Université de Montréal

Neural correlates of affordance competition in dorsal premotor cortex

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To the brave that dare adventure in science,

"… Men Wanted: For hazardous journey. Small wages, bitter cold, long months of complete darkness, constant danger, safe return doubtful. Honour and recognition in case of success …"

— Ernest Shackleton (1874—1922)
Newspaper announcement before his Endurance Expedition

"… No one really starts anything new. Everyone builds on other men's failures. What each man contributes to the sum of knowledge is what counts…"

Daniel Keyes (1927)
Excerpt from Flowers for Algernon

RÉSUMÉ

Le travail présenté dans cette thèse porte sur le rôle du cortex prémoteur dorsal (PMd) au sujet de la prise de décision (sélection d'une action parmis nombreux choix) et l'orientation visuelle des mouvements du bras. L'ouvrage décrit des expériences électrophysiologiques chez le singe éveillé (*Macaca mulatta*) permettant d'adresser une fraction importante des prédictions proposées par *l'hypothèse des affordances concurrentes* (Cisek, 2006; Cisek, 2007a). Cette hypothèse suggère que le choix de toute action est l'issue d'une concurrence entre les représentations internes des exigences et des atouts de chacune des options présentées (*affordances;* Gibson, 1979).

Un intérêt particulier est donné au traitement de l'information spatiale et la valeur des options *(expected value, EV)* dans la prise de décisions. La première étude *(article 1)* explore la façon dont PMd reflète ces deux paramètres dans la période délai ainsi que de leur intéraction. La deuxième étude *(article 2)* explore le mécanisme de décision de façon plus détaillée et étend les résultats au cortex prémoteur ventral (PMv). Cette étude porte également sur la représentation spatiale et l'EV dans une perspective d'apprentissage. Dans un environnement nouveau les paramètres spatiaux des actions semblent être présents en tout temps dans PMd, malgré que la représentation de l'EV apparaît uniquement lorsque les animaux commencent à prendre des décisions éclairées au sujet de la valeur des options disponibles. La troisième étude *(article 3)* explore la façon dont PMd est impliqué aux *"changements d'esprit"* dans un procès de décision. Cette étude décrit comment la sélection d'une action est mise à jour à la suite d'une instruction de mouvement (GO signal).

Les résultats principaux des études sont reproduits par un modèle computationnel (Cisek, 2006) suggérant que la prise de décision entre plusieurs actions alternatives peux se faire par voie d'un mécanisme de concurrence (*biased competition*) qui aurait lieu dans la même région qui spécifie les actions.

Mots-clés: décisions, biais, concurrence, affordances, sélection d'action, spécification des actions, cortex prémoteur, PMd, PMv, EV, valeur relative, valeur absolue, distance, paramètres spatiaux, apprentissage, électrophysiologie, singe.

ABSTRACT

This thesis examines the role of the dorsal premotor cortex (PMd) in the process of decision making (action selection) and visual guidance of arm movements. The work describes electrophysiological experiments conducted in awake monkeys (*Macaca mulatta*) and tests a number of important predictions suggested by the *affordance competition hypothesis* (Cisek, 2006; Cisek, 2007a). This hypothesis suggests that decisions can be viewed as the result of a *competition* between internal representations of conflicting demands and opportunities for actions or *affordances* (Gibson, 1979).

Specific interest is given to the interaction between spatial information and expected value (EV) in a proposed *affordance competition* mechanism for action selection. The first study presented *(article 1)* explores how EV is represented during the delay period in PMd. This study also describes how this area reflects the spatial metrics of the options and examines the interaction between value and spatial information. The second study *(article 2)* explores the mechanism of action selection in more detail and extends the results to ventral premotor cortex (PMv). This study also addresses the nature of value and spatial representations from a learning perspective. In a novel environment the spatial metrics of the actions seem to be invariably present in PMd, meanwhile EV representations appear only once the animals make behaviorally informed decisions about the value of the available options. The third study *(article 3)* explores how PMd is involved in "changes of mind" in which action selection is updated following a movement instruction (GO signal).

The major findings in all these studies are reproduced by a computational model (Cisek, 2006) suggesting that decisions between actions can be made through a biased competition process that takes place in the same region that specifies the actions.

Keywords: decisions, bias, competition, affordances, action-selection, action-specification, premotor cortex, PMd, PMv, EV, relative value, absolute value, distance, spatial parameters, learning, electrophysiology, monkey.

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LIST OF ABBREVIATIONS

ACC: anterior cingulate cortex
AG: angular gyrus
AI: inferior arcuate sulcus
AIP: anterior intraparietal area
AS: superior arcuate sulcus
BG: basal ganglia
C: central sulcus
Ca: calcarine fissure
CHT: center hold time
CVML: conditional visuomotor learning
Cx: cerebral cortex
DA: dopamine
DLPFC: dorsolateral prefrontal cortex
DMPFC: dorsomedial prefrontal cortex
EV: expected value
FEF: frontal eye field
GABA: gamma aminobutyric acid
GPe: external segment of the globus pallidus
GPi: internal segment of the globus pallidus
IDV: initial direction vector
IF: inferior frontal sulcus
IFc: inferior precentral sulcus
IO: inferior occipital sulcus
IP: intraparietal sulcus
IPL: inferior parietal lobe
IPS: intraparietal sulcus
L: lateral fissure
LIP: lateral intraparietal cortex
Lu: lunate sulcus
M1: primary motor cortex
MIP: medial intraparietal area
MST: mediosuperiotemporal cortex
MT: mediotemporal cortex
MTL: medial temporal lobe
OC: striate cortex
OFC: orbitofrontal cortex
OT: occipitotemporal sulcus
P: principal sulcus
PCC: posterior cingulate cortex
PCS: precentral sulcus
PFC: prefrontal cortex
PMd: dorsal premotor cortex
PMv: ventral premotor cortex
PO: parieto-occipital visual area
Pos: parieto-occipital sulcus
PPC: posterior parietal cortex
PT: preferred target
pre-SMA: pre-supplementary motor area
PRR: parietal reach region
RF: receptive field
RSC: retrosplenial cortex
RT: reaction time
RV: relative value
S: spur of the arcuate sulcus
S1: primary somatosensory cortex

S2: secondary somatosensory cortex

SC: superior colliculus

SEF: supplemental eye field.

SF: superior frontal sulcus

SFy: sylvian fissure

SMA: supplementary motor area.

SMG: supramarginal gyrus

SNc/SNpc: substantia nigra pars compacta

SNr: substantia nigra pars reticulata

SNdl: dorsolateral substantia nigra pars reticulata

SPc: superior precentral sulcus

SPD: superior precentral dimple

SPL: superior parietal lobule

SSRT: stop signal reaction time

ST: superior temporal sulcus

STN: subthalamic nucleus

Str: striatum

STS: superior temporal sulcus

TE: rostral inferior temporal cortex

TEO: posterior inferior temporal cortex

Th: thalamus

V1: primary visual cortex

VIP: ventral intraparietal cortex

VLPFC: ventrolateral prefrontal cortex

VTA: ventral tegmental area

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I. PREAMBLE

The organization of this thesis is as follows. A general philosophical introduction lays out the main concepts that will be treated in further detail through the entire work. The introduction is followed by an historical perspective section on the anatomy of the main structure studied here, the dorsal premotor cortex (PMd). Subsequently, a *physiology review section* recapitulates the anatomy and discusses in detail the fundamental concepts presented in the general introduction. This section is split in two parts. The first part introduces the function of PMd according to a "*cognitive view*" and describes its advantages and drawbacks. The second part is more general and describes alternatives to the cognitive view. This part introduces the foundations of the *affordance competition hypothesis*.

The affordance competition hypothesis is central in this dissertation and its main concepts are treated in full detail (i.e. a description of fronto-parietal visual processing pathways, bias competition concepts, source of bias information and supporting data in computational modeling). The general hypothesis makes specific predictions that are described after the physiology review section and are tested in three included articles.

The *discussion section* consists of several parts. The first part consists in a global recapitulation of the predictions and results. The second part addresses the competition hypothesis in PMd and basal ganglia (BG). The third part compares relative value encoding in PMd with other cortical areas such as the lateral intraparietal cortex (LIP) and the frontal eye fields (FEF). A fourth part extends these observations to human

studies. The last part revisits two aspects of the competition process: the location and timing of the process in basis of observations conducted by different research groups.

A *future perspectives* section follows the discussion. This section introduces the notion of effort and action cost in the context of potential upcoming studies within the frame of the *affordance competition hypothesis*. A recent debate about the emerging field of neuroeconomics is briefly inspected. A *conclusion section* finalizes the present work.

II. INTRODUCTION

1. General philosophical introduction

The work presented in this thesis addresses several important aspects of the neurophysiologic process known as decision making. *Decision making* is a deliberative process that results in the commitment to a categorical proposition (Gold and Shadlen, 2007). It can be seen as motivated procrastination (Cisek et al., 2007) or a situation in which one succumbs to the preponderance of one set of influences over another (Bierce, 1911). However, to favour one option over another or to engage in one action or another might be completely different things. We term decisions in a similar fashion whether we deal with an abstract process, such as choice of university or career, or whether we ponder among two concrete actions, such as braking or accelerating upon the sight of an amber light in our drive to work.

The classical view of decision making (Fodor, 1983; Pylyshyn, 1984) has this process belonging to "cognition", a separate process from sensory motor control. For instance, few processes can be as removed from sensory-motor control as playing strategy games such as chess. For a chess player, decisions are portrayed best by the time commitment of one pondered strategy over another with no obvious link between a reported movement and the internal sequences of action-outcomes that the player has in mind (Newell and Simon, 1972). The mental process has to be *covert* if the player wants to stand a chance since guessing is a main feature in the game. The view of decision

making as entirely abstract ("cognitive process") is deeply rooted in history, starting from classic Greek scholarship (Hicks, 1907).

Aristotle for instance, argued that the mechanism responsible for purposive human behavior was conveyed exclusively by a "nonmaterial substrate" like the human soul. This influential idea was not challenged by any alternative view until Descartes (Descartes, 1649, 1664) proposed a dual deterministic and cognitive explanation of human behavior. In contrast with Aristotle, fully deterministic decisions included very elegant and stereotyped sensory-motor reflexes that had a very tangible substrate in the human body. Although cognitive behavior was still relegated to a "nonmaterial substrate", the very foundations for empirical research, binding the neural mechanisms linking sensation and action, were laid down at this time. Notably, the notion of information being transferred from sensory nerves to muscles through basic reflexes flourished with 20th century physiologists such as Sherrington (Sherrington, 1906).

The characterization of the primary sensory and motor systems along with recent physiological data provided the foundations for novel paradigms in psychology like *behaviorism* (Skinner, 1974). Behaviorists attempted to explain even the more abstract process on the basis of essential sensory-motor behaviors and argued that all processes (covert or non-covert such as thinking or walking respectively) should have similar observational correlates. Supporters of behaviorism proposed to treat physical and psychological disorders with qualified experimental methods such as operant-conditioning (Skinner, 1974).

In response to the behaviorist view, Lachman and Butterfield proposed a "cognitive" alternative to explain processes such as decision making (Lachman et al.,

1979). The cognitive view relegates decision making, including decisions among actions, to an exclusive stage of abstract processing that takes place in a serial information processing architecture. This view further suggests a spatial and temporal decoupling of the decision process from perception and action. Although the disagreement between behaviorism and cognitivism went beyond the scope of the decision making it is important to emphasize that this point was particularly crucial.

The dispute between these two psychology schools continued until the second half of the 20th century when it was found that both views could complement each other for the treatment of psychological pathologies such as phobias, posttraumatic stress disorders and addictions (Hofmann and Smits, 2008; Rachman, 1997; Santrock, 2008). Moreover, the interaction of the cognitive and behaviorist points of view led to important advances in developmental child psychology (Piaget, 1954).

However, a certain ambiguity still remains today attending the characterization of decision making. Although the cognitive view might still be popular, from an ecological perspective *decision making* cannot be seen as an entirely abstract process, since the majority of living creatures are faced with a world of actions that need both spatial and temporal overt behavior. The point of view that a decision can be made between overt actions is an outstanding feature that has evolutionary implications as well. All animals display a capacity to decide among actions, whether the decisions are very simple, as it is the case in quasi-reflexive local feeding responses observed in primitive organisms like flatworms (i.e. *Planocera gilchristi,* Gruber and Ewer, 1962) or whether the decisions involve complex foraging behaviour as it is the case in primates and humans (Bautista et al., 2001; Janson, 1998; Kacelnik, 1997; Noser and Byrne, 2007; Tinbergen, 1951;

Stevens et al., 2005). Although decisions among actions can vary greatly in complexity it is reasonable to believe that they are governed by similar principles that allow accumulation of evidence, comparison of the potential options and commitment as more abstracts form of decisions (Glimcher, 2003; Gold and Shadlen, 2007). For instance, early oculomotor studies of saccade selection have shown that even simple kinds of decisions might confer insights into higher cognitive functions (Schall, 2004a). Consequently, a main and very general question regards *how decisions among actions are currently characterized within the existent framework of theoretical, anatomical and physiological knowledge.*

Several attempts to address this question have been proposed and lead to the current debate in neuroeconomics. Neuroeconomics is an emerging discipline that bridges neuroscience and economics and suggest that humans make decisions between different options by integrating all relevant factors such as expected gains, potential risks and action costs, into a single variable reflecting the *subjective value* of each offer (Friedman, 1953; Simon, 1947, 1983). However, some neuroeconomists go a step further in this assumption and postulate that *all decisions are made according to classic economic-utility postulates for economic value* (Padoa-Schioppa, 2011; Von Neumann and Morgenstern, 1944). Among other assumptions, *economic-utility postulates* require decisions to be independent of any contextual parameter such as the metrics and cost of the actions.

The *economic-utility* conjecture appears to be grounded on particular neurophysiology studies suggesting the orbitofrontal cortex (OFC) as the neural correlate for *economic value and economic choice* (Padoa-Schioppa and Assad, 2006, 2008).

According to this point of view, a decision is made exclusively in *abstract* terms and is a serial process dictated by the OFC, wherefrom the outcome of the decision radiates to all other structures. This view is substantiated in the *goods-based model* (Padoa-Schioppa, 2011).

This model has several important caveats as it proposes that decisions are made before action costs can be taken into account for instance, and cannot explain human non-transitive behavior (Güth et al., 1982; Kahneman and Tversky, 1982). Alternatives to this view have been proposed (Cisek, 2012).

In Cisek's view, decisions among actions can be seen as the consequence of a dynamic interaction between perception and action rather than sequestering the decision process to an abstract stage like "cognition". This view proposes that *decisions can be made through a distributed consensus in which action costs and spatial parameters of the action can be taken into account when decisions are made among actions*. The framework in which the decision process is made is the *affordance competition hypothesis*. This hypothesis suggests that decisions can be viewed as the result of a *competition between internal representations of conflicting demands and opportunities for action*, also called *affordances* (Gibson, 1979). The competition between potential actions plays out within reciprocally interconnected areas of the parietofrontal system (Matelli and Luppino, 2000) that can represent different aspects of movement (Jones et al., 1978; Marconi et al., 2001; Pandya and Kuypers, 1969).

Sensorimotor areas such as dorsal premotor cortex (PMd) are sensible candidates for being causally involved in action selection. For instance, Song et al. (2011) showed that reversible inactivation of the superior colliculus (SC), a sensorimotor structure just

two synapses away from the motor neurons that move the eye (Basso and Wurtz, 1998), could affect saccade target selection in non-human primates. The animals performed in a 4-target visual search task and after SC inactivation, made fewer saccades to the targets in the affected zone. These deficits were not simply *motor* as they were mostly absent when only a single target was presented and inactivation was conducted. In this case the animals were still able to saccade to the single target.

The *affordance competition hypothesis* also suggest that multiple potential actions can be represented simultaneously within a given cortical area as has been indirectly shown for the arm system (reach and grasp) and oculomotor system (Baumann et al., 2009; Cisek and Kalaska, 2005; Glimcher, 2003; McPeek and Keller, 2002; Scherberger and Andersen, 2007). For instance, cell population data in PMd suggests that two mutually-exclusive potential reaching actions can be simultaneously represented until a choice can be made, at which time the activity corresponding to the non-chosen option becomes suppressed. This simultaneous specification of multiple potential actions is also supported by several behavioral studies of reaching movements made in presence of distractors (Song and Nakayama, 2006, 2008; Song et al., 2008; Tipper et al., 1992) and lays out the framework for a competition based mechanism for action selection.

