furthermore, accurate decoding can only reflect the voxel spatial activity patterns for different movement plans, and not the overall response amplitudes within each ROI. When we averaged trial responses across all voxels in each ROI (i.e. as done in conventional univariate fMRI analyses), we found only a few significant differences for the four planned movements (see Figure 4.6). In addition to this analysis of response signal amplitudes, we also wanted to topographically characterize both effector-specific and spatially specific (effector-independent) movement planning and execution processes at the group level, in a more similar manner to that done in previous studies. The goals of this additional analysis were to further highlight and differentiate the types of predictive sensorimotor neural information that can be extracted from pattern classification analyses as compared to conventional fMRI subtraction analyses. To do this, we performed a number of group RFX GLM subtraction contrasts.

A) Control ROIs



B) Pattern Decoding



C) % Signal change activity

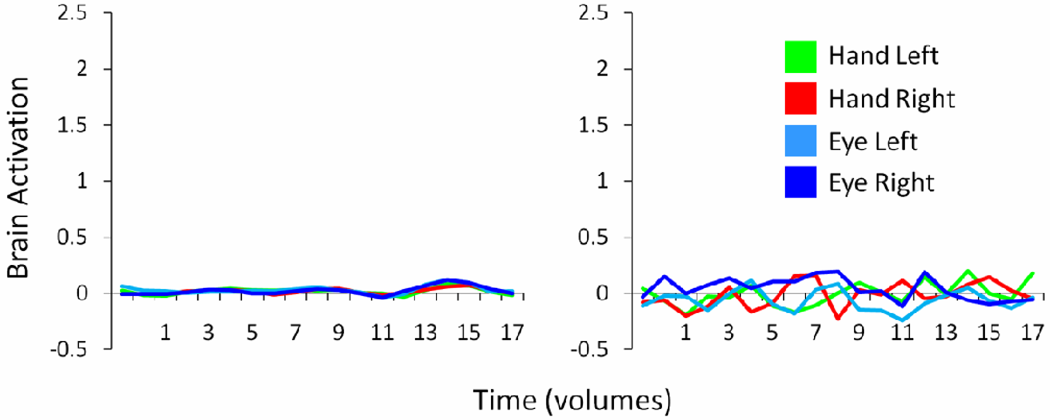


Figure 4.7: Classifier decoding accuracies in non-brain control regions. A) Non-brain control ROIs defined in each subject (denoted in light orange; example subject shown). **B)** Classifier accuracies for the right ventricle (left) and outside the brain ROI (right). Error bars represent SEM across subjects. Solid lines show chance classification accuracy (50%). Note that no significant differences were found with t-tests across subjects with respect to 50% chance. **C)** Percent signal change activity from each selected region, averaged across subjects.

First, in order to characterize the cortical topography of effector-specific movement planning processes (independent of spatial-specificity), we searched for areas that showed higher activity for eye movement planning than the activity elicited by simple visual presentation of the targets, prior to instruction of the eye movement (RFX GLM, $t(7)=3$, $p<0.01$, [Plan(EyeL + EyeR) > Preview(EyeL + EyeR)]; cluster threshold correction: 291 mm^3, Figure 4.8 left panel, shown in yellow). To similarly characterize the areas engaged in the planning of hand movements we performed the equivalent contrast ([Plan(HandL + HandR) > Preview(HandL + HandR)]; same statistical threshold, cluster threshold correction: 284 mm^3, Figure 4.8 left panel, shown in red, overlap for eye and hand shown in orange). We also further characterized movement execution topography for the eye vs. hand (and their overlap) using similar contrasts and the same logic as above ([Execute(EyeL + EyeR) > Preview(EyeL + EyeR)]; [Execute(HandL + HandR) > Preview(HandL + HandR)], same statistical thresholds, same cluster thresholds, Figure 4.8 right panel).

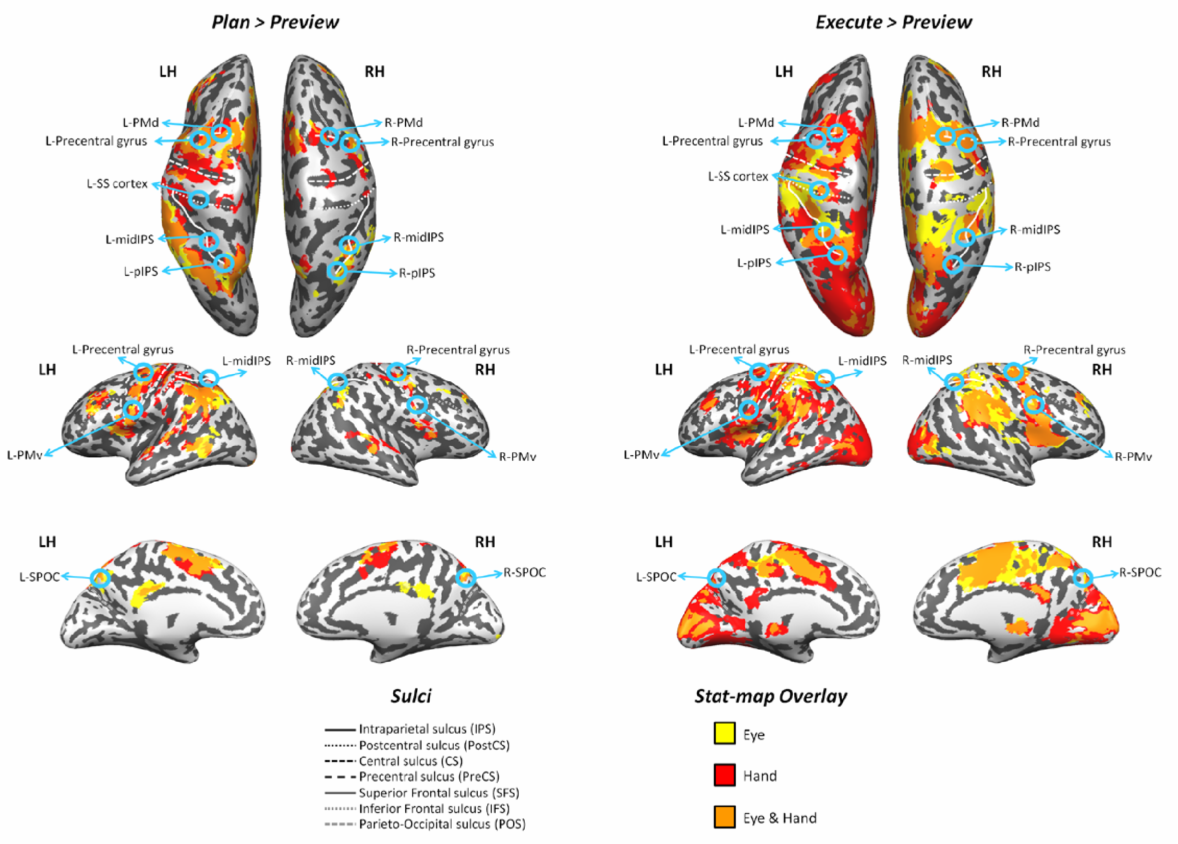


Figure 4.8: Activation topography of effector-selectivity (eye vs. hand) during movement planning and execution with conventional subtraction analyses. (Left) Brain areas that showed significant activation (RFX GLM, t(7)=3, p<0.01, cluster threshold corrected) during movement planning for the eye or hand independent of the spatial target location [Plan(EyeL + EyeR) > Preview(EyeL + EyeR)] in yellow; [Plan(HandL + HandR) > Preview(HandL + HandR)] in red. (Right) Brain areas that showed significant activation (at the same statistical threshold) for movement execution of the eye or hand [Execute(EyeL + EyeR) > Preview(EyeL + EyeR)] in yellow; [Execute(HandL + HandR) > Preview(HandL + HandR)] in red. The overlap of eye and hand movement planning or execution is shown in orange.

Second, we also examined the brain areas recruited for reach planning with respect to the upcoming reach direction (i.e. spatial-specificity for reach movements). We searched for areas with higher activation for planning reaches to the left or right targets vs. visual presentation of the object prior to the reach instruction (RFX GLM, $t(7)=3$, $p<0.01$, [Plan(HandL) > Preview(HandL)], cluster threshold correction: 287 mm^3; [Plan(HandR) > Preview(HandR)], cluster threshold correction: 269 mm^3, Figure 4.9 left panel; leftward reaches in yellow, rightward reaches in red, and the overlap shown in orange). The same type of contrasts were also applied in order to similarly characterize reach execution processes ([Execute(HandL) > Preview(HandL)] ; Execute(HandR) > Preview(HandR)], same statistical thresholds, same cluster thresholds, Figure 4.9 right panel).

Lastly, we wanted to characterize the regions of the brain recruited for saccade planning with respect to the direction of the saccade (i.e. spatial-specificity for eye movements). Consistent with the rationale above, we searched for areas that showed higher activation for the planning of saccades to the left or right vs. visual presentation of the target objects prior to the eye movement instruction (RFX GLM, $t(7)=3$, $p<0.01$, [Plan(EyeL) > Preview(EyeL)], cluster threshold correction: 277 mm^{3,} ; [Plan(EyeR) > Preview(EyeR)], cluster threshold correction: 284 mm^3, Figure 4.10 left panel; leftward saccades in yellow, rightward saccades in red, and the overlap shown in orange). We then also characterized the directionality of the executed saccade movements according to the same logic ([Execute(EyeL) > Preview(EyeL)]; [Execute(EyeR) > Preview(EyeR)], same statistical thresholds, same cluster thresholds, Figure 4.10 right panel).

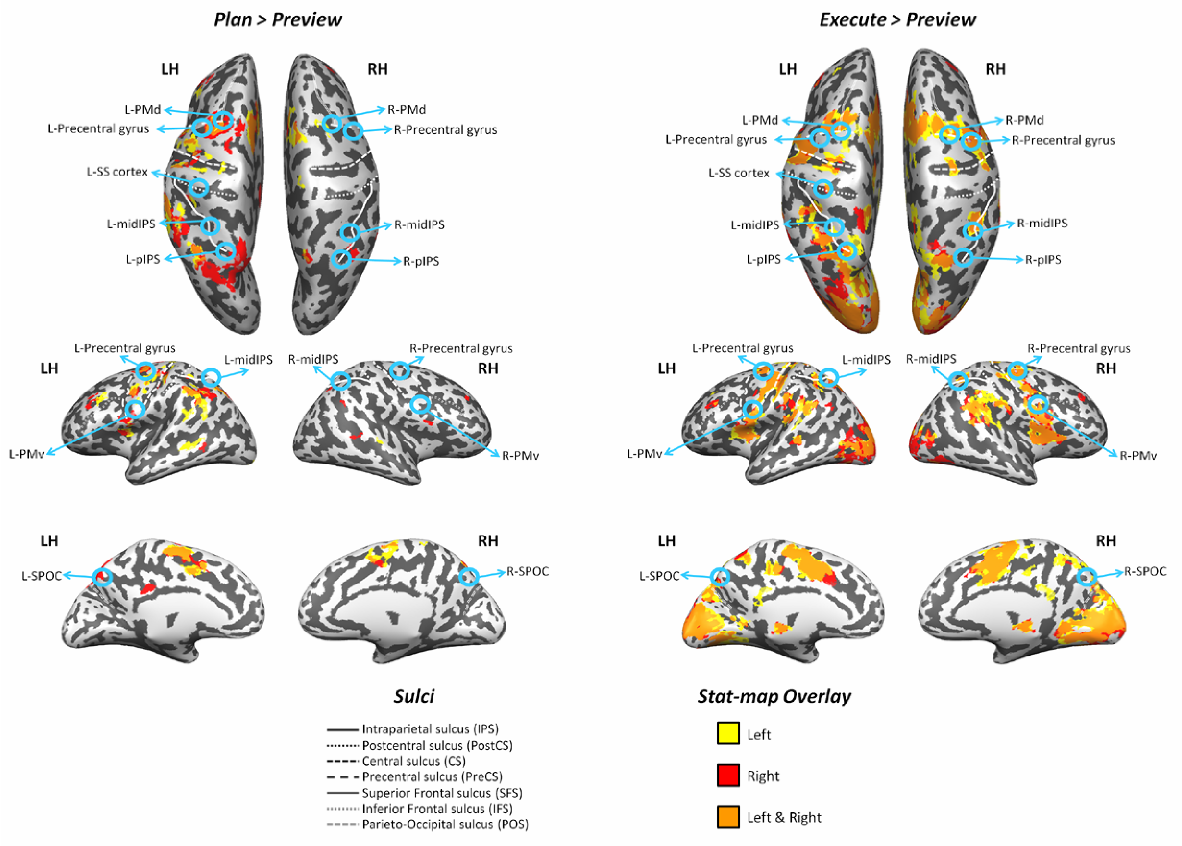


Figure 4.9: Activation topography of spatial-selectivity (left vs. right targets) for reach planning and execution with conventional subtraction analyses. (Left) Brain areas that showed significant activation (RFX GLM, t(7)=3, p<0.01, cluster threshold corrected) during reach planning depending on the spatial target location [Plan(HandL) > Preview(HandL)] in yellow; [Plan(HandR) > Preview(HandR)] in red. (Right) Brain areas that showed significant activation (at the same statistical threshold) for reach execution [Execute(HandL) > Preview(HandL)] in yellow; [Execute(HandR) > Preview(HandR)] in red. The overlap of left and right reach planning or execution is shown in orange.

With respect to the activation topography of hand movements, eye movements, their overlap, and the spatial-specificity of these effector-specific responses, the group findings reported here correspond remarkably well with the parieto-frontal network of areas engaged for planned and executed reaches and/or saccades (Sereno et al., 2001; Curtis et al., 2004; Schluppeck et al., 2005; Curtis and D'Esposito, 2006; Medendorp et al., 2006; Schluppeck et al., 2006; Beurze et al., 2007; Kastner et al., 2007; Beurze et al., 2009; Kagan et al., 2010; Lindner et al., 2010; Van Pelt et al., 2010), planned pointing and saccades (Connolly et al., 2000; Astafiev et al., 2003; Connolly et al., 2003; Connolly et al., 2007; Hagler et al., 2007), reaching and saccade execution (Levy et al., 2007; Filimon et al., 2009), as well as other work from our lab, using actual reaching (Culham et al., 2003; Culham et al., 2006; Culham and Valyear, 2006; see also Filimon, 2010 for review). These previous studies have also found overlapping and topographically mixed saccade and reach responses in the posterior and middle IPS, superior parietal cortex, as well as parts of PMd, precentral gyrus, and PMv. One notable departure from previous findings, however, is that we failed to observe larger response amplitudes for reaching vs. saccade execution in several anterior and superior parts of the PPC, as well as PMv and PMd. In fact, our univariate analysis of response signal amplitudes (for the same time points as those extracted for pattern classification) found no statistical differences between the execution of reaches and saccades (except for SS-cortex, consistent with expectations, see Figure 4.6). The pragmatic explanation of this discrepancy with past findings relates to the contrasts we employed to localize the action-related ROIs to be used for MVPA. In order to localize the ROIs in Figure 4.2, we searched for areas that simply showed higher activity for movement planning and execution compared to the simple transient response that accompanies visual presentation of the object prior to instruction (Plan + Execute > Preview). This type of contrast was in fact necessary, because in addition to specifying ROIs preferentially involved in sensorimotor planning and control, it importantly specifies that the voxels submitted for MVPA are unbiased towards showing univariate differences between reaches and saccades and the movement directions (orthogonality of ROI localization is a critical consideration when interpreting the resultant decoding accuracies, (Kriegeskorte et al., 2009)). This general procedure significantly contrasts with previous approaches, which explicitly search for reach and saccade univariate differences (e.g. Astafiev et al., 2003; Hagler et al., 2007; Levy et al., 2007; Filimon et al., 2009) in order to characterize their topographical relationships and neural organization. In fact, when we directly performed a group subtraction analysis of a similar nature in order to localize our same ROIs (RFX GLM, $t(7)=3$, $p<0.01$, [Execute(HandL + HandR) > Execute(EyeL + EyeR)], cluster threshold correction: 276 mm^3) we found very little activation throughout the brain (of which no voxels survived cluster threshold correction)[Note that this particular null result might initially seem to contradict the findings presented in Figure 4.8, where several regions involved in hand movements (in red) do not overlap with regions in involved in eye movements (in yellow); however, it is important to re-emphasize that the topographical activation maps in Figure 4.8 only show significant reach- and saccade-related activation with respect to the Preview phase and not with respect to each other (i.e. hand vs. eye movements)]. This null finding of course may reflect the reduced statistical power to be expected from a RFX group voxelwise analysis with only eight subjects (minimum group size generally recommended is 12 (Desmond and Glover, 2002)), a point likely further compounded by the fact that all the subject data is unsmoothed (note that although data smoothing is optimal for group voxelwise analysis, it is detrimental to detecting fine-grained spatial activity patterns with MVPA (Mur et al., 2009)). Nevertheless, despite the potential sources of discrepancies with past findings, we find it important to re-emphasize the critical findings from this experiment: despite the absence of signal amplitude differences between different effector- and spatial-movement plans, we are still able to predict in several parieto-frontal areas the chosen effector and spatial location of an upcoming action.

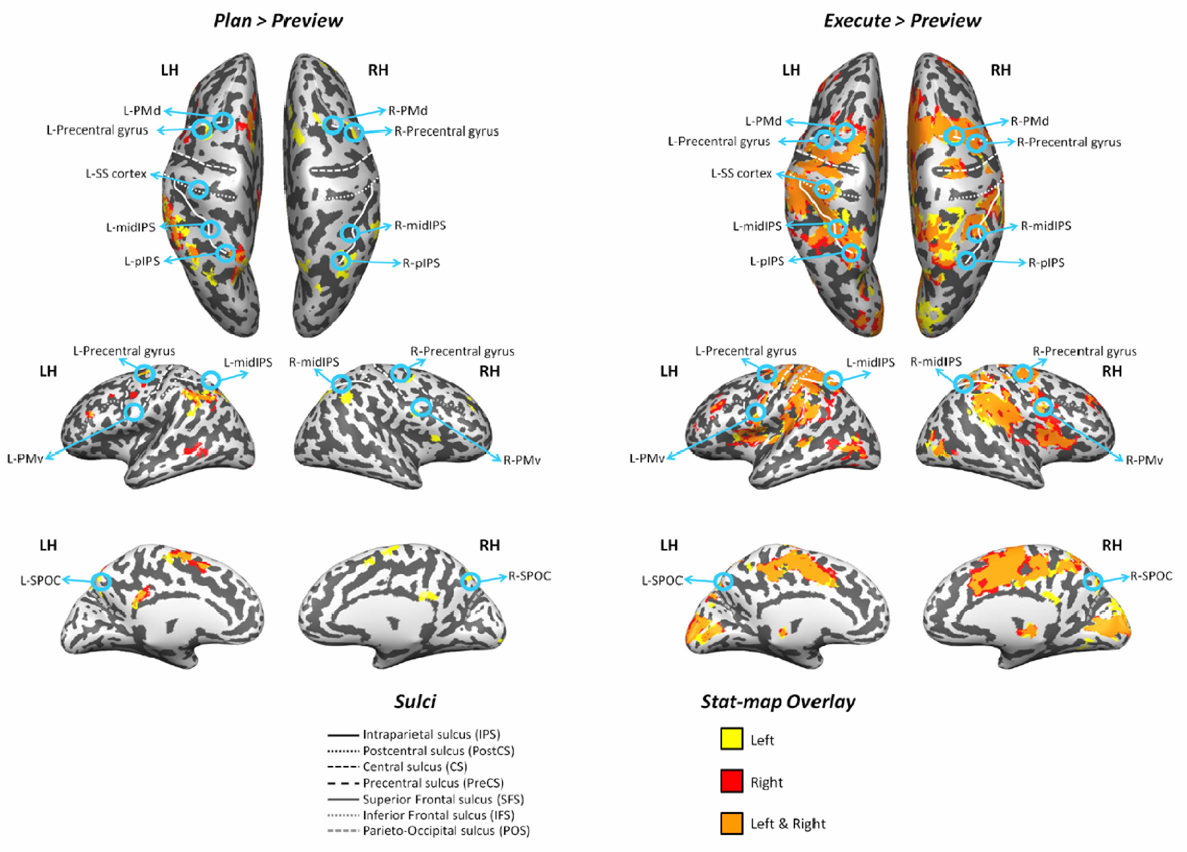


Figure 4.10: Activation topography of spatial-selectivity (left vs. right targets) for saccade planning and execution with conventional subtraction analyses. (Left) Brain areas that showed significant activation (RFX GLM, t(7)=3, p<0.01, cluster threshold corrected) during saccade planning depending on the spatial target location [Plan(EyeL) > Preview(EyeL)] in yellow; [Plan(EyeR) > Preview(EyeR)] in red. (Right) Brain areas that showed significant activation (at the same statistical threshold) for saccade execution [Execute(EyeL) > Preview(EyeL)] in yellow; [Execute(EyeR) > Preview(EyeR)] in red. The overlap of left and right saccade planning or execution is shown in orange.

4.4 Discussion:

Whereas previous fMRI studies have predominantly used MVPA for decoding the perceptual neural responses which accompany (and follow from) the presentation of sensory stimuli (Haxby et al., 2001; Kamitani and Tong, 2005; Formisano et al., 2008; Harrison and Tong, 2009), here we apply MVPA to decode planned target-directed actions, events which have yet to occur. We show in several parieto-frontal brain areas that we can not only decode the *intention* to perform a saccade or reach, but that we can also discern the underlying spatial and non-spatial nature of the movement plan. Importantly, we also find that accurate decoding does not merely reflect an attention-driven modulation: consistent with intention vs. attention distinctions made from monkey neural activity (Snyder et al., 1997), in most of the areas examined, the preparatory signals discriminate whether an eye or arm movement is being planned towards a single spatial target location. Furthermore, we show that this predictive movement information is not revealed from a univariate analysis of signal response amplitudes, a finding that may indicate why previous attempts to identify effector-specific and spatially specific movement plans with fMRI in the human have largely revealed graded or indistinguishable processes.

Beyond applying standard within-trial MVPA analyses to determine which types of planned movements can be decoded in each brain area, we also used cross-trial-type-decoding analyses which allowed us investigate whether 1) planned reach and eye movements were spatially encoded in shared coordinates (*Space-across-effector* decoding) and/or 2) whether the planned movements were coded by non-spatial, motor-specific signals (*Effector-across-space* decoding). Ultimately, the combination of both MVPA approaches (within-trial and cross-trial classification analyses) allowed for the fine-grained differentiation of effector-specific and effector-independent (spatially specific) signals within single parieto-frontal regions, a discrimination directly congruent with the activity profiles of individual parieto-frontal neurons in non-human primates. For instance, in monkey IPS the neural arrangement is highly multiplexed, with many plan-related neurons preferentially responsive to an effector (eye vs. hand) and direction (e.g. left vs. right), whereas others may only carry information related to either the effector or spatial goal (Snyder et al., 1997; Calton et al., 2002; Dickinson et al., 2003). These idiosyncrasies in neural arrangement provide a sensible neurophysiological basis for the complex profiles of predictive activity observed here at the coarse level of distributed parieto-frontal fMRI patterns. In addition, this pattern analysis approach allows for an important theoretical departure from previous human fMRI (and also magnetoencephalography (MEG)) studies. Nearly all prior investigations have relied on the implicit assumption that movement plans for reaches and saccades are topographically organized with respect to the target location (e.g. a target for an eye movement on the right will be encoded by the left hemisphere). This notion emerges from our understanding of the contralateral architecture that governs lower-level cortical structures (e.g. visual cortex, superior colliculus) and has found varying degrees of support in parietal cortex (Sereno et al., 2001; Medendorp et al., 2003; Hagler et al., 2007; Levy et al., 2007; Kagan et al., 2010; Van Der Werf et al., 2010). For several regions, however, there seems no good reason to suspect that simply because the resident neurons may encode stimuli in a particular reference frame (e.g. gaze-centred coordinates), that the entire region will be topographically organized (e.g. retinotopically) in an ordered configuration along similar dimensions (see also Filimon, 2010). In fact, this assumption critically overlooks several important parieto-frontal properties such as its highly distributed/unstructured organization (Andersen and Buneo, 2002), neurons containing ipsilateral or bilateral response fields (Barash et al., 1991; Ben Hamed et al., 2001), and moreover, the fact that movement planning processes are asymmetrically organized (lateralized) in the human, compared to the monkey brain (Kagan et al., 2010)(the latter point is re-emphasized by the generally stronger left-hemisphere decoding of planned movements found here). To further underscore these points, we explicitly examined the topography of planned and executed reaches and saccades using conventional fMRI analyses (see Figures 4.8-4.10) and found, in agreement with previous fMRI investigations containing analyses of a similar nature (Hagler et al., 2007; Levy et al., 2007; Beurze et al., 2009; Filimon et al., 2009), that the cortical topography for reaches, saccades, and goal locations is highly mixed. This result highlights another main benefit of using MVPA for sensorimotor investigations: assumptions of structurally organized cortical topographies are unnecessary.

4.4.1 Posterior Parietal Cortex (PPC) Decoding

Although studies in both humans and monkeys have commonly reported a role for superior parietal cortex in reaching (Andersen and Cui, 2009; Vesia et al., 2010), here we show that L- and R-SPOC preparatory activity also predicts upcoming reach directions, a finding that has only been previously reported with neural recordings in monkeys (e.g. Fattori et al., 2009). Whereas we might only speculate on the underlying organization governing the spatial-selectivity of reaches in SPOC (see Bernier and Grafton, 2010), the decoding profiles found in pIPS and midIPS offer clearer interpretations. pIPS has been implicated in a vast range of human sensorimotor processes: including visual-spatial attention (e.g. Szczepanski et al., 2010) and spatial target and effector integration (Beurze et al., 2009). The middle IPS in contrast, has been more thoroughly characterized in non-human primates (Andersen and Buneo, 2002) of which a prominent feature is its poorly defined functional properties: neurons in the area can support either reaching or saccades or both movement planning processes. For instance, reach-related neurons can be found not only in both V6A and MIP, but also within aspects of cIPS and LIP, areas proximally positioned on the lateral bank of the IPS (Calton et al., 2002; Chang and Snyder, 2010) more prominently implicated in coding action-relevant 3D visual object features (Sakata et al., 1998) and the targets for saccades (Andersen et al., 1985)), respectively. A few human studies to date have attempted to describe the homologous functional locations of these regions, and the pIPS and midIPS decoding results provided here also offer good approximations: L-pIPS, L-midIPS and R-midIPS all predict the direction of both eye and arm movements, and interestingly, this spatial-selectivity is shared across the hand and eye. Although future investigations will require different initial positions of the eye, hand and target locations in order to discriminate whether these shared eye and hand coordinate frames are with spatial reference to the eye, limb, head/body or world (e.g. Snyder et al., 1998; Batista et al., 1999; Buneo et al., 2002; Pertzov et al., 2010), the critical finding here is that we are able to decode and localize for the first time in humans these effector-independent shared reference frames -- known to be present in monkeys for quite some time (Andersen et al., 1985; Batista et al., 1999), but difficult to confirm in humans with conventional fMRI analyses.

4.4.2 Premotor Cortex Decoding

If PPC can be generally described to encode reach targets with reference to the eye (Chang and Snyder, 2010), then by comparison, the reference frames that characterize reach-planning in premotor areas appear more closely linked to the final motor output. A recently emerging view of premotor cortex, and of PMd in particular, suggests that neurons prepare reaching movements by using a relative position code: single neurons can encode the target relative to the eye (eye-centred), the target relative to the hand (hand-centred), the eye relative to the hand, as well as combinations of two or all three (Pesaran et al., 2006). Furthermore, it has more recently been shown that the same relative position code can also characterize the planning of saccades in PMd (Pesaran et al., 2010), presumably facilitating eye-hand coordination given that both saccade and reach movements can be planned in a common spatial reference frame (Pesaran et al., 2010). These recent findings in monkeys seem particularly relevant for interpreting the L-PMd decoding results here: not only are both reach and saccade movement plans spatially tuned to target locations, but we now show in humans that this spatial tuning is *shared* across effectors. Given that the relative positions of the hand, eyes and targets are constant across trials during reach and saccade planning, a compelling suggestion is that the shared L-PMd activity might indicate reliance on this shared relative position code (Pesaran et al., 2006, 2010). Of course, the current study cannot differentiate this possibility from the other, although not mutually exclusive explanation, that the shared patterns across effectors reflect the use of a common eye-, head- or world-centred (absolute) reference frame (e.g. Snyder et al., 1998; Pertzov et al., 2010). Interestingly, in L-PMv, we were able to predict upcoming reach and saccade movement directions but, as an important departure from our PMd results, this spatial-selectivity was not shared across effectors. This result resonates with previous neurophysiological findings suggesting that PMv encodes target locations for saccades and reaches in different coordinates, with eye movements possibly in head- or eye-centred reference frames (Fujii et al., 1998) and hand movements possibly in arm/limb-centred reference frames (Graziano et al., 1994).

4.4.3 Implications:

These findings offer new insights into how saccades and reaches are planned in the human brain. We show that it is possible to decode planned reaches and saccades, the spatial locations they intend on moving towards, and in several cases, we can characterize the coordinate frame and non-spatial, motor-specific nature of the movement plan. Importantly, whereas motor cortex signals are increasingly used to decode motor intentions (Andersen et al., 2010), here we highlight several candidate parieto-frontal brain areas where high-level, intention-related activity can be harnessed to operate and control neural prosthetics in movement-impaired patient populations.

4.5 References

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annual Review of Neuroscience 25:189-220.

Andersen RA, Cui H (2009) Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63:568-583.

Andersen RA, Essick GK, Siegel RM (1985) Encoding of spatial location by posterior parietal neurons. Science 230:456-458.

Andersen RA, Hwang EJ, Mulliken GH (2010) Cognitive neural prosthetics. Annu Rev Psychol 61:169-190, C161-163.

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 23:4689-4699.

Barash S, Bracewell RM, Fogassi L, Gnadt JW, Andersen RA (1991) Saccade-related activity in the lateral intraparietal area. II. Spatial properties. J Neurophysiol 66:1109-1124.

Batista AP, Buneo CA, Snyder LH, Andersen RA (1999) Reach plans in eye-centered coordinates. Science 285:257-260.

Ben Hamed S, Duhamel JR, Bremmer F, Graf W (2001) Representation of the visual field in the lateral intraparietal area of macaque monkeys: a quantitative receptive field analysis. Exp Brain Res 140:127-144.

Bernier PM, Grafton ST (2010) Human posterior parietal cortex flexibly determines reference frames for reaching based on sensory context. Neuron 68:776-788.

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 97:188-199.

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 101:3053-3062.

Buneo CA, Jarvis MR, Batista AP, Andersen RA (2002) Direct visuomotor transformations for reaching. Nature 416:632-636.

Calton JL, Dickinson AR, Snyder LH (2002) Non-spatial, motor-specific activation in posterior parietal cortex. Nat Neurosci 5:580-588.

Caminiti R, Johnson PB, Urbano A (1990a) Making arm movements within different parts of space: dynamic aspects in the primate motor cortex. J Neurosci 10:2039-2058.

Caminiti R, Johnson PB, Burnod Y, Galli C, Ferraina S (1990b) Shift of preferred directions of premotor cortical cells with arm movements performed across the workspace. Exp Brain Res 83:228-232.

Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam TD, Quinlan DJ, Goodale MA, Culham JC (2010) Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. J Neurosci 30:10306-10323.

Chang SW, Snyder LH (2010) Idiosyncratic and systematic aspects of spatial representations in the macaque parietal cortex. Proc Natl Acad Sci U S A 107:7951-7956.

Chang SW, Dickinson AR, Snyder LH (2008) Limb-specific representation for reaching in the posterior parietal cortex. J Neurosci 28:6128-6140.

Chang SW, Papadimitriou C, Snyder LH (2009) Using a compound gain field to compute a reach plan. Neuron 64:744-755.

Connolly JD, Andersen RA, Goodale MA (2003) FMRI evidence for a 'parietal reach region' in the human brain. Exp Brain Res 153:140-145.

Connolly JD, Goodale MA, Cant JS, Munoz DP (2007) Effector-specific fields for motor preparation in the human frontal cortex. Neuroimage 34:1209-1219.

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 84:1645-1655.

Culham JC, Valyear KF (2006) Human parietal cortex in action. Curr Opin Neurobiol 16:205-212.

Culham JC, Cavina-Pratesi C, Singhal A (2006) The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia 44:2668-2684.

Culham JC, Danckert SL, DeSouza JF, Gati JS, Menon RS, Goodale MA (2003) Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Exp Brain Res 153:180-189.

Curtis CE, D'Esposito M (2006) Selection and maintenance of saccade goals in the human frontal eye fields. J Neurophysiol 95:3923-3927.

Curtis CE, Rao VY, D'Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 24:3944-3952.

Desmond JE, Glover GH (2002) Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. J Neurosci Methods 118:115-128.

Dickinson AR, Calton JL, Snyder LH (2003) Nonspatial saccade-specific activation in area LIP of monkey parietal cortex. J Neurophysiol 90:2460-2464.

Dinstein I, Gardner JL, Jazayeri M, Heeger DJ (2008) Executed and observed movements have different distributed representations in human aIPS. J Neurosci 28:11231-11239.

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 29:1928-1936.

Filimon F (2010) Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. Neuroscientist 16:388-407.

Filimon F, Nelson JD, Huang RS, Sereno MI (2009) Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. J Neurosci 29:2961-2971.

Formisano E, De Martino F, Bonte M, Goebel R (2008) "Who" is saying "what"? Brain-based decoding of human voice and speech. Science 322:970-973.

Fujii N, Mushiake H, Tanji J (1998) An oculomotor representation area within the ventral premotor cortex. Proc Natl Acad Sci U S A 95:12034-12037.

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 9:410-413.

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 29:4381-4391.

Graziano MS, Yap GS, Gross CG (1994) Coding of visual space by premotor neurons. Science 266:1054-1057.

Hagler DJ, Jr., Riecke L, Sereno MI (2007) Parietal and superior frontal visuospatial maps activated by pointing and saccades. Neuroimage 35:1562-1577.