The *affordance competition hypothesis* further suggests that the competition process between the options takes place within the same regions that specify the actions (Cisek, 2006, 2007a). This suggestion is in agreement with proposed mechanisms of *selective attention*, in which the selection process also takes place through competition in the very sensory areas that process the percepts (Boynton, 2005; Desimone and Duncan, 1995; Treue, 2001). In both *selective attention* and *affordance competition* mechanisms,

cells with different percept preferences (stimuli orientation or movement preference, respectively) mutually inhibit each other, creating a competition between potential actions or percepts. In the *affordance competition hypothesis*, the competition process is gradually resolved throughout the parieto-frontal system as new information is incorporated into the process: the *bias*. The notion of *bias* arises from the different excitatory inputs that the fronto-parietal system receives from diverse cortical and subcortical structures that project to it (e.g. prefrontal cortex, PFC and BG) conveying particular sets of information (e.g. appetitive, hedonic value) about the options for action. These *biases* become integrated with sensory or motor variables. For instance, LIP integrates expected utility, local income, hazard rate and relative subjective desirability along with specific spatial parameters of the actions such as saccade probability (Dorris and Glimcher, 2004; Janssen and Shadlen, 2005; Platt and Glimcher, 1999; Sugrue et al., 2004). Expected utility is an economic concept that represents the betting preferences of an individual as a function of the payout, probability of outcome, risk and subjective value of the options (i.e. utility of the options). The hazard rate represents the probability of an event to happen in time and local income the reward history (actual vs past rewards).

The mechanism proposed in the *affordance competition hypothesis* is not surprising from the point of view of interactive behavior where decisions among actions must take account of the "dynamic" aspects of the environment in which the actions are played out. Considering, for instance, the situation in ***Figure 1A***, a predator may be initially faced with two potentially useful/attractive pursuit actions, but as soon as the chase begins the metrics of the actions and the estimates of their relative value may change, as it is the case if one of the targets (zebras) splits in two groups. Furthermore,

decisions between actions are strongly dependent upon their geometrical relationship. For example, if an animal seeking escape (zebra in ***Figure 1B***) is faced with two opposite routes (large obstacle ahead), the choice has to be *all-or-none* to a given direction. If the escape routes are similar (small obstacle ahead) then the best strategy may consist in mixing both options and delay making the choice until the last moment. *This implies that* when choosing to reach between two nearby targets the nervous system can mix their neural representation and start moving between them. The observation that decisions among actions can be affected by the metrics of the actions is both consistent with human psychometric data (Chapman et al., 2010; Favilla, 1997; Ghez et al., 1997) and with a number of oculomotor neurophysiology studies (Louie et al., 2011; Schall, 2004a), although this particular issue remains a central topic in the present work and will therefore be examined in detail.

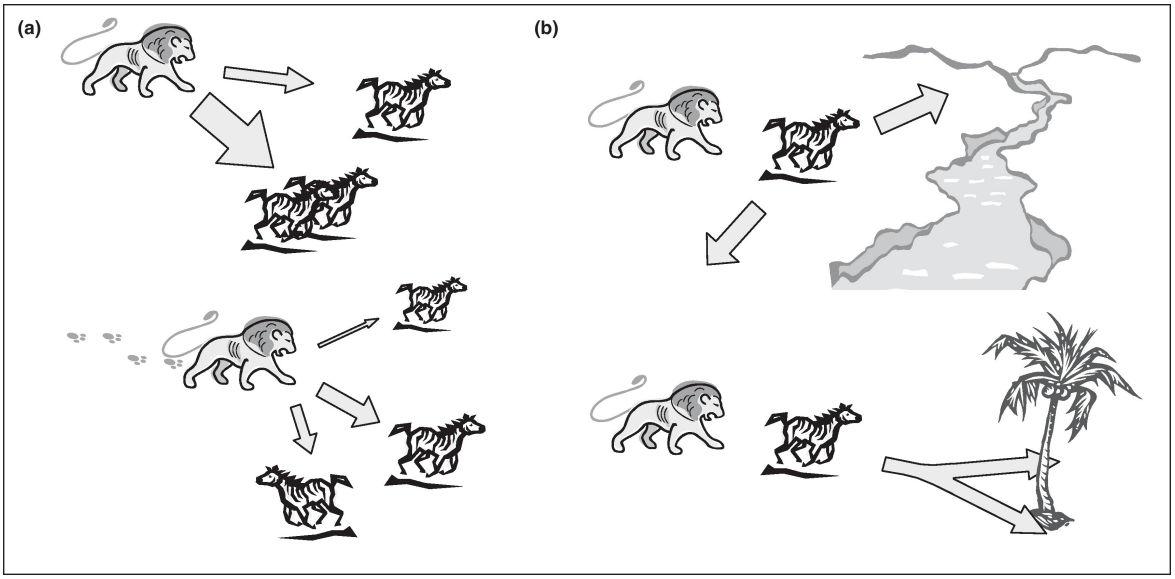


Figure 1. Schematic decision making scenarios during natural behavior.

A. The environment around the lion provides information on both the spatial metrics and relative values of potential pursuit actions (arrows, with value indicated by width). During ongoing activity, this information is constantly changing and what was once a single action may sometimes split into two (bottom). **B.** When faced with two opposite escape routes (top), the zebra must make an all-or-none decision, but when the escape routes are similar (bottom), it may mix them initially and veer toward one or the other in-flight *(adapted from Cisek, 2012).*

2. The motor role of the central nervous system, a brief historical perspective

From the earliest western medical writings, it was thought that the movement of the body was controlled by the brain. In the *Edwin Smith Surgical Papyrus* originating in the Pyramid age (3000 BC) there are a number of descriptions of motor dysfunctions after head injury (Breasted, 1930). A literal citation of one of the cases reads as follows "the subject walks shuffling with the sole on the side of him having that injury which is to the skull". This contralateral symptom was interpreted as the result of a blow to one side of the head causing the brain to impact on the inside of the contralateral skull (contrecoups syndrome). Later on, Hippocratic doctors (500 BC) would write more extensive treaties on head wounds showing good awareness that head injuries could produce contralateral symptoms. However, the primary interest was diagnosis and not the study of the underlying anatomy or physiology (Courville, 1946). Aretaeus, a Greek physician who practiced in Rome and Alexandria (200 BC), went a step further and distinguished paralysis due to head injury from paralysis due to spinal injuries, an observation that led him to postulate that some kind of crossing must take place above the craniovertebral junction. However, where exactly the crossing occurred remained a mystery for centuries (Louis, 1994) only to be revealed much later by the Pisan scholar Domenico Mistichelli (1675-1715) in his "trattato dell'apoplessia" and by the French military surgeon Dr François Pourfour du Petit (1664-1741) with complementary field work (Thomas, 1910).

One of the most important events in the history of the study of the motor functions of the cortex was the discovery by Fritsch and Hitzig in 1870 that electric

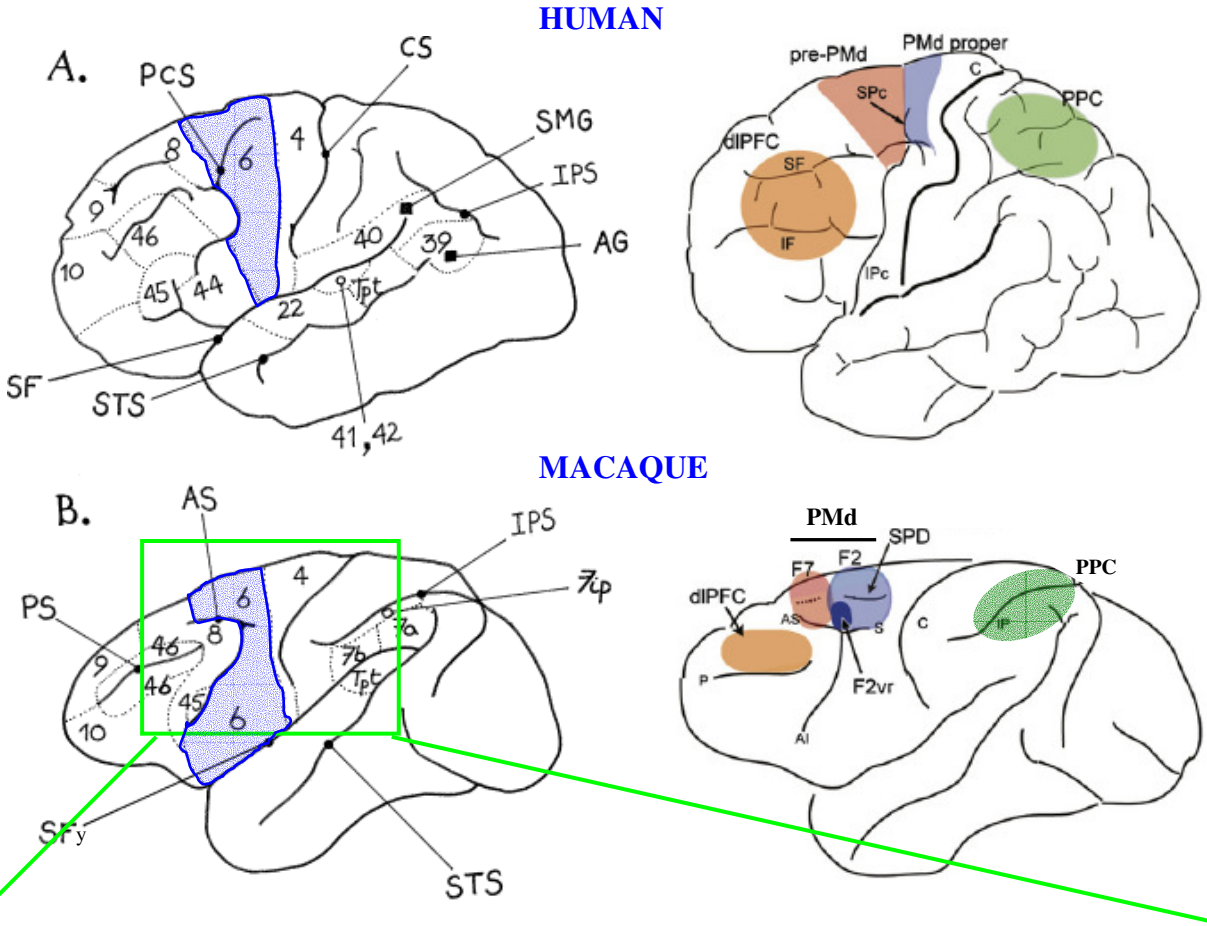
stimulation of the cerebral cortex could produce discrete movements. These results were in agreement with the ideas of John Hughlings Jackson (1815-1911), often considered the "father of English clinical neurology". Hughlings Jackson reasoned that the cortex had basic sensory-motor functions and also gathered clinical evidence substantiating this view (Young, 1970). In studying epileptic seizures, he noticed a systematic spread of convulsions from one body part to its immediate next. These observations led him to suggest that different areas of the cortex could be involved in the control of particular muscle groups and that these areas would be arranged in a way that mimic the organization of the body (Hughlings Jackson, 1873; Temkin, 1971; Young, 1970). Hughlings Jackson's work was notably expanded by Ferrier (1874a, b) who explored the effects of electrical stimulation in extensive areas of the cerebral cortex, well beyond what is considered today's motor cortex (M1) and including prefrontal areas such as FEF.

Ferrier observed that electrical stimulation could induce not only seizures but also discrete movements. The later observation was particularly interesting because these discrete movements seemed to cluster on particular areas. Ferrier reported that electrical stimulation on these areas evoked movements of eyelids, face, mouth, tongue, ear, neck, hand, foot and tail. The early work by Ferrier was conducted in a wide range of animals such as dogs, jackals, rabbits and cats, substantiating the generality of Jackson's assumptions. A growing interest in the primate brain would then lead Ferrier to extend research to non-human primates, delineating not less than 19 centers related to different movements including walking, arm retraction, extension and flexion of the wrist, mouth opening and protrusion of the tongue, sneering expression of the face and eye movements (Ferrier, 1874-1875). Ferrier (1875) also conducted lesion studies of the motor centers

reporting a correlation between the size and location of a lesion with the type and severity of the resulting paralysis. As techniques for electrical stimulation improved, Ferrier's results were confirmed in humans. The Canadian Dr. Penfield and colleagues applied electrical stimulation along the precentral cortex in patients during surgery for the removal of tumors and epileptic foci (Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950). Their results revealed a disproportionate somatotopic map of the body that is commonly depicted as Penfield's motor homunculus with very similar results in non-human primates (*Woolsey's semiusculus*; Woolsey et al., 1952). These pioneering works are the foundation of the modern functional and anatomical definition of the motor and premotor cortices.

3. The anatomical organization of the premotor cortex

Early human anatomical work by Brodmann (1909) revealed that a significant fraction of the frontal lobe lacks a clearly defined internal granular layer (IV) and is commonly referred as agranular cortex. This area can be further parceled into a well defined field with large pyramidal cells including exclusively Betz cells (Betz, 1874), lying in the anterior bank of the precentral sulcus *(area 4)*, and a wide region spanning the precentral gyrus and the posterior portion of the superior frontal gyrus on both the lateral and medial surfaces in the primate brain *(area 6)* (**Figure 2A-B**).


HUMAN
A.
PCS
CS
SMG
IPS
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STS
41,42
pre-PMd
PMd proper
SPc
PPC
dlPFC
SF
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IPc
MACAQUE
B.
AS
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PMd
SPD
F7
F2
dlPFC
PPC
F2vr
C.
ACC
24c
24d
Pre-SMA
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SEF
FEF
DLPFd
DLPFv
PMv
OFC
PGm
PEc
PE
PEip
MIP
VIP
LIP
AIP
V6A
POs
PFG
PG
PF
face
arm
leg
eye

Figure 2. Architectonic areas in the human (A) and macaque brain (B) along with expanded mesial and lateral views of the macaque brain (C). The numbers on the left-side picture correspond to Brodmann and Walker's classification, meanwhile the right-side picture uses the classification of Barbas and Pandya (1987). Notice the consistent mapping of area 6 (blue shades) and area 4 in both humans and macaques despite the different representation of gyrus sulci in both species, in particular for macaque principal sulcus (P) that becomes the superior frontal sulcus (SF) and the inferior frontal sulcus (IF) (orange ellipse in the right-side pictures). The figures on the right show the location of the dorsal premotor cortex (PMd) and its homologous subdivisions in humans and macaques. PMd can be subdivided into rostral PMd (pre-PMd in humans and F7 in the macaque, pink ellipses) and caudal PMd (PMd proper in humans and F2 in the macaque, blue ellipse). On the top left figure: PCS, precentral sulcus; CS, central sulcus; SMG, supramarginal gyrus; IPS, intraparietal gyrus; STS, superior temporal gyrus; SFy, Sylvian fissure; AS, arcuate sulcus; PS, principal sulcus. On the top right figures: dlPFC, dorsolateral prefrontal cortex; SPc, superior precentral sulcus; C, central sulcus; PPC, posterior parietal cortex (green ellipses); IPc, inferior precentral sulcus; AS, superior arcuate sulcus, AI, inferior arcuate sulcus; S, spur of the arcuate sulcus; C, central sulcus; SPD, superior precentral dimple; C, central sulcus; IP, intraparietal sulcus (*adapted from Aboitiz and Garcia, 1997; Abe and Hanakawa, 2009).* The green rectangle depicted in **C** shows the parcellation of the motor cortex, posterior parietal, and cingulate cortices**.** The motor and premotor areas are defined according to Matelli et al. (1985, 1991). IP, intraparietal sulcus, AG, annectant gyrus; C, central sulcus; Ca, calcarine fissure; Cg, cingulate sulcus; IO, inferior occipital sulcus; L, lateral fissure; Lu, lunate sulcus; P, principal sulcus; POs, parieto-occipital sulcus; ST, superior temporal sulcus; FEF, frontal eye field; SEF, supplemental eye field; PMd, dorsal premotor cortex; PMv, ventral premotor cortex, M1; motor cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area. AI, inferior arcuate sulcus; AS, superior arcuate sulcus; C, central sulcus; Cg, cingulate sulcus; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; DLPFd, dorsolateral prefrontal cortex, dorsal; DLPFv, dorsolateral prefrontal cortex, ventral; MIP, medial intraparietal cortex; LIP, lateral intraparietal cortex; VIP, ventral intraparietal area; Anterior intraparietal area, AIP; PE, PEc, PEIp, PF,

PFG and PG are arbitrary names given to cytoarchitectonically distinct areas defined by von Bonin and Bailey (1947). Note that area 6 corresponds roughly to PMd, PMv (green and red shaded areas), SMA and pre-SMA (blue and orange shaded areas). Area 4 corresponds to M1 (beige shaded area F1) *(adapted from Rizzolatti and Luppino, 2001).*

Evidence from clinical observations and cortical ablation experiments conducted by Fulton (1935) led to the original view of a *primary motor cortex corresponding to area 4,* whereas Woolsey et al. (1952) along with Penfield and Welch (1951) further established the concept of a non-primary motor cortex revealing a physiologically distinct region, the *supplementary motor cortex.*

The *supplementary motor cortex* is located in the medial aspect of area 6 and represents today's supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA). Hines (1929) defined the *remaining of area 6 as* "*premotor cortex*", although research in this region would linger for nearly half a century mainly because of experimental shortcomings. For instance, Woolsey et al. (1952) and Travis (1955) concluded that the *premotor cortex* was not a part of the motor system because cortical stimulation of the area in deeply anesthetized monkeys didn't evoke movements. Although it was known that the level of anesthesia is a critical variable for cortical excitability (Bucy and Fulton, 1933), knowledge of the connectivity pattern of the premotor region and spinal cord were at that time very limited and so were the chances to obtain an ideal combination of stimulation parameters and probing locations.

It is known today that low intensity electrical stimulation (≥40μA) of regions of the premotor cortex that have corticospinal projections (F2, PMd, **Figure 2C**) (Dum and Strick, 1991; He et al., 1993) can evoke everything from finger twitches to complex arm-

to-mouth movements (Godschalk et al., 1995; Graziano et al., 2002; Raos et al., 2003). Extensive stimulation of the premotor cortex has also helped characterizing areas involved in oculomotor control such as the supplemental eye field (SEF; Tehovnik and Lee, 1993) and FEF (Bruce et al., 1985; Robinson and Fuchs, 1969; Schlag and Schlag-Rey, 1987). We can parcel the *premotor cortex* of non-human primates in at least seven non-primary motor areas involved in controlling arm movements such as reaching and grasping (Barbas and Pandya, 1987; Geyer et al., 2000; Matelli et al., 1985, 1991; Vogt, 1919; Von Bonin and Bailey, 1947) and two further areas involved in oculomotor control (Barany et al., 1923; Ferrier, 1875) (**Figure 2C**).

The first two regions are located in Brodmann's area 6 and are namely the dorsal and ventral premotor cortices (PMd and PMv) which are caudal to the arcuate sulcus and rostral to M1. The SMA and pre-SMA are located in the superior frontal gyrus and loosely correspond to Woolsey's supplementary motor cortex (Woolsey et al., 1952). Another three non-primary motor areas can be further identified in the banks of the cingulate cortex, namely the rostral, dorsal and ventral cingulate motor areas (CMAr, CMAd and CMAv, respectively)(Dum and Strick, 1991; He and Strick, 1995; Picard and Strick, 1996). The two oculomotor areas are FEF and SEF. The first region, FEF (also called area 8 of Brodmann) is located within the anterior wall of the arcuate sulcus and encompasses a triangular area next to the spur junction of both branches of the arcuate sulcus (Barany et al., 1923; Ferrier, 1875). The second area, SEF is a post-arcuate region located in the rostral bank of the arcuate sulcus close medially to pre-SMA (Schlag and Schlag-Rey, 1987; Woolsey et al., 1952). Although these two areas are classified traditionally as belonging to the prefrontal cortex, the FEF in particular has functional

features that are similar to PMd (Thura et al., 2011). The FEF is involved in action specification and competition-based mechanisms of goal selection in the oculomotor system while the PMd may perform similar functions in the arm system (McPeek et al., 2006; Cisek and Kalaska, 2005).

The modern organization of the premotor cortex is full of nuances and a number of alternative ways of subdividing area 6 have been proposed (Barbas and Pandya, 1987; Matelli et al., 1991; Muakkassa and Strick, 1979). These alternative divisions are worth mentioning in order to address the functional differences observed within the region. For instance, Barbas and Pandya (1987) delineated the premotor cortex (area 6) mainly on the basis of cytoarchitectonic and myeloarchitectonic features and subdivided it into a dorsal sector (PMd) and a ventral sector (PMv) at the spur of the arcuate sulcus.

These authors reported hints of an "emergent" layer IV in PMv and higher myelin content in PMd, although the most striking results were observed studying the connectivity patterns within these two sectors using anterograde and retrograde tracers. *A rostral portion of PMd had specific frontal connections restricted to the neighboring dorsal frontal regions, whereas a caudal portion of PMd sent projections to the motor cortex.* These results would be later complemented by tracing studies conducted by Strick and colleagues detailing inputs from the dorsolateral prefrontal cortex (DLPFC) to rostral PMd (Lu et al., 1994) and projections from the caudal sector of PMd to not only M1 but also directly to the spinal cord (Dum and Strick, 1991; He et al., 1993).

In contrast, the PMv was found to be connected extensively both with PFC and M1. For instance, Carmichael and Price (1995a, b) and Strick and colleagues (Lu et al., 1994) showed that both OFC, DLPFC and the dorsomedial prefrontal cortex (DMPFC)

share reciprocal projections with PMv. The DLPFC projections to PMv are extensive in contrast to the projections of DLPFC to PMd that are limited to only a portion of the arm area. Matsumura and Kubota (1979) and Muakkassa and Strick (1979) also showed projections of PMv to M1.

The idea that anatomical differences could be observed not only in PMd and PMv but also within each of these cortical areas separately motivated yet another parcelation of area 6, incorporating a growing bulk of information from neuroanatomical and physiological studies (Matelli et al., 1985, 1991). According to Matelli et al. (1985, 1991), the dorsal part of the agranular frontal cortex could be subdivided into three areas: area F1, corresponding to the primary motor cortex (M1), and areas F2 and F7 which together correspond to PMd (**Figure 2**). Area F2 occupies the caudal two-thirds of superior area 6 and is bordered caudally by area F1 and extends rostrally up to the border with area F7. Area F7 is located about 3 mm in front of the genu of the arcuate sulcus and extends medially to the superior limb of the arcuate sulcus until area F6 (pre-SMA). Area F7 corresponds roughly with the rostral division of PMd of Barbas and Pandya (1987) and incorporates a distinct eye movement representation in its rostro-medial aspect (SEF) and a motor representation of a forelimb field with a minority of other body parts representations embedded in it (Tachibana et al., 2004).

These results are congruent with physiological studies (Boussaoud et al., 1998; Fujii et al., 2000; Mitz and Godschalk, 1989) suggesting that this area is involved in visual guidance of arm reaches. Area F2 is medially delimited by area F3 (SMA) and laterally by the spur of the arcuate sulcus, which separates it from areas F4 and F5, that together correspond to Barbas and Pandya's PMv. F2 corresponds roughly to the region

referred to as the caudal part of PMd in physiological studies (Wise et al., 1997). The topography of the corticospinal projections (Dum and Strick 1991; He et al. 1993), the data from single-neuron recording studies (Kurata, 1989) and intracortical microstimulation studies (Godschalk et al., 1995; Raos et al., 2003) suggest that area F2 has a gross somatotopic arrangement, with a hindlimb field located medially to the superior precentral dimple and a forelimb field located laterally to it (SPP, Figure 2B). Area F2 contains a significant proportion of cells (16%) with visual responses and seems implicated in visual guidance of arm reaches. The visual responses in area F2 are not just perceptual but appear to be driven by the instructional significance of the stimulus for motor behaviour (Wise et al., 1996a). Most visually driven neurons are concentrated within the rostrolateral sector of the forelimb representation of area F2 (which is the region of F2 spanning from the precentral dimple to the spur (Fogassi et al., 1999).

Tanji's group (Fujii et al., 2000) reported similar visual responses and evoked saccades in the PMd region corresponding roughly to the entire area F7 plus a rostral portion of F2. It has been shown that gaze modulation effects observed in PMd for arm-reaching movements are modest when the animals are instructed to perform in a free gaze condition, in comparison to when the animals have to move the eyes after an oculomotor instruction (Boussaoud et al., 1998; Cisek and Kalaska, 2002). These results are in agreement with the work from Tanji's group (Fujii et al., 2000). Their study reported that saccadic responses elicited by either visual or electrical stimulation in PMd were functionally different from responses observed in SEF and FEF, further indicating the role of PMd in coordination of eye and arm movements in a context that requires cognitive behavioral control.

The border between PMd and its neighboring areas has also been an issue of debate mainly concerning PMv. A precentral polysensory zone caudally located from the spur separating area F2 and F4 (between caudal PMd and PMv) has been recently proposed by Graziano and Gandhi (2000). Graziano suggests a role in the guidance of movements in basis of tactile, visual and auditory information for this particular region.

According to Matelli, PMv can also be subdivided in anatomical and physiologically distinct regions, namely areas F4 and F5. Area F4 constitutes the caudal part of PMv (Matelli et al., 1985). It is connected with posterior parietal areas such as the ventral intraparietal area (VIP), the intraparietal sector of area PE, and the secondary somatosensory cortex (S2) (Rizzolatti and Lupino, 2001, for a review). F4 neurons discharge according to specific body part movements and electrical stimulation of this area evokes neck, arm, and face movements with often a combination of two or three body parts (Fogassi et al., 1996; Gentilucci et al., 1988). Most F4 neurons are activated by somatosensory, visual or auditory stimuli (Fogassi et al., 1996; Gentilucci et al., 1988; Graziano et al., 1999). This area presents bimodal, somatosensory and visual neurons that have RF within a reaching distance (peripersonal space) and code actions in extrinsic (spatial) coordinates, rather than in intrinsic limb coordinates (Kakei et al., 2001). It has therefore been suggested that area F4 transforms specific positions in peripersonal space into arm, neck, and face/mouth movements and is also involved in space perception (Fogassi et al., 1996; Rizzolatti et al., 1996).

Area F5 occupies the most rostral part of PMv in the macaque monkey, and contains a motor representation of distal hand movements (Hepp-Reymond et al., 1994; Kurata and Tanji, 1986; Rizzolatti et al., 1988). The neurons of this area discharge during

specific goal-directed hand movements such as grasping, holding and tearing. This area is also directly connected with M1 and receives rich inputs from S2, parietal area PF (7b), and from a parietal area located inside the intraparietal sulcus, the anterior intraparietal area (AIP) (Godschalk et al., 1984; Luppino et al., 1999; Matelli et al., 1986; Matsumura and Kubota, 1979; Muakkassa and Strick, 1979) which is traditionally associated with grasping (Baumann et al., 2009). There are two classes of visuomotor neurons in monkey area F5: canonical neurons, which respond to the presentation of an object, and "mirror" neurons, which respond when the monkey sees object-directed action (Rizzolatti and Luppino, 2001). "Mirror" neurons require a meaningful interaction between an effector (e.g. hand or mouth) and an object (e.g. edible fruit) in order to be active (Gentilucci et al., 1988).

Early studies characterize these cells according to the naturalistic motor acts that they prefer and classify them into proximal and distal classes involving diverse effectors such as arm, hand and mouth. For instance, Gentilucci et al., (1988) reports "mirror" neurons in the distal classes as "Grasping-with-the-hand-and-the-mouth neurons", "Grasping-with-the-hand neurons", "Holding neurons" and "Tearing neurons". The proximal classes are: "Reaching neurons" and "Bringing-to-the-mouth-or-to-the-body neurons". More recently it has been demonstrated that area F5 also harbors "mirror" neurons that discharge during the execution and observation of mouth actions.

Most of mouth "mirror" neurons become active during the execution and observation of mouth ingestive actions such as grasping, sucking or breaking food. Some of them respond during the execution and observation of oral communicative actions such as lip smacking (Ferrari et al., 2003). In general, "mirror" neurons have gathered

considerable attention in the scientific community as they might be involved in diverse processes such as action understanding, language, communication and learning by imitation (Rizzolatti and Luppino, 2001). Despite the appeal of this hypothesis "mirror" neurons cannot be regarded as the only type of cells in which the observation of external events can generate motor representations of the actions associated with those events. Unlike "mirror" neurons, PMd cells do not respond to direct observation of naturalistic behaviors but are implicated in the prediction of impending actions or events based on arbitrary cue-response associations. However, Cisek and Kalaska (2004) found PMd cells that are active during action observation and seemed involved in mental rehearsal of action plans (Cisek and Kalaska, 2004). This property might contribute to abstract functions underlying the assessment and understanding of observed events and suggest a relation with PMv "mirror" cells: although PMd cells and PMv "mirror" cells may have very different properties, it is plausible that both groups are required in processes such as action learning and understanding.

4. The role of PMd in visual guidance of movements: visual processing pathways

Early studies indicated that the occipital cortex lacks direct access to the primate frontal lobe (Jones and Powell, 1970; Pandya and Kuypers, 1969), although it has been known for a long time that striate and extrastriate visual areas can relay visual information to premotor areas via the parietal cortex (Critchley, 1953a; Milner and Goodale, 1993). The notion of a parietal relay for visual information has its foundations in the classic "dorsal and ventral processing streams" hypothesis proposed by

Ungerlieder and Mishkin (1982). However, the idea that the visual system is divided into two main streams of information may not be entirely novel and can be tracked back to the work of Max Schultze (1866) and to the *Duplicity Theory* proposed by von Kries (1895).

According to Ungerlieder and Mishkin's proposal, visual processing can be segregated into two anatomically and functionally distinct pathways originating in the striate cortex, namely an *occipito-parietal dorsal stream specifying spatial location* and an *occipito-temporal ventral stream specifying object identity* (**Figure 3A***)*.

The dorsal stream travels through the occipitoparietal cortex (V1-V4) to the caudal part of the posterior parietal cortex (PPC), the inferior parietal lobule (IPL), and extends further to DLPFC. The ventral stream travels through the occipitotemporal cortex to the inferior temporal cortex (TE) and extends further to the ventrolateral prefrontal cortex (VLPFC, **Figure 3A).**

Lesions of the ventral and dorsal streams in monkeys produced selective deficits in object vision and spatial vision, respectively, leading to their characterization as 'What' and 'Where' pathways (Macko et al., 1982; Mishkin et al., 1983). Human patients with PPC lesions are able to recognize objects, but not their spatial relationship (Andersen, 1987; Critchley, 1953a, b). For instance, optic ataxia is characterized by a specific deficit in localizing visual targets with respect to the body and results from lesions centered around the intraparietal sulcus (IPS) and the superior parietal lobule (SPL) (Rondot et al., 1977). Consequently, patients suffering from optic ataxia are able to identify objects properly, although they cannot accurately perform a goal directed action. However, it is important to mention that the functional distinction between ventral and dorsal stream is not entirely clear-cut and a number of additional clinical studies in

humans have revealed nuances for grasping actions (James et al., 2003; Milner et al., 1991; Read et al., 2010). For instance, a patient with agnosia (patient D.F.) who had a large bilateral lesion of the occipitotemporal cortex and a small left-sided lesion of the occipitoparietal cortex (James et al., 2003; Milner et al., 1991) presented impaired perception of objects but intact ability to grasp them (**Figure 3B**).

In fact, patients like D.F. can pre-shape the hand to reflect size, shape and orientation of objects and are able to both orient and transport the hand to an intended reach location in space. However they cannot indicate the orientation of their own hand in space (and by extension pantomime an action) despite being aware of spatial depth information (Read et al., 2010). These findings, combined with the connectivity patterns between the posterior parietal and frontal premotor areas (Wise et al., 1997 for a review), have led to the proposal of a 'How' instead of a "Where" function for the dorsal stream (Goodale and Milner, 1992).

Recent studies account better for these nuances by segregating *the dorsal parieto-frontal stream into three functionally and anatomically distinct, major pathways: a parieto–prefrontal pathway, a parieto–premotor pathway and a parieto–medial temporal pathway* (**Figure 3C**). The ***parieto–prefrontal pathway*** has its strongest sources in the LIP, VIP, the mediotemporal (MT) and mediosuperiotemporal (MST) regions, and links the occipito–parietal circuit with two areas, namely a pre-arcuate region (i.e. FEF) and the caudal portions of the banks of the principal sulcus in PFC (i.e. DLPFC) (Cavada and Goldman-Rakic, 1989; Schall et al., 1995). This pathway is basically involved in control of eye movements, spatial working memory and highly cognitive processing. ***The parieto–premotor pathway*** comprises two distinct parallel projections.