Harrison SA, Tong F (2009) Decoding reveals the contents of visual working memory in early visual areas. Nature 458:632-635.

Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293:2425-2430.

Hoshi E, Tanji J (2000) Integration of target and body-part information in the premotor cortex when planning action. Nature 408:466-470.

Kagan I, Iyer A, Lindner A, Andersen RA (2010) Space representation for eye movements is more contralateral in monkeys than in humans. Proc Natl Acad Sci U S A 107:7933-7938.

Kamitani Y, Tong F (2005) Decoding the visual and subjective contents of the human brain. Nat Neurosci 8:679-685.

Kastner S, DeSimone K, Konen CS, Szczepanski SM, Weiner KS, Schneider KA (2007) Topographic maps in human frontal cortex revealed in memory-guided saccade and spatial working-memory tasks. J Neurophysiol 97:3494-3507.

Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI (2009) Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 12:535-540.

Levy I, Schluppeck D, Heeger DJ, Glimcher PW (2007) Specificity of human cortical areas for reaches and saccades. J Neurosci 27:4687-4696.

Lindner A, Iyer A, Kagan I, Andersen RA (2010) Human posterior parietal cortex plans where to reach and what to avoid. J Neurosci 30:11715-11725.

Medendorp WP, Goltz HC, Vilis T (2006) Directional selectivity of BOLD activity in human posterior parietal cortex for memory-guided double-step saccades. J Neurophysiol 95:1645-1655.

Medendorp WP, Goltz HC, Vilis T, Crawford JD (2003) Gaze-centered updating of visual space in human parietal cortex. J Neurosci 23:6209-6214.

Mur M, Bandettini PA, Kriegeskorte N (2009) Revealing representational content with pattern-information fMRI--an introductory guide. Soc Cogn Affect Neurosci 4:101-109.

Pertzov Y, Avidan G, Zohary E (2010) Multiple reference frames for saccadic planning in the human parietal cortex. J Neurosci 31:1059-1068.

Pesaran B, Nelson MJ, Andersen RA (2006) Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. Neuron 51:125-134.

Pesaran B, Nelson MJ, Andersen RA (2010) A relative position code for saccades in dorsal premotor cortex. J Neurosci 30:6527-6537.

Picard N, Strick PL (2001) Imaging the premotor areas. Curr Opin Neurobiol 11:663-672.

Prado J, Clavagnier S, Otzenberger H, Scheiber C, Kennedy H, Perenin MT (2005) Two cortical systems for reaching in central and peripheral vision. Neuron 48:849-858.

Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y, Tsutsui K (1998) Neural coding of 3D features of objects for hand action in the parietal cortex of the monkey. Philos Trans R Soc Lond B Biol Sci 353:1363-1373.

Schluppeck D, Glimcher P, Heeger DJ (2005) Topographic organization for delayed saccades in human posterior parietal cortex. J Neurophysiol 94:1372-1384.

Schluppeck D, Curtis CE, Glimcher PW, Heeger DJ (2006) Sustained activity in topographic areas of human posterior parietal cortex during memory-guided saccades. J Neurosci 26:5098-5108.

Sereno MI, Pitzalis S, Martinez A (2001) Mapping of contralateral space in retinotopic coordinates by a parietal cortical area in humans. Science 294:1350-1354.

Smith FW, Muckli L (2010) Non-stimulated early visual areas carry information about surrounding context. Proc Natl Acad Sci U S A.

Snyder LH, Batista AP, Andersen RA (1997) Coding of intention in the posterior parietal cortex. Nature 386:167-123.

Snyder LH, Grieve KL, Brotchie P, Andersen RA (1998) Separate body- and world-referenced representations of visual space in parietal cortex. Nature 394:887-891.

Szczepanski SM, Konen CS, Kastner S (2010) Mechanisms of spatial attention control in frontal and parietal cortex. J Neurosci 30:148-160.

Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H (2007) Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J Neurosci 27:10259-10269.

Van Der Werf J, Jensen O, Fries P, Medendorp WP (2010) Neuronal synchronization in human posterior parietal cortex during reach planning. J Neurosci 30:1402-1412.

Van Pelt S, Toni I, Diedrichsen J, Medendorp WP (2010) Repetition suppression dissociates spatial frames of reference in human saccade generation. J Neurophysiol 104:1239-1248.

Vesia M, Prime SL, Yan X, Sergio LE, Crawford JD (2010) Specificity of human parietal saccade and reach regions during transcranial magnetic stimulation. J Neurosci 30:13053-13065.

Chapter 5

5. How the brain uses tools: Separate and shared movement plans for the hand and tool in human parieto-frontal cortex

5.1 Introduction

The capacity of the primate brain to abstractly represent high-level action goals separately from the underlying body mechanics necessary to achieve those goals provides an enduring characteristic of highly intelligent behavior. In fact, nearly the entire repertoire of human object-directed behavior is consciously planned at this more abstract level. For instance, when we plan to grab for a cup of coffee (the goal), we are not cognitively concerned with the precise muscle activations or degrees of limb rotation required. Moreover, we can flexibly achieve this same goal completely independent of the specific effector used for movement (e.g., left or right hand, etc.). Understandably, this seemingly simple behavioral capacity must rely on a rather complex goal-directed motor hierarchy, with increasing levels of abstraction. Much is currently known about the lowest levels of this motor hierarchy, including the neural coding of intrinsic and extrinsic muscular dynamics (e.g., velocity, force, direction; (Evarts and Thach, 1969; Todorov, 2000; Kalaska, 2009) as well as the slightly higher-level kinematics of reaching and grasping (Jeannerod et al., 1995; Andersen and Buneo, 2002; Culham et al., 2006; Filimon, 2010). Remarkably little is known, however, about the underlying neural mechanisms that support the highest levels of this motor hierarchy, where abstract movement goals are represented independent of the underlying kinematics required (i.e., goal-centred representations). Perhaps the most exceptional and recognizable example of this high-level goal-centred behavior is when primates use tools.

Tool-use, whether using a stone, stick, rake, or pliers, ultimately functions as an extension of the body (Van Lawick-Goodall, 1970) and requires the transfer of a proximal movement goal (e.g., initiated by the hand) to a more distal goal (desired action with the tool) (Johnson and Grafton, 2003; Johnson-Frey, 2004). Neural evidence suggests that with training, a tool can actually become incorporated into the body schema of the actor. For instance, the receptive fields of bimodal visuo-tactile parietal neurons, originally linked to the hand and arm in monkeys, can expand to encompass the length of a rake following training (Iriki et al., 1996; Hihara et al., 2006). Similarly, parietal patients exhibiting near-space neglect and extinction, following use of a tool, can show a spatial extension of these deficits (Berti and Frassinetti, 2000; Ladavas, 2002;

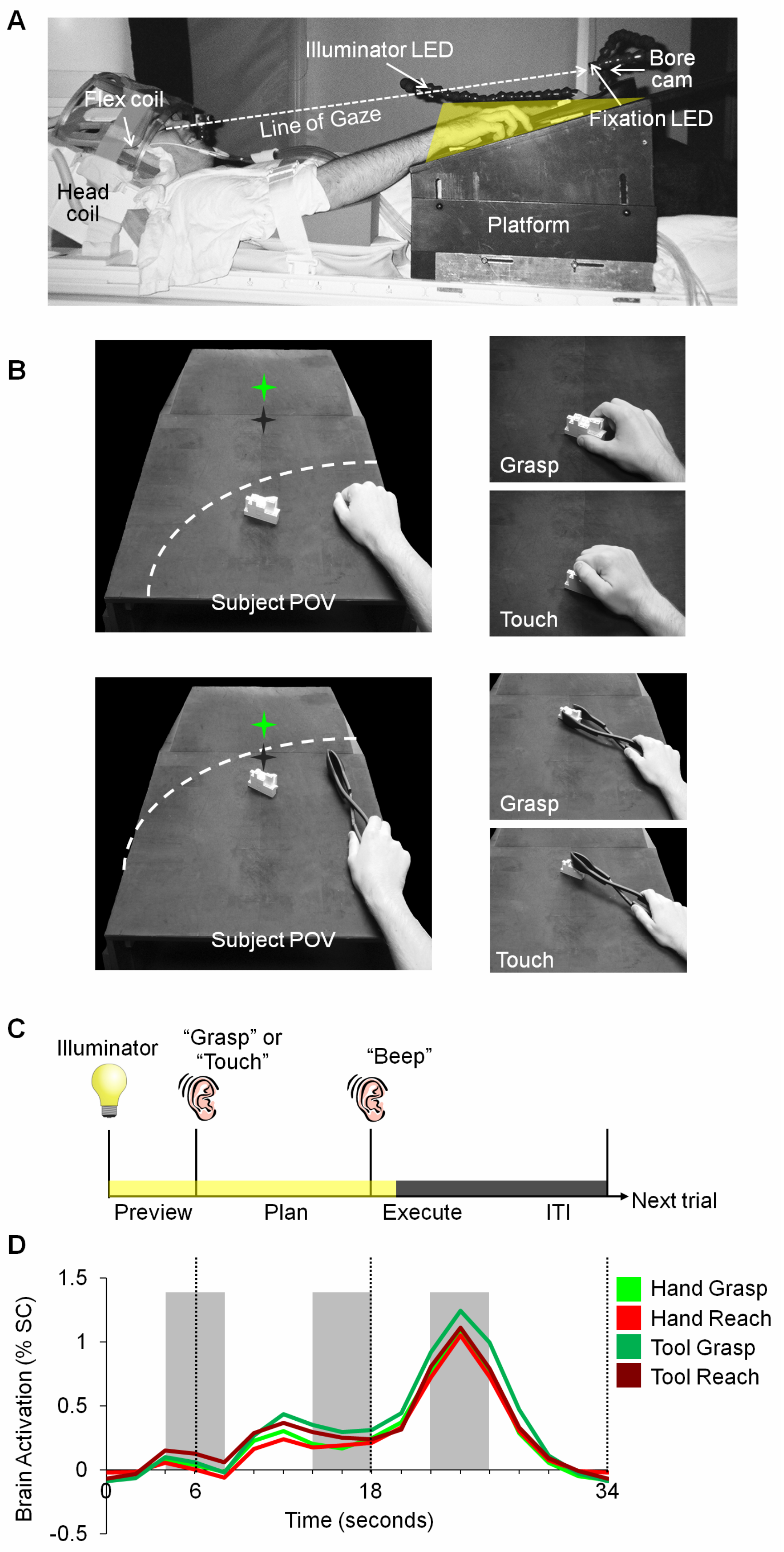
Maravita and Iriki, 2004). This evidence, along with other findings (Umilta et al., 2008; Cardinali et al., 2009; Jacobs et al., 2010), has led to the suggestion that the brain areas recruited for hand actions also come to support tool-use. While this is in part to be expected, given that it is proximal movements of the hand that guide distal movements of the tool, how exactly are planned tool movements coded by the brain regions involved in hand actions?

Previous theories and neural evidence argue that tool-related movements need to be coded at two distinct hierarchical levels. The first is an effector-specific representation, where the hand and tool are separately coded and thus sensitive to the kinematic properties of each effector (Hamilton and Grafton, 2006; Umilta et al., 2008; Jacobs et al., 2010). The second level is a more abstract effector-independent representation, where the tool is then coded as an extension of the hand/limb and the overall goal of the motor act is represented separately from the precise hand/tool kinematics required to achieve the goal (Umilta et al., 2008). This of course begs the question, where in the human brain are these hierarchical representations functionally nested? And furthermore, how can we possibly differentiate effector-specific and effector–independent movement plans from human brain activity?

An important clue to addressing both of these questions comes from neural recordings of grasping neurons in ventral premotor and motor cortex of the macaque monkey trained to use pliers (Umilta et al., 2008). The authors found that in both these areas, many neurons that originally encoded hand grasping subsequently encoded tool grasping, even when the tool required kinematics opposite to those required when grasping with the hand alone (that is, when the tool, “reverse pliers”, required a closing of the hand to open the tool aperture and vice versa). Such results suggest effector-independent representations. At the same time, however, almost half of motor cortex neurons maintained their selectivity for the hand’s kinematics only (i.e., effector-specific representation). While this previous study could only differentiate these two hierarchical representations during movement execution, it is necessary that both effector- and goal-related information also be incorporated into the initial movement plan (Snyder et al., 1997; Andersen and Buneo, 2002; Andersen and Cui, 2009). As such, a major focus of the current study was to determine whether prior to initial movement, both effector-specific and effector-independent motor intentions could be decoded from human preparatory brain activity. Furthermore, based on the sites of neural recording, this previous monkey study did not specify any role for parietal cortex in contributing to or maintaining these distinct representations. Indeed, an overwhelming amount of neural evidence in monkeys strongly implicates parietal cortex in the coding of actions at various levels of abstraction (Andersen and Buneo, 2002; Musallam et al., 2004; Fogassi et al., 2005; Mulliken et al., 2008; Andersen et al., 2010; Bonini et al., 2011) and it remains to be determined -- specifically in the case of target-directed tool-use -- where certain human parietal regions are situated within the motor hierarchy. We addressed these outstanding issues by manipulating the type of action performed on a target object (grasping vs. reaching) and the type of effector used (hand vs. tool). Using fMRI multi-voxel pattern analysis (MVPA) and a delayed-movement paradigm, we directly probed where in parieto-frontal cortex movement plans (grasping vs. reaching) for the hand and tool were distinct (effector-specific) versus where plans were independent of the acting effector (effector-independent).

5.2 Material and Methods

In an event-related design with a delay interval, subjects used either their hand or a tool to execute a precision grasp or reach towards (without hand/tool preshaping) a single centrally-located three-dimensional target object (Figure 5.1B). The tool was a set of reverse tongs; when the hand closed on the grips, the ends of the tongs would open and vice versa. Use of the hand and tool were alternated across experimental runs. The position of the single target object was changed between hand and tool experimental runs in order for the grasps and reaches to be performed at a comfortable distance for each effector (see Figure 5.1B). On each trial, subjects were first cued to the hand/tool action to be carried out then, following a delay period, they performed the instructed action. Importantly, the delay timing of the paradigm allowed us to divide the trial into discrete time epochs and isolate the sustained plan-related neural activity that evolves prior to movement from the transient visual (Preview phase) and movement execution responses (Execute phase; see Figure 5.1 C,D). We implemented multi-voxel pattern analysis (MVPA) in specific parieto-frontal regions-of-interest (ROIs) during movement planning (Plan Phase) and questioned: 1) whether we could predict upcoming grasps vs. reaches with either the hand or tool (or both); and 2) where in the parieto-frontal network predictive patterns of activity where shared across effectors (despite vast differences in the movement kinematics required to control actions with the hand and tool and independent from low-level visual and somatosensory differences related to the object position and its presence/absence in the hand, respectively).


A
Illuminator LED
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Fixation LED
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Touch
C
Illuminator
“Grasp” or
“Touch”
“Beep”
Preview
Plan
Execute
ITI
Next trial
D
1.5
1
0.5
0
-0.5
Brain Activation (% SC)
0
6
18
34
Time (seconds)
Hand Grasp
Hand Reach
Tool Grasp
Tool Reach

Figure 5.1: Experimental methods and evoked neural activity. A) Subject setup shown from side view. **B)** (Left) Experimental apparatus and target object shown from the subject's point of view for experimental runs where either the hand (top) or reverse tool (bottom) were used. The location of the target object (white block) was switched between run types but did not change its position from trial-to-trial within a given run. Dashed line represents the arc of reachability for each run type with respect to the participant. The hand is shown at its starting location. Green star with dark shadow represents the fixation LED and its location in depth. (Right) Hand and tool movements performed by the subject. **C)** Timing of each event-related trial. Trials began with the 3D object being illuminated while the subject maintained fixation (Preview phase; 6 s). Subjects were then instructed via headphones to perform one of two movements: Grasp the object ("Grasp") or Touch the object ("Touch"), initiating the Plan phase portion of the trial. Following a fixed delay interval (12 s), subjects were cued ('beep') to perform the instructed movement (initiating the Execute phase). Two seconds after the Go cue, vision of the workspace was extinguished and participants waited for the following trial to begin (14 s, ITI). **D)** Averaged fMRI activity from left dorsal premotor (PMd) cortex, time-locked to trial length. MVPA was performed using single trials in two ways: 1) based on the windowed average (2 imaging volumes; 4 s) of the % signal change BOLD activation corresponding to the three different time-epochs denoted by each of the gray shaded bars (each corresponding to activity elicited from the three distinct trial phases Preview, Plan and Execute; the time points corresponding to the Plan phase were of critical interest, and provide the focus of this paper) and 2) based on the % signal change BOLD activation evoked for each single time point in the trial (time-resolved decoding), allowing us to pinpoint when exactly predictive movement information was available.

We first localized a common set of action-related ROIs within each individual subject for use in MVPA. These *a priori* ROIs were defined by performing a whole-brain voxel-wise search by contrasting the activity evoked during movement generation (i.e., movement planning (Plan phase) and execution (Execute phase)) versus the activity evoked during simple visual object presentation (Preview phase; when subjects had vision of the target object yet were unaware of which action (grasp vs. reach) to perform). This [Plan & Execute > Preview] contrast revealed activity throughout a well-documented parieto-frontal network of areas (Figure 5.2, see Table 5.1 for coordinates). Within this network, we focused MVPA on ten commonly described human and monkey anatomical ROIs in the left hemisphere (contralateral to the arm used), each previously implicated in either hand-related and/or tool-related visual-motor processing. We localized superior parieto-occipital cortex (SPOC), posterior intraparietal sulcus (pIPS), middle IPS, motor cortex, and dorsal premotor (PMd) cortex – a group of well-known parietal and frontal areas generally implicated in hand-related movement planning processes (Culham et al., 2006; Andersen and Cui, 2009; Cisek and Kalaska, 2010; Filimon, 2010) -- and then defined the posterior anterior IPS (post. aIPS), aIPS, supramarginal gyrus (SMG), and ventral premotor (PMv) cortex -- a group of parietal and frontal areas generally implicated in hand preshaping and tool-related motor planning (Johnson-Frey, 2004; Umilta et al., 2008; Jacobs et al., 2010). One additional area, left somatosensory (SS cortex), was selected as a sensory control region, not expected to accurately decode movements until stimulation of the hand's mechanoreceptors at movement onset (i.e., at the Execute phase).

5.2.1 Subjects

Thirteen right-handed volunteers participated in this study (7 females; mean age: 25.7 years, age range: 20-33 years).

5.2.2 Setup and Apparatus

Participants performed single movements with their hand or a novel tool (reverse tongs) towards a single centrally-located object when required. The target object was made of LEGO pieces (length: 7 cm x depth: 3 cm x height: 3 cm) and was secured to the workspace at one of two locations along the arc of reachability for the effector (hand or tool) to be used during the experimental run. The exact placement of the object on the platform was adjusted for the hand and tool to match each participant's arm/tool length such that all required movements were comfortable. To mark the object location for hand runs, the participant used the right hand to place the target object at a central position on the platform, in line with the point of fixation and oriented to maximize the comfort for grasping. To mark the object location for tool runs, the participant placed the target object within reach of the tool at a further central position, in line with the point of fixation and with the same orientation as that used for the hand. Once specified and prior to the initiation of each run type (Hand or Tool), the target object was secured to the platform at one of these two corresponding locations (see Figure 5.1B).

For each trial, subjects were required to perform one of two actions upon the target object, following a delay period: 1) reach towards and precision grasp (G) the object ("Grasp" auditory command) without lifting and 2) reach towards (R) and manually touch the top of the object ("Touch" auditory command). For experimental runs with the hand, grasping required the subjects to precision grasp the object with their thumb and index finger (Hand-G) without lifting whereas the reaching action required the subject to simply transport their hand to the object without hand pre-shaping (Hand-R). For experimental runs with the tool, grasping required the subjects to precision grasp the object with the set of reverse tongs without lifting, which involved squeezing the grips on the tongs (in order to initially open the distal ends of the tongs) and then subsequently releasing pressure on the grips (in order to close the distal ends of the tongs onto the object; Tool-G). Reaching actions with the reverse tongs simply required the subject to transport the tool to the object without any further manipulation, and touch the top of the target (Tool-R). Participants were instructed to keep the timing of hand movement for grasping and reaching trials as similar as possible. Other than the execution of these hand and tool actions, the hand throughout the other phases of the trial (Preview phase, Plan phase and ITI) was instructed to remain still and in a relaxed 'home' position on the right surface of the platform. For each participant the home/starting position was marked with a small elevation of black tape and subjects were required to always return to this same position following execution of the instructed movement. For experimental runs with the hand, the required home position of the hand was a relaxed fist, and for experimental runs with the tool, the required home position was to have the thumb and index finger gently placed on the grips of the tool (without applying pressure). Importantly, within each experimental run, the target object never changed its centrally-located position, thus eliminating retinal differences across workspace of each effector but quite importantly, maintaining large retinal differences (i.e., position of the object with respect to fixation) and somatosensory differences (presence or absence of the tool in hand) between hand and tool runs. Although including hand and tool trials within the same run would have enabled direct statistical comparisons between them, this would have necessitated insertion and removal of the trial during experimental testing, possibly leading to additional movement artifacts. In between runs, the tool was given to and removed from the subject by the experimenter.

We chose a reverse set of tongs as the tool to be used in this experiment because it provided an opposite mapping between the proximal movements of the hand and the distal movements of the tool (i.e., when the hand closed on the reverse tongs, the end of the tongs opened, and vice versa). This incongruence was imperative to the aims of the study (i.e., decoding higher-level movement goals independent of the muscle activations required) as it allowed the object-directed intentions of both effectors (hand and tool) to be held constant (i.e., grasping and reaching) while at the same time, uncoupling the lower-level hand kinematics required to operate each effector. In contrast, when a normal set of tongs are used, the distal ends of the tool exactly mirror the movements made by the hand (i.e., when the hand closes on the tongs, the distal ends of the tongs also close), and if we had used this type of tool instead, it would have made it difficult to rule out that any tool-related decoding was independent of the hand movements required to operate the tool.

5.2.3 Experiment Design and Timing

We used a slow event-related planning paradigm with 34 s trials, each consisting of three distinct phases: ‘Preview’, ‘Plan’ and ‘Execute’ (see Figure 5.1C). Each trial began with the Preview phase, where the subject’s workspace was illuminated revealing the centrally-located target object. After 6 s of the Preview phase, subjects were given an auditory cue (0.5 s), either “Grasp” or “Touch”, informing them of the upcoming movement required; this cue marked the onset of the Plan phase. After 12 s of the Plan phase, a 0.5 s auditory beep cued participants to immediately execute the planned action (for a duration of approximately 2 s), initiating the Execute phase of the trial. Two seconds following the beginning of this Go cue, the illuminator was turned off, providing the cue for subjects (during both hand and tool runs) to return the hand to its peripheral starting position. After the illuminator was extinguished, subjects then waited in the dark while maintaining fixation for 14 s, allowing the BOLD response to return to baseline prior to the next trial (ITI phase). The two trial types, with ten repetitions per condition (20 trials total) were randomized within a run and balanced across all runs that used the same effector (Hand or Tool) so that each trial type was preceded and followed equally often by every other trial type across the entire experiment. There were four trial types in total: Hand-Grasp (Hand-G), Hand-Reach (Hand-R), Tool-Grasp (Tool-G) and Tool-Reach (Tool-R).

5.2.4 MRI acquisition and preprocessing

Error trials – trials where the participant fumbled with the object, performed the incorrect instruction, or contaminated the plan phase data by slightly moving their limb or eyes or by performing the action before the ‘Go’ cue -- were identified off-line from the videos recorded during the session; only two trials from one subject and one trial from another subject (three trials total) contained such movement errors.

5.2.5 Regions of Interest (ROI)

To specify our pre-defined ROIs and select voxels to submit for MVPA from each subject we searched for brain areas involved in movement generation and contrasted activity for movement planning and execution (collapsed over hand, tool, grasp and touch) vs. the simple visual response to object presentation prior to instruction: (Plan & Execute > Preview) -- ([Plan(Hand-G + Hand-R + Tool-G + Tool-R) + Execute(Hand-G + Hand-R + Tool-G+ Tool-R) > 2*Preview(Hand-G + Hand-R + Tool-G + Tool-R)]. The resulting statistical map of all positively active voxels in each subject ($t(7) = 3$, $p<0.003$, each subject’s activation map was cluster threshold corrected (corrected, $p<0.05$) so that only voxels passing a minimum cluster size were selected; average minimum cluster size across subjects was 111.5 mm^3; for details see *ROI selection*, below) was then used to define ten different ROIs within the left-hemisphere: 1) Superior parieto-occipital cortex (SPOC), 2) posterior intraparietal sulcus (pIPS), 3) middle IPS (mid-IPS), 4) posterior anterior IPS (post. aIPS), 5) anterior IPS (aIPS), 6) Supramarginal gyrus (SMG), 7) Somatosensory (SS) cortex, 8) Motor cortex, 9) Premotor dorsal (PMd) cortex, and 10) Premotor ventral (PMv) cortex. All of these ROIs were selected based on their well-documented involvement in movement planning/generation and we selected the SS cortex ROI as a sensory control region (i.e., known to respond to transient stimuli (i.e., sensory events), but not expected to participate in sustained movement planning/intention-related processes). The voxels included in each ROI were easily defined based on all significant activity within a 3375 mm^3 cube centered on a pre-defined anatomical landmarks that corresponded with functional activity (see *ROI selection* below for criteria).

5.2.6 ROI selection

Left Superior parieto-occipital cortex (SPOC)

- defined by selecting voxels located medially either within or directly anterior to the Parieto-occipital sulcus (POS)(Gallivan et al., 2009)

Left posterior IPS (pIPS)

- defined by selecting activity at the caudal end of the IPS (Sakata et al., 1998; Beurze et al., 2009).

Left middle IPS (midIPS)

- defined by selecting voxels half-way up the length of the IPS, centred on the medial bank (Calton et al., 2002; Chang et al., 2009), near a characteristic ‘knob’ landmark observed consistently within each subject.

Left region located posterior to L-aIPS (L-post. aIPS)

- defined by selecting activity just posterior to the junction of the IPS and Post-central sulcus (PCS), on the medial bank of the IPS (Culham, 2004).

Left aIPS (L-aIPS)

- defined by selecting voxels located directly at the junction of the IPS and PCS (Culham et al., 2003).

Left inferior parietal lobule (L-IPL)

- defined by selecting activity along the supramarginal gyrus, lateral to the anterior segment of the IPS (Lewis, 2006).

Left somatosensory cortex (L-SS cortex)

- defined by selecting voxels medial and anterior to the aIPS, encompassing the Post-central gyrus and PCS.

Left Motor cortex

- defined by selecting voxels around the left ‘hand knob’ landmark in the Central sulcus (CS)(Yousry et al., 1997).

Left Premotor dorsal (PMd)

- defined by selecting voxels at the junction of the Precentral sulcus (PreCS) and Superior frontal sulcus (SFS)(Picard and Strick, 2001).

Left Premotor ventral (PMv)

- defined by selecting activity inferior and posterior to the junction of the Inferior frontal sulcus (IFS) and PreCS (Tomassini et al., 2007).

See Table 5.1 for details about ROI coordinates and sizes, and Figure 5.2 for representative anatomical locations on one subject's brain.

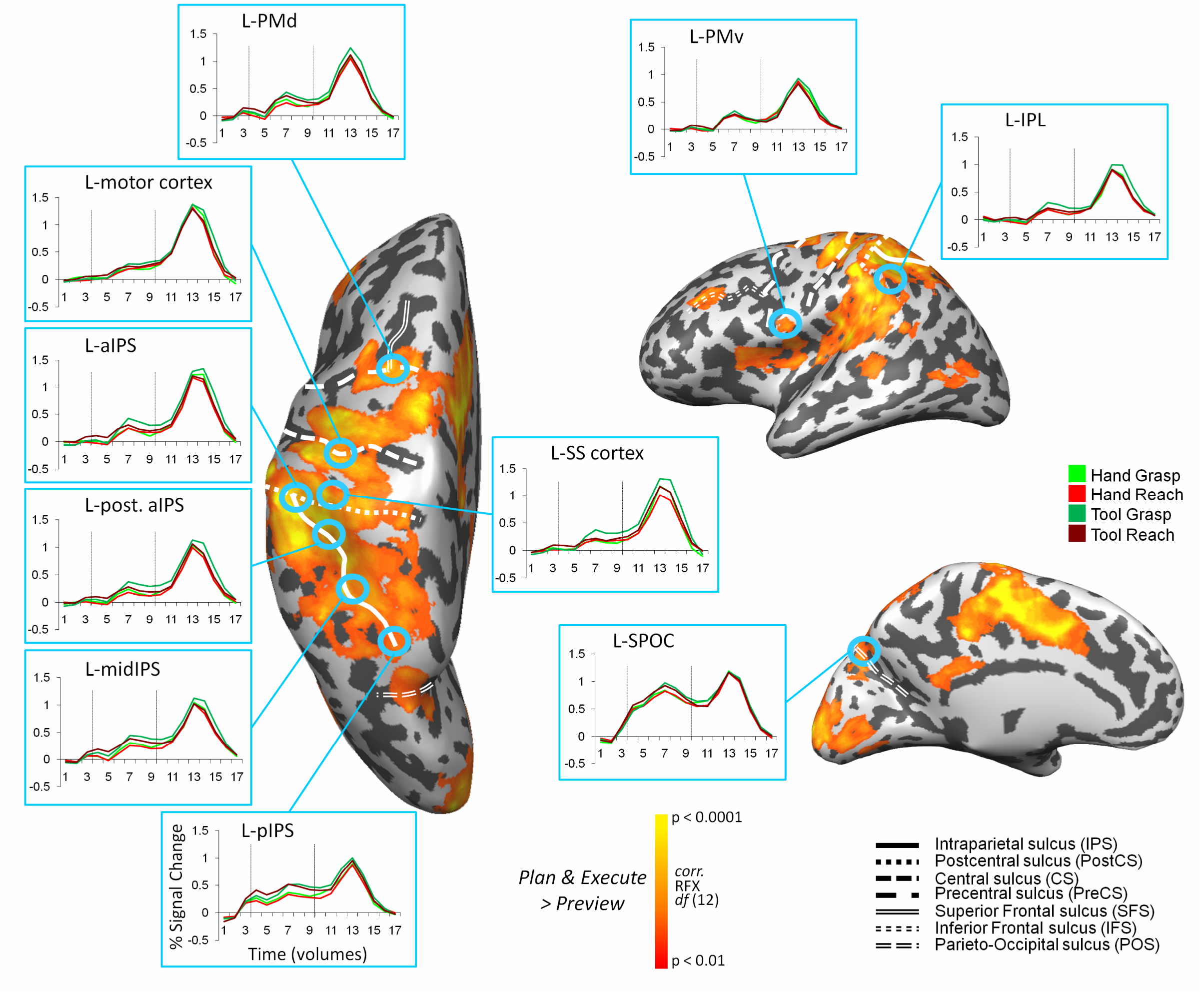

Figure 5.2: Parieto-frontal brain areas selected for movement plan decoding. Cortical areas that exhibited larger responses during movement generation than the preceding visual phase [(Plan + Execute) > 2*(Preview)] are shown in orange/yellow activation. Results calculated across all subjects (Random Effects GLM) are displayed on one representative subject's inflated hemispheres. The general locations of the selected ROIs are outlined in circles (actual ROIs were anatomically defined separately in each subject). Linked to each ROI is the corresponding percent (%) signal change BOLD activity averaged across voxels within each ROI and across subjects and plotted according to trial length (note that time is in imaging volumes, each volume = 2 s). Vertical dashed lines correspond to the onset of the Plan and Execute phases of each trial (from left to right). Sulcal landmarks are denoted by white lines (stylized according to the corresponding legend). ROI acronyms are spelled out in main text.

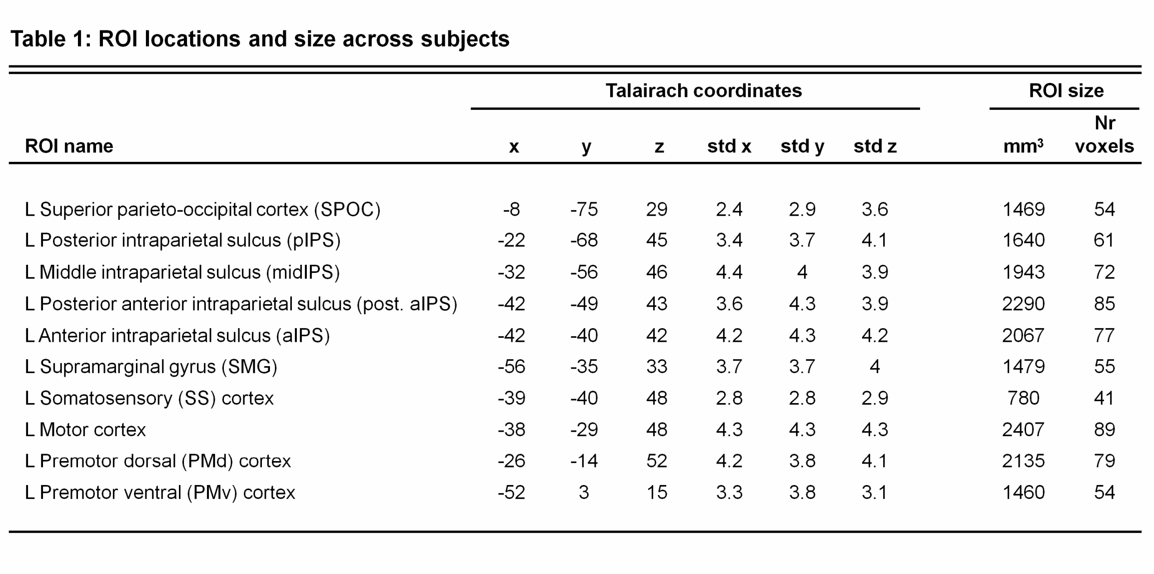

Table 1: ROI locations and size across subjects

	Talairach coordinates						ROI size	
ROI name	**x**	**y**	**z**	**std x**	**std y**	**std z**	**mm³**	**Nr voxels**
L Superior parieto-occipital cortex (SPOC)	-8	-75	29	2.4	2.9	3.6	1469	54
L Posterior intraparietal sulcus (pIPS)	-22	-68	45	3.4	3.7	4.1	1640	61
L Middle intraparietal sulcus (midIPS)	-32	-56	46	4.4	4	3.9	1943	72
L Posterior anterior intraparietal sulcus (post. aIPS)	-42	-49	43	3.6	4.3	3.9	2290	85
L Anterior intraparietal sulcus (aIPS)	-42	-40	42	4.2	4.3	4.2	2067	77
L Supramarginal gyrus (SMG)	-56	-35	33	3.7	3.7	4	1479	55
L Somatosensory (SS) cortex	-39	-40	48	2.8	2.8	2.9	780	41
L Motor cortex	-38	-29	48	4.3	4.3	4.3	2407	89
L Premotor dorsal (PMd) cortex	-26	-14	52	4.2	3.8	4.1	2135	79
L Premotor ventral (PMv) cortex	-52	3	15	3.3	3.8	3.1	1460	54

Table 5.1: ROIs with corresponding Talairach coordinates (mean x, y, and z centre of mass and std). Mean ROI sizes across subjects from AC-PC data (in mm^3 and functional voxels).