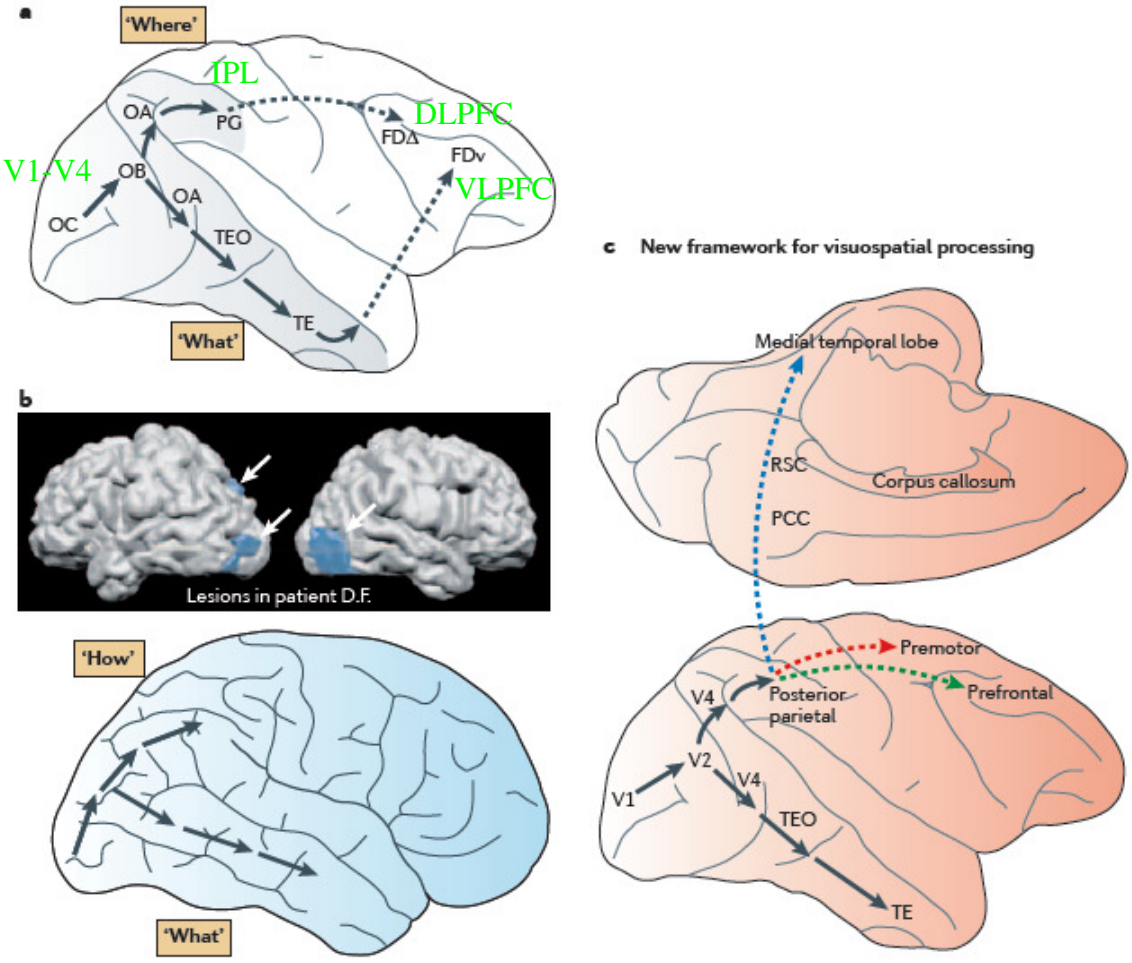
a
'Where'
IPL
DLPFC
V1-V4
OA
PG
FDΔ
FDv
VLPFC
OB
OA
OC
TEO
TE
'What'
b
Lesions in patient D.F.
'How'
'What'
c New framework for visuospatial processing
Medial temporal lobe
RSC
Corpus callosum
PCC
Premotor
Prefrontal
Posterior parietal
V4
V2
V4
V1
TEO
TE

Figure 3 Frameworks of visuospatial processing. A. The original formulation of the dorsal and ventral streams in the macaque monkey. The ventral stream is a multisynaptic pathway projecting from the striate cortex (area OC) to area TE in the inferior temporal cortex, with a further projection from area TE to VLPFC (i.e. FDv from Bonin and Bailey, 1947). The dorsal stream is a multisynaptic pathway projecting from striate cortex to area PG in the inferior parietal lobule, with a further projection from area PG to dorsal DLPFC (i.e. FDD from Bonin and Bailey, 1947). On the basis of the effects of lesions in monkeys, the ventral stream was termed a 'What' pathway supporting object vision, whereas the dorsal stream was labeled a 'Where' pathway supporting spatial vision. **B.** The top panel depicts the location of the lesions in patient D.F. (shown in blue and indicated by white arrows) that led to impairment in object perception but not in the accuracy of orienting her hand when reaching to the same objects. This pattern of results led to the proposal depicted in the bottom panel, that the dorsal stream is more accurately characterized as a 'How' pathway supporting visually guided action than as a perceptual 'Where' pathway. **C.** The new neural framework for dorsal stream function that is proposed by Kravitz et al. (2011). At least three distinct pathways emanate from the posterior parietal cortex. One pathway targets the PFC (shown by a dashed green arrow) and supports spatial working memory (the parieto–prefrontal pathway); a second pathway targets the premotor cortex (shown by a dashed red arrow) and supports visually-guided actions (the parieto–premotor pathway); and the third targets the medial temporal lobe, both directly and through the posterior cingulate and retrosplenial areas (shown by a dashed blue arrow), and supports navigation (the parieto–medial temporal pathway). PCC, posterior cingulate cortex; RSC, retrosplenial cortex; TE, rostral inferior temporal cortex; TEO, posterior inferior temporal cortex; V1, visual area 1. (***A*** *and* ***B*** *are adapted from Kravitz et al., 2011;* ***C*** *is adapted from James et al., 2003).*

One projection has its major source in SPL areas V6A and the medial intraparietal region, MIP. This projection targets PMd areas F2 and F7 (Gamberini et al., 2009; Matelli et al., 1998). The second projection arises primarily from area VIP and projects to PMv areas F4 and F5 (Rozzi et al., 2006). This pathway mediates eye movements (Nachev et al., 2008), as well as numerous forms of visually guided actions such as reach and grasp (Colby and Duhamel, 1991; Duhamel et al., 1998; Fattori et al., 2001, 2009, 2010; Galletti et al., 1991, 1995, 1997, 2001). The ***parieto–medial temporal pathway*** links the IPL with the medial temporal lobe (MTL) including the hippocampus. This pathway is involved in processing of navigationally relevant information, distant-space perception, route learning and spatial long-term memory (Kravitz et al., 2011). The two former pathways traditionally constitute the **parieto-frontal network** which is highly relevant for both visual guidance of movements and decision making processes.

5. The role of PMd in visual guidance of movements: the parieto–frontal network.

The anatomical and functional organization of the parieto-frontal network underlying arm reaching is well documented (Caminiti et al., 1996; Johnson et al., 1993, 1996) and particular emphasis will be given to the role of the main structures in PPC and PMd. The PPC shares with motor and premotor areas a multiplicity of arm, leg and face representations. In particular, the arm skeletomotor region is represented at least 8 times (Rizzolatti et al., 1998). PPC comprises a diverse number of functions including spatial attention, spatial awareness, polysensory integration, coordinate transformation, movement intention and decision making (Andersen et al., 1987, 2009; Andersen and

Buneo, 2002; Burnod et al., 1999; Cohen and Andersen, 2002; Colby and Goldberg, 1999; Critchley, 1953a, b; Desmurget et al., 1999; Gold and Shadlen, 2007; Kalaska et al., 1997; Mishkin et al., 1983; Mountcastle et al., 1975; Rushworth et al., 2001a, b).

Anatomically, the PPC is formed by two lobules: SPL and IPL (**Figure 4**). **SPL** includes area 5d, V6A and MIP in the superiorlateral bank of the intraparietal sulcus (IPS) (Caminiti et al., 1996; Johnson et al., 1996) and area 7m, the medio-dorsal parietal area (MDP) and the parieto-occipital area (PO) in the medial crest of the IPS (Lewis and Van Essen, 2000a, b; Matelli et al., 1995; Shipp and Zeki, 1995). **IPL** includes areas 7a and 7b in its exposed lateral surface and the lateral intraparietal area, LIP (Andersen et al., 1985; Blatt et al., 1990); the ventral intraparietal area,VIP (Colby et al., 1993a, b; Maunsell and van Essen, 1983) and the anterior intraparietal area, AIP (Sakata et al., 1995) in the inferiolateral bank of the IPS (**Figure 4**). The IPL has been classically regarded as the main relay of visual information to the motor areas because it constitutes the main parietal input from the dorsal stream (Jones and Powell, 1970; Pandya and Kuypers, 1969).

However, the projections of the IPL are not mainly addressed to motor and premotor cortices but to prefrontal areas instead (Andersen et al., 1985; Cavada and Goldman-Rakic, 1989; Petrides and Pandya, 1984; Schwartz and Goldman-Rakic, 1984). In fact, visual information is conveyed to PMd by area PO in SPL and to some extent by area 7a in IPL (Tanne et al., 1995). PMd also receives visual information indirectly from PO via area 7m (Cavada and Goldman-Rakic, 1989) and MIP (Blatt et al., 1990). All these areas: PO, 7a, MIP and 7m receive direct extrastriate visual inputs (Felleman and Van Essen, 1991). See **Figure 5** for a summary.

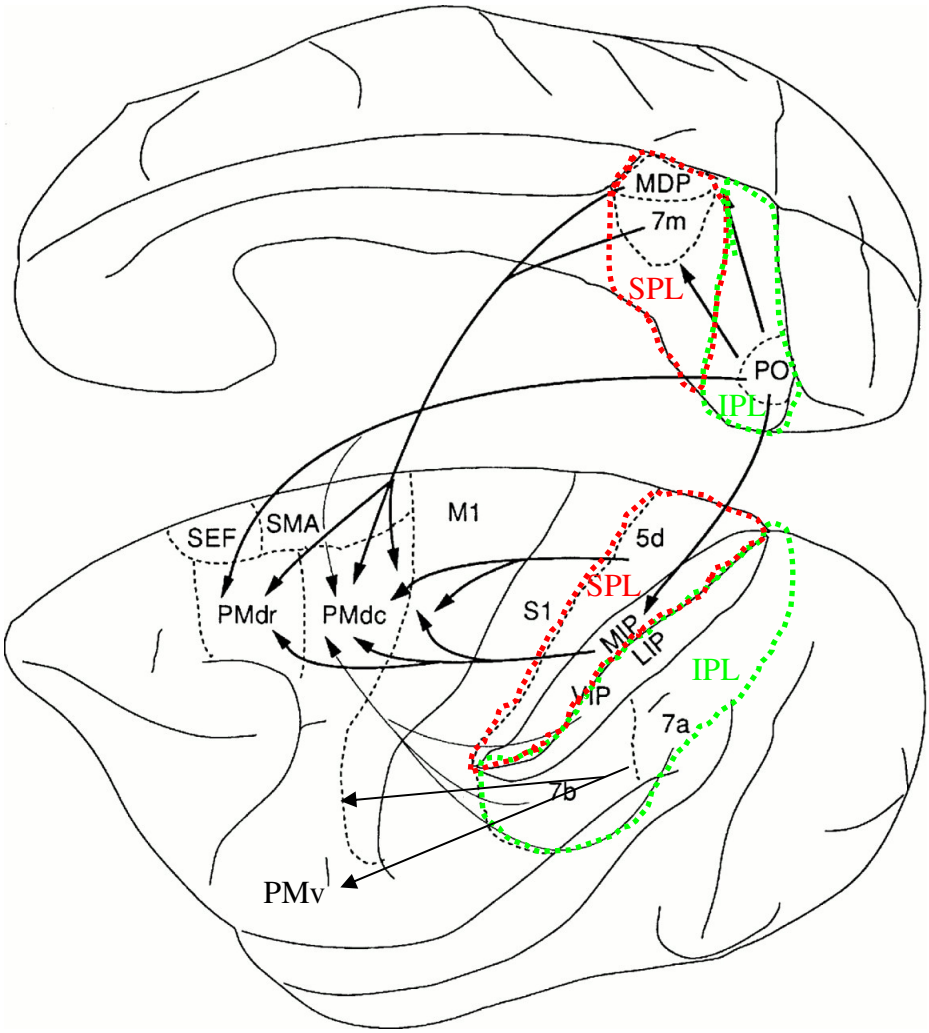

Figure 4. The parietofrontal network: a summary of connectivity from posterior parietal cortex primarily to PMd and M1. (*Bottom*) Lateral view of the left hemisphere. (*Top*) medial view of the hemisphere, depicting areas of the same left hemisphere as the bottom figure. Arrows are shown projecting to PMd, but note that most corticocortical projections are reciprocal. Quantitatively, more significant projections are marked by the thicker lines. Abbreviations are as in Figure 1, with these additions: MIP, LIP, and VIP, medial, lateral, and ventral intraparietal areas, respectively; PO, parieto-occipital visual area; MDP, medial dorsal parietal area; areas 7a, 7b, and 7m, subdivisions of posterior parietal cortex; area 5d, dorsal area 5; S1, somatosensory cortex *(adapted from Wise et al., 1997).*

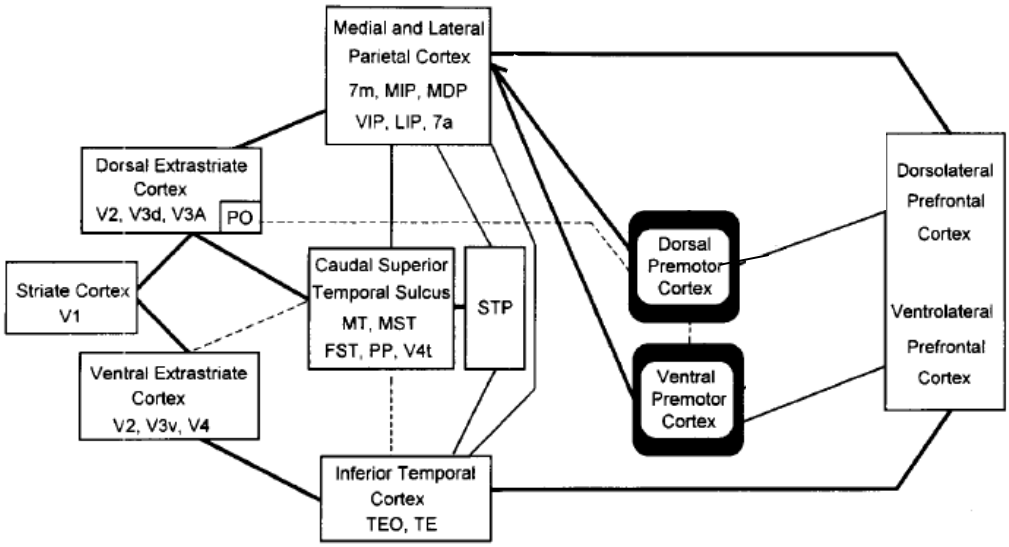

Figure 5. Summary of the major corticocortical visual pathways to premotor cortex. Dashed lines represent sparser connections. In this diagram, the areas are not arranged in a functional hierarchy, but rather in a quasi-regional manner *(adapted from Wise et al., 1996).*

Dorsal stream visual information can also reach PMd through even less direct routes after being relayed by prefrontal areas within the parieto-frontal network. The IPL sends its prefrontal projections predominantly to DLPFC (Cavada and Goldman-Rakic, 1989), whereas the SPL projects more to DMPFC (Petrides and Pandya, 1984). These two prefrontal areas project mostly to the dorsal and medial premotor regions (e.g. PMd, preSMA, SMA) (Barbas and Pandya, 1987; Barbas, 1988). For instance, PMd receives the majority of the prefrontal inputs in its more rostral aspect, area F7 (Barbas and Pandya, 1987; Lu et al., 1994*;* Stepniewska et al., 1993; Tachibana et al., 2004). In contrast PMv receives prefrontal inputs originating from VLPFC that convey *ventral stream information* (Barbas, 1988). However, the dorsal stream and ventral stream prefrontal pathways are not completely separate. Recent evidence suggests that ventral stream information can be also relayed to PMd via VLPFC (Takahara et al., 2012).

Quantitatively, the majority of the parietal input to PMd and M1 originates from SPL area 5 and MIP (Figure 4) (Jones et al., 1978; Jones and Powell, 1970; Pandya and Kuypers, 1969). Additionally, MDP and 7m project exclusively to PMd. It is important to mention that *association projections between PMd and these structures in SPL tend to relate regions sharing similar activity types in a gradient-like fashion indicating a common role in visual planning and coordination of movements* (Johnson et al., 1996; Marconi et al., 2001). In fact, rostral PMd and ventral MIP show similar signal, set-related and directional tuning activities during delay period in spatial visuo-motor tasks, whereas movement and postural-related activities are more prominent in dorsal MIP, area 5d and M1 (Johnson et al., 1996). In contrast, PMv input originates from VIP and area 7b (**Figure 4**) (Caminiti et al., 1996; Colby and Duhamel, 1991; Galletti et al., 2003;

Luppino et al., 1999; Matelli et al., 1998; Pesaran et al., 2008; Shipp et al., 1998; Snyder et al., 1997; Tanne-Gariepy et al., 2002; Tomassini et al., 2007; Wise et al., 1997).

6. Parietal structures implicated in visuo-motor transformations and guidance of movements

Visually guided reaching requires transformation from eye to limb centered coordinates. It has been proposed for PPC, that a direct transformation subtracting the position of the hand from the position of the target (both in eye coordinates) can be used to form a movement vector centered on the arm without stepping in sequential transformations through multiple reference frames (Andersen and Buneo, 2002; Buneo et al., 2002). To this purpose, a brief account of the functional peculiarities of PPC areas involved in visual guidance of movements is useful.

Studies conducted in the *parietal reach region* (PRR, a term used by Andersen's group to define the area encompassing MIP, 7a and PO; Andersen and Buneo, 2002; Cohen and Andersen, 2002) have shown that it contains neurons representing visual targets in eye coordinates (Batista et al., 1999; Buneo et al., 2002; Pesaran et al., 2006). This is in contrast with area 5 where cells can be found coding simultaneously eye and limb coordinates (Batista et al., 1999; Buneo et al., 2002; Caminiti et al., 1991). MIP reflects limb movement and position (Johnson et al., 1996), although cells are also sensitive to both visual and somatosensory stimuli (Colby and Duhamel, 1991). MIP neurons display a gradient of responses that range from purely visual to proprioceptive, with occasional representation of both (Colby and Duhamel, 1991; Eskandar and Assad,

1999; Snyder et al., 1997). As mentioned previously, MIP neurons have similar functional gradient responses as observed in the region ranging from rostral PMd to M1, supporting the hypothesis that both areas participate in visual guidance of movements.

A study conducted by Snyder's group (Chang and Snyder, 2010; Chang et al., 2009) in the PRR is particularly pertinent to the above observations. Although PRR represents space using *multiple reference frames* (E.g. cells having either hand centered, gaze centered or intermediate tuning responses) this heterogeneous representation cohexist with a *systematic compound gain field* that modulates activity proportional to the distance between eyes and hand. This compound gain field consists of a distinct eye position gain effect and a hand position gain effect that have similar magnitude but opposite sign. It is important to mention that the compound gain field was present in the majority of cells systematically and regardless from their reference frame encoding. These results can be interpreted from a computational point of view. Whereas multiple-reference frame representations may be pertinent to optimally compute non-linear sensorimotor transformations in visually guided reachings, the compound gain effect may be more pertinent for linear transformation between eye and hand reference frames.

Area **5d**, which primarily projects to M1 and the caudal parts of PMd, appears to encode arm position in a shoulder-centered coordinate system (Lacquaniti et al., 1995) or eye-and-limb coordinates (Buneo et al., 2002). This area processes proprioceptive information and contains neurons that reflect movement kinematics (Hyvarinen, 1982; Mountcastle, 1975) and contributes to the visuomotor coordination of complex sequences of movements such as locomotion (Drew et al., 2008). Cells in this region are modulated

by the direction of reach movements just like in M1 (Ashe and Georgopoulos, 1994). However, some differences have been observed since area 5d seem to only weakly encode forces and movement dynamics (Kalaska et al., 1990).

It has also been reported that parallel representations of azimuth, elevation, and distance of the hand relative to the shoulder occur in largely segregated neuronal populations in area 5 (Lacquaniti et al., 1995). These results suggest a role for this area for the encoding of hand position and movement in 3D space and perhaps in visuo-motor reference frame transformation processes (Ferraina et al., 2009). PMd was found to encode the target of reach relative to the eye, to the hand, or both (hand relative to the eye; Pesaran et al., 2006) and this form of encoding suggest a coordinate frame based on the "work-space" defined by eye, hand and target rather than each of them separately.

Other areas of PPC that do not project directly to PMd are nonetheless important for the visual guidance of movement. For instance, area **LIP**, also called the "parietal eye field" (Andersen et al., 1992) is part of a visuo-saccadic system of the monkey and has been intensively studied over the past three decades as a model for understanding sensory-motor control in general (Andersen and Buneo, 2002; Colby and Goldberg, 1999). For instance, both PRR and LIP encode the position of objects in the same eye-centered reference frame and both areas show effector-specific modulation suggesting that a communication within different parietal areas might contribute to movement planning (Batista et al., 1999; Cohen and Andersen, 2000, 2002; Cohen et al., 2002; Stricanne et al., 1996).

7. Parietal structures implicated in action-selection and guidance of movements

In addition of sensory-motor functions, PPC areas are notably involved in decision making and action selection processes. Notably, area LIP has been studied in the context of perceptual decision making, saccade target selection, working memory, allocation of attention, behavioral intention, representation of reward, expected value and elapsed time (Assad and Maunsell, 1995; Chafee and Goldman-Rakic, 2000; Dorris and Glimcher, 2004; Eskandar and Assad, 1999; Hanks et al., 2006; Leon and Shadlen, 1999; Platt and Glimcher, 1999; Roitman and Shadlen, 2002; Shadlen and Newsome, 2001; Sugrue et al., 2004). *It is important to mention that LIP, FEF, and SC together comprise the core of a heavily interconnected network that plays a critical role in visuo-saccadic decision making* (Glimcher, 2003; Gold and Shadlen, 2007). There is also a growing body of evidence suggesting a parallel role in non-saccadic decision making for M1, PMd, SMA and MIP (Cisek and Kalaska, 2005; Cui and Andersen, 2011; Nakayama et al., 2008). Notably, cognitive signals from MIP representing expected value and reach target location have been used in context of neural prosthetic studies (Mulliken et al., 2008a, b; Musallam et al., 2004) with similar results in motor and premotor areas (Bansal et al., 2011; Santhanam et al., 2006). Potential action representations (action plans) for reaches and anti-reaches can be also represented in PRR (Kalaska, 1996; Kalaska and Crammond, 1995; Klaes et al., 2011) with similarities with action plan representations in PMd (Cisek and Kalaska, 2005), SC (Basso and Wurtz, 1998) and other parietal structures such as LIP (Platt and Glimcher, 1997). The similarities between parietal and premotor regions

for decision and executive functions suggest a parallel if not complementary role of these areas in action selection and visual guidance of movements.

8. The basal ganglia and premotor cortex

The basal ganglia (BG) are a complex network of subcortical nuclei involved in control of skeletal movement, sensorimotor integration, and cognitive and motivational processes (Bolam et al., 2000; Gerfen, 1996). It has been also suggested that the BG could be involved in selection of motor programs (Chevalier and Deniau, 1990; Mink and Thach, 1991; Mink, 1996; Redgrave et al., 1999; Turner and Anderson, 1997) and in reinforcement learning (Apicella et al., 1991; Bar-Gad and Bergman, 2001; Schultz et al., 1993). BG receive inputs from wide areas of the cerebral cortex in basically two main structures, the striatum and the subthalamic nucleus (STN). The information processed in these two structures returns primarily to the cerebral cortex via the thalamus and constitutes what is commonly known as BG loops (Alexander et al., 1986, 1990; Alexander and Crutcher, 1990a). BG loops are composed of several parallel, segregate, and functionally distinct, but homologous circuits (Alexander et al., 1986; Middleton and Strick, 2000) (**Figure 6).**

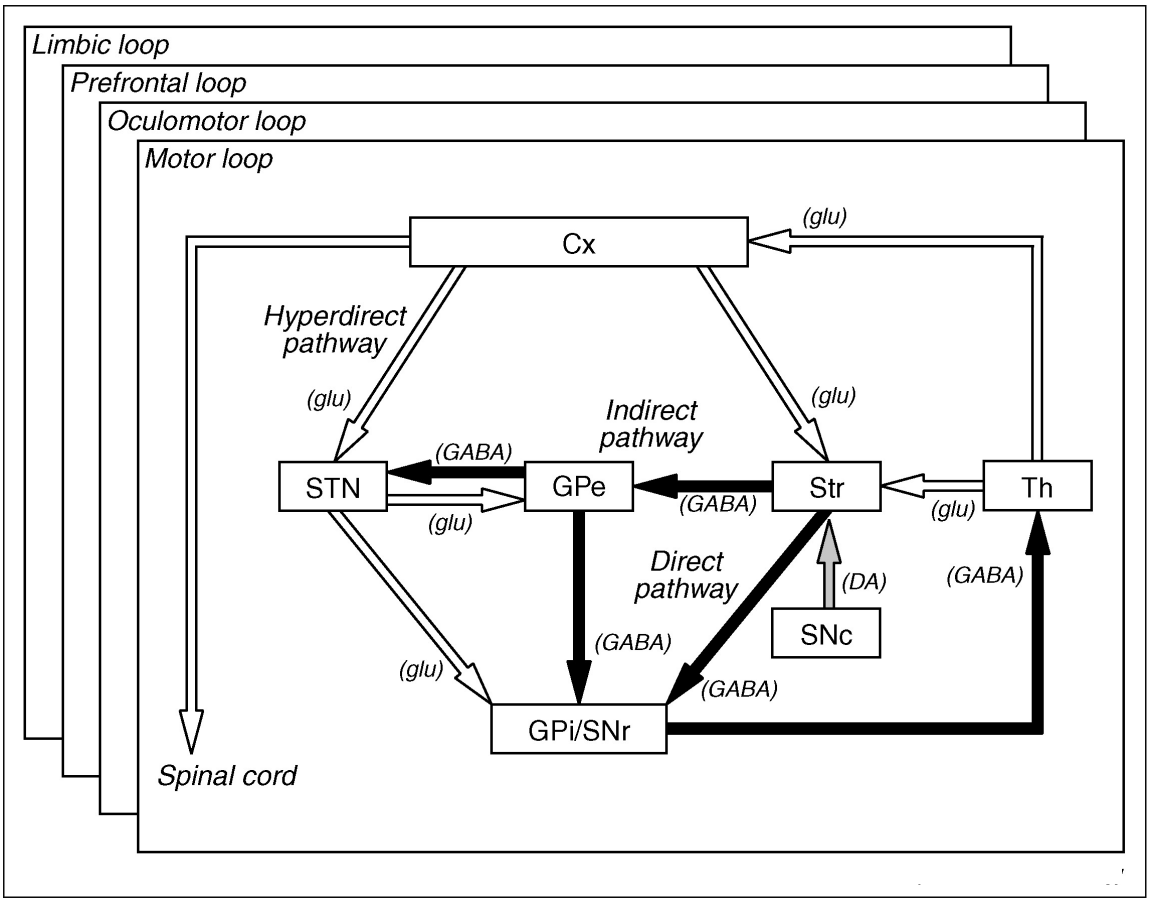

Figure 6. Basic circuitry of the basal ganglia. This diagram includes the Cx–STN–GPi/SNr hyperdirect, Cx–Str–GPi/SNr direct, and Cx–Str–GPe–STN–GPi/SNr indirect pathways. Open and filled arrows represent excitatory glutamatergic (glu) and inhibitory GABAergic (GABA) projections, respectively. The gray arrow represents dopaminergic (DA) projections. Cx, cerebral cortex; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus *(adapted from Nambu, 2008).*

The limb motor loops, which control voluntary limb movements, originate from the motor cortices, such as M1, SMA, PMd, PMv and project to somatotopic motor territories of BG. The outputs structures from BG are the internal segment of the globus pallidus, (GPi) and the substantia nigra pars reticulata, (SNpr). These two structures convey information to the thalamus, which then project back to M1, SMA, PMd and PMv (Akkal et al., 2007; Hoover and Strick, 1999; Middleton and Strick, 2000; Miyachi et al., 2006). It is also important to mention that the anatomical distribution of particular motor loops support the functional differences observed in areas such as PMd and PMv (Boussaoud and Wise, 1993; Hoshi and Tanji, 2007).

These two areas seem to have partially segregated cortico-basal loops in rhesus macaques and owl monkeys (Dum and Strick, 2005; Morel et al., 2005; Nakano, 2000a, b; Stepniewska et al., 2007). The input projections from the PMd and PMv largely overlap in the medial aspect of the STN, whereas they segregate laterally (Nambu et al., 1997). The thalamic outputs for these two areas show partial overlaps with important nuances (Morel et al., 2005). PMd receives the majority of its thalamic projections from the more dorsal portion of nucleus ventralis anterior (VAd) and the posteriodorsal ventrolateral nucleus (VLpd). In contrast, PMv receives its main projections from the ventral portion of the nucleus ventralis anterior (VAv), the posterioventral lateral nucleus (VLpv), and the ventral medial nucleus (VM). Both areas receive largely overlapping projections from the medial dorsal nucleus (MD) and anterior ventrolateral nucleus (VLa), the first being selective for rostral-PMd (F7) and PMv (F5) and the later for caudal-PMd (F2) and PMv (F4)(Stepniewska et al., 2007).

In addition to the motor and premotor loops, the oculomotor, prefrontal, and limbic loops connect the cerebral cortical areas (FEF, SEF, PFC and limbic cortex) with the corresponding parts of BG and thalamic nuclei. Through these multiple loops, BG control eye movements, higher brain functions and emotions, as well as limb movements. The BG loops consist of three major projection systems linking the input nuclei (striatum, STN) to the output nuclei (GPi/SNpr), namely the '*direct*', the *'hyperdirect'* and the '*indirect*' pathways (**Figure 6**) (Alexander and Crutcher, 1990a; Alexander et al., 1990).

The *direct* pathway arises from GABAergic striatal neurons and projects monosynaptically to GPi/SNr. The *indirect* pathway arises from GABAergic striatal neurons that projects polysynaptically to GPi/SNr by way of sequential connections with the globus pallidus pars externa, (GPe) and the STN. The STN receives direct cortical inputs, and is considered another input station of BG, in addition to the striatum. The cortico–STN–GPi/SNr '*hyperdirect*' pathway conveys strong excitatory signals from the cortex to the GPi/SNr with faster conduction velocity than the *direct* and *indirect* pathways (Nambu et al., 2002) and seems to be important for inhibiting irrelevant motor programs and/or changing motor plans (Isoda and Hikosaka, 2008; Leblois et al., 2006).

In general, a transient cessation in tonic inhibition supplied by BG to motor structures *releases* movements via the *direct* pathway, whereas a transient increase in inhibition by the basal ganglia to motor structures via the *indirect and hyperdirect* pathways *prevents* the release of selected motor programs (Leblois et al., 2006; Mink, 1996; Nambu et al., 2002). This observation can be explained on the basis of the circuitry diagram shown in **Figure 6.** Considering that the projections of BG to thalamus are always inhibitory, a stronger suppression of the BG via the direct pathway results in

disinhibition of the thalamus and cortical sensorimotor targets. The converse situation is observed if BG receives stronger excitatory inputs via the direct or hyperdirect pathway.

Based on these properties it has been suggested that BG is perhaps involved in action-selection (Leblois et al., 2006; Redgrave et al., 2011) as it has been reported in cortical motor areas such as PMd (Cisek and Kalaska, 2005; Klaes et al., 2011).

9. PMd role in visual guidance of movements: learning studies

People apply associations between arbitrary visual cues and body movements on a daily basis (for example, pushing the brake pedal when stopping at a red light). Learning these arbitrary associations relates to conditional visuomotor learning (CVML). This type of learning establishes a solid foundation for understanding abstract-rule learning mechanisms. CVML has been studied extensively in motor, premotor and prefrontal areas (Brasted and Wise, 2004; Buch et al., 2006; Chen and Wise, 1995a, b; Hadj-Bouziane and Boussaoud, 2003; Mitz et al., 1991; Watanabe, 1990) and PMd is essential for this type of learning.