5.2.7 Multi-voxel pattern analysis (MVPA)

5.2.7.1 Voxel Pattern Preparation

To prepare the data for spatial pattern classification, the percent signal change was computed from the time-course at a time point(s) of interest with respect to the time-course at a common baseline, for all voxels in the ROI. This was done using two approaches. The first approach involved extracting the percent signal change values for a windowed-average at three different epochs over the course of the trial (Preview, Plan and Execute phases of the trial; called epoch-related decoding). The second approach involved extracting percent signal change values for each time point in the trial (time-resolved decoding). For the details of both approaches, see Materials and Methods in Chapter 2.

5.2.7.2 Single-Trial classification

For each subject and for each of the ten action-related ROIs, separate binary support vector machine (SVM) classifiers were estimated for MVPA (i.e., for each of the pair-wise comparisons examined, Hand-G vs. Hand-R and Tool-G vs. Tool-R, and for each of the *Preview*, *Plan* and *Execute* phases in the epoch-related decoding approach and for each individual time point in the time-resolved decoding approach). We used a “leave-four-trials-out” cross-validation to test the accuracy of the binary SVM classifiers (i.e., four trials from each of the conditions being compared (i.e. eight trials total) were reserved for testing the classifier and the remaining trials were used for classifier training (i.e. 26 or 36 or 46 remaining trials per condition, depending on whether the subject participated in six, eight, or ten experimental runs, respectively). Single trials in the independent test data set (eight total), prior to classifier testing, were averaged according to condition (i.e. creating an averaged spatial patterns of activity for each condition), improving voxel pattern signal-to-noise in the test data set (see also Smith and Muckli, 2010). Because a full cross validation is not entirely reasonable with a “leave-four-trials-out” design due to the ~10^4 possible iterations, to provide a highly reliable estimate of decoding accuracies we performed a minimum of 1008 train-and-test iterations for each pair-wise discrimination. In the subject with six runs, each trial was used exactly 134 times to train the classifier, in subjects with eight runs, 1010 iterations were used and each trial was used exactly 100 times to train the classifier, and in the subject with ten runs, 1032 iterations were used and each trial was used exactly 82 times to train the classifier.

5.3 Results

5.3.1 Movement plan decoding

During movement planning (where we examined the final 4 s prior to movement initiation) we found a full range of decoding profiles across the network of specified parieto-frontal regions. For instance, activity patterns in SPOC accurately predicted upcoming grasping vs. reaching actions with the hand only whereas in contrast, voxel patterns in SMG successfully predicted the same actions with the tool only (Figure 5.3, red and blue bars and traces). Interestingly, in nearly all the remaining regions, we were able to successfully predict the movement goal (grasping vs. reaching) for both the hand and tool effector (see Figures 5.4 and 5.5, red and blue bars and traces). For instance, in parietal cortex, preparatory activity in pIPS, midIPS, post. aIPS and aIPS could be used to accurately discriminate which object-directed hand or tool movement was to be performed moments later. Consistent with these parietal findings, in frontal cortex, predictive activity for hand and tool actions were also found in motor cortex, PMd, and PMv. Importantly, consistent with expectations, our sensory control region, SS cortex, failed to decode planned movements and only discriminated the different actions once executed (see Figure 5.3, red and blue bars and traces). This latter finding substantiates the notion that predictive movement information is constrained within action-related parieto-frontal brain areas. As an additional type I error control of our decoding accuracies, we ran the same classification analyses in two non-brain ROIs where decoding should never be expected: the right ventricle and outside the brain. Indeed, MVPA in these two areas showed no accurate decoding for any trial phase (see Figure 5.8).

Critically, our results show that decoding revealed during the Plan phase can only be attributed to the *intention* to perform a grasp vs. reach movement. This is reflected in the absence of decoding observed during the preceding Preview phase, when movement-planning information was unavailable to the participant (see Figure 5.6). Furthermore, we find that accurate decoding predominantly reflects the voxel spatial activity patterns for the two different movement plans, and not the overall response amplitudes within each ROI. When we averaged trial responses across all voxels in each ROI (i.e., the same approach done in conventional univariate fMRI analyses), we primarily only found significant differences between hand and tool conditions (data not shown); this of course, is to be expected given the range of visual and somatosensory differences between trials with the two effectors (e.g., Hand-G vs. Tool-G, Hand-R vs. Tool-R).

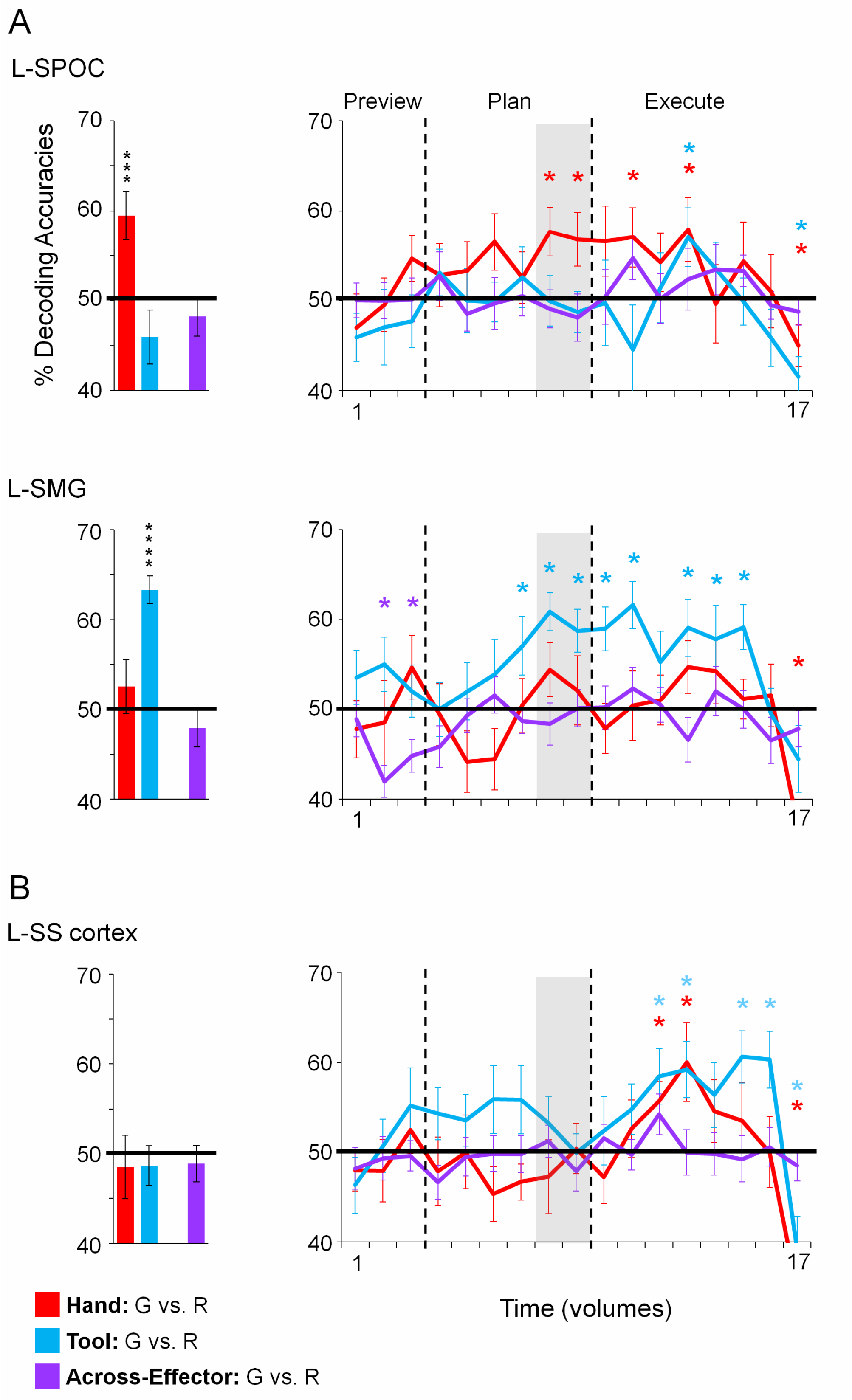
A
L-SPOC
% Decoding Accuracies
70
60
50
40
Preview
Plan
Execute
1
17
L-SMG
B
L-SS cortex
Time (volumes)
🟥 **Hand:** G vs. R
🟦 **Tool:** G vs. R
🟪 **Across-Effector:** G vs. R

Figure 5.3: Movement plans for the hand or tool decoded from parietal cortex. Decoding accuracies are shown for the Plan phase only (epoch-related decoding; left column) or for each time point in the trial (time-resolved decoding; right column). The epoch-related decoding plots are based on a windowed average of the spatial activity patterns denoted by the gray shaded bars in the time-resolved decoding plots. In the time-resolved decoding plots, vertical dashed lines correspond to the onset of the Plan and Execute phases of the trial (from left to right). For decoding accuracies discriminating grasp vs. reach actions with the Hand (in red) and Tool (in blue) classifier training was done on single trials and tested on the average activity patterns of the single trials for each condition in the independent test data set. Across-effector decoding accuracies (in purple) were computed using the same approach but from training classifiers on Hand-G vs. Hand-R trials and testing on Tool-G vs. Tool-R trials and then averaging these values with the opposite train-and-test ordering, within each subject. **A)** Decoding accuracies for SPOC (which predicts hand actions only) and SMG (which predicts tool actions only). **B)** Decoding accuracies for our sensory control region, SS-cortex.. Note also that decoding accuracies are color-coded according to pair-wise discriminations and not trial types. Error bars represent standard error of the mean (SEM) across subjects. Solid black lines are chance accuracy level (50%). Asterisks assess statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=p<0.05; **=p<0.01; ***=p<0.005; ****=p<0.001). Note that to minimize the number of asterisks presented for time-resolved decoding (plots in right column), statistical significance is shown only at p<0.05 (note also that the color of each asterisk denotes which pair-wise discrimination is significant at each point in time).

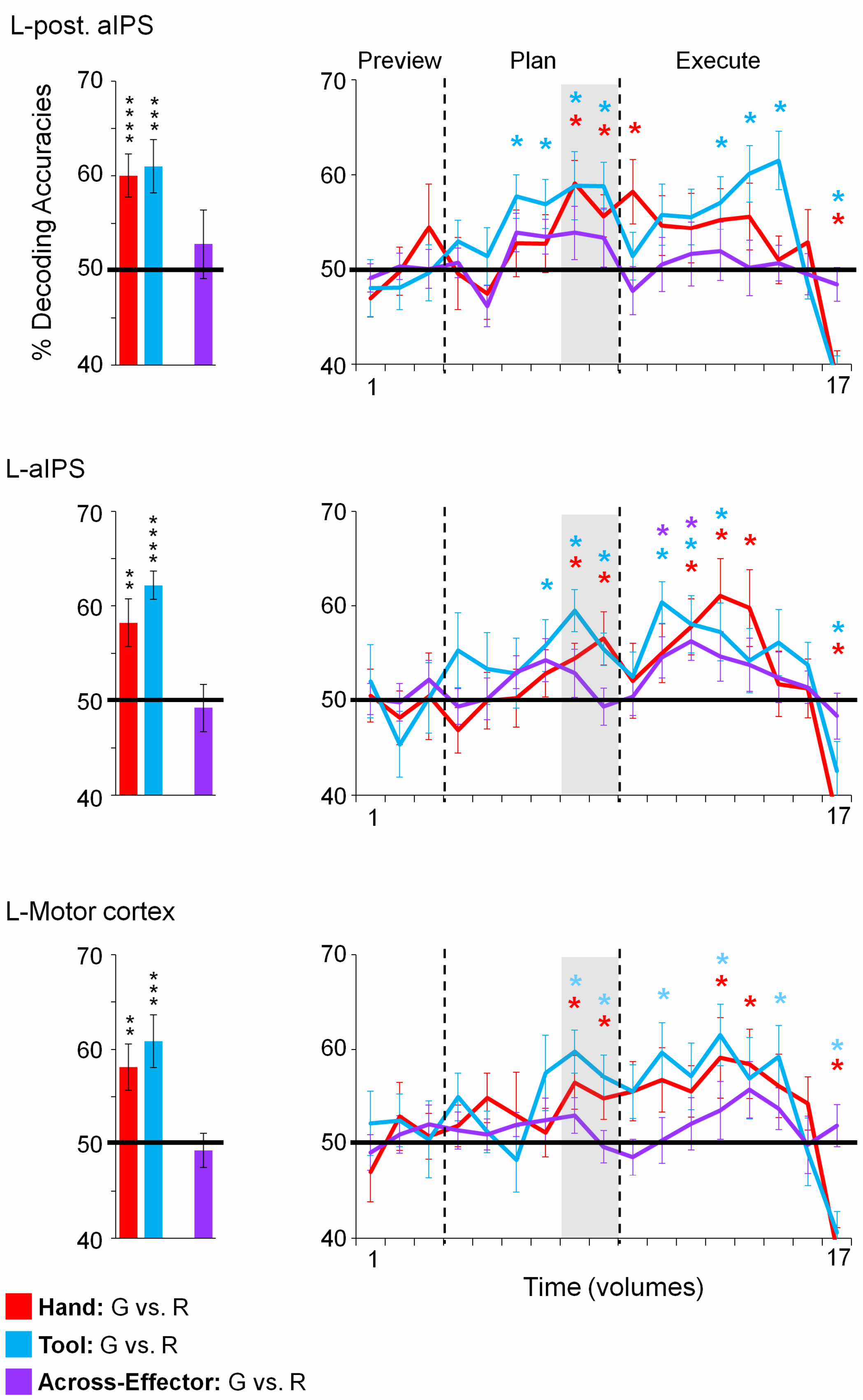
L-post. aIPS
L-aIPS
L-Motor cortex
% Decoding Accuracies
70
60
50
40
Preview
Plan
Execute
1
17
Time (volumes)
****
***
**
*
Hand: G vs. R
Tool: G vs. R
Across-Effector: G vs. R

Figure 5.4: Separate movement plans for the hand and tool decoded in anterior parietal and motor cortex. Decoding accuracies are shown for the Plan phase only (epoch-related decoding; left column) or for each time point in the trial (time-resolved decoding; right column). All accuracies are computed the same as in Figure 5.3. Error bars represent standard error of the mean (SEM) across subjects. Solid black lines are chance accuracy level (50%). Asterisks assess statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=p<0.05; **=p<0.01; ***=p<0.005; ****=p<0.001). Note that to minimize the number of asterisks presented for time-resolved decoding (plots in right column), statistical significance is shown only at p<0.05 (note also that the color of each asterisk denotes which pair-wise discrimination is significant at each point in time).

5.3.2 Separate and shared representations

Expanding on the within-effector MVPA -- and perhaps more important to the overall interpretation of our findings -- we next examined in which areas the end movement goal (grasping vs. reaching) was being represented independent of the effector to be used (i.e., separate from lower-level kinematics required to perform the movement). To do this, we trained pattern classifiers using Hand-G and Hand-R trials and tested the accuracy of the classifiers using Tool-G and Tool-R trials (the opposite train-and-test process -- train set: Tool-G vs. Tool-R, test set: Hand-G vs. Hand-R -- was also performed, and then we averaged the accuracies from both approaches)(for this technique, see also Dinstein et al., 2008; Formisano et al., 2008; Harrison and Tong, 2009). We found accurate across-effector classification in four regions during planning: two areas in posterior parietal cortex, pIPS and midIPS, and two areas in premotor cortex, PMd and PMv (see purple bars and traces in Figure 5.5). Recall that because the object location was changed (with respect to fixation) between hand and tool experimental runs, successful across-effector classification of upcoming grasping vs. reaching movements cannot be simply attributed to low-level visual similarities between hand and tool trials, and therefore must instead reflect the encoding of a more abstract movement goal (grasping vs. reaching). Note also that accurate cross-trial-type classification does not simply result from any area where the classifiers are able to successfully discriminate grasp vs. reach movements for both the hand and tool. In fact, although several other areas can accurately differentiate the two upcoming movements for both effectors (e.g., post. aIPS, aIPS, and motor cortex), the predictive spatial patterns of activity in these areas were not sufficiently similar between the hand and tool trials (see Figure 5.4). This latter finding is in itself notable, as it alternatively suggests that these particular areas contain separate movement plans for the hand and tool, providing a neural instantiation of the effector-specificity required for complex tool-use.

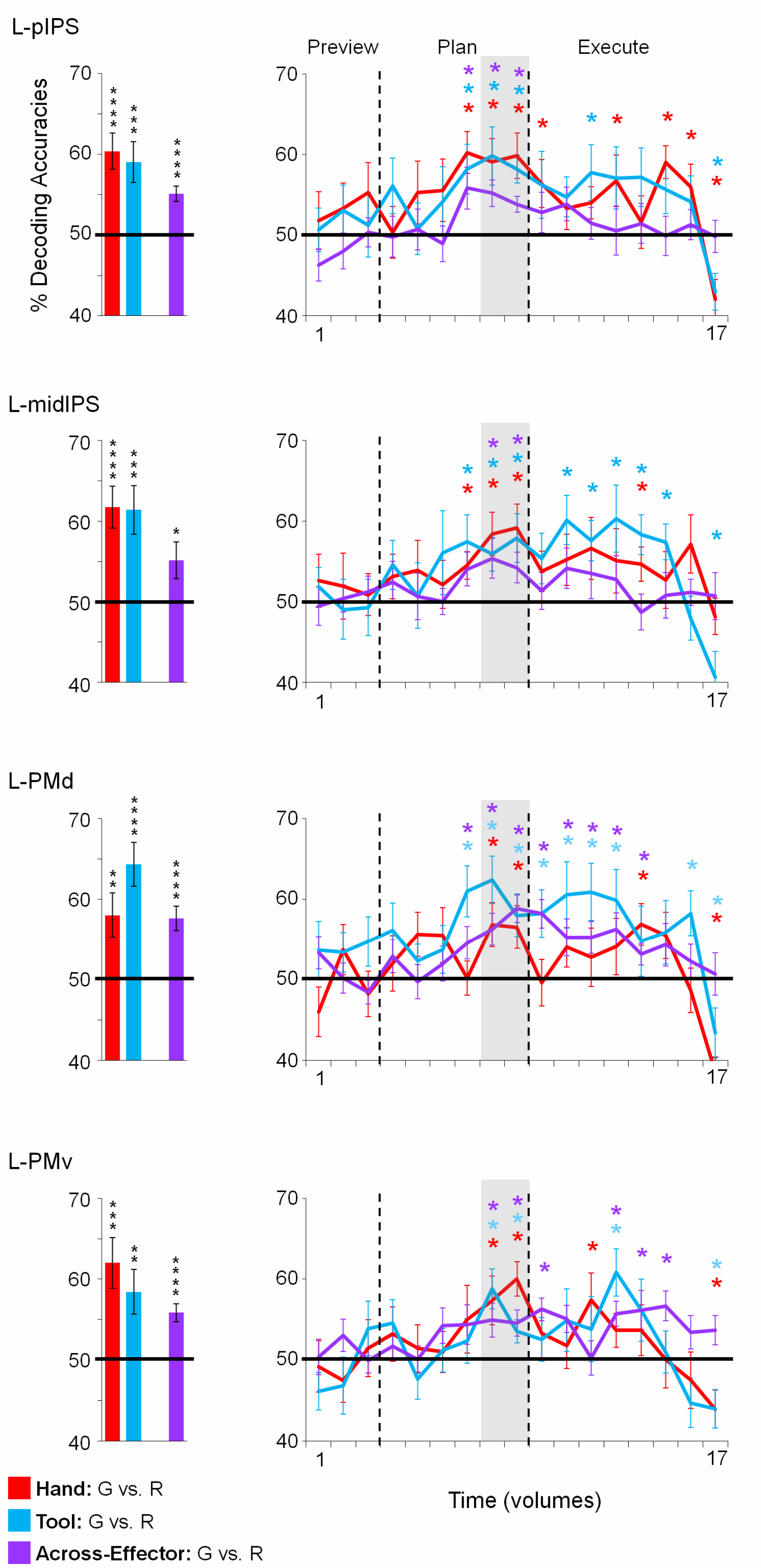
L-pIPS
L-midIPS
L-PMd
L-PMv
% Decoding Accuracies
Preview
Plan
Execute
70
60
50
40
1
17
Time (volumes)
🟥 **Hand:** G vs. R
🟦 **Tool:** G vs. R
🟪 **Across-Effector:** G vs. R

Figure 5.5: Shared movement plans for the hand and tool decoded in posterior parietal and premotor cortex. Decoding accuracies are shown for the Plan phase only (epoch-related decoding; left column) or for each time point in the trial (time-resolved decoding; right column). All accuracies are computed the same as in Figure 5.3. Significant decoding for the cross-trial-type (across-effector) approach shows that the movement goal (Grasp vs. Reach) is being represented independent of the effector (Hand vs. Tool) to be used in the action. Error bars represent standard error of the mean (SEM) across subjects. Solid black lines are chance accuracy level (50%). Asterisks assess statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=$p<0.05$; **=$p<0.01$; ***=$p<0.005$; ****=$p<0.001$). Note that to minimize the number of asterisks presented for time-resolved decoding (plots in right column), statistical significance is shown only at $p<0.05$ (note also that the color of each asterisk denotes which pair-wise discrimination is significant at each point in time).

5.3.3 Time-Resolved Decoding

In order to verify the observations made with the epoch-related decoding approach and more precisely pinpoint when exactly predictive movement information was available in the spatial voxel patterns, we additionally ran a decoding analysis for each point in time over the course of the trial (see Soon et al., 2008 for a similar approach; Harrison and Tong, 2009). This analysis (both within-effector and across-effector decoding) was performed in exactly the same way as that done in the epoch-related analysis presented above, except that here, the train-and-test iterations were performed using the spatial voxel activity patterns found at each individual imaging volume (TR). The results of this analysis are found in Figures 5.3-5.5 (right columns) and they largely confirm two general observations from the plan epoch-related analysis: 1) predictive movement information, if it is ever made available during planning, generally arises in the two time points prior to initiation of the movement (although note that in a few areas, pIPS, midIPS, post. aIPS, aIPS, SMG and PMd, this information is also available prior to these two time points) and 2) in further support that this predictive motor information is directly related to the *intention* to make a movement, accurate classification never arises prior to the subject being aware of which action to execute (i.e., prior to initiation of the Plan phase).

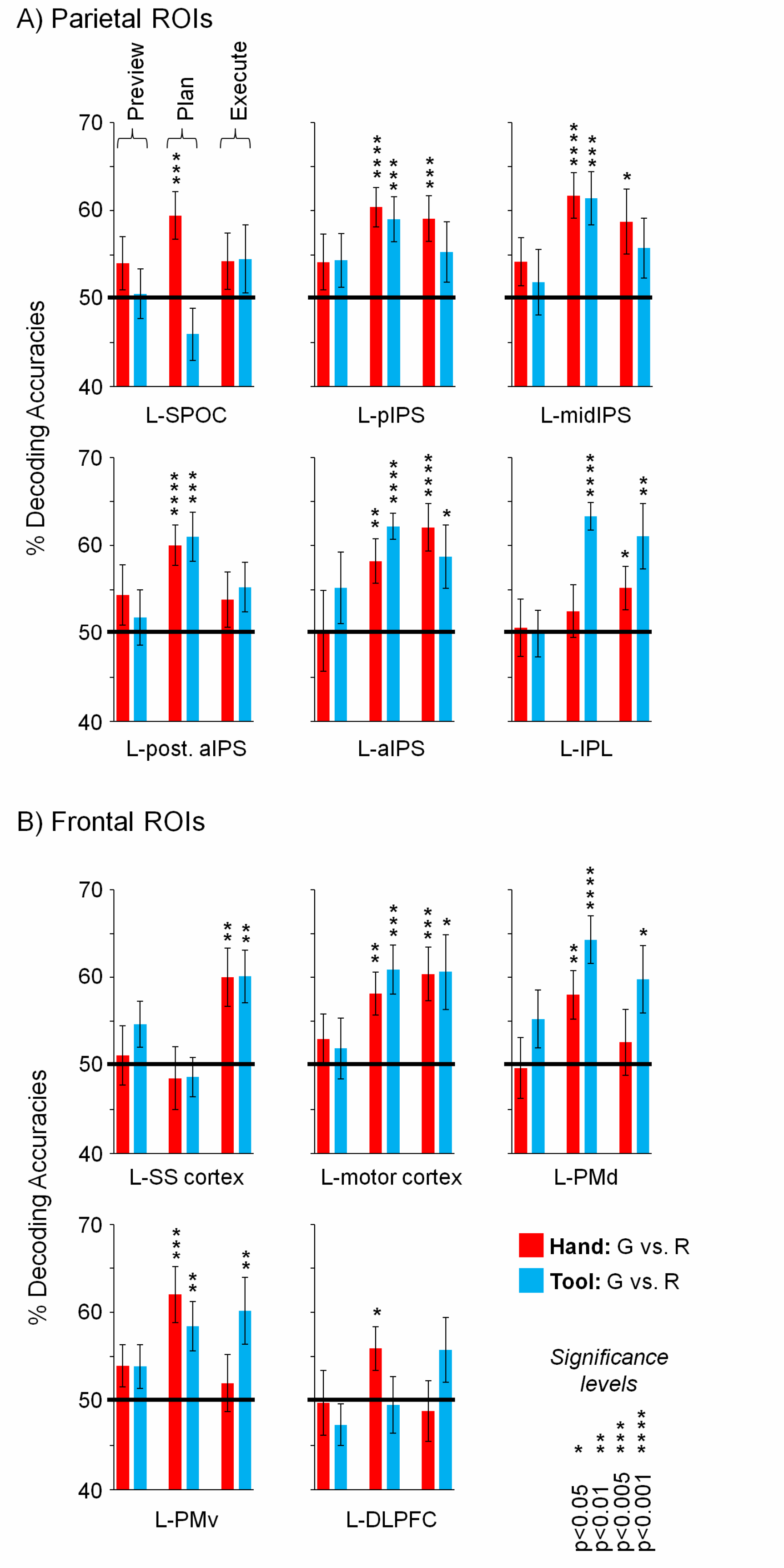
A) Parietal ROIs
Preview
Plan
Execute
% Decoding Accuracies
70
60
50
40
L-SPOC
L-pIPS
L-midIPS
L-post. aIPS
L-aIPS
L-IPL
B) Frontal ROIs
L-SS cortex
L-motor cortex
L-PMd
L-PMv
L-DLPFC
Hand: G vs. R
Tool: G vs. R
Significance levels
* p<0.05
** p<0.01
*** p<0.005
**** p<0.001

Figure 5.6: Movement plans for the hand and tool decoded from parieto-frontal cortex. Decoding accuracies are shown for each trial time phase (Preview, Plan, and Execute) for the parietal ROIs **(A)** and frontal ROIs **(B)**. Classifier training was done on single trials and tested on the average activity patterns of the single trials for each condition in the independent test data set. Note that only standard pattern classification is shown here; cross-trial-type decoding between the hand and tool for each trial time phase is shown in Figure 5.7. Error bars represent standard error of the mean (SEM) across subjects. Solid black lines are chance accuracy level (50%). Asterisks assess statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=p<0.05; **=p<0.01; ***=p<0.005; ****=p<0.001).

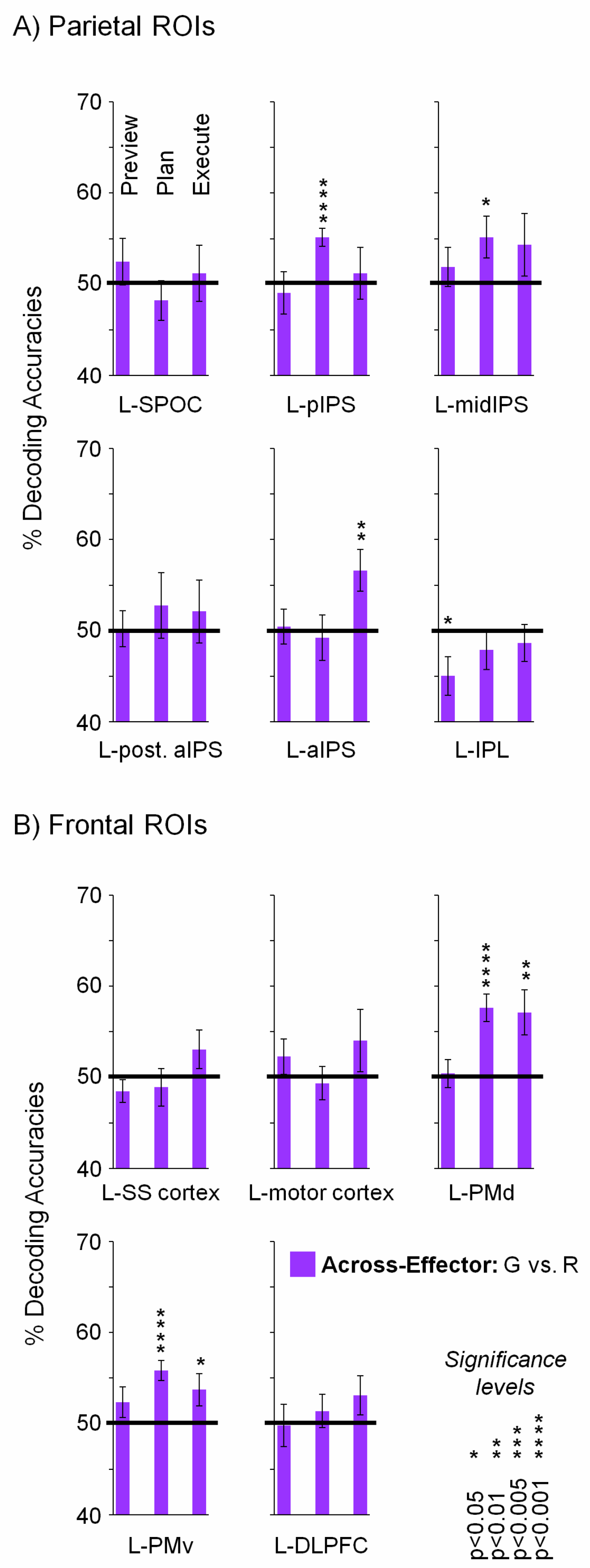
A) Parietal ROIs
B) Frontal ROIs
% Decoding Accuracies
70
60
50
40
Preview
Plan
Execute
L-SPOC
L-pIPS
L-midIPS
L-post. aIPS
L-aIPS
L-IPL
L-SS cortex
L-motor cortex
L-PMd
L-PMv
L-DLPFC
Across-Effector: G vs. R
Significance levels
* p<0.05
** p<0.01
*** p<0.005
**** p<0.001

Figure 5.7: Cross-trial-type decoding reveals shared movement plans for the hand and tool in parieto-frontal cortex. Cross-trial-type decoding accuracies are shown for each trial time phase (Preview, Plan, and Execute) for the parietal ROIs **(A)** and frontal ROIs **(B).** Across-effector decoding accuracies were computed from training classifiers on Hand-G vs. Hand-R trials and testing on Tool-G vs. Tool-R trials and then averaging these values with the opposite train-and-test ordering, within each subject. ROIs with significant decoding for this cross-trial-type approach show where the movement goal (Grasp vs. Reach) is being encoded independent of the effector (Hand vs. Tool) used. Error bars represent standard error of the mean (SEM) across subjects. Solid black lines are chance accuracy level (50%). Asterisks assess statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=p<0.05; **=p<0.01; ***=p<0.005; ****=p<0.001).