The studies of Passingham (1986) and Petrides (1982) showed that ablations of the monkeys' PMd specifically caused serious deficits in retention and learning of novel arbitrary visuo-motor mappings (Halsband and Passingham, 1982, 1985; Passingham, 1986; Petrides, 1982, 1985, 1997). Humans who have frontal lobe lesions including PMd are also impaired in this task (Petrides, 1997). Neuroimaging studies confirm that PMd is normally activated during CVML tasks (Grafton et al., 1998). However, task impairment

can only be detected when conditional motor associations are instructed by contextual visual cues. Monkeys are able to perform well in conditional motor—motor associations such as sequences of three finger movements to obtain reward (Passingham, 1986). On a sequence task of this sort the cue for the next movement can be given by joint information (proprioceptive input) from the last movement, whereas, on the visuo-motor mapping task the cue has to be visual.

Mitz et al. (1991) trained monkeys in a CVML task in which monkeys were presented with novel and familiar visual stimuli. Novel stimuli were never the same across two different sessions in contrast to familiar stimuli for which the animals had learned the visuo-motor mapping thoroughly during training. This randomization was done in order to ensure pertinent learning for all novel stimuli. Cell recordings were conducted in PMd while the animals were learning mappings for the novel stimuli by trial and error. Criterion *(i.e. behavioral measure to assess successful learning of an association)* was achieved when the monkeys made a correct choice three consecutive times. Learning-related effects were seen across cells in several epochs (i.e. set, delay period, movement, and reward); although some could show effects only in particular ones.

The group of Wise (Chen et al., 1995a, b, 1996; Mitz et al., 1991) classified these cells according to the type of changes observed in each epoch. A general observation was that during learning many cells showed an increase in cell activity at any epoch, and this modulation closely paralleled the improvement in task performance of the animals. These types of cells were defined as **learning dependent.** These cells showed trial outcome selectivity, and fired more for correct responses in the preferred direction of the cell than in the opposite direction. Plotting average cell activity across trials for entire epochs (e.g.

delay period) indicated that cell activity increased as learning progressed and stabilized at comparable levels to what was observed with presentation of familiar stimuli.

According to Mitz and colleagues (1991), learning effects were similar for different sets of novel stimuli presented, and therefore, independent of the particular visual features of the stimuli. This suggests that the effects described reflect learning of visuomotor mapping and not sensory responses to novel stimuli. Similar results were obtained in subsequent studies in PMd for oculomotor (Brasted and Wise, 2004) or arm reaching tasks (Buch et al., 2006).

Learning dependent cells were also observed in other cortical areas such as SEF in addition to other type of cells defined as **learning selective cells** (Chen et al., 1995a). This particularly interesting type of cell is characterized by an unusually high firing rate during the early stages of learning and activity decay with behavioral performance. Learning selective cells show stable and very low baseline activity both at later stages of learning and when presented with familiar stimuli. A correlation between the evolution of the directional tuning properties of theses cells and learning has also been observed. Learning selective cells are transiently tuned during early stages of learning but become unmodulated in later stages of learning or when exposed to familiar stimuli (Chen et al., 1996). These results suggest that cells that are normally not directionally tuned can take part of a learning process.

Different groups have reported similar types of responses in CVML in very diverse cortical areas including PMd, SEF, FEF, PFC and BG (Brasted and Wise, 2004; Buch et al., 2006; Chen and Wise, 1995a, b; Hadj-Bouziane and Boussaoud, 2003; Mitz et al., 1991; Watanabe, 1990). It is noteworthy that learning effects in frontal lobe

structures (such as PMd, SEF) and BG had very modest qualitative and quantitative differences, and similar post-stimulus onset latencies (Brasted and Wise, 2004; Buch et al., 2006; Chen and Wise, 1995a, b, 1996; Hadj-Bouziane and Boussaoud, 2003). This is in contrast with areas M1 and FEF in which CVML effects were comparatively scarce (Chen et al., 1996; Germain and Lamarre, 1993; Mitz et al., 1991).

These results are consistent with the idea that CVML is mainly driven by a parallel modular network that involves certain frontal lobe and BG structures (Alexander and Crutcher, 1990a; Alexander et al., 1986; Houk and Wise, 1995). A few functional interpretations have been proposed for the role of the different learning types of cells. For instance, Wise and Boussaoud proposed that long-lasting effects in learning dependent cells could reflect long-term storage of learned associations (Chen and Wise, 1995a; Hadj-Bouziane and Boussaoud, 2003; Mitz et al., 1991). In contrast, learning selective cells might play a role in short-term plasticity changes and strengthen the connectivity between BG and PMd in early stages of learning (Hadj-Bouziane and Boussaoud, 2003). Some indirect evidence of this has also been suggested in a imaging study conducted in humans (Toni et al., 2002).

10. Role of dorsal premotor cortex in guidance of arm reaching movements: a traditional cognitive view

Cognitive neuroscience proposes that complex behavior can be explained in terms of neural mechanisms of *perception*, *cognition* and *action* that are traditionally organized within a serial input-output framework such as information processing theory (Albright et

al., 2000; Fodor, 1983; Gazzaniga, 2000; Johnson-Laird, 1988; Keele, 1968; Marr, 1982; Miller et al., 1960; Pylyshyn, 1984).

According to this view *perception* collects sensory information to build and update a stable and unified internal representation of the external world (Marr, 1982; Riesenhuber and Poggio, 2002) that is subsequently used as input to *cognitive* processes in order to make informed judgments about the course of action (Johnson-Laird, 1988; Newell and Simon, 1972; Shafir et al., 1995). Once cognitive processes have decided *what to do*, a single program is prepared for execution. The resulting plan is tailored by the motor system (e.g. grasp an apple or a raisin) through a process of action specification (*how to do*) that is used to generate a desired trajectory of movement through muscle activation (Keele, 1968; Miller, 1960). The motor system perform these executive functions borrowing formalisms from control theory in which a predetermined motor program is passed to a controller that executes it (Keele, 1968; Miller, 1960). As a consequence of this serial-processing view, the functions of PMd have been traditionally studied in the context of independent processing stages, namely: *action selection, action planning, movement preparation and movement execution.*

10.1. Decisions among actions in PMd

Decisions among actions typically refer to the task of choosing "what to do" and can also be called *action selection.* The process of selection among available potential options is one of the hallmarks of cognitive neuroscience, namely decision making, and is the subject of intense research in the motor system. Neural correlates for motor decisions

in the arm system have been observed in sensory motor areas such as PMd (Cisek and Kalaska, 2005; Klaes et al., 2001), PMv (Acuna and Pardo-Vazquez, 2011; Hoshi and Tanji, 2002; Pardo-Vazquez et al., 2011; Romo et al., 2004) and PRR (Batista and Andersen, 2001; Cui and Andersen, 2007; Scherberger and Andersen, 2007). Neural correlates of perceptual decisions are also well documented for the eye system in LIP (Coe et al., 2002; Dorris and Glimcher, 2004; Platt and Glimcher, 1997; Shadlen and Newsome, 200; Yang and Shadlen, 2007), FEF (Coe et al., 2002; Gold and Shadlen, 2000; Schall and Bichot, 1998) and SC (Basso and Wurtz, 1998; Carello and Krauzlis, 2004; Glimcher and Sparks, 1992; Horwitz and Newsome, 1999; Keller et al., 2005; Shen and Pare, 2007). According to the traditional view action selection is an entirely abstract process that does not incorporate information about the metrics of the actions. Additionally, the traditional view implies that action selection is an independent stage in which a *single goal* is always selected before a particular action can be planned and released for execution (Keele, 1968; Miller, 1960). However, recent physiology studies in PMd have shown otherwise (Cisek and Kalaska, 2005; Klaes et al., 2011). For instance, when the available sensory information is insufficient to define a particular goal among several options, premotor delay activity in PMd can represent instead *all potential goals* (Cisek and Kalaska, 2005).

Cisek and Kalaska (2005) trained monkeys with an instructed delay task where spatial-information (two potential targets) and non-spatial information (color) were required for correct performance in the task. The team presented these two sets sequentially during the delay period. When the spatial cue was presented to the animals the PMd population activity reflected *both* options until the appearance of the subsequent

non-spatial cue specified the correct one. At this time the directional signal for correct reach direction increased meanwhile the signal for the rejected target became suppressed. The authors proposed that *multiple reach options are initially represented in PMd and a competition process between the option representations resolving the selected target for overt execution can take place within the same region that specify the actions* (Cisek and Kalaska, 2004; Cisek, 2006).

10.2. Action planning in PMd

Action planning is the process that determines "*how*" an action has to be performed and is also called *action specification*. Action planning typically involves integration of sensory percepts and information specifying the components of a particular action during an instructed delay period (e.g. reach to grasp a cup or a peanut are two similar actions but might require different muscle activation sequences and the usage of contextual knowledge about the action goal and its features, Ansuini et al., 2006). It is known that PMd activity signals the information carried by sensory stimuli about the nature and the metrics of the impending action suggesting that the visual responses are not isolated percepts but are signals that become integrated in the process specifying the actions (Wise et al., 1992). PMd is modulated by spatial cues instructing the monkey to reach in a particular direction (Weinrich and Wise, 1982; Weinrich et al., 1984; Wise, 1985), although when the stimulus location does not match the direction of movement (anti-reach or redirected reach studies) neural activity in PMd first appears to encode the location of a stimulus and later reflect the movement direction instructed by that stimulus

(Crammond and Kalaska, 1994; Gail et al., 2009; Georgopoulos et al., 1989a, b; Georgopoulos and Grillner, 1989).

This is similar to what has been observed in other areas such as FEF during visual search tasks (Schall and Bichot, 1998) indicating that PMd retrieves the information concerning a given operant rule as, for example, in reach/antireache (Klaes et al., 2011) or match/non-match tasks (Wallis and Miller, 2003a). For instance, PMd neurons also discharge after presentation of an arbitrary cue whose features instruct the monkey to execute a particular movement (Kurata and Hoffman, 1994; Kurata and Wise, 1988a, b; Mitz et al., 1991). The ability of PMd to integrate sensory-motor information is also observed in lesion and learning studies. The studies of Passingham (1986), Petrides (1982) and Kurata and Hoffman (1994) have shown that ablation or transient inactivation of monkey's PMd with muscimol (GABAa agonist) specifically causes deficits in retention and learning of novel arbitrary visuo-motor mappings (Halsband and Passingham, 1982; 1985; Passingham, 1986; Petrides, 1982; 1985).

Neuroimaging studies have also confirmed that PMd is normally activated during CVML tasks in humans (Grafton et al., 1998) and that patients with PMd lesions are impaired in these tasks (Petrides, 1997). However, the impairments can only be detected when conditional motor associations are instructed by contextual visual cues. For instance, monkeys are able to perform well in conditional motor-motor associations where sequences of three finger movements are required in order to obtain a reward (Passingham, 1986). A sequence task of the sort can be solved using only intrinsic information. The cue for the next movement can be given by joint information (proprioceptive input) from the last movement, whereas on a visuo-motor mapping task

processing using an extrinsic reference frame is normally required. These results further indicate the particular role of PMd in specification of visually-guided movements. However, there is also some evidence that PMd does not only integrate visuo-spatial information but also other percepts like auditory information (Germain and Lamarre, 1993; Weinrich and Wise, 1982). It has also been shown that PMd integrates intrinsic motor information, such as the effector used (Cisek et al., 2003; Hoshi and Tanji, 2000, 2002, 2006). For instance, Hoshi and Tanji (2000, 2002, 2006) used a sequentially instructed delay task to dissociate target location from effector information (arm to be used). PMd reflected arm use or target location independently of the order of cue presentation and integrated both sets of information before action specification (action selective cells). This is in contrast with PMv that was mainly selective for the physical location of the cues representing either arm or target choice and did not integrate the two sets of information. However, it is arguable that the results could be task dependent, as PMv is typically active in tasks involving 3D object manipulation and grasping. Indeed, neural correlates of motor planning in PMv have also been reported (Murata et al., 1997; Raos et al., 2006).

The group of Hoshi and Tanji (Nakayama et al., 2008; Yamagata et al., 2009) conducted additional studies and used a set of sequential instructions in order to further dissect the process of action planning when the information provided is incomplete. In one variant of the task (*virtual action plan*) a symbolic cue provided *partial information* about the spatial metrics of the rewarded movement. Each symbolic cue was associated to a particular motor rule (e.g. a *square* maps to a “right” reach location while a *cross* maps to a “left” reach location). The symbolic target was followed by a spatial cue consisting

of a couple of choice targets presented at different positions on the screen (e.g. a pair appears either on the left, the middle or the right side of the screen). In this task the animals were rewarded for reaching the correct target *relative to the pair* presented and not in the absolute metrics of the display. In a variant of the same study (*direct* action *plan)* a single symbolic cue provided the information about the target location in the display and the animals were rewarded for reaching the actual position of the target there.

The *virtual action task* is similar to the one conducted by Cisek and Kalaska's study (2005) where a color cue provided partial information about the identity of the rewarded target and a subsequent spatial cue presented metric information about the options. In Hoshi's *virtual action plan,* PMd activity was initially selective for the partial instruction (left or right) and integration of spatial information provided by the second cue was observed in cells that had a combined selectivity for the first partial instruction and subsequent target location in the display. This result is important because it suggests that *PMd could reflect the spatial metrics of the options relative to each other rather than in the absolute metrics of the display* which is the case when there is stimulus-response compatibility (i.e. *direct action plan*). All these studies substantiate the notion that PMd can integrate partial sensory-motor information to specify an action.

10.3. Movement preparation in PMd

The involvement of the PMd in motor preparation was first described as *set-related activity*, which is defined as the neural activity that starts once a forthcoming movement is instructed and continues until the movement is executed (Weinrich and

Wise, 1982, 1984, 1985). The set-related activity in PMd reveals the motor significance of a visual instruction rather than its sensory or attentional significance (di Pellegrino and Wise, 1993). This is in contrast with the activity in PMv which represents better the attentional significance of spatial cues, the shape of motor targets and peri-personal space (Gentilucci et al., 1988; Graziano et al., 1997; Murata et al., 1997; Mushiake et al., 1997). The PMd set-related activity typically reflects the spatial aspects of a forthcoming movement such as its intended direction (Kalaska and Crammond, 1995; Kurata, 1993), amplitude (Fu et al., 1993; Messier and Kalaska, 2000; Riehle and Requin, 1989) and trajectory (Archambault et al., 2009; 2011; Hocherman and Wise, 1991; Shen and Alexander, 1997) as well as non-spatial aspects of a movement such as speed (Churchland et al., 2006) or impending forces (Xiao et al., 2006).

10.4. Movement execution in PMd

At the stage of motor execution, neurons in PMd exhibit activity that resembles M1, suggesting that this area is involved in movement execution as well (Lee and van Donkelaar, 2006) and is influenced by hand trajectory (Hocherman and Wise, 1991; Shen and Alexander, 1997) and limb orientation (Scott et al., 1997). However, PMd is in general less sensitive than M1 to limb-related motor output details such as joint posture and force (Crammond and Kalaska, 1996; Kakei et al., 1999; Riehle et al., 1994; Scott et al., 1997) although certainly more than PMv (Kakei et al., 2001). This result is not surprising since PMd tends to reflect abstract aspects of the task (Caminiti et al., 1998; Cisek et al., 2003; Crammond and Kalaska, 2000; Shen and Alexander, 1997). During an

instructed-delay task where arm reaches could be instructed with either the ipsilateral or contralateral limb, Cisek et al. (2003) revealed that neural activity in PMd was not effector-selective but reflected the abstract goal or direction of targets to be reached. Similar observations have been made by Hoshi's group in their study dissociating virtual action plans from direct motor plans (Nakayama et al., 2008; Yamagata et al., 2009).

A reach goal location can be computed with respect to an external reference frame *(extrinsic reference frame)* or with respect to constituent parts of the body such as joints or muscles *(intrinsic reference frame)*. PMd represents reaching goals both in *extrinsic* and *intrinsic* reference frames although the latter to much less extent than in M1, in agreement with the functional differences observed between the two areas. Cells in PMd are modulated by hand, eye or a combination of hand-and-eye position (Batista et al., 2007; Boussaoud et al., 1998; Caminiti et al., 1991; Cisek and Kalaska, 2002; Pesaran et al., 2006). However, the group of Georgopoulos has also observed coding of reach targets in extrinsic coordinates (hand) in M1 and has suggested a less evident difference in reference conding between the two areas (Georgopoulos, 1986; Georgopoulos et al., 1986). Altogether, these data suggests that *although PMd is a sensory-motor integration region involved in abstract aspects of motor guidance it has a close correspondence with M1, an area more implicated in the details of motor execution*.