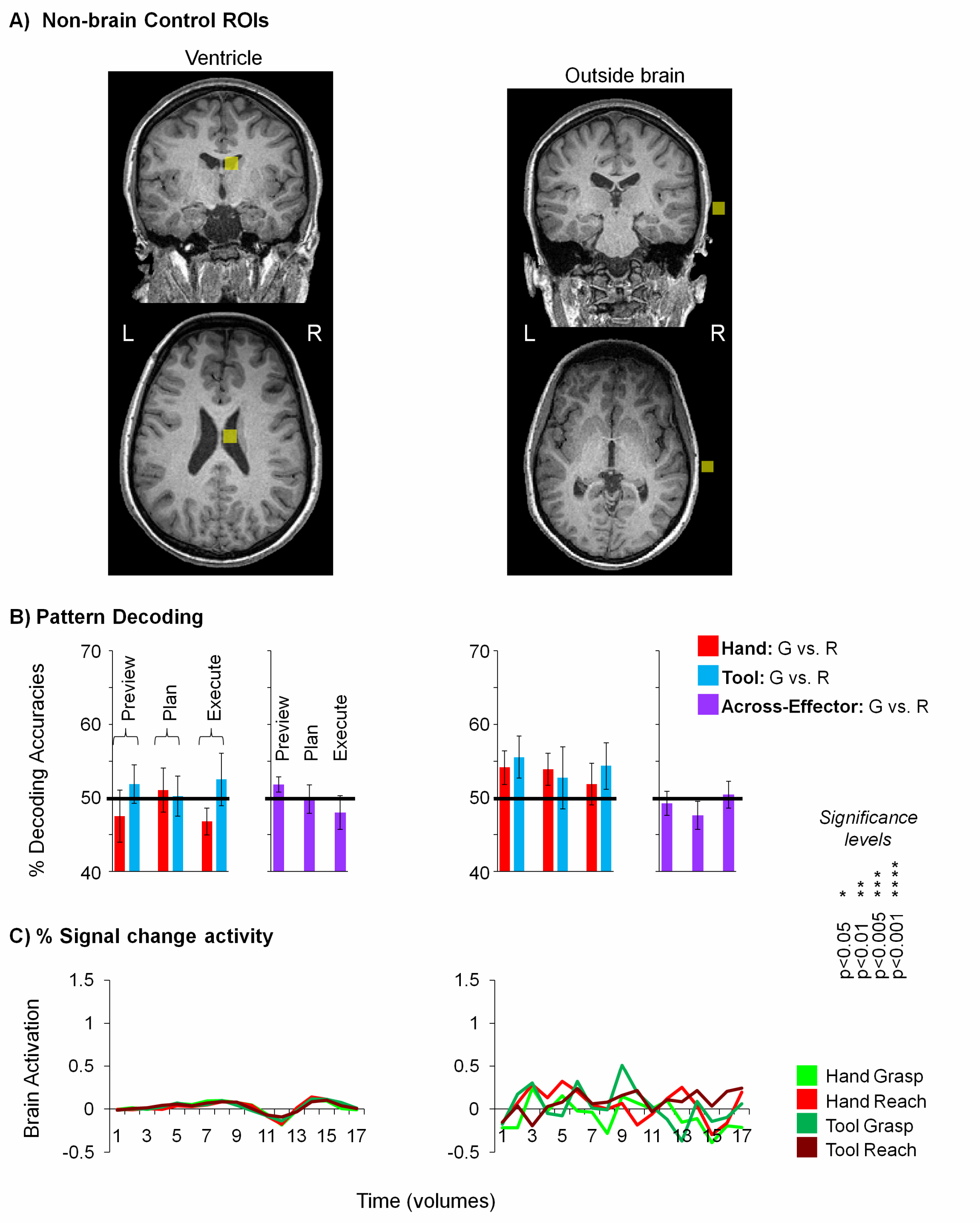

Figure 5.8: Classifier decoding accuracies in non-brain control regions. A) Non-brain control ROIs defined in each subject (denoted in light yellow; example subject shown). **B)** Classifier accuracies for the right ventricle (left) and outside the brain ROI (right) for each of the trial epochs. Error bars represent SEM across subjects. Solid lines show chance classification accuracy (50%). Note that no significant differences were found with 2-tailed t-tests across subjects with respect to 50% chance. **C)** Percent signal change activity from each selected region, averaged across voxels and subjects.

5.4 Discussion

Behavioral, neuropsychological and neurophysiological evidence demonstrates that a central and governing feature of movement planning, and indeed of higher-level cognition in general, is the linking together of overarching action goals with the precise underlying kinematics required by the body to achieve those goals (Alexander and Crutcher, 1990; Crutcher and Alexander, 1990; Kakei et al., 1999; Haaland et al., 2000; Kakei et al., 2001; Andersen and Buneo, 2002; Gentilucci et al., 2004; Fogassi et al., 2005; Grafton and Hamilton, 2007; Umilta et al., 2008; Ingram et al., 2010; Bonini et al., 2011). Yet exactly how the human brain is able to do this, specifically in the everyday case of tool-use, has been challenging to answer. Here we manipulated the type of object-directed action that was planned (grasping vs. reaching) as well as the effector (hand vs. tool) used to implement the action. Notably, the tool-effector required the planning of hand movements that were mirror opposite to the kinematics required when the hand was used alone. We employed the fine-grained sensitivity afforded by fMRI MVPA in order to directly examine where in human parietal and premotor cortex the target-directed movement goals were represented in an effector-specific or effector-independent manner. We found that these two distinct representations simultaneously coexisted in the moments prior to movement initiation, each localized to specific regions within parietal and premotor cortex. In doing so, these findings identify a highly distributed, goal-directed hierarchical neural architecture from human intention-related brain activity that spans the parieto-frontal network.

We showed that both anterior parietal (post. aIPS, aIPS) and motor cortex contained effector-specific representations, where the preparatory voxel activity patterns predicted upcoming grasping vs. reaching movements for both the hand and tool but were not shared across effectors. In contrast, in posterior parietal (pIPS, midIPS) and premotor cortex (PMd, PMv) areas, we found that in addition to decoding upcoming hand and tool movements, these activity patterns were similar enough to allow cross-trial-type classification. In addition, we also found one brain area, SPOC, that only discriminated planned hand actions and one other area, SMG, which only discriminated planned tool actions. These findings argue for a neuroanatomical segregation of visual-motor processing across parieto-frontal brain areas, with some regions, prior to movement onset, coding for effector-specific kinematic properties and low-level dissimilarities between hand and tool movements (different object position etc.) with other areas instead coding for the higher-level object-directed goals of the movement (grasping vs. reaching). Importantly, we show that these distinct hierarchical representations can be revealed in the intention-related signals of specific brain areas and not just in execution-related neural responses, as shown previously (Umilta et al., 2008). Moreover, we show that these two representations are temporally maintained in parallel, residing in different regions of the parieto-frontal network. In addition, while nearly all evidence to date has emphasized the transformative influence of tool-use on neural firing patterns and body schema representations (Iriki et al., 1996; Berti and Frassinetti, 2000; Maravita and Iriki, 2004; Umilta et al., 2008; Cardinali et al., 2009), importantly, we also report sensorimotor brain areas whose preparatory patterns of activity remain linked to either the hand (i.e., SPOC) or tool (i.e., SMG).

Nearly all previous studies using human fMRI to examine the neural substrates of tool-use and goal-centred coding have used tasks that require the observation of others' actions, in which most commonly, 2D static images or movies of action-related behaviors are passively viewed by participants (Lewis, 2006; Grafton and Hamilton, 2007; Valyear and Culham, 2010). Alternatively, in many fMRI studies of tool use, participants make "pantomimed" hand actions (such as pretending to use a hammer with the hand held out of view) within the scanner. In fact, of the scores of fMRI studies of tool use (Lewis, 2006), only a very small number have employed actual use of real tools (e.g., Imazu et al., 2007; Gallivan et al., 2009), as we did here. This fact is not coincidental; given the inherent difficulties of performing real object-directed movements in the scanner (e.g., arm and head movement-related artifacts in the fMRI signal), examining the neural mechanisms that support self-generated goal-directed behavior is challenging (Culham, 2004). Admittedly, the aims of some of these previous investigations has not necessarily been to reveal how the brain plans and executes different movement goals, but instead to reveal how, as an observer of a motor act, the brain understands the goals and intentions of the actor. This particular line of research has been primarily motivated by the discovery of so-called 'mirror-neurons' in the monkey (Rizzolatti et al., 2001), located in inferior parietal and ventral premotor cortex (Fogassi et al., 2005; Umilta et al., 2008), and which discharge both when the monkey performs a motor act and when the monkey views the same act performed by another individual (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 2001). Nevertheless, past human neuroimaging research has largely left open the intruiguing question of how tools are incorporated into neural representations of goal-directed actions. As a departure from these previous observation-related studies in humans, the focus of the present paper was to understand first how self-generated goal-related movements are encoded. Understanding neural events at this level (i.e., the individual who is actually planning the action goal) is likely to provide a pragmatic starting point for interpreting findings from observation-related fMRI studies.

5.4.1 Representation of the motor hierarchy across parieto-frontal cortex

Hierarchical theories of motor control have existed for more than a century (Jackson, 1889; Sherrington, 1906; Hebb, 1949; Bernstein, 1996; Grafton and Hamilton, 2007), distinguishing between the various levels of abstraction required for action planning -- for example, at the level of muscles, joints, motor kinematics (e.g., reaching), and movement goals. The present findings offer substantive insights into precisely where different parieto-frontal regions might be situated within such a hierarchy. For instance, at some mid-level along this hierarchy we likely have regions like SPOC and SMG, which as shown here, respectively decode planned actions with the hand and tool only. SPOC is most often implicated in reaching actions (Prado et al., 2005; Cavina-Pratesi et al., 2010) although recent evidence suggests that it may also serve some grasp-related function (Fattori et al., 2009; Fattori et al., 2010). The fact that we are unable to decode tool-related movement plans from this region suggests that human SPOC activity may only encode single/distinct motor acts with the hand. If this is the case, then other brain regions are required to code for the more complex action sequences required by the reverse tool (i.e., hand closing to first open the tongs and then hand release to close the tongs on the object). One such area may be the SMG, also localized here, a region notably implicated in the more abstract coding of movement goals and tool-related behaviors. For instance, inferior parietal cortex shows mirror-neuron-related properties (Fogassi et al., 2005; Grafton and Hamilton, 2007; Valyear and Culham, 2010), encodes the final goal of an action sequence in which grasping is embedded (Fogassi et al., 2005; Bonini et al., 2011), becomes activated when human subjects view (Lewis, 2006; Valyear et al., 2007; Peeters et al., 2009) and pantomime (Rumiati et al., 2004; Johnson-Frey et al., 2005) tool-related actions, and damage to the area creates difficulty in pantomiming or performing tool-use actions (Haaland et al., 2000; Johnson-Frey, 2004). Thus, the fact that the SMG, as shown here, is able to predict upcoming tool actions provides a noteworthy extension of these previous findings.

At a slightly higher-level along this motor hierarchy, we found a few parietal and frontal brain regions that although able to predict upcoming grasping vs. reaching movements with the hand and tool, the preparatory activity patterns in each of these areas were specific to the effector used (i.e., no across-effector decoding). When considering the special case of tool-use provided here -- where the operating mechanics of the tool are mirror opposite to those of the hand alone -- this effector-specific level of action planning is critical. It not only provides kinematic sensitivity to these different effector properties (Umilta et al., 2008; Jacobs et al., 2010) but in addition, specificity to the other low-level sensory differences between hand and tool trials (e.g., retinotopic position of target). Three brain areas in our parieto-frontal network match this effector-specific description: post. aIPS, aIPS, and motor cortex. Certainly, the most expected of these areas is motor cortex. The area provides the largest source of descending motor commands to the spinal neurons that implement the specific mechanics of the action plan (Evarts and Thach, 1969; Porter and Lemon, 1993; Chouinard and Paus, 2006) and correspondingly, much of its activity can be explained in low-level muscle control terms (Todorov, 2000; Kalaska, 2009). As such, the fact that it decodes upcoming kinematics with the hand and tool was largely anticipated (see also Project 1) and in a way, this finding provides a good positive control of data quality (i.e., similarly to how the preparatory voxel patterns from SS-cortex can effectively function as a negative control). In parietal cortex, both post. aIPS and aIPS are strongly implicated in grasp planning and execution (Taira et al., 1990; Sakata et al., 1997; Murata et al., 2000; Culham et al., 2003; Frey et al., 2005; Tunik et al., 2005; Baumann et al., 2009). More notably, the anterior aspect of the IPS has also previously been implicated in tool-use (Gallivan et al., 2009; Jacobs et al., 2010), but to date, its precise role in planning tool-directed actions has remained unclear. The current findings substantially clarify this role and provide further evidence that tool-use is supported by the same brain regions used for hand actions (see also Umilta et al., 2008; Gallivan et al., 2009; Jacobs et al., 2010). Moreover, our results clearly indicate that this fact in itself is not sufficient evidence for the presence of effector-independent representations, as previously interpreted (Rijntjes et al., 1999; Castiello et al., 2000).

At the highest and most abstract level of the motor hierarchy noted in the present study, we have several areas that in addition to discriminating movement plans for the hand and tool contain predictive voxel activity patterns that allow for accurate across-effector classification. That is, we find regions where the overall plan of the movement (grasping vs. reaching) is represented independently of the mirror opposite kinematics required by the two effectors to achieve the goal. Previous human behavioral (Gentilucci et al., 2004) and monkey neural recording studies (Umilta et al., 2008) provide compelling evidence for the existence of effector-independent representations during movement execution, but to our knowledge, no prior human neural evidence has provided empirical support for this observation. Our data shows that effector-specific representations are also present in the action *intention*, revealed in the preparatory activity evoked moments before movement onset. In posterior parietal cortex (PPC), the activity in both pIPS and midIPS fits this effector-independent description. In the human and macaque monkey, the PPC serves a variety of high-level visual-motor- and cognitive-related functions, such as integrating target- and effector-related information for movement (Snyder et al., 1997; Andersen and Buneo, 2002; Calton et al., 2002; Beurze et al., 2007; Chang and Snyder, 2010), representing forthcoming movement decisions (Gold and Shadlen, 2007), and encoding 3D features of objects for hand actions (Sakata et al., 1998; Katsuyama et al., 2010). Given this diverse range of cognitive-related properties, PPC seems well situated to abstractly represent higher-level movement goals related tool-use, as shown here. We also find evidence for effector-independent representations in premotor areas, PMd and PMv. Based on previous investigations of tool-use (Umilta et al., 2008; Jacobs et al., 2010) and action understanding (Rizzolatti and Craighero, 2004; Hamilton and Grafton, 2008), we initially hypothesized that perhaps only PMv would encode movement goals for the hand and tool. PMv is a motor area critically involved in grasping in both the monkey (Jeannerod et al., 1995; Rizzolatti and Luppino, 2001; Raos et al., 2006; Fluet et al., 2010) and human (Davare et al., 2006; Davare et al., 2008; Cavina-Pratesi et al., 2010) and its implication in higher-level goal-related processing (Rizzolatti and Luppino, 2001; Bonini et al., 2011) -- particularly in the case of tool-use (Umilta et al., 2008) -- seems commensurate with the findings reported here. A somewhat unanticipated result, however – at least within the context of the previous tool-related literature -- was that the same abstract representation of hand and tool movement plans would be found in PMd. PMd is most often implicated in reach-related processes (Weinrich and Wise, 1982; Caminiti et al., 1990; Cisek and Kalaska, 2005; Pesaran et al., 2006), however, emerging evidence from our lab and others suggests that this description may be overly one-dimensional. We have recently shown that preparatory activity in PMd can predict upcoming grasping vs. reaching movements with the hand (Project 1) and several other groups have also reported grasp-related properties in the area (Raos et al., 2004; Grol et al., 2007; Stark et al., 2007; Verhagen et al., 2008; Hendrix et al., 2009). The present findings, however, go beyond these previous descriptions and offer a more specific role for PMd: the high-level abstract coding of movement goals.

Networks of brain areas are required to connect the abstract goals of an action with the lower-level motor commands required to implement the goals (Kakei et al., 2003; Jubault et al., 2007; Grafton, 2010). Beyond localizing brain regions where distinct levels of the motor hierarchy may reside, in the specific cases where the same types of movement-related information are found (e.g., effector-independent), our results necessarily fall short of being able to specify or differentiate the unique contribution of each region, to the upcoming movement. This is certainly understandable, given the fact that, at the most general anatomical level, parietal and premotor cortex are highly interconnected (Matelli and Luppino, 2000; Tanne-Gariepy et al., 2002; Cisek and Kalaska, 2010) and despite specific cases being made for the directionality or serial nature of processing between these two regions (Kalaska and Crammond, 1995; Lawrence and Snyder, 2006; Buschman and Miller, 2007; Pesaran et al., 2008), the emergence of high-level goal-directed behavior is largely seen as a complex interplay between both general areas (Cisek and Kalaska, 2010; Grafton, 2010). Nevertheless, the distinct patterns of interconnectivity and specialized subdivisions of parietal and premotor cortex (Andersen and Buneo, 2002; Tanne-Gariepy et al., 2002; Culham et al., 2006) may provide clues as to what types of movement-related information are contained in several of the specified areas. For instance, increasing evidence suggests that prehension is largely supported by two parallel parieto-frontal pathways, with a SPOC-midIPS-PMd circuit -- thought to be specialized for reaching and proximal movements of the arm -- interacting alongside a separate pIPS-AIP-PMv circuit -- thought to be specialized for grasping and distal movements of the fingers (Matelli and Luppino, 2000; Andersen and Buneo, 2002; Tanne-Gariepy et al., 2002; Borra et al., 2008; Grafton, 2010). From this standpoint, it might seem intuitive that effector-independent representations emerge within interconnected regions like pIPS and PMv (Koch et al., 2010) as well midIPS and PMd (Andersen and Cui, 2009). Yet the absence of effector-independent responses in both anterior IPS and SPOC regions (areas that also form part of these parallel pathways) might also suggest a further differentiation of function or some effector-specific to –independent gradient within each circuit (Beurze et al., 2007; Stark and Zohary, 2008; Filimon, 2010).

Much effort is currently directed towards developing cognitive neural prosthetics, robotic devices operable by intention-related brain signals related to high-level movement goals (Schwartz, 2004; Andersen et al., 2010). A critical consideration in this field, however, is not only where in the human brain should these signals be recorded but also more generally, what types of signals beyond the simple kinematics of reaching and grasping can convey the more complex goal-directed behaviors of tool-use (e.g., eating with a fork, cutting with a pair of scissors, playing tennis, etc.)? The findings provided here offer possible answers to both these questions and show where the high-level goals of an action are encoded, independent of the specific motor acts needed to implement these goals.

5.5 References

Alexander GE, Crutcher MD (1990) Preparation for movement: neural representations of intended direction in three motor areas of the monkey. J Neurophysiol 64:133-150.

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annual Review of Neuroscience 25:189-220.

Andersen RA, Cui H (2009) Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63:568-583.

Andersen RA, Hwang EJ, Mulliken GH (2010) Cognitive neural prosthetics. Annu Rev Psychol 61:169-190, C161-163.

Baumann MA, Fluet MC, Scherberger H (2009) Context-specific Grasp Movement Representation in the Macaque Anterior Intraparietal Area. J Neurosci 29:6436-6448.

Bernstein NA (1996) On dexterity and its development. In: Dexterity and its development (Latash ML, Turvey MT, eds), pp 3-207. Mahway, NJ: Lawrence Earlbaum Associates.

Berti A, Frassinetti F (2000) When far becomes near: remapping of space by tool use. Journal of Cognitive Neuroscience 12:415-420.

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 97:188-199.

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 101:3053-3062.

Bonini L, Ugolotti Serventi F, Simone L, Rozzi S, Ferrari PF, Fogassi L (2011) Grasping Neurons of Monkey Parietal and Premotor Cortices Encode Action Goals at Distinct Levels of Abstraction during Complex Action Sequences. J Neurosci 31:5876-5886.

Borra E, Belmalih A, Calzavara R, Gerbella M, Murata A, Rozzi S, Luppino G (2008) Cortical connections of the macaque anterior intraparietal (AIP) area. Cereb Cortex 18:1094-1111.

Buschman TJ, Miller EK (2007) Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315:1860-1862.

Calton JL, Dickinson AR, Snyder LH (2002) Non-spatial, motor-specific activation in posterior parietal cortex. Nat Neurosci 5:580-588.

Caminiti R, Johnson PB, Burnod Y, Galli C, Ferraina S (1990) Shift of preferred directions of premotor cortical cells with arm movements performed across the workspace. Exp Brain Res 83:228-232.

Cardinali L, Frassinetti F, Brozzoli C, Urquizar C, Roy AC, Farne A (2009) Tool-use induces morphological updating of the body schema. Curr Biol 19:R478-479.

Castiello U, Bennett KM, Egan GF, Tochon-Danguy HJ, Kritikos A, Dunai J (2000) Human inferior parietal cortex "programs" the action class of grasping. Cognitive Systems Research 1:140-145.

Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam TD, Quinlan DJ, Goodale MA, Culham JC (2010) fMRI reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. Journal of Neuroscience.

Chang SW, Snyder LH (2010) Idiosyncratic and systematic aspects of spatial representations in the macaque parietal cortex. Proc Natl Acad Sci U S A 107:7951-7956.

Chang SW, Papadimitriou C, Snyder LH (2009) Using a compound gain field to compute a reach plan. Neuron 64:744-755.

Chouinard PA, Paus T (2006) The primary motor and premotor areas of the human cerebral cortex. Neuroscientist 12:143-152.

Cisek P, Kalaska JF (2005) Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. Neuron 3:801-814.

Cisek P, Kalaska JF (2010) Neural Mechanisms for Interacting with a World Full of Action Choices. Annu Rev Neurosci.

Crutcher MD, Alexander GE (1990) Movement-related neuronal activity selectively coding either direction or muscle pattern in three motor areas of the monkey. J Neurophysiol 64:151-163.

Culham JC (2004) Human brain imaging reveals a parietal area specialized for grasping. In: Attention and Performance XX: Functional Brain Imaging of Human Cognition (Kanwisher N, Duncan J, eds). Oxford, U.K.: Oxford University Press.

Culham JC, Cavina-Pratesi C, Singhal A (2006) The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia 44:2668-2684.

Culham JC, Danckert SL, DeSouza JF, Gati JS, Menon RS, Goodale MA (2003) Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Exp Brain Res 153:180-189.

Davare M, Lemon R, Olivier E (2008) Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. J Physiol 586:2735-2742.

Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E (2006) Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci 26:2260-2268.

di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G (1992) Understanding motor events: a neurophysiological study. Exp Brain Res 91:176-180.

Dinstein I, Gardner JL, Jazayeri M, Heeger DJ (2008) Executed and observed movements have different distributed representations in human aIPS. J Neurosci 28:11231-11239.

Evarts EV, Thach WT (1969) Motor mechanisms of the CNS: cerebro-cerebellar interrelations. Annu Rev Physiol 31:451-498.

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 29:1928-1936.

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 30:342-349.

Filimon F (2010) Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. Neuroscientist 16:388-407.

Fluet MC, Baumann MA, Scherberger H (2010) Context-specific grasp movement representation in macaque ventral premotor cortex. J Neurosci 30:15175-15184.

Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G (2005) Parietal lobe: from action organization to intention understanding. Science 308:662-667.

Formisano E, De Martino F, Bonte M, Goebel R (2008) "Who" is saying "what"? Brain-based decoding of human voice and speech. Science 322:970-973.

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 23:397-405.

Gallese V, Fadiga L, Fogassi L, Rizzolatti G (1996) Action recognition in the premotor cortex. Brain 119:593-609.

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 29:4381-4391.

Gentilucci M, Roy AC, Stefanini S (2004) Grasping an object naturally or with a tool: are these tasks guided by a common motor representation? Exp Brain Res 157:496-506.

Gold JI, Shadlen MN (2007) The neural basis of decision making. Annu Rev Neurosci 30:535-574.

Grafton ST (2010) The cognitive neuroscience of prehension: recent developments. Exp Brain Res 204:475-491.

Grafton ST, Hamilton AF (2007) Evidence for a distributed hierarchy of action representation in the brain. Hum Mov Sci 26:590-616.

Grol MJ, Majdandzic J, Stephan KE, Verhagen L, Dijkerman C, Bekkering H, Verstraten F, Toni I (2007) Parieto-frontal connectivity during visually guided grasping. J Neurosci 27:11877-11887.

Haaland KY, Harrington DL, Knight RT (2000) Neural representations of skilled movement. Brain 123 (Pt 11):2306-2313.

Hamilton AF, Grafton ST (2006) The motor hierarchy: from kinematics to goals and intentions. In: Attention and performance (Rosetti Y, Kawato M, Haggard P, eds).

Hamilton AF, Grafton ST (2008) Action outcomes are represented in human inferior frontoparietal cortex. Cereb Cortex 18:1160-1168.

Harrison SA, Tong F (2009) Decoding reveals the contents of visual working memory in early visual areas. Nature 458:632-635.

Hebb DO (1949) The organization of behavior: a neuropsychological theory. New York: Wiley.

Hendrix CM, Mason CR, Ebner TJ (2009) Signaling of grasp dimension and grasp force in dorsal premotor cortex and primary motor cortex neurons during reach to grasp in the monkey. J Neurophysiol 102:132-145.

Hihara S, Notoya T, Tanaka M, Ichinose S, Ojima H, Obayashi S, Fujii N, Iriki A (2006) Extension of corticocortical afferents into the anterior bank of the intraparietal sulcus by tool-use training in adult monkeys. Neuropsychologia 44:2636-2646.

Imazu S, Sugio T, Tanaka S, Inui T (2007) Differences between actual and imagined usage of chopsticks: an fMRI study. Cortex 43:301-307.

Ingram JN, Howard IS, Flanagan JR, Wolpert DM (2010) Multiple grasp-specific representations of tool dynamics mediate skillful manipulation. Curr Biol 20:618-623.

Iriki A, Tanaka M, Iwamura Y (1996) Coding of modified body schema during tool use by macaque postcentral neurones. Neuroreport 7:2325-2330.

Jackson JH (1889) On the comparative study of diseases of the nervous system. British Medical Journal 2:355-362.

Jacobs S, Danielmeier C, Frey SH (2010) Human anterior intraparietal and ventral premotor cortices support representations of grasping with the hand or a novel tool. J Cogn Neurosci 22:2594-2608.

Jeannerod M, Arbib MA, Rizzolatti G, Sakata H (1995) Grasping objects: the cortical mechanisms of visuomotor transformation. Trends in Neurosciences 18:314-320.

Johnson-Frey SH (2004) The neural bases of complex tool use in humans. Trends Cogn Sci 8:71-78.

Johnson-Frey SH, Newman-Norlund R, Grafton ST (2005) A distributed left hemisphere network active during planning of everyday tool use skills. Cereb Cortex 15:681-695.

Johnson SH, Grafton ST (2003) From 'acting on' to 'acting with': the functional anatomy of object-oriented action schemata. Prog Brain Res 142:127-139.

Jubault T, Ody C, Koechlin E (2007) Serial organization of human behavior in the inferior parietal cortex. J Neurosci 27:11028-11036.

Kakei S, Hoffman DS, Strick PL (1999) Muscle and movement representations in the primary motor cortex. Science 285:2136-2139.

Kakei S, Hoffman DS, Strick PL (2001) Direction of action is represented in the ventral premotor cortex. Nat Neurosci 4:1020-1025.

Kakei S, Hoffman DS, Strick PL (2003) Sensorimotor transformations in cortical motor areas. Neurosci Res 46:1-10.

Kalaska JF (2009) From intention to action: motor cortex and the control of reaching movements. Adv Exp Med Biol 629:139-178.

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 5:410-428.

Katsuyama N, Yamashita A, Sawada K, Naganuma T, Sakata H, Taira M (2010) Functional and histological properties of caudal intraparietal area of macaque monkey. Neuroscience 167:1-10.

Koch G, Cercignani M, Pecchioli C, Versace V, Oliveri M, Caltagirone C, Rothwell J, Bozzali M (2010) In vivo definition of parieto-motor connections involved in planning of grasping movements. Neuroimage 51:300-312.

Ladavas E (2002) Functional and dynamic properties of visual peripersonal space. Trends in Cognitive Sciences 6:17-22.

Lawrence BM, Snyder LH (2006) Comparison of effector-specific signals in frontal and parietal cortices. J Neurophysiol 96:1393-1400.

Lewis JW (2006) Cortical networks related to human use of tools. Neuroscientist 12:211-231.

Maravita A, Iriki A (2004) Tools for the body (schema). Trends Cogn Sci 8:79-86.

Matelli M, Luppino G (2000) Parietofrontal circuits: parallel channels for sensory-motor integrations. Adv Neurol 84:51-61.

Mulliken GH, Musallam S, Andersen RA (2008) Decoding trajectories from posterior parietal cortex ensembles. J Neurosci 28:12913-12926.

Murata A, Gallese V, Luppino G, Kaseda M, Sakata H (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. J Neurophysiol 83:2580-2601.

Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA (2004) Cognitive control signals for neural prosthetics. Science 305:258-262.

Peeters R, Simone L, Nelissen K, Fabbri-Destro M, Vanduffel W, Rizzolatti G, Orban GA (2009) The representation of tool use in humans and monkeys: common and uniquely human features. J Neurosci 29:11523-11539.

Pesaran B, Nelson MJ, Andersen RA (2006) Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. Neuron 51:125-134.

Pesaran B, Nelson MJ, Andersen RA (2008) Free choice activates a decision circuit between frontal and parietal cortex. Nature 453:406-409.

Picard N, Strick PL (2001) Imaging the premotor areas. Curr Opin Neurobiol 11:663-672.

Porter R, Lemon RN (1993) Corticospinal function and voluntary movement. Oxford, UK: Clarendon Press.

Prado J, Clavagnier S, Otzenberger H, Scheiber C, Kennedy H, Perenin MT (2005) Two cortical systems for reaching in central and peripheral vision. Neuron 48:849-858.

Raos V, Umilta MA, Gallese V, Fogassi L (2004) Functional properties of grasping-related neurons in the dorsal premotor area F2 of the macaque monkey. J Neurophysiol 92:1990-2002.

Raos V, Umilta MA, Murata A, Fogassi L, Gallese V (2006) Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. J Neurophysiol 95:709-729.

Rijntjes M, Dettmers C, Buchel C, Kiebel S, Frackowiak RS, Weiller C (1999) A blueprint for movement: functional and anatomical representations in the human motor system. J Neurosci 19:8043-8048.

Rizzolatti G, Luppino G (2001) The cortical motor system. Neuron 31:889-901.

Rizzolatti G, Craighero L (2004) The mirror-neuron system. Annual Review of Neuroscience 27:169-192.

Rizzolatti G, Fogassi L, Gallese V (2001) Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci 2:661-670.

Rumiati RI, Weiss PH, Shallice T, Ottoboni G, Noth J, Zilles K, Fink GR (2004) Neural basis of pantomiming the use of visually presented objects. Neuroimage 21:1224-1231.

Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y (1997) The TINS Lecture. The parietal association cortex in depth perception and visual control of hand action. Trends Neurosci 20:350-357.

Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y, Tsutsui K (1998) Neural coding of 3D features of objects for hand action in the parietal cortex of the monkey. Philos Trans R Soc Lond B Biol Sci 353:1363-1373.

Schwartz AB (2004) Cortical neural prosthetics. Annu Rev Neurosci 27:487-507.

Sherrington CS (1906) The integrative action of the nervous system. New Haven, CT: Yale University Press.

Smith FW, Muckli L (2010) Non-stimulated early visual areas carry information about surrounding context. Proc Natl Acad Sci U S A.

Snyder LH, Batista AP, Andersen RA (1997) Coding of intention in the posterior parietal cortex. Nature 386:167-123.

Soon CS, Brass M, Heinze HJ, Haynes JD (2008) Unconscious determinants of free decisions in the human brain. Nat Neurosci 11:543-545.

Stark A, Zohary E (2008) Parietal mapping of visuomotor transformations during human tool grasping. Cereb Cortex 18:2358-2368.

Stark E, Asher I, Abeles M (2007) Encoding of reach and grasp by single neurons in premotor cortex is independent of recording site. J Neurophysiol 97:3351-3364.

Taira M, Mine S, Georgopoulos AP, Murata A, Sakata H (1990) Parietal cortex neurons of the monkey related to the visual guidance of hand movement. Exp Brain Res 83:29-36.

Tanne-Gariepy J, Rouiller EM, Boussaoud D (2002) Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp Brain Res 145:91-103.

Todorov E (2000) Direct cortical control of muscle activation in voluntary arm movements: a model. Nat Neurosci 3:391-398.

Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H (2007) Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J Neurosci 27:10259-10269.

Tunik E, Frey SH, Grafton ST (2005) Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. Nat Neurosci 8:505-511.

Umilta MA, Escola L, Instkirvell I, Grammont F, Rochat M, Caruana F, Jezzini A, Gallese V, Rizzolatti G (2008) When pliers become fingers in the monkey motor system

Proc Natl Acad Sci U S A 105:2209-2213.

Valyear KF, Culham JC (2010) Observing learned object-specific functional grasps preferentially activates the ventral stream. J Cogn Neurosci 22:970-984.

Valyear KF, Cavina-Pratesi C, Stiglick AJ, Culham JC (2007) Does tool-related fMRI activity within the intraparietal sulcus reflect the plan to grasp? Neuroimage 36 Suppl 2:T94-T108.

Van Lawick-Goodall J, ed (1970) Advances in the Study of Behavior. New York: Academic.

Verhagen L, Dijkerman C, Grol MJ, Toni I (2008) Perceptuo-motor interactions during prehension movements. J Neurosci 28:4726-4735.

Weinrich M, Wise SP (1982) The premotor cortex of the monkey. J Neurosci 2:1329-1345.

Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P (1997) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 120:141-157.

Chapter 6

6. General Discussion

Although the ability to predict goal-directed sensorimotor behaviors from preceding changes in intention-related brain activity has been almost exclusively confined to the domain of non-human primate research and largely limited to methodologies that require invasive neural recordings, the current set of projects asked whether it would be possible to accomplish the same feat in human subjects using a non-invasive technique. Our voxel pattern fMRI analyses present two important findings with broad implications: First, we show that different upcoming object-directed movements can be decoded from the intention-related activity within several parieto-frontal areas of the human brain. Methodologically speaking, this finding is significant in many respects, because it shows that intentions can be studied not only with invasive neural recordings in non-human species, but also with fMRI in humans and that the same general ‘types’ of high-level motor-related signals are discriminable. Second, and more importantly from a theoretical perspective, we show that several parieto-frontal network areas involved in movement planning can be differentiated based on the types of effector-specific movements that they can predict. Cortically mapping the effector-specificity of movement intention-related signals across monkey parieto-frontal cortex has provided several important breakthroughs into understanding the neural mechanisms and anatomical organization that supports goal-directed behavior and our findings in many cases both reinforce and expand upon the success of this approach. At a more general level, these results also impart a new appreciation for the highly detailed movement information contained in the human brain’s preparatory signals, provide significant developments in our understanding of human visual-motor control, and perhaps most importantly, offer a useful springboard for further investigations into higher-level cognitive and abstract processes like motor intentions.

In Project 1, I used fMRI MVPA to first examine whether the *intention* to perform a specific hand action could be decoded from preparatory brain activity in different human parieto-frontal regions. Using a delayed-movement paradigm, we had our subjects first plan and then execute hand movements requiring different degrees of finger precision (grasping a small object, grasping a large object, and touching the object without hand preshaping). We found that despite an absence of signal amplitude differences between different planned movements, we were able to predict in several parieto-frontal areas which hand action the subject was going to execute. In addition, we further showed that a subset of brain areas could also predict the object size to be grasped (small vs. large).

In Project 2, fMRI MVPA was used to examine whether we could predict the effector to be used and the spatial location to be acted upon from preparatory brain signals in parieto-frontal cortex. Using a similar delayed-movement paradigm to Project 1, we had our subjects plan and then execute either reaches or eye movements towards two different spatial target locations. We found that again, even in the absence of signal amplitude differences, the spatial activity patterns preceding movement onset were predictive of upcoming reaches and saccades, and their intended directions. Moreover, using a cross-trial-type decoding approach, we found suggestive evidence in certain parieto-frontal regions that these predictive activity patterns were reflective of a shared spatial reference frame for the hand and eye. Within some of the same regions, we further showed that these preparatory spatial signals could be discriminated from non-spatial, effector-specific signals.

In Project 3, I used fMRI MVPA and a delayed-movement paradigm to examine how and where in the human brain high-level movement goals were encoded independent of the kinematics needed to achieve those goals. To this aim, I had subjects plan and then execute either grasp or reach actions (two different motor goals) using either their hand or reverse tool (requiring two different movement kinematics). We found that while only a few parieto-frontal areas predicted hand or tool movements only, the majority of examined regions decoded grasp vs. reach actions with both effectors. In these latter regions, using a cross-trial-type decoding approach, we found that the discriminatory patterns of activity were either shared or separate across effectors. We speculated that areas containing separate preparatory patterns of activity for the hand and tool were likely to encode the distinct kinematics required to operate the two effectors whereas in contrast, the areas containing shared activity patterns across effectors were likely to represent the abstract goals of the movement (grasping vs. reaching), independent of how those goals were mechanically implemented by the hand.

My general discussion is divided into four main sections. First, I will consider what exactly significant intention-related decoding might mean within the context of an fMRI action-related movement task. This general question will be addressed by attempting to answer two more focused and specific questions: 1) from a more methodological standpoint, what is the underlying neural basis and nature of the information being represented in the spatial voxel patterns of activity? And 2) from a more theoretical standpoint, what types of movement-related information are contained in specific parieto-frontal ROIs and what does this information reveal about the underlying hierarchical organization that governs the planning of goal-directed actions? I will also briefly discuss how the intention-related account of the present findings, offered in the previous pages, might compare with an attention-related account of the same findings (section 6.1). Second, I will outline a few minor methodological and theoretical issues that should be taken into consideration when interpreting the findings of the current projects. In particular, I will attempt to reconcile some of the discrepancies in decoding found between movement planning and execution and also briefly highlight some limits to the explanatory power of MVPA (section 6.2). Third, I will offer some interesting future avenues for investigation based on the findings provided here – some of which is currently underway in our lab and several other directions that remain to be explored (section 6.3). Lastly, I will offer some brief concluding remarks and highlight several of the new and important contributions offered in the previous pages.

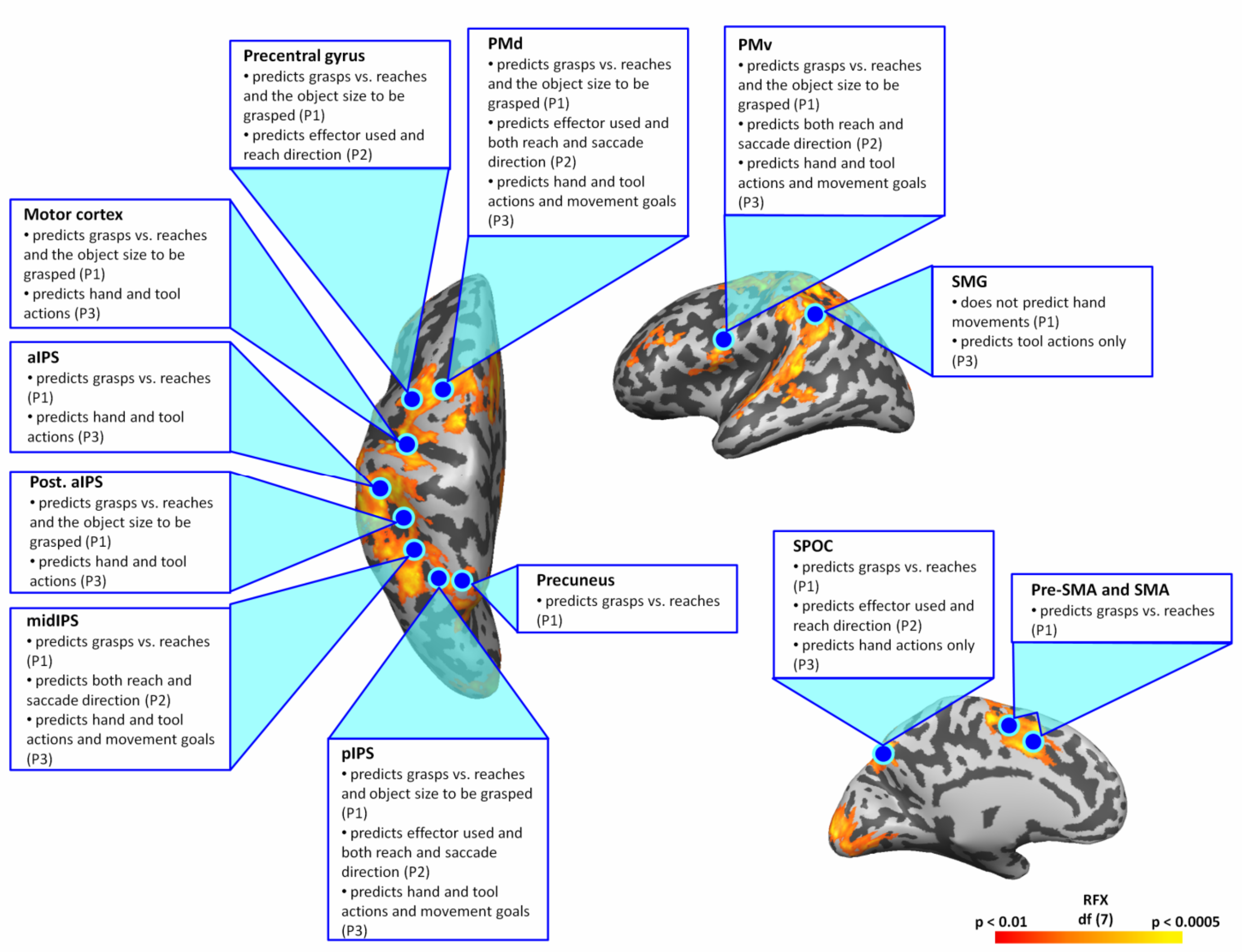

Figure 6.1: Summary of findings from the three projects. Linked to each parieto-frontal brain area is a brief description of the intention-related decoding profiles discovered in that particular region across the three projects (P1, P2, and P3, where applicable).

6.1 What do these spatial activity patterns mean?

Multivariate pattern recognition techniques have recently proven to be exceptionally useful in revealing fine-grained spatial differences in fMRI activity distributed across multiple voxels (Haxby et al., 2001; Haynes and Rees, 2005; Kamitani and Tong, 2005; Kriegeskorte et al., 2006; Kay et al., 2008; Soon et al., 2008; Harrison and Tong, 2009; Stokes et al., 2009; Meyer et al., 2010), spatial information often ignored in traditional univariate analyses because statistics are run on single voxels (Norman et al., 2006; Mur et al., 2009; Pereira et al., 2009; Raizada and Kriegeskorte, 2010). Given the highly overlapping and distributed nature of sensorimotor activity within parieto-frontal networks (Andersen and Buneo, 2002; Andersen and Cui, 2009; Filimon, 2010) this important methodological consideration makes pattern analysis a particularly beneficial technique for studying visual-motor interactions and movement planning processes. With this in mind, coupled with our recent ability to localize and decode intention-related signals from human parieto-frontal activity, it would seem that two seperate but intimately related questions need to be addressed: *1) what is the neural organization that gives rise to the observed spatial pattern differences? and 2) from a more theoretical point of view, what type(s) of neural information might be gleaned from the predictive spatial patterns of activity?* Although it remains unclear whether these two questions actually permit dissociations, based on previous findings in the human and macaque monkey, I will provide some discussion and speculation which aims to disentangle them. With regards to the second question, I will then also briefly offer some speculations as to how and where different parieto-frontal brain regions may be situated within the hierarchical neural architecture that produces goal-directed behavior.

6.1.1 What is the neural basis of the local spatial patterns?

Although interest in the neural basis of spatial activity patterns is not new to visual-perceptual investigations (Haxby et al., 2001; Kamitani and Tong, 2005; Haynes and Rees, 2006; Haynes, 2009; Freeman et al., 2011), it is certainly an issue which has yet to be explored in visual-motor research. In the visual-perceptual domain, the decoding of viewed faces and objects from overlapping neural representations in ventral temporal cortex has led to notions that pattern differences might reflect a distributed population code, being sampled in a task-specific manner (Haxby et al., 2001). Alternatively, the decoding of fine-grained activity patterns in early visual cortex elicited by differences in stimulus orientation (Haynes and Rees, 2005; Kamitani and Tong, 2005) has led to the suggestion that such discriminations might instead reflect the measurement of underlying feature-specific columns or small fine-grained clusters of cells containing similar functional properties (Haynes and Rees, 2006; Soon et al., 2008; Haynes, 2009) – an organizational principle, which on its own, has generated considerable debate (Mountcastle, 1997; Horton and Adams, 2005). More recent fMRI evidence, however, shows that there actually exists a far coarser topographic map of orientation preference in early visual cortex, arguing against interpretations that successful decoding necessarily exploits an underlying columnar architecture at the sub-voxel level (Freeman et al., 2011). Regardless of which one of these explanations turns out to be correct (or whether they are in fact mutually exclusive), it currently remains unclear how or whether any of these hypotheses can directly account for the findings provided here, and moreover, whether such neuroanatomical organizational principles extend to higher-level brain areas with more abstract and cognitive properties like parietal and premotor cortex.

One thing we do know about the parieto-frontal network is that its neural organization is multiplexed: single brain areas in the macaque monkey can contain several highly-specialized and intermingled populations of neurons, each with different blends of sensory properties related to the reference frames they use to encode stimuli and motor movements. For instance, the neurons in one area can encode information in a variety of different coordinate frames – for example, eye-, head-, limb- or body-centered reference frames or even intermediates between these different coordinates - while neurons in another brain area may predominantly represent spatial information according to only one of these (e.g., eye-centered coordinates)(Andersen et al., 1997; Andersen and Buneo, 2002; Andersen and Cui, 2009). Moreover, these neurons can be highly-complex, showing relative frames of reference (e.g., eye-relative to the hand) and partially-shifting receptive fields gain-modulated by the position of the head, limb and eyes (Graziano, 2001; Andersen and Buneo, 2002; Cohen and Andersen, 2002; Graziano, 2006; Pesaran et al., 2006; Cassanello and Ferrera, 2007; Andersen and Cui, 2009). In addition, recent neural evidence and computational models suggest that the reference frames used to plan reach movements can flexibly adapt to the available sensory input (Pouget and Snyder, 2000; Sober and Sabes, 2005; McGuire and Sabes, 2009; Bernier and Grafton, 2010). To further complicate matters, a variety of recording techniques show that single premotor neurons can be specific for either a reach direction or grasp type, and from their synchronous interactions, specific for different combinations of reach and grasp (e.g., Stark et al., 2007). In addition, these neural populations are highly intermixed with selectivity for either proximal (e.g., elbow) or distal (e.g., finger) movements (Stark and Abeles, 2007; Stark et al., 2007; Stark et al., 2008). Assuming some homologies with the monkey (Grefkes and Fink, 2005) we should expect to find, in the parieto-frontal network of humans, the same heterogeneous mixture of both sparse and distributed neural codes related to separate reference frames and/or movement types. In relation to the larger scale signal changes observed with BOLD fMRI, it seems plausible that these neurophysiological properties might be encoded in the hemodynamic spatial response patterns discriminated by pattern recognition techniques.

It certainly stands to reason ,however, given that the neurovascular coupling mechanisms relating neural responses with BOLD signal changes are far from being well understood (Logothetis et al., 2001; Logothetis and Wandell, 2004; Viswanathan and Freeman, 2007; Maier et al., 2008; Sirotin and Das, 2009), that the fMRI activity patterns generated by our planning-related task need not directly correspond with the planning-related activity observed at the single neuron level. Recall that each functional voxel (3 mm x 3 mm x 3 mm) contains somewhere on the order of 1.35-1.62 million neurons (Pakkenberg and Gundersen, 1997; Koch, 2004) and thus if anything is to be interpreted from spatial voxel patterns, it is that we are measuring the coordinated activity of multiple specialized and distributed sub-populations of neurons. While this fact in itself complicates the direct transfer and inference of neural properties from one species to the other -- for instance, our present results are necessarily limited in addressing the types of reference frames used for action planning or revealing particulars about the underlying multiplexed organization of the parieto-frontal neurons – the pattern analysis method in many respects provides a complementary approach to monkey neural recordings and as shown here, particularly in Project 3, it allows us to explore the neural representation of motor hierarchies across the brain. Monkey neural studies, for all their benefits (and there are many), are often limited by the fact that in most cases only one brain region and only a single neuron can be tested at a time. In addition, the recorded activity from neurons is largely biased towards larger cells. Unquestionably, this makes it challenging to fully explore how the brain, as a functioning and interacting network, guides goal-directed action. Indeed, complex visual-motor behaviors like reaching and grasping are not limited to the outputs of individual neurons nor the workspace defined by a single neuron’s receptive field but instead rely on the outputs of large neural populations governed by short- and long-range interconnections between different anatomical regions.

Unfortunately, beyond demonstrating that the same general ‘types’ of intention-related signals can be found in similar areas of the human and monkey parieto-frontal network and also showing how we can use voxel pattern information to explore new types of experimental questions (hierarchical motor architectures, see Project 3), at present, it remains difficult to pin down the specific neural origin for these fMRI spatial pattern signals. Exactly where multivariate activity patterns fit within this continuum from single neuron responses to large scale hemodynamic changes across multiple voxels, particularly within parieto-frontal cortical regions, remains an interesting and open question for future investigations.

6.1.2 What is the information contained in the local spatial patterns?

Although we can only speculate on the information represented in the predictive spatial patterns of activity, the different plan-related decoding profiles found across several of the parietal and premotor areas (e.g., grasps vs. reaches, reaches vs. eye movements, hand vs. tool) coupled with previous human- and monkey-related activations reported in these regions, appears to provide some important clues. Instead of simply re-hashing the types of plan-related decoding profiles found in several parieto-frontal areas (for a detailed summary of this information, see Figure 6.1, and for a more detailed account, see the specific Discussion sections of each project) the aims of this particular discussion will be to speculate on the more generalized function of each brain area, and in particular, how the coordinated activity of these different parieto-frontal areas leads to the planning and implementation of high-level goal-directed behaviors. Instrumental in this discussion will be the concept of a motor hierarchy (described in some detail in Project 3) -- where at a general schematic level, the planning of any complex visual-motor behavior or goal (e.g., pouring a glass of wine) can be viewed as being supported by increasingly specialized modules or networks, each linked to the completion of individual sub-goals (Shallice and Burgess, 1996; Dehaene and Changeux, 1997) and each more intimately related to the output or kinematics of the final action (Grafton and Hamilton, 2007). For instance, in the given example of pouring a glass of wine, some lower-level of the motor hierarchy would need to be concerned with the specific muscle activations required to position the limb, forearm, and finger muscles (e.g., activation of flexors and extensors, joint angles, etc.) whereas at some slightly higher-level of the motor hierarchy there would also need to be a detailed coding for the precise movement kinematics needed to complete the action (e.g., the hand preshaping required to grasp the wine bottle and the temporal and spatial coordination of the arm and hand needed to pour). Of course, located above these two levels, there also needs to be an overall movement plan -- some sort of abstract representation[5] of the overarching goal or intention of the action or actor (in the case here for example, pouring the glass of wine to be served to a dinner guest) -- that then successively calls upon the lower-levels of the motor hierarchy to actually implement the desired act. Although the concept of a motor hierarchy has a long, distinguished history (Jackson, 1889; James, 1890; Sherrington, 1906; Hebb, 1949) and resonates with several universally acknowledged organizational principles of the central nervous system – for example, parieto-frontal cortex plans movements at a higher-level than motor cortex, and motor cortex plans movements at a higher-level than the spinal cord, and so forth – a basic question in visual-motor neuroscience is whether this largely descriptive hierarchical organization has a cognitive counterpart, directly situated in the underlying neuroanatomy of parieto-frontal cortex. As already mentioned, the PPC and premotor cortex are highly multiplexed and interconnected structures, thought to provide an integral neural interface between sensation and goal-directed movement, and it remains an important and open question whether different levels of a motor hierarchy can be functionally localized to specific regions within this network.

Before moving ahead, a critical point worth re-emphasizing here and one that becomes immediately obvious when reflecting upon the adaptability of goal-directed actions to current environmental contexts is that there is no strict one-to-one mapping between the different hierarchical levels of motor control. That is, the same kinematic and muscular components need not always lead to the same motor goal, and attainment of the same motor goal need not necessarily require the exact same kinematic and muscular components. The best example of this latter case is when we grasp a coffee cup; while the goal of grasping the cup need not change, we can flexibly achieve this goal by using either the left or right hand (which necessitate different muscle activations) or with an object already in hand, like a pencil (necessitating compensatory hand kinematics to grasp the coffee cup). It was really through using derivations of this second case in Projects 2 and 3 -- where the general goals of an action could remain constant but the ways in which those goals were kinematically achieved could change – that provided a tractable approach for studying hierarchical motor control and for framing several of the experimental hypotheses. It should be noted that although Project 1 was in many ways informative of the types of intention-related hand signals that could be decoded and provided a good measure of the

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[5] Note that the term ‘abstract’, as used throughout this thesis, is only meant to denote a neural coding or representation that is not directly linked to a detailed specification of the movement kinematics to be performed.

sensitivity of MVPA (i.e., as a general proof-of-principle and springboard for Projects 2 and 3), beyond showing simple intention decoding within a given brain area we were unable to provide any substantial insights into an underlying hierarchical neuroanatomical organization in parieto-frontal cortex (except of course, to perhaps argue that some brain regions may additionally encode the finger precision required for grasping the smaller object). In Project 2, however, we used a task often employed in monkey neural recording experiments (e.g., Snyder et al., 1997) that had subjects act upon one of two different spatial target locations (two different goal positions) using one of two different effectors for movement (hand vs. eyes); thus, different low-level muscle activations were required to act at the same spatial locations. Project 3 was similar in principle but used a task where subjects planned and executed one of two different movement goals (grasping vs. reaching an object) using either their hand or a reverse tool. In this way, the same two motor goals – grasping vs. reaching – were held constant but the movement kinematics differed greatly depending on the effector to be used. Critical to separating the neural representations pertaining to higher-level abstract movement goals vs. lower-level movement kinematics was the results of our cross-trial-type decoding analyses (applied in Projects 2 and 3). Cross-classification analysis allowed us to ask the question of whether the voxel patterns of activity discriminating two different movement plans (i.e., acting left vs. acting right, grasping vs. reaching) were either *similar* or *different* across effectors (e.g., arm vs. eyes, hand vs. reverse tool).

To facilitate the discussion of these findings, we have subdivided the different parieto-frontal brain areas according to whether they encode the higher-level movement goals or lower-level movement kinematics required to achieve those goals. While this decoding-based division of the parieto-frontal network intuitively permits a functional characterization of different regions, a critical question of interest that I will aim to address is whether areas showing the same types of decoding profiles are necessarily engaged in the same types of movement-planning processes.

6.1.2.1 Higher-level goal representations in parieto-frontal cortex

Four brain regions in particular show the types of response patterns suggestive of a more prominent role in abstract, goal-related movement planning: two areas in the PPC – pIPS and midIPS – and two areas in premotor cortex – PMd and PMv. In Project 2, pIPS, midIPS and PMd were found to encode the effector to be used (eye vs. arm) and the spatial location to be acted upon (left vs. right) for an upcoming movement. With cross-trial-type decoding, however, we were able to reveal a far more complex underlying pattern of activity: each of the three areas represented the goal target location independent of the effector to be used in the movement. In Project 2 we took this as suggestive evidence that these three brain areas may use a common coordinate frame for reaches and saccades (highly consistent with past and recent neural evidence from monkeys)(Batista et al., 1999; Pesaran et al., 2006, 2010) but of course, because we did not manipulate the initial positions of the eyes, head or limb, we could only speculate on which body part this common reference frame was anchored. In PMv, although we found that its activity could accurately predict the spatial target location to be acted upon, these activity patterns did not allow for cross-trial-type decoding. We took this latter finding to suggest that the reference frames used for planning arm movements and saccades were separate within this area (e.g., Graziano et al., 1994; Fujii et al., 1998). In Project 3, we found that all four brain areas also predicted upcoming grasp vs. reach movements with both the hand and tool. Although this type of finding is to be largely expected from any brain region discriminating the hand kinematics required for movement (and also consistent with the expectations from Project 1) cross-trial-type decoding further revealed that the activity patterns discriminating grasp vs. reach movements were highly similar across the two effectors. This instead suggests that these areas might represent more abstract higher-level movement goals rather than the specific muscle activations and hand kinematics required.

It is worth recognizing that in a general sense, the findings from these two projects are quite compatible. Despite large differences in the tasks employed, most of these areas contain representations of the overall movement goal separate from the effector to be used, highly consistent with expectations from neurophysiology. For instance, neurons in the posterior aspect of the IPS show a variety of encoding schemes: some encode the target location to be acted upon, some the effector to be used and some the conjunction of both pieces of information (e.g., Calton et al., 2002; Dickinson et al., 2003). Our findings in pIPS and midIPS appear to reflect this general underlying organization of PPC. Similarly, monkey premotor areas like PMd and PMv also largely represent movement goals related to target location and action type, rather than specifying details of the muscle activations required (e.g., Rizzolatti and Luppino, 2001; Pesaran et al., 2006).

A possible discrepancy that arises between the two projects, however, concerns how it is that these four areas can be tuned to motor goals like spatial location (left vs. right target) in Project 2 but in Project 3 show tuning for the motor goal of the object-directed action (grasping vs. reaching) independent of the object's location (recall that the position of the object changes between hand and tool experimental runs)? Stated more succinctly, how can the same brain areas represent target locations in one experiment and then show motor selectivity independent of target location in the other experiment? It is important to first emphasize that this latter point is not necessarily true; when we compared grasping with the hand vs. grasping with the tool (i.e., planning grasp vs. grasp actions at two different spatial locations) we found highly significant decoding in each of these four brain regions. To complicate matters, however, in many of these same regions we also found significant decoding during the Preview phase (i.e., prior to the motor instruction being given to the subject). This latter finding, however, is sensible when considering the large visual differences that exist between hand and tool experimental runs (e.g., tool present vs. absent, change in object position, etc.) and the highly sensitive nature of MVPA to detect small task-related visual differences (e.g. Kamitani and Tong, 2005). As such, in this case, we could not unequivocally attribute any action-related spatial-specificity to only the *intention* to perform the action (although, certainly some location-selectivity is expected based on the findings of Project 2 [6]). Nevertheless, to return to the question posed, it is important to emphasize that spatial- and motor-specific response properties are not mutually exclusive. For goal-directed behavior, it is not enough to merely specify the target location of an action; it is equally important to specify how it is going to be acted upon. Indeed, some of the areas in Project 2 specify this latter information: pIPS, midIPS and PMd, in addition to target location, specify which effector will be used for movement (hand vs. eye; note that pIPS and PMd also encode this information independent of the spatial location to be acted upon as shown with cross-trial-type decoding). Based on these findings it seems entirely sensible then that these same areas also encode the motor goal of grasping vs. reaching independent of the effector/kinematics (hand vs. tool) and independent of the object's position in space. Taken together, the results from these two projects demonstrate and re-affirm a distinguishing feature of neural response properties in the PPC and premotor cortex: the motor goal being represented can flexibly adapt to the current

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[6] It is worth restating that the primary objective of Project 3 was to examine where in the brain a motor goal like grasping vs. reaching is represented despite the presence of so many low-level task-related differences (i.e., hand kinematics required, retinal position of the object, etc.), and thus, some level of caution should be applied when directly comparing the two projects.

context of the experimental task (e.g., Calton et al., 2002; Beurze et al., 2007; Baumann et al., 2009; Bernier and Grafton, 2010; Davare et al., 2010; Fluet et al., 2010). In the context of Project 2, both the spatial target location and effector to be used are highly relevant to successful completion of the task (given that both targets are simultaneously present on the platform and the subject needs to know how and which target to act upon) and so it is expected that various forms of these movement parameters be represented. In the context of Project 3, only completion of the motor goal (grasping vs. reaching) is relevant for any single trial (given that only one object appears on the platform for each experimental run and these action goals remain constant regardless of whether the hand or tool is being used) and so it is expected that this also be correspondingly represented at various hierarchical levels, similar to what we have shown.

The question to immediately follow from this discussion then -- specifically given that I have denoted these four areas as being ‘high-level’ and involved in ‘goal’ encoding -- is what types of abstract motor goals are actually being represented in PPC and premotor cortex? The answer to this question has been a matter of ongoing debate and extensive research in both monkeys and humans (e.g., Fagg and Arbib, 1998; Colby and Goldberg, 1999; Rizzolatti and Luppino, 2001; Andersen and Buneo, 2002; Musallam et al., 2004; Rizzolatti and Craighero, 2004; Fogassi and Luppino, 2005; Graziano, 2006; Beurze et al., 2007; Grafton and Hamilton, 2007; Andersen and Cui, 2009; Bisley and Goldberg, 2010) and in some ways, the projects provided here fall short of being able to specifically address this question given that the same ‘types’ of preparatory patterns of activity (at least at the level of detail revealed with cross-trial-type decoding) are found in both premotor and PPC areas. What we do know for certain from these findings, however, is that the preparatory activity patterns clearly reflect the *intention* to perform an action. This notion is supported by the fact that we fail to find any significant decoding prior to the instruction being given to the subject (Preview phase) and importantly, no visual information in the subject’s workspace changes prior to, during, or after the movement instruction is given. Moreover, because the spatial patterns of activity allow for cross-trial-type decoding between effectors, we also know that these actions are not planned with any specification of the kinematics or muscle activations required and therefore they must in some way be abstractly linked to the final goal of the movement. In the case of planning arm vs. eye movements, a sensible and well-supported interpretation is that the intended spatial targets in both PPC and premotor cortex are being represented within a particular sensory frame(s) of reference (e.g., linked to the position of the eye, see Project 2 for a more detailed discussion). In the case of planning hand vs. tool movements, it may be that the abstract action plan only specifies the grasping vs. reaching points on the object (e.g., Baldauf and Deubel, 2010), a notion intimately linked to a more narrowed focus of attention (Rizzolatti et al., 1987; Moore et al., 2003; Bisley and Goldberg, 2010). Alternatively, the action plan may specify general particulars about how the object will be interacted with (e.g., grasping vs. reaching), a notion closely related to some kind of forward state estimation or motor prediction based on efference copies of motor signals detailing what movements the limb will be engaged in moments later (Wolpert et al., 1998; Wolpert and Ghahramani, 2000; Wolpert and Flanagan, 2001; Shadmehr and Wise, 2005). Most commonly in the literature, these types of abstract goal-related representations are ascribed to the functions of the PPC, where presumably the earliest plans for movement are first formed (Andersen and Buneo, 2002). Indeed, PPC movement-related activity is often linked to the retinal coordinates provided by early visual cortex, and these visual reference frames are often independent of the effector to be used (reaches vs. saccades) and sensory cues given (Andersen and Buneo, 2002; Cohen and Andersen, 2002). In many respects, the activity in premotor areas appears to be a further continuation of this abstract processing, except at this level, additional movement related factors are accounted for like the position of the limb and/or position of body in space (Scott et al., 1997; Graziano, 1999; Pesaran et al., 2006; although see Chang et al., 2009 for evidence that this information is also coded in PPC; Bernier and Grafton, 2010) and whether or not a decision has been made to move (Kalaska and Crammond, 1995). As such, unlike the PPC which seems intimately involved in specifying the visual goals of a movement (Fagg and Arbib, 1998; Rizzolatti and Luppino, 2001; Andersen and Buneo, 2002; Culham et al., 2006; Andersen and Cui, 2009) premotor cortex may play a greater role in response selection and directly binding together different pieces of action-related information (Kalaska and Crammond, 1995; Kalaska et al., 1997; Pesaran et al., 2006; Filimon, 2010). Indeed, the anatomical proximity of premotor cortex to higher cognitive centres in prefrontal cortex and lower motor control centres in M1 makes it ideally positioned to receive higher-order signals related to decisions and motivation (from prefrontal cortex) and transform incoming visual features of potential targets from PPC into goal-directed movement commands to be deconstructed by M1.

6.1.2.2 Lower-level kinematic representations in parieto-frontal cortex

Four brain regions in particular show the types of response patterns suggestive of a more prominent in coding the lower-level kinematics of planned actions: three areas in parietal cortex

– SPOC, SMG and aIPS – and one area in the frontal lobe, motor cortex. In Project 1 we found that all areas, with the exception of SMG, predicted grasp vs. reach actions with the hand. This general finding was confirmed in Project 3, with the exception that here we showed that SMG instead codes for movement plans with the tool, consistent with its well known involvement in tool action-related processing (e.g., Johnson-Frey, 2004; Lewis, 2006). Only SPOC activity was examined in Project 2, and consistent with its well established role in reach-related planning, it successfully predicted upcoming reach movements and their directions. It was only in Project 3, however, where we actually had the opportunity to fully characterize the activity patterns in all these four areas with cross-trial-type decoding. We interpreted non-significant cross-classification to mean that the voxel patterns differentiating grasp vs. reach movement plans were too dissimilar across effectors and therefore likely linked to the kinematic differences required to operate the hand and tool. As described in some detail in the Project 3 discussion, effector-specific representations are critical to goal-directed behavior as they allow for the precise muscle-specific implementation of different movements. Frequently this type of kinematic role is largely attributed to a brain area like motor cortex (M1) given its direct anatomical projections to spinal cord neurons (Porter and Lemon, 1993; Chouinard and Paus, 2006) and that much of its neural activity seems to directly reflect intrinsic (e.g., force, velocity) and extrinsic (e.g., location) factors related to movement (Kalaska, 2009). Similarly, to our knowledge, little evidence to date has implicated SPOC in higher-level goal-related processing (although see Bernier and Grafton, 2010). More often than not, its activity is associated with the on-line control of movement (see Grafton, 2010 for review) and more recently, in addition to reach execution, a role in wrist orientation and hand preshaping (Fattori et al., 2009; Fattori et al., 2010). One finding of particular interest, however, is that the activity in aIPS (both post. aIPS and aIPS) appears so closely linked to the planned movement kinematics.

AIP has been often implicated in goal-related processing due to its close anatomical proximity to goal-related activations in the inferior parietal lobule of the macaque monkey (Fogassi et al., 2005; Rozzi et al., 2008; Bonini et al., 2011) and the fact that the area is activated during action observations in humans (Hamilton and Grafton, 2006a; Hamilton and Grafton, 2006b; Hamilton et al., 2006; Dinstein et al., 2008; Hamilton and Grafton, 2008; Oosterhof et al., 2010). This latter finding, however, relies on implicit assumptions of a mirroring or motor simulation between the observation of a motor act and performance of that same act (Rizzolatti et al., 2001; Rizzolatti and Craighero, 2004, see also Project 3 discussion for a brief overview of this literature). It is worth recognizing, however, that the anatomical location of aIPS – situated directly adjacent to somatosensory cortex – optimally positions it to receive proprioceptive feedback signals related to grasping (Culham, 2004) and maintain sensitivity to kinematic properties like grip force and scaling (Ehrsson et al., 2003; , see also Johansson and Flanagan, 2009 for review). Moreover, increasing neural evidence has noted a more prominent role for aIPS in stereoscopic vision, showing that its activity is modulated by spatial target features like position in depth and in the fronto-parallel plane (Sakata et al., 1999; Durand et al., 2007; Joly et al., 2009; Srivastava et al., 2009). In addition, fMRI activity in aIPS increases as the grasp precision and grasp difficulty increases (Begliomini et al., 2007; Verhagen et al., 2008). These types of visual-motor neural response properties would seem unlikely to appear in a brain region more abstractly removed from the kinematic properties of the task. Thus, if aIPS is involved in goal-centred coding – which it very well may be -- then it might instead provide some sort of link or interface between low-level kinematic and high-level abstract representations of movement. This type of arrangement might help reconcile previous fMRI work from our lab showing that aIPS is selective for both the object (goal) and the kinematics used for grasping during the execution phase of the movement (Kroliczak et al., 2008), and in Project 3, why grasp vs. reach action planning in aIPS might still evoke voxel activity patterns that fail to transfer between movement effectors (like the hand and tool). More generally of course, these disparate findings in human aIPS (i.e., goal-encoding during action observation and kinematic encoding during grasping) may also suggest that the area plays complementary yet different roles in the both the understanding and generation of action intentions.

Compared to the more abstract goal-related representations found in PPC and premotor cortex (noted in the previous section), the activity in the areas reported here provide for a more straightforward and less speculative interpretation. Preparatory voxel patterns in motor cortex likely represent the muscle activations and detailed mechanics required by the hand/limb for the upcoming movements (Kalaska, 2009). Similarly, SPOC and aIPS likely encode specific parameters related to the integration and coordination of the reach and grasp components of the planned action (Grafton, 2010) but by all accounts (Andersen and Buneo, 2002; Chouinard and Paus, 2006; Cisek and Kalaska, 2010; Filimon, 2010), specify these movements at a higher-level than motor cortex. SMG activity, as suggested in the Project 3 discussion, instead seems specialized for coding tool-use and its associated actions (Lewis, 2006; Valyear et al., 2007; Peeters et al., 2009; Valyear and Culham, 2010). Specifying actions at these intermediate kinematic levels is central to the transformation of abstract movement goals into the displacement of muscles and limbs.