This is in contrast with PMv that despite being a major source of inputs to M1 (Matsumura and Kubota, 1979; Muakkassa and Strick, 1979) is heavily devoted to visual processing and does not typically represent intrinsic parameters of movement such as arm posture (Kakei et al., 2001). Moreover, PMv reflects mostly the *perceived* trajectory of motion in visual space (Schwartz et al., 2004) or the direction of image motion rather

than the *actual direction* of the moving arm itself (Ochiai et al., 2005). Kurata and Hoshi (2002) used shift-prisms to dissociate the motor space from the visual space and found an important proportion of cells (2/3rd) representing target location in visual space (exclusively or in combination with motor space). It has been additionally proposed that PMv contains cells involved in peripersonal perception of space (area F4) and "mirror" representation of goal-oriented actions (area F5). There are however some similarities between PMd and PMv when it comes to execution of reach to grasp movements (Raos et al., 2004, 2006). There are two regions involved in preparing and executing similar grasping movements of three-dimensional objects: one located in PMv (area F5) and one in PMd (ventral and rostral portion of F2, close or in juxtaposition to Grazianos polysensory zone, Graziano and Gandhi, 2000). PMv has a larger proportion of reach-to-grasp cells than PMd although this can be explained based on the functional properties of the area and the visual processing requirements needed for grasping.

11. Inconsistencies in the traditional cognitive view: perception, cognition and action

Studies on the cerebral cortex have encountered difficulties interpreting neural activity in belonging to discrete perceptual, cognitive or motor systems. For example, Ungerlieder and Mishkin (1982) observed that visual processing diverges in the cortex into two separate pathways: an occipito parietal dorsal stream specifying spatial location, and an occipito-temporal ventral stream specifying object identity. In addition, color, shape and motion are further processed separately within these streams (Felleman and Van Essen, 1991) and multiple representations of space co-exist suggesting a non-unified

representation of the world (Colby and Goldberg, 1999; Stein and Glickstein, 1992). The sensory representations are strongly influenced by attentional changes (Boynton, 2005; Moran and Desimone, 1985) or by decision variables (Platt and Glimcher, 1999) and are far from being static even when the observer scans a familiar and stable scene (Bushnell et al., 1981; Gottlieb et al., 1998).

The neural representations of the visual world seem to be dominated by the behavioral relevance of information in higher visual areas further suggesting that perception and cognition are not two clearly independent processing stages (Coe et al., 2002; Dorris and Glimcher, 2004; Gold and Shadlen, 2000; Platt and Glimcher, 1997; Schall and Bichot, 1998; Shadlen and Newsome, 2001; Treue, 2001; Yang and Shadlen, 2007). For instance, Gardner's group has shown that attention enhances behavioral performance by enabling efficient selection of behaviorally relevant sensory signals (Pestilli et al., 2011).

The search for discrete cognitive stages has been even more problematic. For instance, traditional cognitive theories propose that action selection precedes action planning (Tversky and Kahneman, 1981) and that these two functions are carried out by distinct physical correlates and without any timing overlaps: there is only a single program prepared for execution before a movement begins (Keele, 1968; Miller, 1960). However, it is difficult to dissociate action selection from action planning even conceptually. Animals are continuously faced with opportunities and demands for action and must make decisions about *what* to do (action selection) and *how* to do it (action specification).

At least from the perspective of overt behavior, continuous interaction with the world often does not allow one to procrastinate *ad-libitum* and collect all information needed to build a *complete* knowledge of the surroundings. A hostile environment (*e.g. approaching predator*) motivates us to build representations of potential actions which the environment currently affords (*e.g. escape running down the valley or fight back using the cutting capacity of a sharp stone*) even if these representations are partial and can be at times misleading (*e.g. the sharp stone may be of little use on a mammoth's thick fur)*. There is growing evidence that decisions among actions in the arm system are found within the same sensory-motor circuits that are responsible for planning and even executing the actions (Cisek and Kalaska, 2005; Gold and Shadlen, 2007; Pesaran et al., 2008; Romo et al., 2004; Scherberger and Andersen, 2007).

Oculomotor decisions also seem to involve the same sensory-motor areas involved in saccade generation (Coe et al., 2002; Dorris and Glimcher, 2004; Gold and Shadlen, 2000; Platt and Glimcher, 1997; Schall and Bichot, 1998; Shadlen and Newsome, 2001; Yang and Shadlen, 2007) and within "less integrated" areas barely two synapses away from the muscle like SC (Basso and Wurtz, 1998; Carello and Krauzlis, 2004; Glimcher and Sparks, 1992; Horwitz and Newsome, 1999; Keller et al., 2005; Shen and Pare, 2007; Thevarajah et al., 2009).

In all these areas, the same neurons that reflect decision variables (e.g. visuo-motor rule in a reach decision task or accumulated evidence in a perceptual decision task) also encode later the metrics of the actions to report the decision (Cisek and Kalaska, 2005; Kim and Basso, 2008; Nakayama et al., 2008; Roitman and Shadlen, 2002; Yamagata et al., 2009; Yang and Shadlen, 2007). It is therefore plausible that *action*

selection and specification involve the same circuits and are performed in an integrated manner: a parallel decision/planning process (Cisek, 2006, 2007b; Fagg and Arbib, 1998; Shadlen and Newsome, 2001). Associative regions also do not correspond well with the segregated topology view suggested by traditional cognitivism (Lebedev and Wise, 2002). For instance, PPC contains cells related to *perception, cognition* and *action* (Andersen and Buneo, 2003; Colby and Duhamel, 1996; Kalaska and Crammond, 1995). PPC is modulated by a wide range of variables associated with decision making such as expected utility (Platt and Glimcher, 1999), local income (Sugrue et al., 2004), log-likelihood of estimates (Yang and Shadlen, 2007) at the same time that it represents intended saccades or reaches (Andersen and Buneo, 2003; Kalaska and Crammond, 1995; Snyder et al., 1997, 2000a, b) and is strongly modulated by attention and behavioral context information (Colby and Duhamel, 1996; Colby et al., 1996; Colby and Goldberg, 1999).

12. Alternatives to the cognitive view

Interactive behaviour cannot be broken down into a sequence of distinct and self-contained events that each starts with a discrete stimulus and ends with a specific response. The deficits of the traditional view have been pointed out several times (Dewey, 1896; Gibson, 1979; Hughlings Jackson, 1884). Gibson for instance, argued that perception does not involve constructing a static representation of the external world but rather is an active process that selects information pertinent to one's behavior.

For instance, the notion that perception can be gated by the significance of the action is well rooted in the processes of selective attention (Desimone and Duncan, 1995).

Interactive behavior could be viewed as a distributed system that involves continuous modification of on-going actions, evaluation of alternative options and updating of sensory information from the external world. Additionally, it does not seem to be the result of a static interaction of independent and highly specialized modules such as it is proposed in the traditional view. From an engineering point of view, interactive processes can be managed with a distributed control system (Parunak and Vanderbok, 1997) with sensori-motor feedback loops instead of using a serial and local control architecture (Ashby, 1965; Brooks, 1991; Sahin et al., 2007). This is precisely what is observed physiologically: the cerebral cortex incorporates considerable functional redundancy *(*e.g. *motor regions with overlapping functions,* Wise, 1985*)*, parallel processing *(*e.g. *visual information pathways*, Ungerlieder and Mishkin, 1982*)* and loop processing architecture *(*e.g. *striatal-pallido-thalamo-cortical pathways*, Alexander et al., 1990; Middleton and Strick, 2000*)*.

Having some functional redundancy along with parallel processing confers important advantages. For instance, redundancy provides robustness to the system towards perturbations or lesions and possibilities for compensation after stroke (Dancause and Nudo, 2011; Nudo and Milliken, 1996; Nudo et al., 1996). Parallel processing contributes to facilitate action selection by filtering relevant from non-relevant information of the impending actions (Aglioti et al., 1995; Desimone and Duncan, 1995; Kusunoki et al., 2000; Treisman and Gelade, 1980).

Temporal processing in a dynamic system is *ecological* in the sense that the system has the ability to respond *any time* that it is requested, since there is no beginning or end of processing but a continuum. This assumption implies that partial

representations simultaneously *coexist,* allowing flexible decision behavior. Indeed, there is growing evidence that the brain begins to prepare several actions in parallel while collecting evidence for selection between them (Cisek and Kalaska, 2005; Gold and Shadlen, 2007; Kalaska et al., 1998; Kim and Basso, 2008; Kim and Shadlen, 1999; Platt, 2002; Ratcliff et al., 2007). From this perspective*, interactive behaviour can be viewed as a constant competition between internal representations of conflicting demands and opportunities of the available actions,* in other words *a competition between "affordances".*

13. Frontoparietal specification of potential actions and the foundations of the affordance competition hypothesis

Ungerlieder and Mishkin (1982) observed that visual processing diverges in the cortex into two separate pathways. An occipito-temporal ventral stream specifies object identity and answers to a *what* question, meanwhile an occipito-parietal dorsal stream specifies spatial location (*where* question) (**Figure 3**). Goodale and Milner were the first to suggest that *the predominant role of the dorsal stream is not only to build a representation of the environment but also to specify the spatial parameters of potential and on-going actions in visually guided behavior* (Goodale and Milner, 1992; Milner and Goodale, 1995). This view directly involves structures lying in the dorsal pathway and reciprocally interconnected areas in specifying the parameters of potential actions (Andersen, 1997; Andersen and Buneo, 2003; Goodale and Milner, 1992; Kalaska, 1996; Kalaska and Crammond, 1995; Wise et al., 1996b, 1997).

The interconnected areas in the ventral stream provide instead information for action selection (Andersen and Buneo, 2003; Cisek, 2007b; Kalaska et al., 1998; Sakagami and Pan, 2007). Perceptual information is transformed into parameters of action along the dorsal stream and information diverges into a number of parallel subsystems each specialized towards the needs of different types of actions (Andersen and Buneo, 2003; Andersen et al., 1987; Colby and Goldberg, 1999; Stein and Glickstein, 1992; Wise et al., 1997). For example, LIP is concerned with the control of gaze (Snyder et al., 2000b), represents the space in a body-centered reference frame (Colby and Duhamel, 1996; Colby et al., 1996; Snyder et al., 1998) and is interconnected with other parts of the gaze control system such as FEF and superior colliculus (Pare and Wurtz, 2001). MIP is involved in guidance of arm reaching movements (Cui and Andersen, 2007; Kalaska and Crammond, 1995; Pesaran et al., 2008), represents target locations with respect to the direction of gaze (Buneo et al., 2002) and is interconnected with frontal regions that are involved in reaching such as PMd (Johnson et al., 1996; Wise et al., 1997). The anterior intraparietal area (AIP) is involved in grasping (Baumann et al., 2009), represents object features such as size and orientation (Nakamura et al., 2001) and is interconnected with the grasp-related area of PMv (Rizzolatti and Luppino, 2001). These observations suggest that all these areas represent a large distributed system for action specification for visually guided actions (Fagg and Arbib, 1998; Goodale and Milner, 1992).

14. Sources of biasing signals for action selection

14.1. The dopamine system

Biasing signals can represent very diverse variables (e.g. EV, local income, hazard rate, discounted value, action cost and utility) and are closely related to different aspects of reward processing (Croxson et al., 2009; Kennerley et al., 2009; Kim et al., 2008; Louie and Glimcher, 2010; Padoa-Schioppa and Assad, 2006, 2008; Platt and Glimcher, 1999; Roesch et al., 2006; Rushworth and Behrens, 2008; Schultz, 2010; Sugrue et al., 2004; Yang and Shadlen, 2007).

According to the predominant theory in modern psychology, we can distinguish two main types of reward: primary and secondary rewards (Mowrer, 1960). Primary rewards are those that meet direct biological needs (eg. water, food, sex and sleep), while secondary rewards are stimuli that have acquired rewarding properties through their association with primary rewards (conditioned reinforcers). Animals can treat these reward signals in completely different and contextually dependent ways leading to a fairly rich and dynamic reward-seeking behaviour (e.g. patient vs impatient foraging, safe vs risky gambling behaviour).

However, the simplest type of biasing signal, *reward value*, hinges on a unique computation: the comparison between a predicted and obtained reward. This computation has been observed in the dopamine system (Schultz, 2006, 2007) and enables reinforcement learning, a process by which animals deal with secondary rewards by assigning a reinforcing value to a neutral stimulus. The dopamine system and BG are two

fundamental structures involved in reward processing and reinforcement learning (Murray et al., 2012 for a review).

The dopamine system is a phylogenetically well conserved structure that can be traced back to primitive vertebrates. Diencephalic structures in primitive fish such as the lamprey seem to be homologous to the midbrain dopamine system in tetrapods (Smeets et al., 2000). Consequently, it would be reasonable to observe reward biasing signals for action selection in these structures.

It is worthy mentioning that the dopamine system and BG are not the only structures that are able of reward valuation and reinforcement learning. It has been observed that invertebrates (with whom we do not share any telencephalic structures) can also learn associations through reinforcement learning (Carew and Sahley, 1986; Samarova and Balaban, 2007, 2009; Zhang et al., 2005). However, it is uncertain wether invertebrates use reward value in a similar way that vertebrates do. Certain invertebrates like *Aplysia* do not take account well for the temporal structure of reward and fit better with the Rescorla-Wagner model (Hawkins and Kandel, 1984).

In contrast, the learning features of vertebrate's dopamine system are best described by a temporal difference model (TD model). This suggests that vertebrates can not only predict the reward associated with a condition stimulus (CS) but also can predict *when* the reward will actually occur in time (Suri and Schultz, 2001; Sutton and Barto, 1990). Higher-order conditioning is also a notable feature of this system (Schultz, 1997; Suri and Schultz, 2001).

Although the previous mentioned distinctions between invertebrate and vertebrate reward valuation and learning might seem attractive, there is substantial evidence that

social insects (e.g. bees) can learn novel associations through a hebbian-learning mechanism such as the TD model (Montague et al., 1995, 1996). These animals can also predict reward through higher order conditioning (Abramson et al., 2009; Hussaini et al., 2007) suggesting that functional analogues to the dopamine system might exist.

14.2. The basal ganglia

The basal ganglia (BG) are particularly interesting from the point of view of a competition based model of action selection because of their particular anatomical organization (Nambu, 2008). Afferent pathways relay information from nearly the entire cerebral cortex and limbic system to the input nuclei, namely the striatum (caudate nucleus, putamen, nucleus accumbens), and STN, which then converge to the output nuclei (GPi/SNr) before they relay back to the cerebral cortex through the thalamus. This type of closed loop organization is typical of BG's modular network and segregates in large parallel channels running through motor areas, limbic areas, associative areas and highly cognitive areas such as PFC (Alexander and Crutcher, 1990a; Alexander et al., 1986; Middleton and Strick, 2000; Nakano, 2000a, b). For instance, the primary motor cortex (M1) projects through the striatum to the motor part of GPi (Alexander et al., 1986; Parent and Hazrati, 1995a, b) and relays information from GPi through the thalamus back to M1 (Hoover and Strick, 1999; Kayahara and Nakano, 1996). These motor loops are additionally somatotopically organized (Alexander et al., 1986; Deniau et al., 1996) and fine parallel subcircuits can be distinguished with regards to the effector used. For

instance, arm-related areas in M1, striatum and GPi are connected in a closed loop starting and finishing in M1 (Kelly and Strick, 2004).

In addition to the structures taking part in cortico-basal loops, BG incorporates fundamental dopaminergic structures, namely the dorsolateral substantia nigra SNdl (area A8), the substantia nigra pars compacta SNpc (area A9) and the ventral tegmental area VTA (area A10) that convey reward related information (dopaminergic inputs) directly to the striatum (Nambu, 2008). In fact, dopaminergic inputs provide the scaffolding material for *action-value* signals encoded in BG (Samejima et al., 2005).

The input nuclei in the striatum are involved both in the organization of movement (Alexander and Crutcher, 1990a; Alexander et al., 1990; Middleton and Strick, 2000) and processing of reward information (Fiorillo et al., 2003; Hollerman and Schultz, 1998; Morris et al., 2004; Satoh et al., 2003). This duality is important for decision making processes because reward information (and in particular reward prediction errors) can be used to learn about stimuli in the environment and select profitable courses of action (Montague and Berns, 2002).