6.1.3 Intention vs. Attention

Despite several decades of considerable psychological and neuroscientific research into understanding attention and its related processes, William James' classic description in his seminal work, Principles of Psychology (1890), remains just as pertinent and explanatory today as it did more than a century ago:

> "Everyone knows what attention is...the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, and consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others."

This rather broad description seemingly encompasses nearly all aspects of our own internal, subjective experience of the world around us, and this fact, among other things, has made attention a particularly difficult process to study within the confines of the laboratory. Some traction on this front, however, has been gained by studying not attention per se (after all, any reasonable description of attention emphasizes that it is, by and large, a highly covert process) but rather the overt, easily observable behaviours that can result from internal attentional processes and their associated cognitive states. Indeed, the tight linkage between attention and action was also noted by James (1890) himself: "When we look or listen we accommodate our eyes and ears involuntarily, and we turn our head and body as well." This important observation, along with significant experimental evidence showing that attention is often directed to the location of planned movements (Deubel and Schneider, 1996; Moore and Fallah, 2001; Bisley and Goldberg, 2003) and that the focus attention can affect the metrics of movements (Kustov and Robinson, 1996), has lead to several suggestions that the processes subserving attention and movement planning may rely upon or share common mechanisms (Rizzolatti et al., 1987; Bisley and Goldberg, 2003; Baldauf and Deubel, 2010). Several attempts have been made to explicitly test these notions by examining whether the processes of action planning and attention selection can be dissociated. Despite innumerable investigations into this matter, the seperability of these two mechanisms remains a matter of considerable and ongoing debate.

The source of primary contention in the field of sensorimotor neuroscience is whether the preparatory responses that form prior to movement execution in several brain regions in both humans and monkeys reflect an intentional response to perform the upcoming movement or alternatively, some sort of sensory and/or top-down attentional response. Put another way, and framed as a question: Does the persistant activity in a given brain region reflect a movement *intention* or the focus of *attention* for the location of the action? While on the surface this distinction might appear fairly subtle, the answer to this question can provide fundamental insights into what drives the persistent activity in neurons and ultimately, how the brain produces goal-directed behaviour. To disambiguate these two processes (i.e., intention vs. attention) many investigators have opted to use some variant of a delay memory task ((Hikosaka and Wurtz, 1983), note that this task was described in some detail in the Introduction, see Figure 1.5). In this task the monkey (or human) is cued to the location of a movement, but the cue quickly disappears and the subject is required to perform a movement (e.g., with the eye or hand) to the remembered target location after some delay period. As such, the sensory/attentional response of the cue can be dissociated from any persistant activity that develops prior to movement (Snyder et al., 1997). Another popular task employed to dissociate attention- vs. intention-related responses is the anti-movement task. In this type of task the visual stimulus cuing the movement and the final destination of the movement are incongruent. For instance, in some studies, monkeys (or humans) will be trained to perform an action in the direction opposite the appearance of a stimulus. Importantly, this manipulation further allows the experimenter to uncouple the sensory and motor consequences of the task and examine whether this sensory vs. motor separation is observable at the level of individual neurons (or large populations of neurons in the case of fMRI). Findings from these types of tasks have been largely mixed, with some labs reporting parietal neurons with a primarily sensory-related or attentional coding for the location of the stimulus (Gottlieb et al., 1998; Colby and Goldberg, 1999; Gottlieb and Goldberg, 1999; Bisley and Goldberg, 2003) with other groups instead finding primarily movement-related or intentional coding for the direction of the movement (Snyder et al., 1997; Zhang and Barash, 2000, 2004). Interestingly, many of the interpretations of these findings are complicated by the fact that neurons in several parietal structures – and the lateral intraparietal area (LIP) in particular – show large transient neural responses for flashed irrelevant cues (Powell and Goldberg, 2000; Bisley and Goldberg, 2003). Certainly, these transient-type sensory responses would be expected in areas involved in shifting attention or creating salience/priority maps of visual space (presumably in order to guide future attentional resources), but perhaps not necessarily in areas directly linked to intention-related processes (that is, unless the transient response reflects a brief shift in *intention* or a default movement plan for the flashed target (for further discussion of this fact, see Andersen and Cui, 2009).

Another substantial contribution to this debate has been the discovery of effector-specific neural responses (described in some detail in this thesis, but its direct implications were not fully developed and emphasized). That is, some brain areas code not only the spatial location of an upcoming target (spatial specificity), but also rather importantly, how that target will be interacted with (effector-specificity, for example, eye vs. limb effector, see Snyder et al., 1997; Cui and Andersen, 2007, see also the Project 2 findings). This is an important distinction to be made, because if neural responses in areas like parietal or premotor cortex were purely attentional or sensory in nature, then they should not be expected to discriminate the effector that will be used to act upon that sensory stimulus. The multiplexing of these spatial and non-spatial (where and how) signals within single neurons fits well within an intentional framework (Andersen and Buneo, 2002). Nevertheless, this finding, and others, has also lead to an expansion of the definition of attention to include what might be considered ‘motor attention’ (Rushworth et al., 2001), an attention specific to the effector to be used.

While more on this ongoing debate could be discussed, it is probably becoming clear to the reader that similar questions might be posed for the findings reported in this thesis. For instance, could the effects I have reported as being *intentional* in nature, not simply be re-framed and discussed as being merely *attentional*? Hopefully I have been able to briefly overview the difficulty of disambiguating these two processes, and indeed, at present, it remains unclear – at least from my viewpoint -- whether attempts to separate attention and intention are actually helpful from the perspective of understanding brain function and organization. More to the point, it seems worth reconsidering whether or not these proposed intention vs. attention distinctions, which exist in our language, actually have a cognitive counterpart in the underlying neural mechanisms that guide behaviour. Certainly, just because it aids discussions and helps investigators to think about neural events as being parcelled/categorized into strictly sensory-, cognitive-, or motor-related divisions, this does not in itself necessitate that the brain, which has been largely conserved throughout evolution, respects these theoretical distinctions (for further discussions on these similar issues, see Culham and Kanwisher, 2001; Cisek and Kalaska, 2010).

The neural processes characterized in the present set of experiments have been described as motor intentions for the very reason that I am interested in investigating how goal-directed actions are coded in the human brain, and it is often much more useful to describe these types of processes as being products of one's intentions. In contrast, descriptions of attention generally not only subsumes processes related to action planning but also commonly encompasses a much larger and far more inclusive range of cognitive processes (Bisley and Goldberg, 2003), where sensory stimuli are further selected for many different and diverse facets of additional neuronal processing. I tend to agree with previously noted distinctions which emphasize that while behaviours like eye movements may allow one to infer certain aspects related to the underlying attentional states of an individual (e.g., shifts in the focus of attention), this does not therefore necessitate that an examination of the neural mechanisms that underlie eye movements is an examination of attention itself (e.g., Andersen and Buneo, 2002; Andersen and Cui, 2009). Indeed, as noted by Andersen and Cui (2009): "...asserting that the oculomotor neurons in the brainstem control attention rather than move the eyes would not be a useful construct" and, "...over-generalizing attention to encompass a large variety of different neural processes weakens the concept and undercuts the ability to develop a robust understanding of other cognitive functions."

6.2 Methodological and minor theoretical considerations

There remain just a few outstanding issues and caveats to the interpretation of the present findings that require some attention. I will now briefly turn to discuss some of these in the sections that follow.

6.2.1 Planning- vs. Execution-related activity:

An important finding illustrated by the current set of projects is that, despite what might be intuitive, the decoding of movement intentions is far more reliable than the decoding of the executed movements. One possible interpretation of this finding is that it might emphasize dissociations within an area with respect to its role in motor planning vs. execution. For instance, it has been argued that the dorso-lateral circuit might be specialized for movement planning and goal-directed processing, while the dorso-medial circuit might alternatively be specialized for the on-line visual-motor control of a movement (for example, see Desmurget et al., 1999; Pisella et al., 2000; Glover, 2004; Grafton, 2010). Moreover, the tuning of individual motor-related neurons can shift between the time where the action is planned and the movement is initiated (e.g., Baumann et al., 2009; Churchland et al., 2010). While these options are certainly possible, the far more parsimonious explanation for the additional sensitivity we observe during movement planning vs. execution is that motion artifacts are introduced into the data when the limb perturbs the magnetic field of the scanner (Culham, 2006, we noted this as providing a great challenge for movement-related fMRI studies in the Introduction). While these motion artifacts do not appear to affect the fMRI signal amplitudes shown here (note the absence of fMRI data spikes in Figures 3.3, 4.3. 5.2), it remains unclear how they might affect the spatial patterns of the signals being measured[7]. In addition to this important motion-related consideration, the differences in decoding observed during the execution phase of the trial (with respect to the Plan phase) might also be reflective of pattern differences which emerge from the preceding Plan phase. That is, any trial-specific spatial pattern differences accrued during the Plan phase may negatively bias or influence the extent to which pattern differences can be elicited following movement execution (similar to the issues created by baseline differences in standard voxel-wise univariate analyses). While the level of contamination on the Execute phase spatial patterns from either the limb movement or the preceding Plan phase are difficult to assess from a multivariate perspective, there are certainly cases in our data where Execute phase decoding seems sensible. For instance, a highly reasonable finding is that our somatosensory ROI only shows accurate decoding following the execution of the different hand actions in all three projects, notably the only time when the hand's mechanoreceptors are activated. Nevertheless, because of the apparent disconnect between Plan and Execute phase decoding in several of the areas, and in light of the methodological and theoretical considerations mentioned above, I believe that convincing interpretations can only be applied with respect to the plan-related function of a given area.

6.2.2 Caveats to interpretations from standard decoding analyses

While accurate decoding strongly argues for different underlying neural representations with respect to two conditions (Norman et al., 2006), a lack of decoding (~50% chance classification) or null effect, could either mean 1) neural/pattern differences exist but these differences are not picked up by our support vector pattern classifiers (i.e., limit of methodology, Pereira and Botvinick, 2011), 2) the two conditions being compared engage the area in similar or

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[7] Note that this execution-related artifact problem was an additional motivating factor (i.e., in addition to the novel theoretical questions being asked in each project) to examine whether we could decode motor intentions prior to initiation of the movement.

indistinguishable processes (i.e., same neural recruitment) or 3) the area is not recruited for either of the two conditions (i.e., indifferent to task). With respect to the current set of projects, given that we selected all of our parieto-frontal regions based on showing higher activity for action planning (and execution) than the simple visual transient responses which accompany presentation of the object, it stands to reason that all of the defined areas are in some way utilized during movement generation (note that this suggestion seems overwhelmingly confirmed by the highly overlapping and higher than baseline response amplitudes in each region across the three projects, see Figures 3.3, 4.3, and 5.2). Thus, it is reasonable to assume that an area that fails to decode between two planned movements is either 1) likely to contain real pattern differences that we cannot detect with our current SVM methodology *or* 2) perhaps more intuitively, play a similar functional role in their generation. Although I cannot definitively rule out this first possibility, the pattern of decoding profiles noted in Projects 1 and 2 – namely, that the distinguishing feature of nearly all parieto-frontal regions was whether or not the area could additionally discriminate precision grasps upon objects of different sizes or discriminate eye movement directions, respectively -- seems to suggest that many of the non-decoding pair-wise comparisons are indicative of shared functional role for the motor plans examined (e.g., in the case of Project 1, a general non-discriminative role in precision grasping and in the case of Project 2, a largely non-discriminate role in the planning of eye movements).

6.2.3 Caveats to interpretations from cross-trial-type decoding analyses (emphasis on Project 3 findings)

Although straightforward interpretations can be applied to accurate cross-trial-type classification results in an brain area where the patterns of activity already discriminate the movement goals within effector (i.e., Hand-G vs. Hand-R *AND* Tool-G vs. Tool-R trial types) – that is, in these areas it must be that the higher-level goals of grasping vs. reaching are represented given that the kinematics of the hand differ appreciably between effectors -- there are a few instances in our data where these same types of interpretations are difficult. For instance, note in Figure 5.7 that during the execute phase of the trial we find significant cross-trial-type decoding in PMd and PMv while at the same time both these regions fail to show accurate decoding using within-effector MVPA for Hand-G vs. Hand-R trials (see Figure 5.6; also note that a similar disconnect can be found in a few time points in the time-resolved decoding analysis shown in Figures 5.4, 5.5). Similar to statistically significant below chance decoding (which we do report in a few brain areas, see Figures 5.3, 5.4, and 5.5), one cannot claim success of the pattern classifier in these cases and we appreciate that no firm conclusions can be drawn from these outlier observations (Pereira et al., 2009).

6.2.4 Corrections for multiple comparisons?

For the decoding accuracies presented throughout Projects 1-3, we did not employ corrections for multiple comparisons (i.e., the number of t-tests or ROIs) given a variety of important methodological and theoretical considerations that we present here. First and foremost, it is not intuitively clear, given the goals of this experiment, which level of Bonferroni correction is appropriate. That is, should we be correcting for the number of total pair-wise comparisons made within an ROI, the number of comparisons made within a single time-phase, or correcting for the total number of action-related ROIs in which we implemented pattern analyses? It is important to note that while the initial aim of such corrections would be to reduce type I errors (false positives), the far more likely outcome would be a drastic increase in the number of type II errors committed (false negatives; for detailed discussion see (Lieberman and Cunningham, 2009)). An alternate solution to limit the number of corrections required might be to also reduce the number of ROIs reported (e.g., only report parietal *or* premotor regions, and not both), but again this approach would greatly facilitate Type II errors. Due to these issues, we report several quantitative and qualitative results ensuring that our findings are unlikely due to chance while at the same time, avoiding Type II errors.

First, given the aims of this study (i.e., to decode object-directed movement plans and pinpoint exactly when the predictive information arises), I knew it was imperative to find no significant decoding during the Preview phase, when subjects were naïve with respect to the upcoming action (for confirmation of this fact, see Figure 3.4, 4.4, for example). In addition, we might expect areas showing significant decoding above 50% during planning to also have significantly higher decoding than the preceding Preview phase. To assess this we performed within-trial paired t-tests to determine whether movement planning accuracies were significantly higher than those elicited earlier in the same trial by the object's visual presentation (note that this was only done as a proof-of-concept in Project 1, see Figure 3.4). In effect, by applying the conjunction of these two tests to assess significance (Plan vs. 50% and Plan vs. Preview), it seems reasonable to interpret with great confidence the particular planning or intention-related role of a brain region.

Second, recall the results of our randomization tests which empirically defined true chance classification based on a random shuffling of the test labels (~50% based on an average of the one hundred permutations of Test trial identities within each subject). Critically, these non-parametric permutation tests largely confirmed our parametric t-test findings (i.e., the brain regions which showed significant decoding with t-tests also showed highly significant decoding (p<0.001) based on an empirical probability distribution), with the only exception being that the permutation tests revealed significant decoding in areas not detected with conventional parametric analyses (see also Chen et al., 2010; Smith and Muckli, 2010). Importantly, this latter finding in itself suggests that parametric t-tests may already be highly conservative. Nevertheless, the additional rigor provided by this empirical test provides further evidence that the significant decoding results reported in several parieto-frontal areas across the three projects are not purely random occurrences.

Third, and rather importantly, we report no significant pattern classification (vs. 50%) in any of our sensory control regions during movement planning (a Type I error control) in any of the three projects. Moreover, for the several brain areas within the parieto-frontal network that do allow for the accurate decoding of movement plans, their accuracy profiles are largely intuitive. For instance, in the case of Project 1, a brain area differentiating an upcoming grasp movement from a touch movement should be expected to show significant decoding for GT vs. Touch *and* GB vs. Touch trials. Moreover, a brain area discriminating the precision required by the two planned grip types (GT vs. GB) should *also* certainly be expected to decode the less subtle differences required by the grasp vs. touch movements (see Figure 3.4 for verification). In addition, a strong argument can be made for the reliability of these findings based on the consistency of movement plan decoding in both Projects 1 and 3 and across two separate populations of fMRI subjects. For instance, all of the parieto-frontal brain areas in Project 1 able to predict upcoming grasp vs. reach actions were also found to predict the same two actions in Project 3 (when subjects used their hand).

Taken together, these three main observations provide strong arguments as to why the decoding accuracies we report in the three projects from our delayed-movement task are likely to reflect genuine plan-related neural differences. As such, instead of applying strict Bonferroni corrections for accuracies elicited during the Plan (and Execute) phase of the trial, we report the different levels of significance within each ROI (* = p<0.05, ** = p<0.01, *** = p<0.005, **** = p<0.001; with respect to 50%), ultimately allowing the reader, given the several important considerations above, to apply their own estimates of statistical significance.

6.3 Future Directions

Several different experimental questions were asked in the present research projects and I would argue that many of them have been answered. For instance, can we decode intentions related to goal-directed actions from human brain activity? Unequivocally, yes. Can we characterize different brain areas according to the types of action intentions they decode? I think we have provided good evidence for that fact here. Furthermore, can we describe the hierarchical level at which a particular brain region represents upcoming movements? Again, I believe we have provided sufficient evidence for this to be the case. But for every question we have answered, newer questions are revealed. For instance, what other types of action-related or object-related information is contained in these intention-related signals? In what specific contexts can we disambiguate the neural coding between PPC and premotor cortex? Why are these intention-related signals maintained several seconds prior to the action actually being initiated? Is there additional movement-related information contained in the *temporal* profile with which these spatial patterns of activity change? I should also emphasize that my three projects have focused rather exclusively on the role of parieto-frontal cortex in coding sensorimotor behaviors -- namely because a long and rich literature suggests that this is the first place we should look – but this does not of course exclude the possibility that intention-related signals are present elsewhere in the brain. For instance, it seems reasonable to suspect that several highly cognitive areas in prefrontal cortex might also encode the upcoming choices and behaviors of an individual. After all, prefrontal cortex is generally thought to provide the neural substrate for most aspects of higher-level cognition and decision-making (Purves et al., 2008, pp 663-686) and directly influence both perceptual and action-related representations in ventral-temporal cortex and premotor cortex, respectively (Rizzolatti and Luppino, 2001; Cisek and Kalaska, 2010). Moreover, while most lines of research in systems neuroscience focus on feed-forward or ‘bottom-up’ functional connections between brain structures and their coordination in goal-directed movement (e.g., those that originate from early visual cortex to PPC), we know relatively little about the extensive web of feedback connections that link higher cortical areas with lower-level areas (e.g., back projections from PPC to early visual cortex). These ‘top-down’ projections are thought to facilitate perceptual processes like attention and object recognition by selecting visual items of interest in the world for additional processing by lower-level visual cortical areas (Hupe et al., 1998; Super et al., 2001; Ress and Heeger, 2003; Jehee et al., 2007).

A particularly important component of nearly all theories of feedback connections in perceptual processing is that the destination of the feedback projection is the same cortical location as the origin of the feed-forward representation (although see Williams et al., 2008). In this way, processing of the initial neural representation in visual cortex is directly modulated (e.g., sharpened, enhanced) by descending feedback connections, allowing a direct one-to-one mapping of the stimulus-related and attention-related neural responses. But this is all related to perception; what about action?

As I hope I have managed to make clear in my projects, the brain does much more than simply perceive and attend to objects in the world; it provides us with the capability of changing our environment. So, do feedback projections related to action intentions from PPC also influence early visual representations of targets? There is already some evidence from human fMRI and neural recordings in non-human primates to suggest that this may in fact be the case. For instance, during eye movements it has been demonstrated that early visual cortex remaps the previous cortical location of a briefly presented stimulus to a newly updated location corresponding with the most current position of the eye (Nakamura and Colby, 2002; Merriam et al., 2007). This cortical updating presumably allows for a stable visual perception of our surroundings despite multiple shifts in the retinal image caused by voluntary eye movements. We of course, however, do not just act on our surrounding environment with our eyes but also with hand movements, like reaching and grasping (indeed, eye movements by themselves are unable to actually manipulate objects within our proximity). Do early visual cortical areas also contain this information prior to an action being initiated? More specifically, can visual cortex activity predict whether the subject will make a grasp, reach or eye movement to a specific target location?

6.3.1 Does early visual cortex provide a 'read-out' of a subject's intentions?

We have already begun investigating this intriguing question with a re-analysis of the data collected for Projects 1 and 2. Recall that in both of these projects, prior to the movement being initiated, the object position(s) never changed and thus any prediction of the subject's upcoming movements from early visual cortex activity can only reflect differences in the planned action (presumably reflecting feedback projections from visual-motor-related structures in parieto-frontal cortex). Using the exact same MVPA methods employed in each project and by approximately mapping the retinal positions of the target objects in visual cortex (based on previously collected retinotopic data in two subjects and combined with some knowledge of the visual angles of the targets) we found that we could decode the subject's motor intentions, several seconds prior to the action being performed (see Figures 6.2 and 6.3). A somewhat more unexpected finding, however, was that in project 2, unilateral visual cortex activity could also predict the effector to be used for movement into the ipsilateral visual field. Based on the well-established contralateral organization of lower-level visual cortex (Purves et al., 2008, pp 289-312) this necessitates that unilateral visual cortex contains effector-specific movement information for actions to targets that remain 'unseen' or hidden from its field of view. One possible reconciliation of this discrepancy is to assume that in addition to visual cortex 'selecting' which movement to perform (left vs. right target) it also at the same time 'de-selects' the uncued target location (i.e., if the left target is selected, the right target is de-selected), but does so in a way that is specific to the cued effector (for more on target de-selection see Baldauf and Deubel, 2010; Bisley and Goldberg, 2010; Chapman, 2010; Cisek and Kalaska, 2010). While further experiments are currently being run in order to validate these startling observations, the present results would seem to substantially alter currently held views on the types of neural processing and feedback connections present in visual cortex. For instance, visual cortex has a well-documented role in attention-related processing but why would visual cortex receive differential feedback signals (e.g., from eye- and arm-related areas in PPC) depending on the type of effector to be used in an upcoming movement? More to the point, what purpose would this effector-specific feedback modulation serve? One possible explanation is that different amounts of object-directed attention are needed for saccades vs. reaches (e.g., saccades requiring more precision than reaches) and this is what is being reflected in the preparatory activity patterns in visual cortex. Alternatively, this finding might reflect some anticipatory response or the arrival of efference copy signals in preparation for an impending whole visual field shift (in the case of a saccade) vs. movement of only the arm in the visual field (in the case of a reach movement), allowing the early visual system to easily disambiguate the two types of actions once executed. Whatever the reason, it remains to be determined how these preparatory visual signals differ from the plan-related responses observed in parieto-frontal cortex. Certainly, it would be perculiar to suggest that both visual and parieto-frontal cortex are doing the exact same thing in the context of action planning but nevertheless, both areas are equally predictive (perhaps visual cortex even more so when taking into account the high % decoding accuracies) of a subject's upcoming movement and this finding leads to the odd notion that with the appropriate brain decoder, movement-impaired patient populations could control neural prosthetic devices with early visual cortex signals.

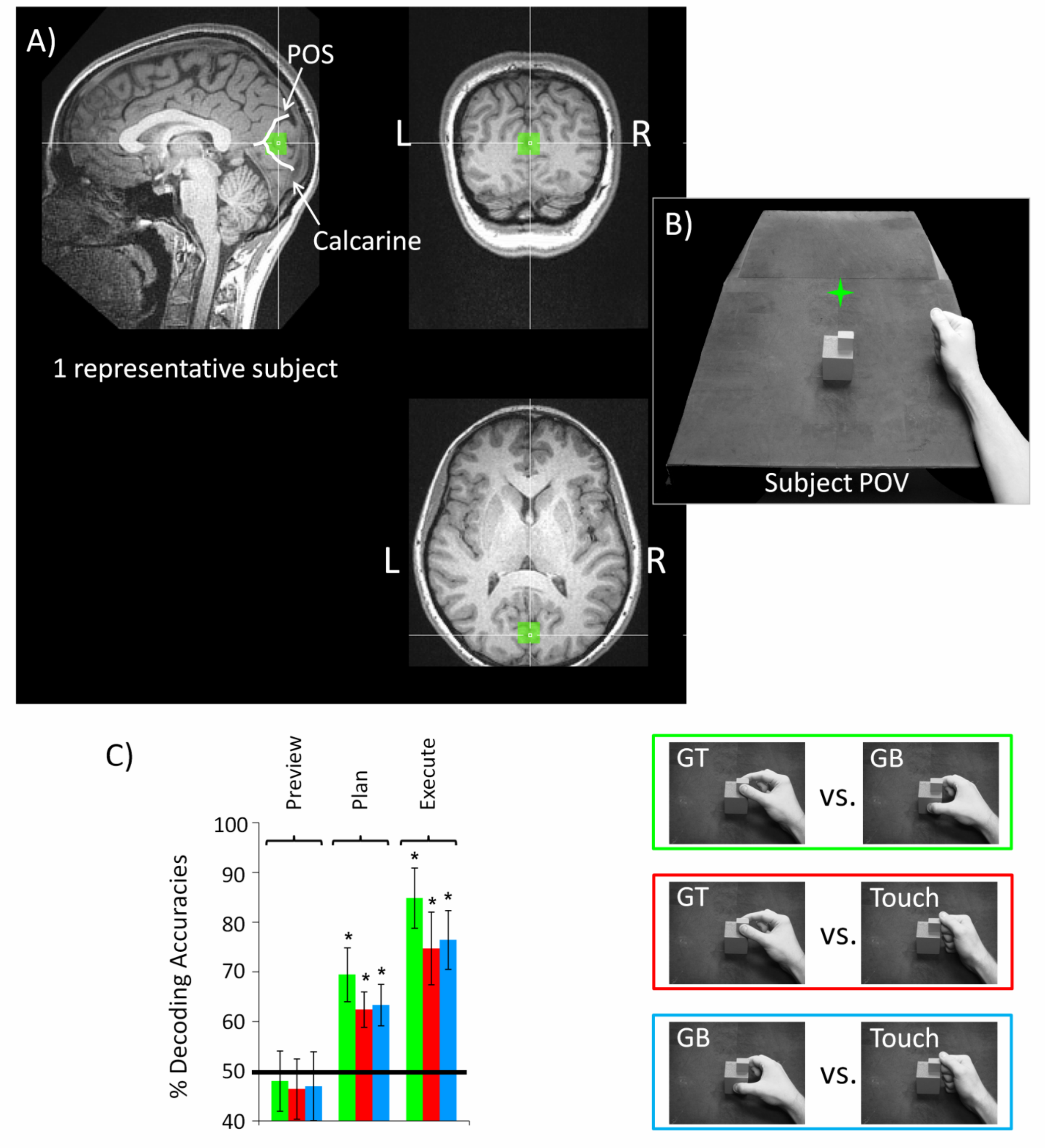


Figure 6.2: Upcoming grasp and reach movements predicted from early visual cortex activity based on a re-analysis of Project 1 data. Non-foveal early visual cortex activity shown in the brain of one representative subject (**A**) corresponding to the approximate lower visual field location of the centrally-located object (**B**). Visual cortex activity in **A** was localized by the contrast of Preview > Baseline. **C**) Classifier decoding accuracies (left) correspond to the visual cortex activity in **A** for the three trial phases examined in Project 1 (Preview, Plan and Execute) according to the three possible pair-wise comparisons (right). Errors bars represent SEM across subjects. Solid black lines are chance accuracy level (50%). Black asterisk assesses statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=$p<0.05$). L = Left, R =

Right, POS = parieto-occipital sulcus, GT = Grasp Top, GB = Grasp Bottom. See Project 1 for further details.

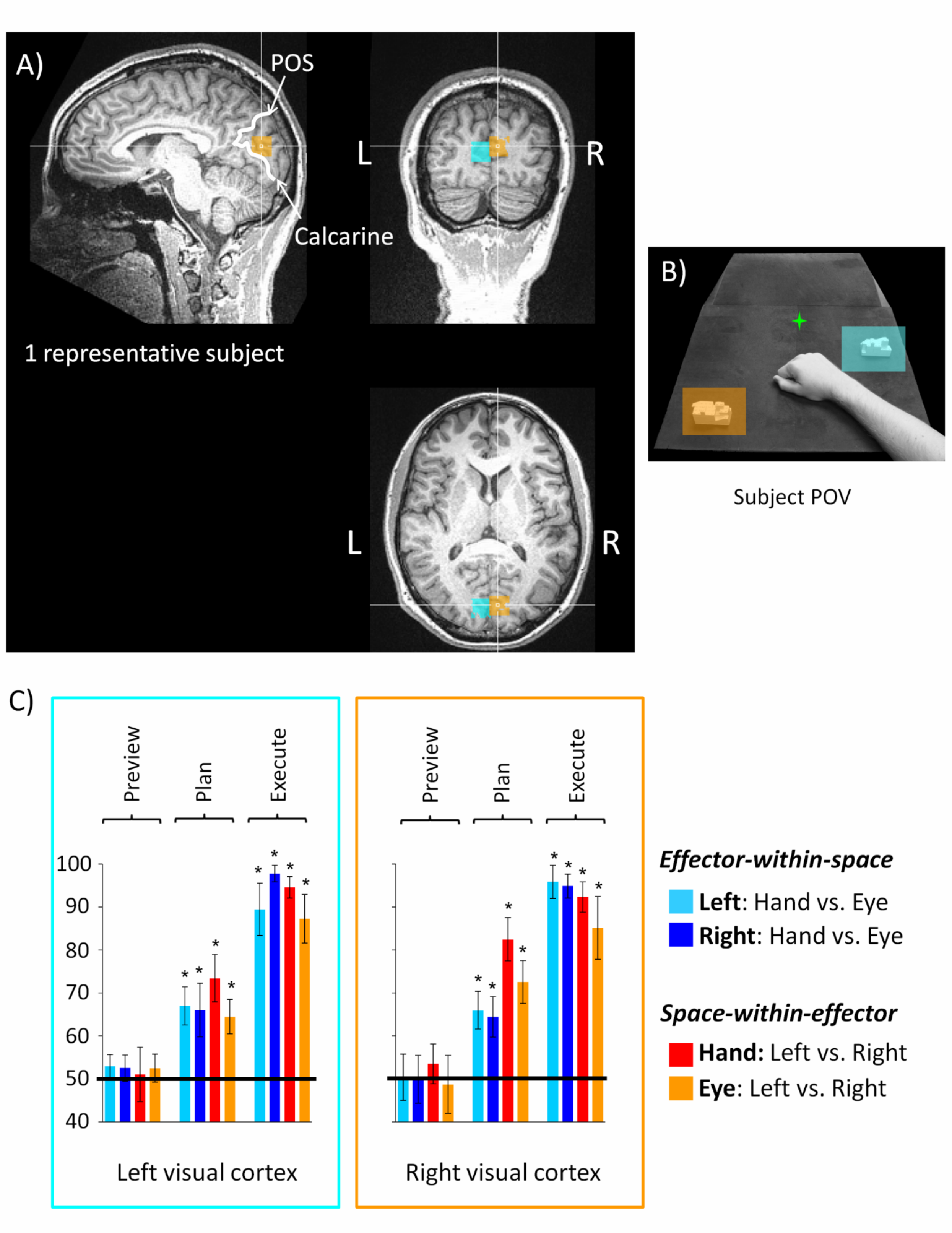


Figure 6.3: Upcoming reach and eye movements predicted from early visual cortex activity based on a re-analysis of Project 2 data. Non-foveal visual cortex activity shown in the brain of one representative subject **(A)** corresponding to the approximate lower visual field locations of both the left- (in orange) and right- (in turquoise) positioned objects **(B)**. In **B**, objects are

shown from subject point of view. Visual cortex activity in **A** was localized by the contrast of Preview > Baseline. **C)** Classifier decoding accuracies (left) correspond to the visual cortex activity in **A** for the three trial phases examined in Project 2 (Preview, Plan and Execute) according to four pair-wise comparisons (right). Note that color-coded borders around each set of decoding accuracies in **C** correspond to the visual cortex activity from one hemisphere. Interestingly, also note that in both early visual areas there is a decoding for planned movements in the 'unseen' ipsilateral visual field. Errors bars represent SEM across subjects. Solid black lines are chance accuracy level (50%). Black asterisk assesses statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=$p<0.05$). L = Left, R = Right, POS = parieto-occipital sulcus. See Project 2 for further details.

Beyond early visual cortex and more broadly speaking, these findings also have fundamental and far-reaching implications for our understanding of action-related processing in the brain. For instance, in light of these most recent findings, I have also just begun exploring whether movement intention-related information can also be decoded from more traditional perceptual structures involved in object-related visual processing located in ventral visual cortex. I will now briefly highlight some promising findings from these additional investigations.

6.3.2 Do object-processing perceptual regions provide a 'read-out' of a subject's intentions?

These exciting and largely unexpected findings in early visual cortex led us to a somewhat unusual prediction: That object-processing perceptual areas in the ventral visual pathway might also predict upcoming goal-directed actions. This prediction is based on the assumption that the intention-related signals in early visual cortex (originating from feedback projections in parieto-frontal cortex) would feed-forward and influence the neural processing in anterior ventral visual areas. This finding, at least within the context of our current understanding of human and monkey ventral visual stream function, would be rather surprising since these areas are traditionally assumed to serve largely perceptual roles (e.g., shape recognition, etc. Malach et al., 1995; Grill-Spector et al., 2001; Kanwisher, 2001; Kanwisher et al., 2001; Grill-Spector, 2003; Grill-Spector and Malach, 2004) and to our knowledge, no direct neural evidence to date has specified any sort of movement planning-related function. If any particular ventral stream visual area were to contain signals related to motor intentions we hypothesized that the lateral occipital complex (LOC) area would be the most likely. LOC is a central visual processing region intimately linked to object perception and highly interconnected with more anterior regions in ventral temporal cortex involved in higher-level perceptual processing (e.g., face recognition, visual scene processing, etc. Grill-Spector and Malach, 2004). Moreover, LOC shares direct anatomical connections with aIPS in parietal cortex (Borra et al., 2008), and is thus likely to share important visual target-related information with neurons involved in grasping. As such, apart from possibly receiving intention-related signals from early visual cortex structures it is also reasonable to suspect that LOC may be privy to grasp-related information being represented in aIPS.

We have recently begun investigating whether LOC contains intention-related signals by re-analyzing the hand movement data from Project 1. After localizing left and right LOC activity in each of our Project 1 subjects and implementing the exact same MVPA analyses, we found that

LOC could decode, similar to visual cortex, the different movement plans for the hand (see Figure 6.4). This finding suggests a far more prominent role for LOC in action encoding than initially thought and will prompt us to reconsider what particular types of object-related information are being represented in ventral cortex. We are currently following up on this novel finding with a second fMRI experiment in order to replicate these LOC findings but also ask new additional questions. For instance, is the activity in more anterior brain areas involved in face processing and visual scene recognition also predictive of a subject's upcoming behaviors? The answers to these questions will no doubt have a profound impact on the way we view visual processing in ventral visual cortex, perhaps expanding our working definition of what visual-perceptual or visual-motor processing actually means and in doing so, open the door for a more complete knowledge of brain function.

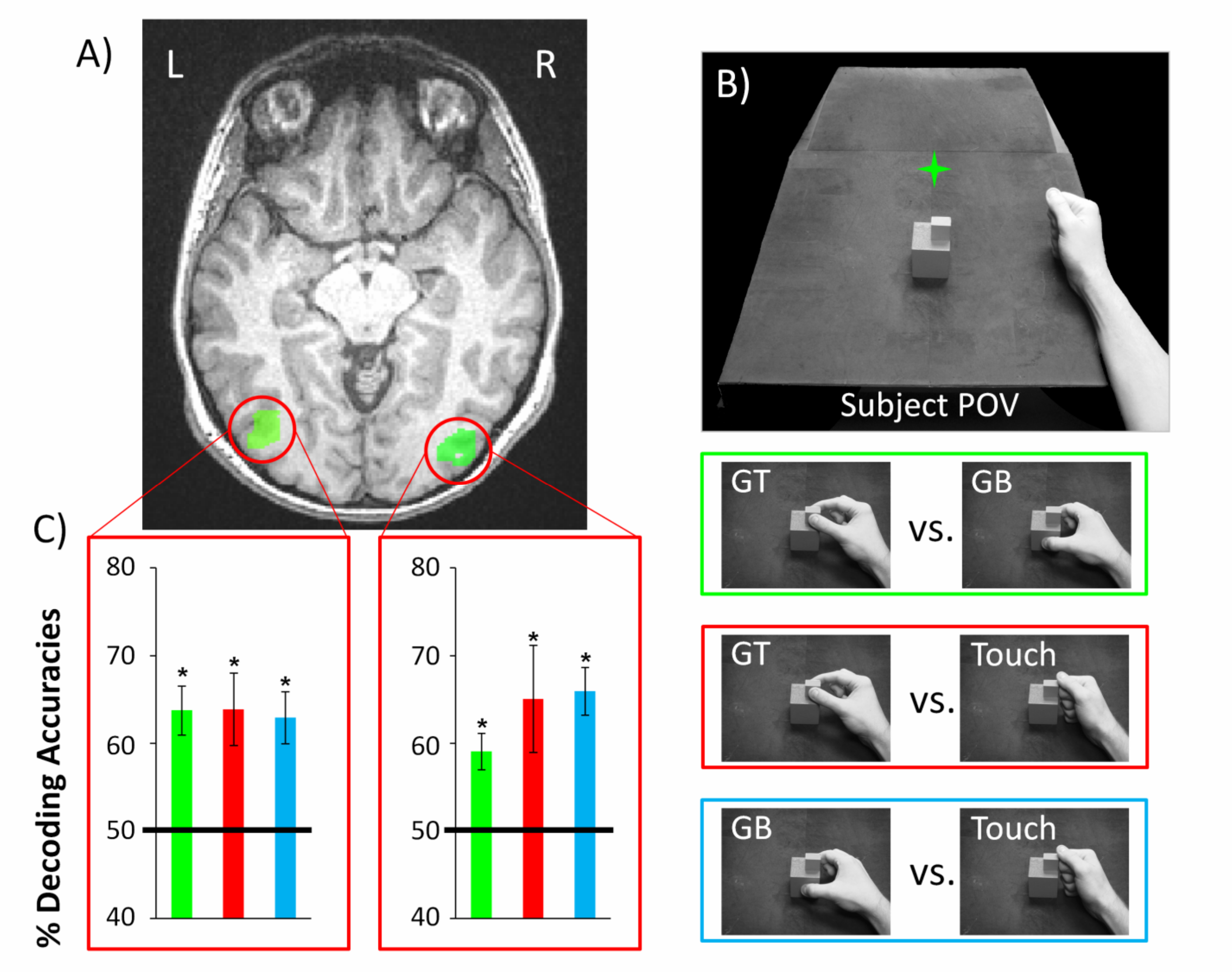


Figure 6.4: Upcoming grasp and reach movements predicted from the Lateral Occipital Complex (LOC) area based on a re-analysis of Project 1 data. **A)** Left and right LOC (shown in green) localized by the contrast of Preview > Baseline and shown on the brain of one representative subject. **B)** Experimental setup shown from subject point of view. **C)** Classifier decoding accuracies (left) correspond to the left and right LOC activity in **A** for the plan phase only, according to the three possible pair-wise comparisons (right). Errors bars represent SEM across subjects. Solid black lines are chance accuracy level (50%). Black asterisk assesses statistical significance with 2-tailed t-tests across subjects with respect to 50% (*=p<0.05). L = Left, R = Right, GT = Grasp Top, GB = Grasp Bottom. See Project 1 for further details.

6.3.3 Other future directions: Examining ecologically-relevant behavior

A highly challenging but critical next step in moving forward will be to map out the intention-related signals and neural organization that subserves more natural, ecologically-relevant behavior. In the real-world, object-directed reach and grasp movements -- those which I have studied so far -- rarely on their own constitute the completion of a planned action. More often the case, the end-goal is further object manipulation (e.g., to lift the object) and initiating a more complex sequence of movements, in which only the single acts of grasping and lifting are embedded. At these higher, more abstract levels of movement planning additional factors need to be taken into consideration -- like not only the object's dynamics required for lifting (e.g., weight), but also the proper sequencing of distinct motor acts (reaching, grasping, lifting, etc.) needed to achieve the desired end-goal. Characterizing human neural activity at these more complex stages of action planning remains largely uncharted territory and yet understanding the hierarchical neural architecture that underlies these seemingly simple, everyday object-directed behaviors remains critical to understanding many aspects of higher-level human cognition. I intend to pursue this line of research in my post-doctoral studies.

6.4 Concluding remarks

Neurophysiological recordings in awake, behaving non-human primates represent the gold-standard in systems neuroscience. Undoubtedly, the ability to record from the activity of individual neurons has provided much of our current understanding of sensorimotor brain function and indeed in many ways, most human fMRI studies with investigations of a similar nature have been largely playing 'catch-up', determined to replicate several findings and observations noted in the monkey. A perfect example of this fact is provided in the motivation of Projects 1 and 2 here. These studies were largely designed with the basic premise of being able to map out intention-related signals in the human brain similarly to that shown in the macaque monkey (i.e., the intention-related signals of grasping, reaching, and eye movements). While this endeavor has been largely successful, and we think that we have provided strong, convincing evidence for homologies between brain areas in the monkey and human, many of the findings reported here were largely hypothesized in some form or another. Where I do think a breakthrough has been made, however, is through the development of a rather robust fMRI paradigm and application of a cutting-edge analysis technique to explore brain signals and neural processes that have unquestionably been constrained to experimental investigations with far more invasive neural techniques. The approach taken here will not only allow us to examine and pinpoint several other homologies with the monkey, but more importantly from my perspective, provide us with the capacity to ask the types of experimental questions that have not been previously addressed. I believe that Project 3 provides a good example of this capacity; while some of the motivation of this particular project was based on previous tool-related findings in the monkey, our results and their implications extend far outside any species-specific domain or simple characterization of tool-related behavior. For the first time in humans we are able to localize exactly where in the brain specific levels of the motor hierarchy are functionally nested. Moreover, we demonstrate that this hierarchical architecture can be revealed several moments prior to the subjects actually initiating their action, a finding notoriously difficult to reveal in the firing rates of individual neurons (Rizzolatti & Luppino, 2001). Furthermore, instead of simply providing largely vague, unfocused and far-off future directions of study, I have outlined in some detail an immediate future research program that potentiates considerable alternatives towards our current view of action-encoding. For instance, I have provided preliminary evidence that intention-related signals can be decoded from brain structures not traditionally implicated in action planning processes (e.g., visual cortex, LOC; shown in the previous section). This type of finding provides a particularly important contribution to the field of sensorimotor neuroscience because it is unlikely to have been uncovered with monkey neural studies alone. Due to the invasive nature of neurophysiological recordings, for investigations to be fruitful, researchers often examine brain areas where signals have been previously well-characterized and the findings provided here not only offer several other candidate brain regions for further exploration in monkeys but at the same time, provide far-reaching implications for our understanding of goal-directed movement planning.

Taken together, the set of fMRI projects provided here offers substantial insights into how different areas of the parieto-frontal network contribute to a broad range of goal-directed behaviors. To review, I first showed, as a general proof-of-principle, that it is possible to decode the intention to perform a specific action from brain activity, movements prior to any action actually be executed. I then showed that different movement-related intentions could be functionally mapped across human cortex and that specific brain areas could be generally characterized based on these preparatory signals. Lastly, I provided evidence for a hierarchical neural architecture across cortex, showing where kinematic signals related to movement were represented and where higher-level abstract movement goals were encoded. I expect that a continuation of the research efforts provided here will offer great promise for understanding the cognitive underpinnings of human behavior.

6.5 References

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annual Review of Neuroscience 25:189-220.

Andersen RA, Cui H (2009) Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63:568-583.

Andersen RA, Snyder LH, Bradley DC, Xing J (1997) Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annual Review of Neuroscience 20:303-330.

Baldauf D, Deubel H (2010) Attentional landscapes in reaching and grasping. Vision Res 50:999-1013.

Batista AP, Buneo CA, Snyder LH, Andersen RA (1999) Reach plans in eye-centered coordinates. Science 285:257-260.

Baumann MA, Fluet MC, Scherberger H (2009) Context-specific Grasp Movement Representation in the Macaque Anterior Intraparietal Area. J Neurosci 29:6436-6448.

Begliomini C, Wall MB, Smith AT, Castiello U (2007) Differential cortical activity for precision and whole-hand visually guided grasping in humans. Eur J Neurosci 25:1245-1252.

Bernier PM, Grafton ST (2010) Human posterior parietal cortex flexibly determines reference frames for reaching based on sensory context. Neuron 68:776-788.

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 97:188-199.

Bisley JW, Goldberg ME (2003) Neuronal activity in the lateral intraparietal area and spatial attention. Science 299:81-86.

Bisley JW, Goldberg ME (2010) Attention, intention, and priority in the parietal lobe. Annu Rev Neurosci 33:1-21.

Bonini L, Ugolotti Serventi F, Simone L, Rozzi S, Ferrari PF, Fogassi L (2011) Grasping Neurons of Monkey Parietal and Premotor Cortices Encode Action Goals at Distinct Levels of Abstraction during Complex Action Sequences. J Neurosci 31:5876-5886.

Borra E, Belmalih A, Calzavara R, Gerbella M, Murata A, Rozzi S, Luppino G (2008) Cortical connections of the macaque anterior intraparietal (AIP) area. Cereb Cortex 18:1094-1111.

Calton JL, Dickinson AR, Snyder LH (2002) Non-spatial, motor-specific activation in posterior parietal cortex. Nat Neurosci 5:580-588.

Cassanello CR, Ferrera VP (2007) Computing vector differences using a gain field-like mechanism in monkey frontal eye field. J Physiol 582:647-664.

Chang SW, Papadimitriou C, Snyder LH (2009) Using a compound gain field to compute a reach plan. Neuron 64:744-755.

Chapman CS (2010) Mental Blocks: The behavioral effects and neural encoding of obstacles when reaching and grasping. In: Psychology, p 265. London, Ontario: University of Western Ontario.

Chen Y, Namburi P, Elliott LT, Heinzle J, Soon CS, Chee MW, Haynes JD (2010) Cortical surface-based searchlight decoding. Neuroimage.

Chouinard PA, Paus T (2006) The primary motor and premotor areas of the human cerebral cortex. Neuroscientist 12:143-152.

Churchland MM, Cunningham JP, Kaufman MT, Ryu SI, Shenoy KV (2010) Cortical Preparatory Activity: Representation of Movement or First Cog in a Dynamical Machine? Neuron 68:387-400.

Cisek P, Kalaska JF (2010) Neural Mechanisms for Interacting with a World Full of Action Choices. Annu Rev Neurosci.

Cohen YE, Andersen RA (2002) A common reference frame for movement plans in the posterior parietal cortex. Nat Rev Neurosci 3:553-562.

Colby CL, Goldberg ME (1999) Space and attention in parietal cortex. Annu Rev Neurosci 22:319-349.

Culham JC (2004) Human brain imaging reveals a parietal area specialized for grasping. In: Attention and Performance XX: Functional Brain Imaging of Human Cognition (Kanwisher N, Duncan J, eds). Oxford, U.K.: Oxford University Press.

Culham JC (2006) Functional neuroimaging: Experimental design and analysis. In: Handbook of Functional Neuroimaging of Cognition, 2nd Edition (Cabeza R, Kingstone A, eds), pp 53-82. Cambridge MA: MIT Press.

Culham JC, Kanwisher NG (2001) Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol 11:157-163.

Culham JC, Cavina-Pratesi C, Singhal A (2006) The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia 44:2668-2684.

Davare M, Rothwell JC, Lemon RN (2010) Causal connectivity between the human anterior intraparietal area and premotor cortex during grasp. Curr Biol 20:176-181.

Dehaene S, Changeux JP (1997) A hierarchical neuronal network for planning behavior. Proc Natl Acad Sci U S A 94:13293-13298.

Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST (1999) Role of the posterior parietal cortex in updating reaching movements to a visual target. Nat Neurosci 2:563-567.

Deubel H, Schneider WX (1996) Saccade target selection and object recognition: evidence for a common attentional mechanism. Vision Res 36:1827-1837.

Dickinson AR, Calton JL, Snyder LH (2003) Nonspatial saccade-specific activation in area LIP of monkey parietal cortex. J Neurophysiol 90:2460-2464.

Dinstein I, Gardner JL, Jazayeri M, Heeger DJ (2008) Executed and observed movements have different distributed representations in human aIPS. J Neurosci 28:11231-11239.

Durand JB, Nelissen K, Joly O, Wardak C, Todd JT, Norman JF, Janssen P, Vanduffel W, Orban GA (2007) Anterior regions of monkey parietal cortex process visual 3D shape. Neuron 55:493-505.

Ehrsson HH, Fagergren A, Johansson RS, Forssberg H (2003) Evidence for the involvement of the posterior parietal cortex in coordination of fingertip forces for grasp stability in manipulation. J Neurophysiol 90:2978-2986.

Fagg AH, Arbib MA (1998) Modeling parietal-premotor interactions in primate control of grasping. Neural Netw 11:1277-1303.

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 29:1928-1936.

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 30:342-349.

Filimon F (2010) Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. Neuroscientist 16:388-407.

Fluet MC, Baumann MA, Scherberger H (2010) Context-specific grasp movement representation in macaque ventral premotor cortex. J Neurosci 30:15175-15184.

Fogassi L, Luppino G (2005) Motor functions of the parietal lobe. Curr Opin Neurobiol 15:626-631.

Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G (2005) Parietal lobe: from action organization to intention understanding. Science 308:662-667.

Freeman J, Brouwer GJ, Heeger DJ, Merriam EP (2011) Orientation decoding depends on maps, not columns. J Neurosci 31:4792-4804.

Fujii N, Mushiake H, Tanji J (1998) An oculomotor representation area within the ventral premotor cortex. Proc Natl Acad Sci U S A 95:12034-12037.

Glover S (2004) Separate visual representations in the planning and control of action. Behavioral and Brain Sciences 27:3-24; discussion 24-78.

Gottlieb J, Goldberg ME (1999) Activity of neurons in the lateral intraparietal area of the monkey during an antisaccade task. Nat Neurosci 2:906-912.

Gottlieb JP, Kusunoki M, Goldberg ME (1998) The representation of visual salience in monkey parietal cortex. Nature 391:481.

Grafton ST (2010) The cognitive neuroscience of prehension: recent developments. Exp Brain Res 204:475-491.

Grafton ST, Hamilton AF (2007) Evidence for a distributed hierarchy of action representation in the brain. Hum Mov Sci 26:590-616.

Graziano M (2006) The Organization of Behavioral Repertoire in Motor Cortex. Annu Rev Neurosci.

Graziano MS (1999) Where is my arm? The relative role of vision and proprioception in the neuronal representation of limb position. Proc Natl Acad Sci U S A 96:10418-10421.

Graziano MS (2001) Is reaching eye-centered, body-centered, hand-centered, or a combination? Rev Neurosci 12:175-185.

Graziano MS, Yap GS, Gross CG (1994) Coding of visual space by premotor neurons. Science 266:1054-1057.

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

Grill-Spector K (2003) The neural basis of object perception. Curr Opin Neurobiol 13:159-166.

Grill-Spector K, Malach R (2004) The human visual cortex. Annu Rev Neurosci 27:649-677.

Grill-Spector K, Kourtzi Z, Kanwisher N (2001) The lateral occipital complex and its role in object recognition. Vision Res 41:1409-1422.

Hamilton A, Grafton ST (2006a) The motor hierarchy: from kinematics to goals and intentions. In: Attention and performance (Rosetti Y, Kawato M, Haggard P, eds).

Hamilton AF, Grafton ST (2006b) Goal representation in human anterior intraparietal sulcus. J Neurosci 26:1133-1137.

Hamilton AF, Grafton ST (2008) Action outcomes are represented in human inferior frontoparietal cortex. Cereb Cortex 18:1160-1168.

Hamilton AF, Wolpert DM, Frith U, Grafton ST (2006) Where does your own action influence your perception of another person's action in the brain? Neuroimage 29:524-535.

Harrison SA, Tong F (2009) Decoding reveals the contents of visual working memory in early visual areas. Nature 458:632-635.

Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293:2425-2430.

Haynes JD (2009) Decoding visual consciousness from human brain signals. Trends Cogn Sci 13:194-202.

Haynes JD, Rees G (2005) Predicting the orientation of invisible stimuli from activity in human primary visual cortex. Nat Neurosci 8:686-691.

Haynes JD, Rees G (2006) Decoding mental states from brain activity in humans. Nat Rev Neurosci 7:523-534.

Hebb DO (1949) The organization of behavior: a neuropsychological theory. New York: Wiley.

Hikosaka O, Wurtz RH (1983) Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. J Neurophysiol 49:1268-1284.

Horton JC, Adams DL (2005) The cortical column: a structure without a function. Philos Trans R Soc Lond B Biol Sci 360:837-862.

Hupe JM, James AC, Payne BR, Lomber SG, Girard P, Bullier J (1998) Cortical feedback improves discrimination between figure and background by V1, V2 and V3 neurons. Nature 394:784-787.

Jackson JH (1889) On the comparative study of diseases of the nervous system. British Medical Journal 2:355-362.

James W (1890) Principles of Psychology. New York: Holt.

Jehee JF, Roelfsema PR, Deco G, Murre JM, Lamme VA (2007) Interactions between higher and lower visual areas improve shape selectivity of higher level neurons-explaining crowding phenomena. Brain Res 1157:167-176.

Johansson RS, Flanagan JR (2009) Coding and use of tactile signals from the fingertips in object manipulation tasks. Nat Rev Neurosci 10:345-359.

Johnson-Frey SH (2004) The neural bases of complex tool use in humans. Trends Cogn Sci 8:71-78.

Joly O, Vanduffel W, Orban GA (2009) The monkey ventral premotor cortex processes 3D shape from disparity. Neuroimage 47:262-272.

Kalaska JF (2009) From intention to action: motor cortex and the control of reaching movements. Adv Exp Med Biol 629:139-178.

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 5:410-428.

Kalaska JF, Scott SH, Cisek P, Sergio LE (1997) Cortical control of reaching movements. Curr Opin Neurobiol 7:849-859.

Kamitani Y, Tong F (2005) Decoding the visual and subjective contents of the human brain. Nat Neurosci 8:679-685.

Kanwisher N (2001) Faces and places: of central (and peripheral) interest. Nat Neurosci 4:455-456.

Kanwisher N, Downing P, Epstein R, Kourtzi Z (2001) Functional neuroimaging of visual recognition. In: Handbook of Functional Neuroimaging of Cognition (Cabeza R, Kingstone A, eds), pp 109-152. Cambridge, MA: MIT Press.

Kay KN, Naselaris T, Prenger RJ, Gallant JL (2008) Identifying natural images from human brain activity. Nature 452:352-355.

Koch C (2004) The quest for consciousness: a neurobiological approach: Roberts & Company Publishers.

Kriegeskorte N, Goebel R, Bandettini P (2006) Information-based functional brain mapping. Proc Natl Acad Sci U S A 103:3863-3868.

Kroliczak G, McAdam TD, Quinlan DJ, Culham J (2008) The human dorsal stream adapts to real actions and 3D shape processing: a functional magnetic resonance imaging study. J Neurophysiol 100:2627-2639.

Kustov AA, Robinson DL (1996) Shared neural control of attentional shifts and eye movements. Nature 384:74-77.

Lewis JW (2006) Cortical networks related to human use of tools. Neuroscientist 12:211-231.

Lieberman MD, Cunningham WA (2009) Type I and Type II error concerns in fMRI research: re-balancing the scale. Soc Cogn Affect Neurosci 4:423-428.

Logothetis NK, Wandell BA (2004) Interpreting the BOLD signal. Annual Review of Physiology 66:735-769.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150-157.

Maier A, Wilke M, Aura C, Zhu C, Ye FQ, Leopold DA (2008) Divergence of fMRI and neural signals in V1 during perceptual suppression in the awake monkey. Nat Neurosci 11:1193-1200.

Malach R, Reppas JB, Benson RR, Kwong KK, Jiang H, Kennedy WA, Ledden PJ, Brady TJ, Rosen BR, Tootell RBH (1995) Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. Proc Natl Acad Sci U S A 92:8135-8139.

McGuire LM, Sabes PN (2009) Sensory transformations and the use of multiple reference frames for reach planning. Nat Neurosci 12:1056-1061.

Merriam EP, Genovese CR, Colby CL (2007) Remapping in human visual cortex. J Neurophysiol 97:1738-1755.

Meyer K, Kaplan JT, Essex R, Webber C, Damasio H, Damasio A (2010) Predicting visual stimuli on the basis of activity in auditory cortices. Nat Neurosci 13:667-668.

Moore T, Fallah M (2001) Control of eye movements and spatial attention. Proc Natl Acad Sci U S A 98:1273-1276.

Moore T, Armstrong KM, Fallah M (2003) Visuomotor origins of covert spatial attention. Neuron 40:671-683.

Mountcastle VB (1997) The columnar organization of the neocortex. Brain 120 (Pt 4):701-722.

Mur M, Bandettini PA, Kriegeskorte N (2009) Revealing representational content with pattern-information fMRI--an introductory guide. Soc Cogn Affect Neurosci 4:101-109.

Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA (2004) Cognitive control signals for neural prosthetics. Science 305:258-262.

Nakamura K, Colby CL (2002) Updating of the visual representation in monkey striate and extrastriate cortex during saccades. Proc Natl Acad Sci U S A 99:4026-4031.

Norman KA, Polyn SM, Detre GJ, Haxby JV (2006) Beyond mind-reading: multi-voxel pattern analysis of fMRI data. Trends Cogn Sci 10:424-430.

Oosterhof NN, Wiggett AJ, Diedrichsen J, Tipper SP, Downing PE (2010) Surface-based information mapping reveals crossmodal vision-action representations in human parietal and occipitotemporal cortex. J Neurophysiol 104:1077-1089.

Pakkenberg B, Gundersen HJ (1997) Neocortical neuron number in humans: effect of sex and age. J Comp Neurol 384.

Peeters R, Simone L, Nelissen K, Fabbri-Destro M, Vanduffel W, Rizzolatti G, Orban GA (2009) The representation of tool use in humans and monkeys: common and uniquely human features. J Neurosci 29:11523-11539.

Pereira F, Botvinick M (2011) Information mapping with pattern classifiers: A comparative study. Neuroimage.

Pereira F, Mitchell T, Botvinick M (2009) Machine learning classifiers and fMRI: a tutorial overview. Neuroimage 45:S199-209.

Pesaran B, Nelson MJ, Andersen RA (2006) Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. Neuron 51:125-134.

Pesaran B, Nelson MJ, Andersen RA (2010) A relative position code for saccades in dorsal premotor cortex. J Neurosci 30:6527-6537.

Pisella L, Grea H, Tilikete C, Vighetto A, Desmurget M, Rode G, Boisson D, Rossetti Y (2000) An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. Nat Neurosci 3:729-736.

Porter R, Lemon RN (1993) Corticospinal function and voluntary movement. Oxford, UK: Clarendon Press.

Pouget A, Snyder LH (2000) Computational approaches to sensorimotor transformations. Nat Neurosci 3 Suppl:1192-1198.

Powell KD, Goldberg ME (2000) Response of neurons in the lateral intraparietal area to a distractor flashed during the delay period of a memory-guided saccade. J Neurophysiol 84:301-310.

Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia AS, McNamara JO, White LE (2008) Neuroscience. Sunderland, Mass.: Sinauer Associates, Inc.

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

Ress D, Heeger DJ (2003) Neuronal correlates of perception in early visual cortex. Nat Neurosci 6:414-420.

Rizzolatti G, Luppino G (2001) The cortical motor system. Neuron 31:889-901.

Rizzolatti G, Craighero L (2004) The mirror-neuron system. Annual Review of Neuroscience 27:169-192.

Rizzolatti G, Fogassi L, Gallese V (2001) Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci 2:661-670.

Rizzolatti G, Riggio L, Dascola I, Umilta C (1987) Reorienting attention across the horizontal and vertical meridians: Evidence in favor of premotor theory of attention. Neuropsychologia 25:31-40.

Rozzi S, Ferrari PF, Bonini L, Rizzolatti G, Fogassi L (2008) Functional organization of inferior parietal lobule convexity in the macaque monkey: electrophysiological characterization of motor, sensory and mirror responses and their correlation with cytoarchitectonic areas. Eur J Neurosci 28:1569-1588.

Rushworth MF, Ellison A, Walsh V (2001) Complementary localization and lateralization of orienting and motor attention. Nat Neurosci 4:656-661.

Sakata H, Taira M, Kusunoki M, Murata A, Tsutsui K, Tanaka Y, Shein WN, Miyashita Y (1999) Neural representation of three-dimensional features of manipulation objects with stereopsis. Exp Brain Res 128:160-169.

Scott SH, Sergio LE, Kalaska JF (1997) Reaching Movements With Similar Hand Paths but Different Arm Orientations. II. Activity of Individual Cells in Dorsal Premotor Cortex and Parietal Area 5 J Neurophysiol 78:2413-2426.

Shadmehr R, Wise SP, eds (2005) The Computation Neurobiology of Reaching and Pointing. Cambridge, MA: MIT Press.

Shallice T, Burgess P (1996) The domain of supervisory processes and temporal organization of behaviour. Philos Trans R Soc Lond B Biol Sci 351:1405-1411; discussion 1411-1402.

Sherrington CS (1906) The integrative action of the nervous system. New Haven, CT: Yale University Press.

Sirotin YB, Das A (2009) Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity. Nature 457:475-479.

Smith FW, Muckli L (2010) Non-stimulated early visual areas carry information about surrounding context. Proc Natl Acad Sci U S A.

Snyder LH, Batista AP, Andersen RA (1997) Coding of intention in the posterior parietal cortex. Nature 386:167-123.

Sober SJ, Sabes PN (2005) Flexible strategies for sensory integration during motor planning. Nat Neurosci 8:490-497.

Soon CS, Brass M, Heinze HJ, Haynes JD (2008) Unconscious determinants of free decisions in the human brain. Nat Neurosci 11:543-545.

Srivastava S, Orban GA, De Maziere PA, Janssen P (2009) A distinct representation of three-dimensional shape in macaque anterior intraparietal area: fast, metric, and coarse. J Neurosci 29:10613-10626.

Stark E, Abeles M (2007) Predicting movement from multiunit activity. J Neurosci 27:8387-8394.

Stark E, Asher I, Abeles M (2007) Encoding of reach and grasp by single neurons in premotor cortex is independent of recording site. J Neurophysiol 97:3351-3364.

Stark E, Globerson A, Asher I, Abeles M (2008) Correlations between groups of premotor neurons carry information about prehension. J Neurosci 28:10618-10630.

Stokes M, Thompson R, Cusack R, Duncan J (2009) Top-down activation of shape-specific population codes in visual cortex during mental imagery. J Neurosci 29:1565-1572.

Super H, Spekreijse H, Lamme VA (2001) Two distinct modes of sensory processing observed in monkey primary visual cortex (V1). Nat Neurosci 4:304-310.

Valyear KF, Culham JC (2010) Observing learned object-specific functional grasps preferentially activates the ventral stream. J Cogn Neurosci 22:970-984.

Valyear KF, Cavina-Pratesi C, Stiglick AJ, Culham JC (2007) Does tool-related fMRI activity within the intraparietal sulcus reflect the plan to grasp? Neuroimage 36 Suppl 2:T94-T108.

Verhagen L, Dijkerman C, Grol MJ, Toni I (2008) Perceptuo-motor interactions during prehension movements. J Neurosci 28:4726-4735.

Viswanathan A, Freeman RD (2007) Neurometabolic coupling in cerebral cortex reflects synaptic more than spiking activity. Nat Neurosci 10:1308-1312.

Williams MA, Baker CI, Op de Beeck HP, Shim WM, Dang S, Triantafyllou C, Kanwisher N (2008) Feedback of visual object information to foveal retinotopic cortex. Nat Neurosci 11:1439-1445.

Wolpert DM, Ghahramani Z (2000) Computational principles of movement neuroscience. Nat Neurosci 3 Suppl:1212-1217.

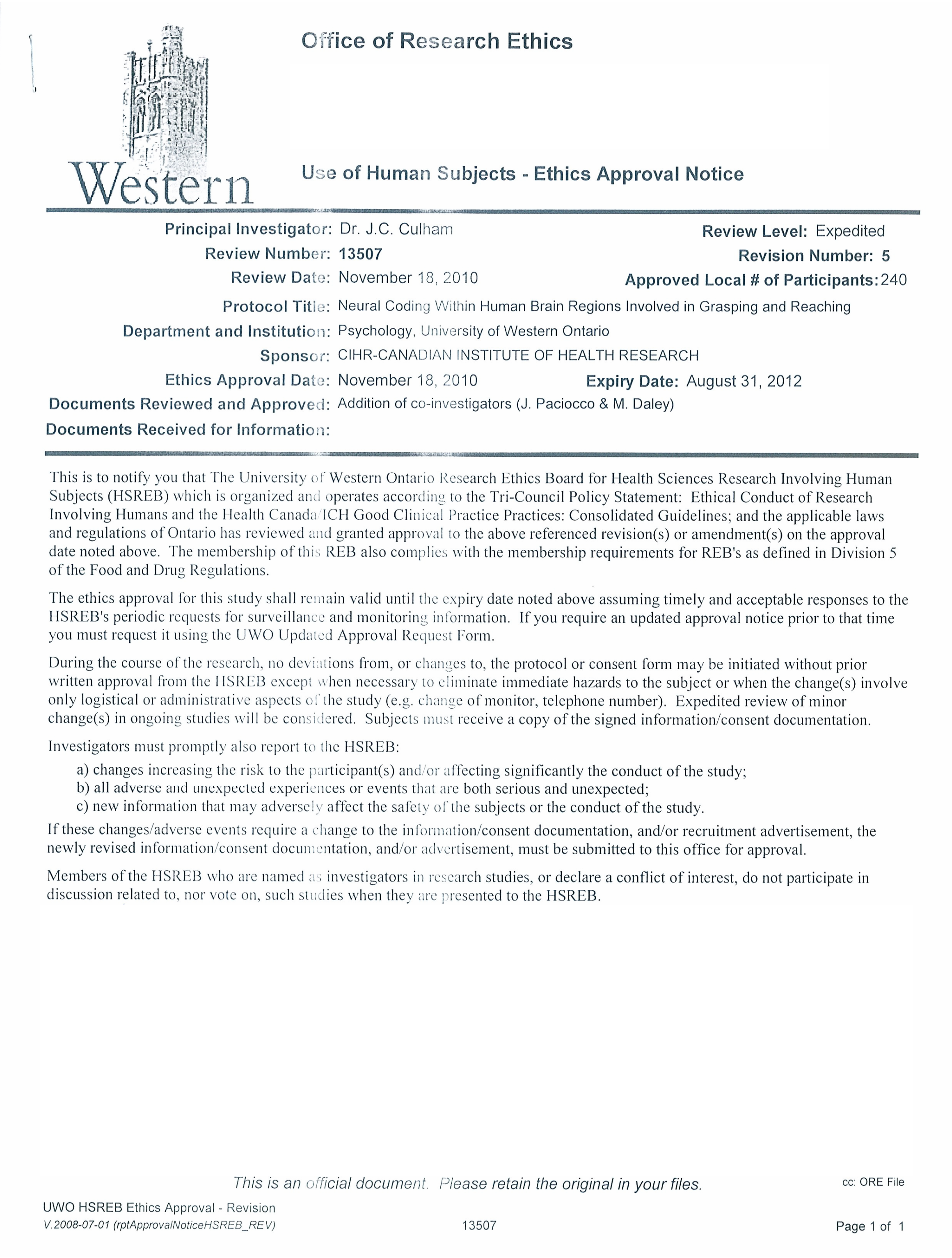
Wolpert DM, Flanagan JR (2001) Motor prediction. Curr Biol 11:R729-732.

Wolpert DM, Goodbody SJ, Husain M (1998) Maintaining internal representations: The role of the human superior parietal lobe. Nature neuroscience 1:529-533.

Zhang M, Barash S (2000) Neuronal switching of sensorimotor transformations for antisaccades. Nature 408:971-975.

Zhang M, Barash S (2004) Persistent LIP activity in memory antisaccades: working memory for a sensorimotor transformation. J Neurophysiol 91:1424-1441.

Appendix A



Western

Office of Research Ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. J.C. Culham
Review Level: Expedited
Review Number: 13507
Revision Number: 5
Review Date: November 18, 2010
Approved Local # of Participants: 240
Protocol Title: Neural Coding Within Human Brain Regions Involved in Grasping and Reaching
Department and Institution: Psychology, University of Western Ontario
Sponsor: CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH
Ethics Approval Date: November 18, 2010
Expiry Date: August 31, 2012
Documents Reviewed and Approved: Addition of co-investigators (J. Paciocco & M. Daley)
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

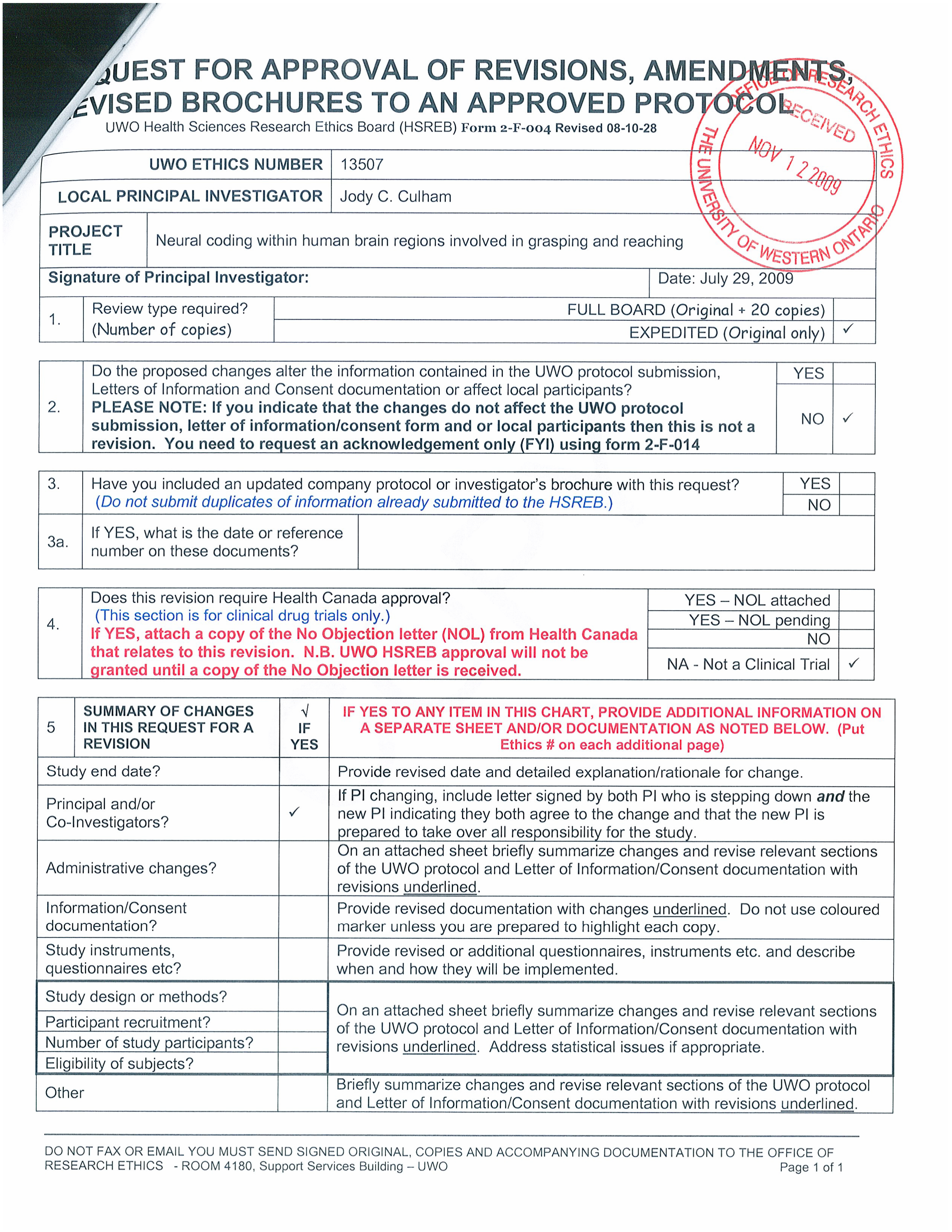
If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

This is an official document. Please retain the original in your files.

cc: ORE File

UWO HSREB Ethics Approval - Revision
V.2008-07-01 (rptApprovalNoticeHSREB_REV)
13507
Page 1 of 1



QUEST FOR APPROVAL OF REVISIONS, AMENDMENTS, EVISED BROCHURES TO AN APPROVED PROTOCOL

UWO Health Sciences Research Ethics Board (HSREB) Form 2-F-004 Revised 08-10-28

OFFICE OF RESEARCH ETHICS
RECEIVED
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THE UNIVERSITY OF WESTERN ONTARIO

UWO ETHICS NUMBER	13507
LOCAL PRINCIPAL INVESTIGATOR	Jody C. Culham
PROJECT TITLE	Neural coding within human brain regions involved in grasping and reaching
Signature of Principal Investigator:	Date: July 29, 2009

1.	Review type required? (Number of copies)	FULL BOARD (Original + 20 copies)	
		EXPEDITED (Original only)	✓

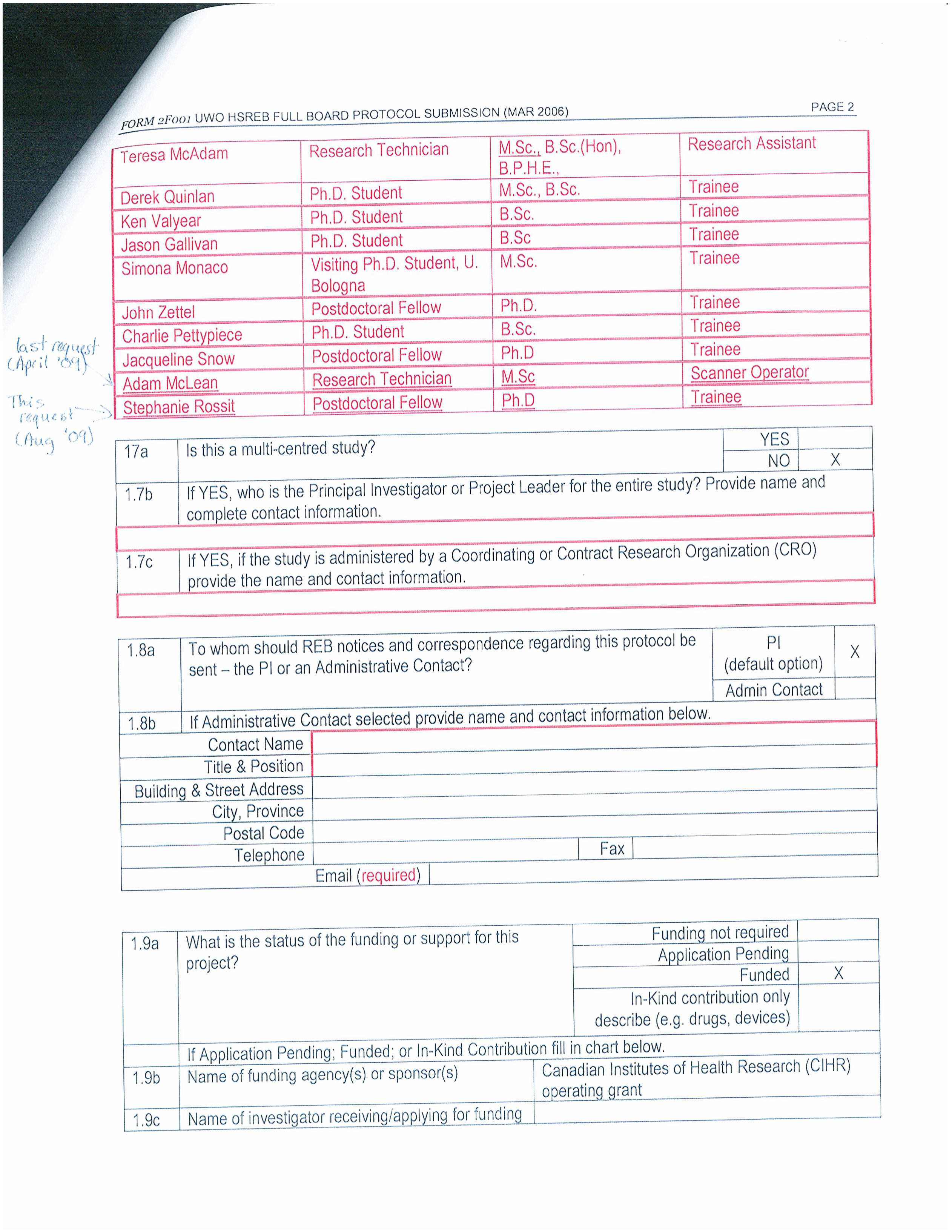
2.	Do the proposed changes alter the information contained in the UWO protocol submission, Letters of Information and Consent documentation or affect local participants? **PLEASE NOTE: If you indicate that the changes do not affect the UWO protocol submission, letter of information/consent form and or local participants then this is not a revision. You need to request an acknowledgement only (FYI) using form 2-F-014**	YES	
		NO	✓

3.	Have you included an updated company protocol or investigator's brochure with this request? *(Do not submit duplicates of information already submitted to the HSREB.)*	YES	
		NO	
3a.	If YES, what is the date or reference number on these documents?		

4.	Does this revision require Health Canada approval? (This section is for clinical drug trials only.) **If YES, attach a copy of the No Objection letter (NOL) from Health Canada that relates to this revision. N.B. UWO HSREB approval will not be granted until a copy of the No Objection letter is received.**	YES – NOL attached	
		YES – NOL pending	
		NO	
		NA - Not a Clinical Trial	✓

5 **SUMMARY OF CHANGES IN THIS REQUEST FOR A REVISION**	**√ IF YES**	**IF YES TO ANY ITEM IN THIS CHART, PROVIDE ADDITIONAL INFORMATION ON A SEPARATE SHEET AND/OR DOCUMENTATION AS NOTED BELOW. (Put Ethics # on each additional page)**
Study end date?		Provide revised date and detailed explanation/rationale for change.
Principal and/or Co-Investigators?	✓	If PI changing, include letter signed by both PI who is stepping down ***and*** the new PI indicating they both agree to the change and that the new PI is prepared to take over all responsibility for the study.
Administrative changes?		On an attached sheet briefly summarize changes and revise relevant sections of the UWO protocol and Letter of Information/Consent documentation with revisions underlined.
Information/Consent documentation?		Provide revised documentation with changes underlined. Do not use coloured marker unless you are prepared to highlight each copy.
Study instruments, questionnaires etc?		Provide revised or additional questionnaires, instruments etc. and describe when and how they will be implemented.
Study design or methods?		On an attached sheet briefly summarize changes and revise relevant sections of the UWO protocol and Letter of Information/Consent documentation with revisions underlined. Address statistical issues if appropriate.
Participant recruitment?		
Number of study participants?		
Eligibility of subjects?		
Other		Briefly summarize changes and revise relevant sections of the UWO protocol and Letter of Information/Consent documentation with revisions underlined.

DO NOT FAX OR EMAIL YOU MUST SEND SIGNED ORIGINAL, COPIES AND ACCOMPANYING DOCUMENTATION TO THE OFFICE OF RESEARCH ETHICS - ROOM 4180, Support Services Building – UWO



Teresa McAdam	Research Technician	M.Sc., B.Sc.(Hon), B.P.H.E.,	Research Assistant
Derek Quinlan	Ph.D. Student	M.Sc., B.Sc.	Trainee
Ken Valyear	Ph.D. Student	B.Sc.	Trainee
Jason Gallivan	Ph.D. Student	B.Sc	Trainee
Simona Monaco	Visiting Ph.D. Student, U. Bologna	M.Sc.	Trainee
John Zettel	Postdoctoral Fellow	Ph.D.	Trainee
Charlie Pettypiece	Ph.D. Student	B.Sc.	Trainee
Jacqueline Snow	Postdoctoral Fellow	Ph.D	Trainee
Adam McLean	Research Technician	M.Sc	Scanner Operator
Stephanie Rossit	Postdoctoral Fellow	Ph.D	Trainee

last request (April '09)

This request (Aug '09)

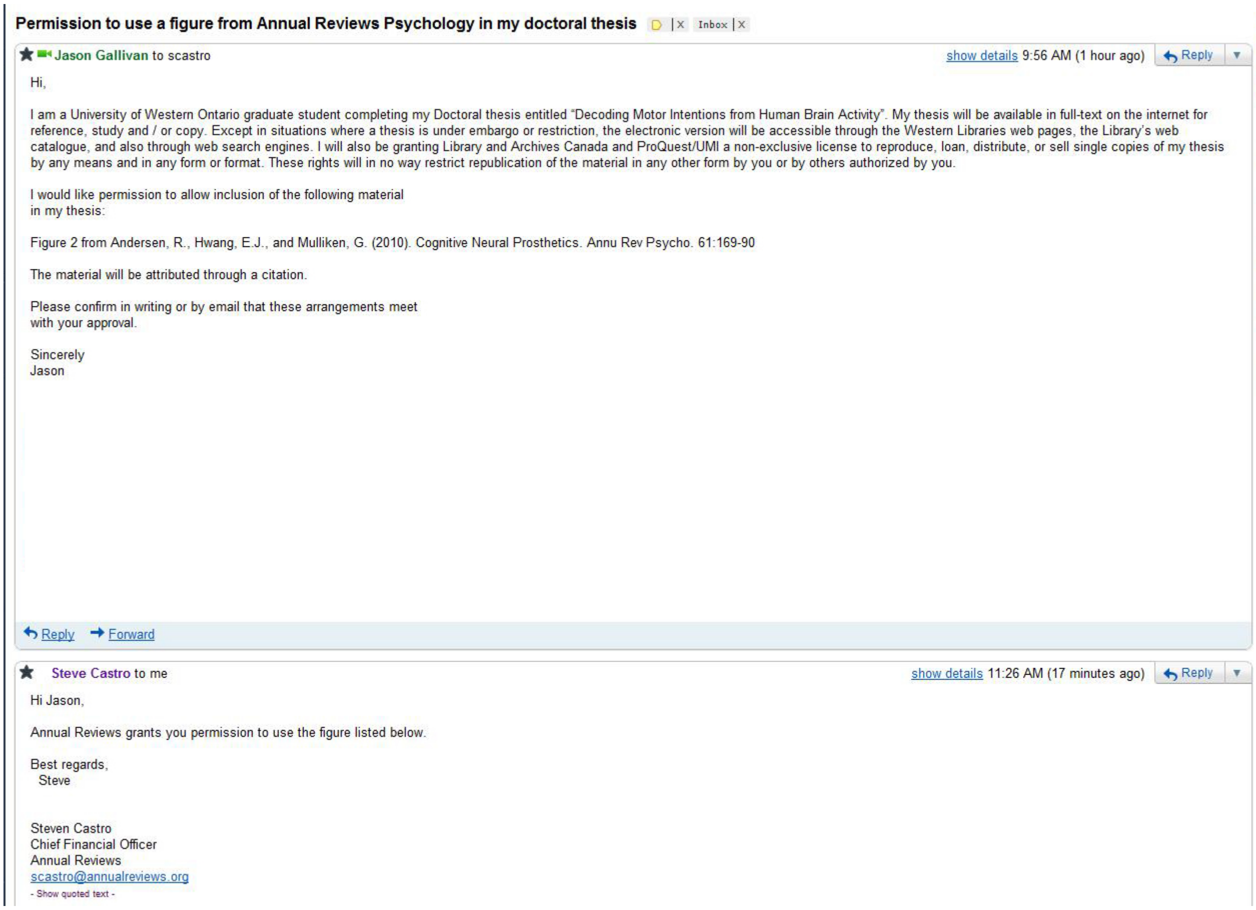
17a	Is this a multi-centred study?	YES	
		NO	X
1.7b	If YES, who is the Principal Investigator or Project Leader for the entire study? Provide name and complete contact information.		
1.7c	If YES, if the study is administered by a Coordinating or Contract Research Organization (CRO) provide the name and contact information.		

1.8a	To whom should REB notices and correspondence regarding this protocol be sent – the PI or an Administrative Contact?	PI (default option)	X
		Admin Contact	
1.8b	If Administrative Contact selected provide name and contact information below.		

Contact Name			
Title & Position			
Building & Street Address			
City, Province			
Postal Code			
Telephone		Fax	
Email (required)			

1.9a	What is the status of the funding or support for this project?	Funding not required	
		Application Pending	
		Funded	X
		In-Kind contribution only describe (e.g. drugs, devices)	
	If Application Pending; Funded; or In-Kind Contribution fill in chart below.		
1.9b	Name of funding agency(s) or sponsor(s)	Canadian Institutes of Health Research (CIHR) operating grant	
1.9c	Name of investigator receiving/applying for funding		

Appendix B



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Jason Gallivan to scastro 9:56 AM (1 hour ago)

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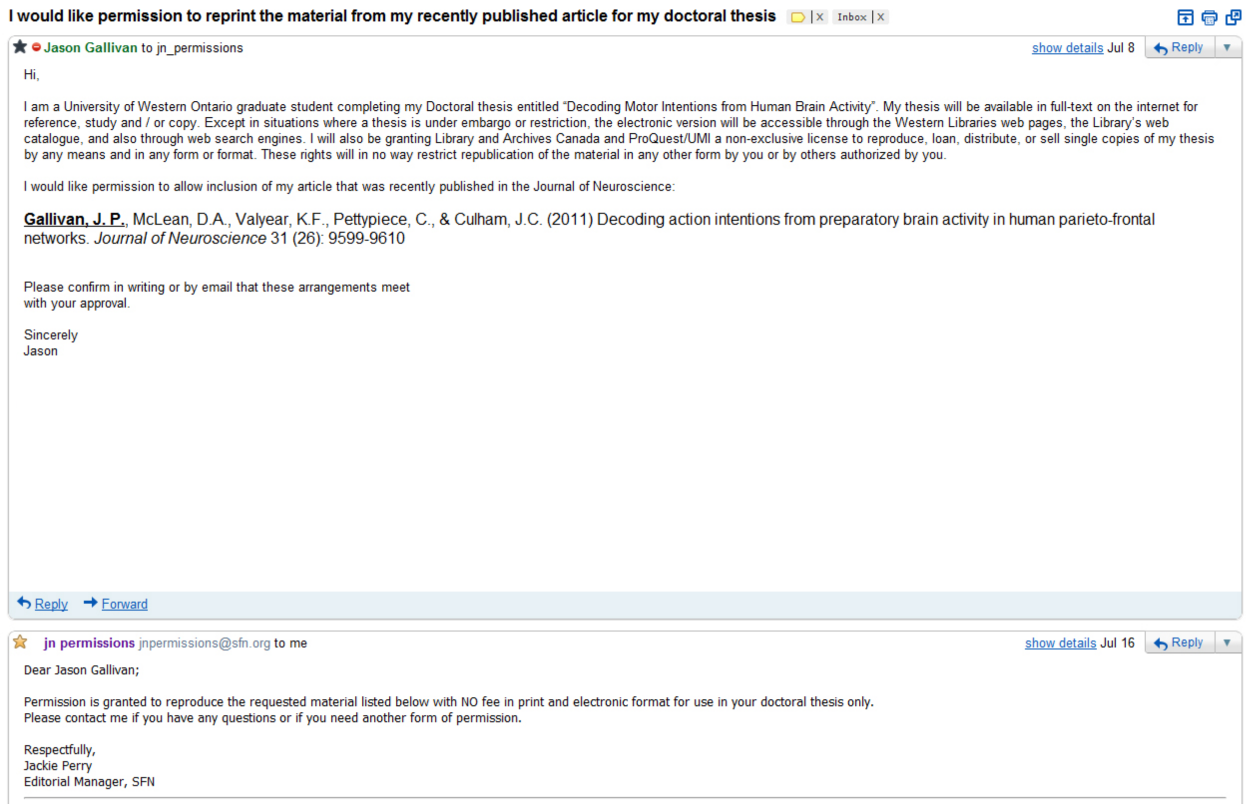

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Jason Gallivan to jn_permissions — Jul 8

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Gallivan, J. P., McLean, D.A., Valyear, K.F., Pettypiece, C., & Culham, J.C. (2011) Decoding action intentions from preparatory brain activity in human parieto-frontal networks. *Journal of Neuroscience* 31 (26): 9599-9610

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with your approval.

Sincerely
Jason

jn permissions jnpermissions@sfn.org to me — Jul 16

Dear Jason Gallivan;

Permission is granted to reproduce the requested material listed below with NO fee in print and electronic format for use in your doctoral thesis only.
Please contact me if you have any questions or if you need another form of permission.

Respectfully,
Jackie Perry
Editorial Manager, SFN

Curriculum Vitae

Jason P. Gallivan

Date of Birth: June 15, 1982
Citizenship: Canadian

Research Interests: Cognitive neuroscience, fMRI, multi-voxel pattern analysis, action planning and control, intention coding, tool-use, parietal cortex, premotor cortex

Publications (10): 8 empirical papers (3 first authorships); 1 review paper; 1 book chapter (detailed below).

Education:

University of Western Ontario, London, ON Ph.D Candidate: Neuroscience Advisor: Dr. Jody Culham	2007-present
University of Western Ontario, London, ON M.Sc: Neuroscience Advisor: Dr. Jody Culham	2005-2007
University of Western Ontario, London, ON B.Sc.: Honours Biology	2001-2005

Honours and Awards:

Canadian Institute of Health Research (CIHR) Brain Star Award	2010
Graduate Thesis Research Awards Fund	2009-present
Natural Sciences and Engineering Research Council (NSERC) Scholar (PGS-D)	2009-2011
Teaching Assistant Award	2009
Ontario Graduate Scholarship for Sciences and Technology	2007-2009
Ontario Graduate Scholarship	2006-2007
Western Graduate Research Scholarship	2005-present
Nominations for Graduate Teaching Assistant Award	2005-2010
Laurene Paterson Estate Scholarship	2004-2005

Dean’s Honour Student in Science 2001-2005

Aiming for the Top Tuition Scholarship 2001

Entrance Scholarship 2001

Research Experience:

Graduate Student 2005-present
Advisor: Dr. Jody Culham
University of Western Ontario
My research uses neuroimaging (fMRI) & behavioural kinematic techniques to examine how the brain encodes movements.

Lab Assistant 2003-2005
Advisor: Dr. David Cechetto
University of Western Ontario
Used several molecular techniques & rat surgical procedures for Alzheimer’s Disease research.

Supervisory Experience:

Undergraduate Honour’s Thesis Co-Advisor (University of Western Ontario):
Jennifer Milne (2008-2009)
Department of Psychology
Maryam Khami (2009-2010)
Department of Physiology and Pharmacology

Advisor for volunteer students:
James Dusten (2nd year student)
Steve Beukema (1st year student)
Debbie Boswell (1st year student)
Kevin Stubbs (1st year student)

Teaching Experience:

Teaching Assistantships, University of Western Ontario
Physiology 4710a: Physiology of the Senses 2009
Dept. of Physiology & Pharmacology 2008
2007

Neuroscience 500:Principles of Neuroscience 2008-2009
Neuroscience Program
Graduate-level neuroscience course

Psychology 380: Psychological Statistics using Computers 2008
Dept. of Psychology

Psychology 023: Biologically oriented introduction to psychology Dept. of Psychology	2006
Psychology 020: Introduction to Psychology Dept. of Psychology	2005
Biology 332a: Parasitology Dept. of Biology	2006 2005 2004

Publications:

Peer-reviewed Journal Articles (9):

Gallivan, J.P., McLean, D.A., Valyear, K.F., Pettypiece, C., and Culham, J.C. (2011) Decoding action intentions from preparatory brain activity in human parieto-frontal networks. *Journal of Neuroscience.* 31 (26): 9599-9610. [Journal Impact factor: 7.2]

Valyear, K.F., Chapman, C.S., **Gallivan, J.P.**, Mark, R.S., & Culham, J.C. (2011) To use or to move: Goal-set modulates priming when grasping real tools. *Experimental Brain Research.* 212/1: 125-142. [Journal Impact factor: 2.3]

Chapman, C.S., **Gallivan, J.P.**, Culham, J.C., & Goodale, M.A. (2011) Mental Blocks: fMRI reveals top-down modulation of early visual cortex when obstacles interfere with grasp planning. *Neuropsychologia* 49 (7): 1703-1717. [Journal Impact factor: 4.3]

Gallivan, J.P., Chapman, C.S., Wood, D.K., Milne, J.L., Culham, J.C., & Goodale, M.A. (2011) One to four, and nothing more: Non-conscious parallel individuation of objects during action planning. *Psychological Science* (2011) 22(6): 803-811. [Journal Impact factor: 5.1]

Chapman, C.S., **Gallivan, J.P.**, Wood, D.K., Milne, J.L., Culham, J.C., & Goodale, M.A. (2010) Short term motor plasticity revealed in a visuomotor decision-making task. *Behavioural Brain Research,* 214 (1): 130-134. [Journal Impact factor: 3.2]

Chapman, C.S., **Gallivan, J.P.**, Wood, D.K., Milne, J.L., Culham, J.C., & Goodale, M.A. (2010) Reaching for the unknown: Multiple target encoding and real-time decision making in a rapid reach task. *Cognition,* 116 (2): 168-176. [Journal Impact factor: 3.5]

Barry, R.L., Williams, J.M., Klassen, L.M., **Gallivan, J.P**., Culham, J.C., & Menon, R.S. (2010) Evaluation of preprocessing steps to compensate for magnetic field distortions due to body movements in BOLD fMRI. *Magnetic Resonance Imaging,* 28 (2): 235-244. [Journal Impact factor: 2]

Gallivan, J.P. & Wood, D.K. (2009) Simultaneous encoding of potential grasping movements in the anterior intraparietal area. *Journal of Neuroscience, 29 (39): 12031-12032*. [Journal Impact factor: 7.2]

Gallivan, J.P., Cavina-Pratesi, C., & Culham, J.C. (2009) Is that within reach? fMRI reveals that the human superior parieto-occipital cortex encodes objects reachable by the hand. *Journal of*

Neuroscience, 29 (14), 4381-91. [Journal Impact factor: 7.2]

Peer-reviewed Book chapter (1):

Culham, J. C., **Gallivan, J.P.**, Cavina-Pratesi, C., & Quinlan, D. J. (2008). fMRI investigations of reaching and ego space in human superior parieto-occipital cortex. In R. L. Klatzky, M. Behrmann, & B. MacWhinney (Eds.), *Embodiment, Ego-space and Action*. New York: Psychology Press. pp. 247-274.

Articles submitted or under revision for resubmission (3):

Gallivan, J.P., McLean, D.A., Smith, F.W., & Culham, J.C. Decoding effector-dependent and effector-independent movement intentions from human parieto-frontal brain activity. *In revision for resubmission at Journal of Neuroscience* (JN-RM-1058-11). Submitted: February, 28th, 2011. [Journal Impact factor: 7.2]

Gallivan, J.P., McLean, D.A., & Culham, J.C. Neuroimaging reveals enhanced activation in a reach-selective brain area for objects located within participants' typical hand workspace. *Under review at Neuropsychologia* (NSY-D-11-00378). Submitted: May, 3rd, 2011. [Journal Impact factor: 4.3]

Wood, D.K., **Gallivan, J.P.**, Chapman, C.S., Milne, J.L., Culham, J.C., and Goodale, M.A. Visual salience dominates early visuomotor competition in reaching behaviour. *Under review at Journal of Vision* (JOV-02652-2011). Submitted: June, 23rd, 2011 [Journal Impact factor: 3.0]

In preparation (3):

In order of expected submission date (soonest first). Most works have been (or will soon be) presented at scientific meetings.

Milne, J.L., Chapman, C.S., **Gallivan, J.P.**, Wood, D.K., Culham, J.C., and Goodale, M.A. Object connectedness influences perceptual comparisons but not the planning or control of rapid reaches to multiple goals.

Gallivan, J.P., McLean, D.A., Valyear, K.F., Pettypiece, C., and Culham, J.C. How the brain uses tools: Separate and shared movement plans for the hand and tool in human parieto-frontal cortex.

Valyear, K. F., **Gallivan, J.P.**, McLean, D.A., Culham, J.C. Neural priming of tool use.

International and National Conference Presentations

Talks (9):

Culham, J. C. & **Gallivan, J. P.** (2011). Decoding of human hand and tool actions using functional magnetic resonance imaging. Centre for Mind/Brain Sciences (CiMeC) Colloquium, University of Trento.

Gallivan, J.P., McLean, A., Smith. F.W., and Culham, J.C. (2011) Decoding effector-dependent and effector-independent movement intentions from human parieto-frontal brain activity. Talk presented at the *CPS/CAPnet conference*, Sainte-Adele, QUE.

Culham, J. C. & **Gallivan, J. P.** (2011). Decoding of human hand actions using functional magnetic resonance imaging. Federation of European Neuroscience Societies – International Brain Research Organization (FENS-IBRO) Hertie Winter School. Obergurgl, Austria.

Gallivan, J.P., McLean, A., Valyear, K.F., Pettypiece, C., and Culham, J.C. (2010) Decoding movement intentions from preparatory activity in human parietal and premotor cortex. Talk presented at the *Society for Neuroscience*, San Diego, CA.

Culham, J.C., Monaco, S, and **Gallivan, J.P.** (2010) Parietal coding of movement components and object properties in reaching and grasping. Talk presented at the International Conference on Parietal Lobe Function, Amsterdam, The Netherlands.

Gallivan, J.P., D.A. McLean, and Culham, J.C. (2009) fMRI shows that the extent of reachable space encoded within superior parieto-occipital cortex depends on handedness. Talk presented at the Society for Neuroscience, Chicago, IL.

Valyear, K.F., Chapman, C.S., **Gallivan, J.P.,** & Culham, J.C. (2009) Tool identity can prime grasping, but only when the goal is to use. Talk presented at the *Society for Neuroscience*, Chicago, IL.

Chapman, C.S., **Gallivan, J.P**., Culham, J.C., and Goodale M.A. (2009) Mental blocks: Using fMRI to reveal the encoding of obstacles during reach-to-grasp movements. Talk presented at the *Society for Neuroscience*, Chicago, IL.

Gallivan, J.P., Cavina-Pratesi, C., & Culham, J.C. (2007). Is that within reach? The human Superior Parieto-Occipital Cortex (SPOC) shows greater fMRI activation for reachable objects. Talk presented at the*Society for Neuroscience*, San Diego, CA.

Posters (8):

Chapman, C.S., **Gallivan, J.P.**, Wood, D.K., Milne, J.L., Culham, J.C., & Goodale, M.A. (2010) Rapid reaching task ‘points’ toward different representations of number. Poster presented at the *Society for Neuroscience*, San Diego, CA.

Wood, D.K., Chapman, C.S., **Gallivan, J.P.**, Milne, J.L., Culham, J.C., & Goodale, M.A. (2010) Visual salience of potential targets overrides spatial probabilities in a rapid visuomotor task. Poster presented at the *Society for Neuroscience*, San Diego, CA.

Valyear, K. F., **Gallivan, J.P.**, McLean, A., Chapman, C.S., Culham, J.C. (2010) Neural priming of tool use.Poster presented at the *Society for Neuroscience*, San Diego, CA.

Gallivan J.P., Chapman C.S., Wood D.K., Milne J., Culham J.C., and Goodale M.A. (2009) Stuck in the middle: Kinematic evidence for optimal reaching in the presence of multiple potential reach targets. Poster presented at the *Vision Sciences Society* meeting in Naples, FL.

Chapman C.S., **Gallivan J.P.,** Wood D.K., Milne J., Culham J.C., and Goodale M.A. (2009) Dynamic Target Acquisition: Rapid reach responses in the presence of multiple potential reach targets. Poster presented at the *Canadian Neuroscience* Meeting, Vancouver, BC.

Gallivan, J.P., Chapman, C.S., & Culham, J.C. (2008). Do objects within reach prime the visuomotor system for action? Poster presented at the *Canadian Neuroscience* Meeting, Montreal, QUE

Gallivan, J.P., Cavina-Pratesi, C., & Culham, J.C. (2007). The effects of reachability and tool use on fMRI activation for brain regions involved in hand actions. Poster presented at the *Canadian Neuroscience*Meeting, Toronto, ONT.

Gallivan, J. P., Cavina-Pratesi, C., & Culham, J. C. (2006). Do objects within reach activate human brain regions involved in hand actions?: An fMRI study. Poster presented at the *Society for Neuroscience*, Atlanta, GA.

Invited Talks/Presentations (4):

Culham, J. C. & **Gallivan, J. P.** (2011). Decoding of human hand actions using functional magnetic resonance imaging. Department of Psychology, York University, Toronto, ONT.

Gallivan, J.P. (2011) Decoding motor intentions from human brain activity. Talk presented at *Queens University*, Kingston, ONT.

Gallivan, J.P., Chapman, C.S., & Culham, J.C. (2008). Do objects within reach prime the visuomotor system for action? Talk given to the Group on Action and Perception in Elmhurst, Ontario.

Gallivan, J.P., Cavina-Pratesi, C., & Culham, J.C. (2007). How does reachability affect fMRI activation for brain regions involved in hand actions? Talk given to the Group on Action and Perception in Elmhurst, Ontario.

Workshops:
Neural Correlates of Object Recognition and Action Workshop. Atlanta, Georgia.

Professional Affiliations:

Member of the Centre for Brain and Mind, UWO (2009 – Present)
Member of the Society for Neuroscience (2006 – Present)
Member of the Vision Sciences Society (2008 – Present)

Contributions:

Ad hoc co-reviewer of submitted manuscripts: Experimental Brain Research (2), Journal of Neuroscience (3), Journal of Neurophysiology (1), Journal of Cognitive Neuroscience (1), Neuron (1), Cognition (1).

Youth Outreach and Community Service:

London Ontario Brain Bee (http://www.uwomeds.com/ncog/main.php), in association with the Canadian Institutes of Health Research Canadian National Brain Bee (**http://www.science.mcmaster.ca/brainbee/**) – I gave the Brain Bee winner a tour of our lab and gave a demonstration of the basics of fMRI and behavioural kinematics, held February 28, 2009