In fact, different types of reward signals have been identified in BG. For instance, neurons in striatum show modulation by *reward magnitude* (Cromwell and Schultz, 2003) and similar responses have also been observed in dopamine neurons (SNpc, SNdl, VTA) (Satoh et al., 2003; Tobler et al., 2005) which are known for encoding reward prediction errors (Hollerman and Schultz, 1998; Morris et al., 2004; Schultz et al., 1997).

Reward expectation signals have also been described in striatum with some heterogeneity as they can integrate information concerning the modality of the stimulus (taste) as well as space information (goal direction) (Hassani et al., 2001). The dorsal

striatum (caudate nucleus and putamen) offers less pure-reward responses than the ventral striatum (accumbens) (Apicella et al., 1991; Schultz et al., 1992), consistent with the notion that motivational functions such as appetitive behaviour are more strongly represented in this nucleus (Kelley, 1999, 2004; Stratford and Kelley, 1999). This is in contrast with reward responses associated with goal-directed behavior that is widely represented in the dorsal nuclei (Hollerman and Schultz, 1998; Kawagoe et al., 1998). In fact, the integration of reward and goal-related information has been proposed as a core feature of BG suggesting an important role in reinforcement-driven decision making (Cromwell et al., 2005; Samejima et al., 2005).

Samejima et al. (2005) have shown that the specific *reward value of an action* (*action-value or spatial-reward encoding*) is represented by striatal neurons. It is therefore not surprising that *spatial-reward magnitude* (Cromwell and Schultz, 2003; Kawagoe et al., 1998), *spatial-reward probability* (Samejima et al., 2005) and *spatial-reward adaptative coding* (Cromwell et al., 2005) have been reported in this structure. In addition, striatal neurons show modulation during movement preparatory delay suggesting that the striatum is to some extent involved in *movement preparation* (Hollerman and Schultz, 1998) and can predict the animal's choice (Samejima et al., 2005). Furthermore, striatal activity evolves in concert with PMd activity to indicate the selected movement during learning of arbitrary visuomotor mappings (Buch et al., 2006) and striatal activity can reflect "virtual action plans" when only partial information is available for movement preparation *(*Arimura et al., 2010*).*

Traditionally, the major output of BG (e.g. pallidum) has been linked to motor activity (Arkadir et al., 2004; Mink, 1996; Turner and Anderson, 1997). The pallidum

encodes movement direction in a similar way as M1 (eg. cosine tuning functions; Georgopoulos et al., 1982; Turner and Anderson, 1997) and focal inactivation of this structure clearly disrupts motor programs such as reaching and grasping (Wenger et al., 1999).

Bergman's group (Arkadir et al., 2004) conducted recordings in globus pallidus (GPe) with monkeys trained in a probabilistic visuomotor task and reported *spatial reward* encoding in this structure. Namely 34% of pallidal neurons were modulated solely by direction of movement while the activity of a comparatively large number of cells (41%) was modulated by both expected trial outcome and direction of arm movement.

Further work by Boraud's group demonstrated important differences between the BG input and output nuclei precisely at the level of the interaction between reward value and motor parameter representations (Pasquereau et al., 2007). Boraud's group recorded simultaneously in the major input structure of the motor striatum, namely the putamen, and the major output nucleus, GPi. Both structures were modulated by movement parameters (direction) and cognitive parameters (reward probability) both during the delay period and movement execution. Approximately the same numbers of cells in both structures represent the spatial location of the targets during the delay period. However, only cells in GPi are modulated by the chosen target. This suggests that the GPi integrates spatial information and goal information (movement plan) as has also been reported in PMd during the delay period (Crammond and Kalaska, 1994, 2000).

14.3. Prefrontal cortex

The ability to select actions on the basis of very abstract criteria may suggest the participation of phylogenetically recent cognitive structures in the prefrontal lobe (Hauser, 1999). Prefrontal structures are strongly implicated in decision making and action selection (Fuster et al., 2000; Kim and Shadlen, 1999; Miller, 2000; Tanji and Hoshi, 2001). Neurons in the DLPFC integrate very diverse stimulus features and make the area particularly versatile (di Pellegrino and Wise, 1991; Hoshi et al., 1998; 2000; Kim and Shadlen, 1999). Prefrontal decisions appear to involve accumulation of votes for the categorical selection of one choice over another (Buschman and Miller, 2007; Cromer and Miller, 2009; Hoshi et al., 2000; Kim and Shadlen, 1999).

Kim and Shadlen (1999) showed that DLPFC activity reflects initially the quality of evidence in favor of a given target and later the chosen target. Upon presentation of an incomplete set of information for action selection, Hoshi et al. (2000) showed that DLPFC cells reflect first all potentially relevant stimulus features such as shape and location but compute rule-selection (i.e. shape-match or location-match) and intended movement only once this information is provided.

It is generally thought that prefrontal structures are responsible for implementing higher-order rules and strategies (Collins et al., 1998; Ragozzino et al., 1999; Wise et al., 1996a). In addition, prefrontal areas are more active during learning of new tasks rather than during performance in familiar tasks (Asaad et al., 1998; Raichle et al., 1994). These results suggest that PFC plays a stronger role in rule acquisition rather than in rule

retrieval (Asaad et al., 1998; Dias et al., 1996; Wallis and Miller, 2003a). When a rule becomes familiar it tends to be encoded more strongly in "downstream" motor system structures (Wallis and Miller, 2003a; Wise et al., 1996a).

Prefrontal areas are particularly important for performance in novel visuo-motor mappings, and therefore, subjects with PFC lesions are not impaired on already known mappings (Bussey et al., 2001). Moreover, neurological lesion and imaging studies suggest an involvement of PFC in rule-switching tasks (Asaad et al., 1998; Dias et al., 1996; Mansouri et al., 2006; Stuss et al., 2000; Wise et al., 1996a). Taken altogether, this data suggests that PFC is responsible for learning novel, higher-order rules such as rule-switches.

However, two different areas, DLPFC and OFC, might be involved in different aspects of high-order rule learning. For instance, rule-switching on the basis of reward contingencies or spatial contingencies involves OFC and DLPFC very differently. Humans with OFC damage are impaired in gambling tasks; meanwhile, humans with DLPFC lesions are impaired in learning spatial working memory tasks (Bechara et al., 1998). A similar dissociation has been observed in monkeys (Dias et al., 1996; Wallis et al., 2001). These results can be due to the strikingly different cortical inputs that are received by DLPFC and OFC. OFC receives information from all sensory modalities (Carmichael and Price, 1995a, b; Cavada et al., 2000; Romanski et al., 1999), including highly processed information from inferior temporal cortex (ITC) and has extensive connections with the limbic system and very notably with the amygdala. Therefore, OFC encodes reward in terms of magnitude (number of drops of juice), incentive value (taste), emotional value and visual preference (Wallis, 2007). In contrast, DLPFC densely

connects with premotor cortex (Chiba et al., 2001; Lu et al., 1994; Wallis, 2007; Wallis and Miller, 2003b) and receives "dorsal-stream" visuo-spatial information (Goodale and Milner, 1992). DLPFC encodes reward amount, visual preferences and spatial information (Chen et al., 2001; Leon and Shadlen, 1999; Mushiake et al., 2006), although visual preference effects are less represented than in OFC (Wallis and Miller, 2003b).

Multiple aspects of reward are encoded in OFC. Tremblay and Schultz (1999) have shown that OFC has *range adaptation* properties. In this study the monkey was presented with two different arbitrary visual cues simultaneously, each of which was associated with one of three different types of reward (raisin, apple or cereal). The value associated with each cue was reflected in the modulation of cell firing rate and was contingent on the pair presented. A cell fired for the *raisin* cue when both *raisin* and *apple* cues were presented, although the same cell fired for *apple* cue when *apple* was presented together with *cereal* cue.

Padoa-Schioppa and Assad (2006) showed *economic value* encoding in OFC (offer value, chosen value and taste cells (the later two being subjective-value correlates) (Padoa-Schioppa and Assad, 2006). OFC also shows differences in firing rate between reward and punishments (Roesch and Olson, 2004). Another interesting observation is that OFC encodes the value of a reward-predictive cue earlier than other prefrontal areas do, DLPFC (Wallis, 2007; Wallis and Miller, 2003b).

OFC plays also a unique role as well in the learning of reward contingency reversals (Leon and Shadlen, 1999; Thorpe et al., 1983; Wallis and Miller, 2003b). Monkeys with OFC lesions fail to perform correctly in a rule-switching task and continue to perform according to a preoperatively learned contingency. This persevering behaviour

is very specific to OFC injuries (McEnaney and Butter, 1969; Wallis, 2007, for a review). In contrast, DLPFC bilateral lesions do not cause strong impairments in rule-switching task performance in both monkeys and humans (Clarke et al., 2004, 2007; Dias et al., 1996; Fellows and Farah, 2003; Rolls et al., 1994). Rule-switching in OFC depends on serotonergic innervation (Clarke et al., 2004, 2007; Dias et al., 1996).

Other studies have shown that OFC is also involved in gambling tasks and compulsive behaviour (Volkow and Fowler, 2000). For instance, human subjects that had damage in OFC showed performance deficits in the Iowa gambling task (Bechara et al., 1994, 1998; Malloy et al., 1993). Such subjects were unable to "play safe". Moreover, OFC lesions in monkeys produce a marked difficulty in suppressing the NO-GO response in a GO/NO-GO task (Butters et al., 1973; Iversen and Mishkin, 1970; Lawicka et al., 1975), similar to what is observed in human patients with OFC damage (Leimkuhler and Mesulam, 1985; Malloy et al., 1993). In contrast, DLPFC damage in humans does not impair GO/NO-GO performance (Decary and Richer, 1995; Drewe, 1975). This demonstrates the selectivity of the ventral orbito-frontal region in the inhibitory control of impulsive behavior.

14.4. Ventral stream structures

Biasing information for visually-based action selection could also come from the ventral visual stream (Cisek, 2007a; Kalaska et al., 1998; Sakagami and Pan, 2007). The ITC is sensitive to visual features of stimuli (Brincat and Connor, 2004, 2006; Desimone et al., 1984; Tanaka et al., 1991; Verhoef et al., 2012) and the behavioural context in

which these features are presented (Eskandar et al., 1992). However, ITC is also modulated by attention (Mo et al., 2011). Thus, the selectivity that ITC shows for particular object identity features could subserve other roles than object recognition such as an attentional based pre-selection oriented to actions.

The detection of particular stimulus that release specific behaviors has been first observed by ethologists (Ewert, 1997; Tinbergen, 1950). This is consistent with Gibson's (1979) notion that perception is an active process of picking up behaviorally relevant cues. Duncan and Desimone (1995) proposed a model where action selection could be based either on target features and saliency (bottom up control) or by the locus of attention (top down). Bottom-up processes are dominated by stimuli that stand out from their background. For instance, new and unfamiliar stimuli become processed preferentially at nearly all levels of the visual system (Allman et al., 1985; Desimone et al., 1985). In a top-down situation the locus of attention can guide action selection.

In one of their studies, Moran and Desimone (1985) conducted recordings in area V4 and ITC in a visual search task designed explicitly to address this dichotomy. In one task variant the target and distractor cues were simultaneously presented within the receptive field of the cells (RF), while in another variant one of the two stimuli was placed outside RF. The effects reported in area V4 and ITC were congruent between these two areas. When both the target and distractor were presented within RF, the cells were modulated primarily by the target and the responses to the distractor were greatly attenuated. The cells responded as if their RF had shrunk around the target (Desimone and Duncan, 1995). However, in the second task variant there was no modulation by the

presence of the distractor outside of the RF of the cells, as if the presence of the distractor didn't matter (Moran and Desimone, 1985).

These results are consistent with a *biased competition model of visual attention* in which target and distractor are competing for the cells response when they are close to each other (Desimone and Duncan, 1995). The findings have been extended by other recent studies (Monosov et al., 2010) indicating that spatial selection can precede object identification during visual search tasks. This observation suggests that the role of the ventral stream may not be only pure perception but also collection of visual information useful for action selection (Milner and Goodale, 1993; Passingham, 1985; Lebedev and Wise, 2002).

15. The affordance competition hypothesis

Behavior can be viewed as a constant *competition between internal representations of conflicting demands and opportunities, of the potential actions* that Gibson (1979) termed "affordances". **Figure 7** depicts a schematic representation of how the ''affordance competition'' framework may be used to interpret neural data on visually guided behavior (Cisek, 2007a, b; Cisek and Kalaska, 2010). According to this hypothesis, visual information in stimulus-response tasks (SR) is processed at the level of cortex through at least two waves of activity. A first wave of visually driven activation quickly sweeps through thalamocortical projections and through the occipitoparietal ''dorsal stream''. The information processed in this wave leads to the *specification* of potential actions in fronto-parietal structures.

The second wave sweeps through the ventral stream and travels through the limbic system, BG and PFC. The information processed by this wave is gradually conveyed to fronto-parietal structures and leads to the *selection* of a winning action that is released for execution (Mishkin et al., 1983; Milner and Goodale, 1995; Pisella et al., 1998). The first wave activates neurons in occipital, parietal, and frontal cortical areas within 40–60 ms of stimulus onset (Ledberg et al., 2007; Schmolesky et al., 1998; Thompson et al., 1996). It is striking for instance, that integrated oculomotor areas such as FEF can respond to visual stimulation as early as 50ms (Schmolesky et al., 1998).

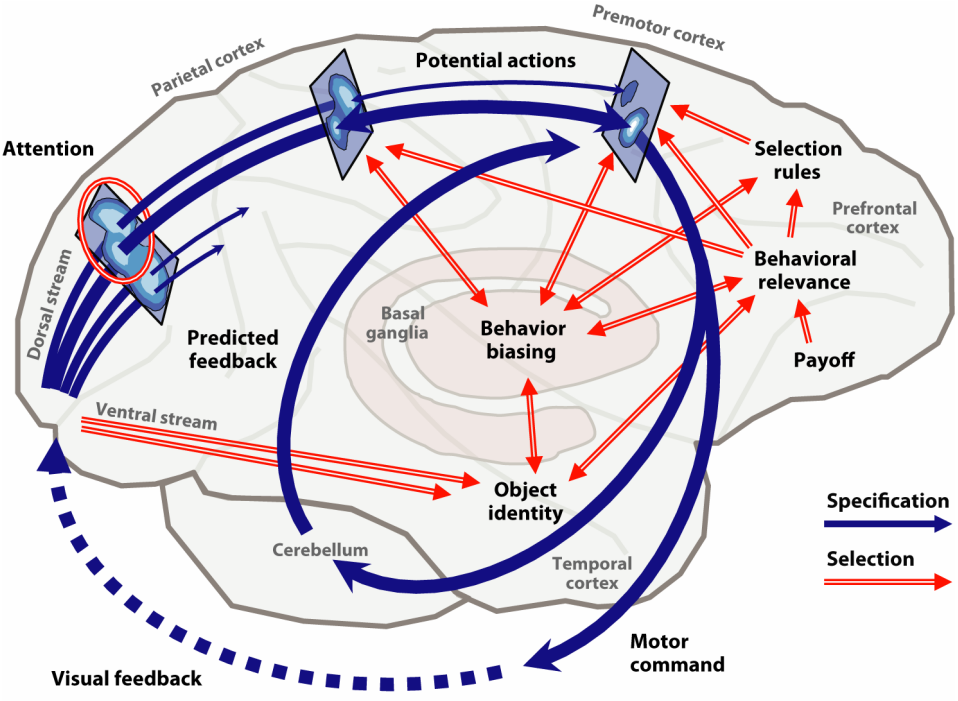

Figure 7. Sketch of the proposed neural substrates of the affordance competition hypothesis, in the context of visually guided movement. The primate brain is shown, emphasizing the cerebral cortex, cerebellum and BG. Filled dark arrows represent processes of action specification, which begins in the visual cortex and proceed rightward across the parietal lobe, transforming visual information into representations of potential actions. Polygons represent three neural populations along this route: the leftmost represents the encoding of potential visual targets, modulated by attentional selection; the middle represents potential actions encoded in parietal cortex; and the rightmost represents activity in premotor regions. Each population is depicted as a map of neural activity with activity peaks corresponding to the lightest regions. As the action specification occurs across the fronto-parietal cortex, distinct potential actions compete for further processing. This competition is biased by input from BG and prefrontal cortical regions which collect information for action selection (double-line arrows). This biasing influences the competition in a number of loci, and owing to reciprocal connectivity, these influences are reflected over a large portion of the cerebral cortex. The final selected action is released into execution and causes both overt feedback through the environment (dashed blue arrow) and internal predictive feedback through the cerebellum (*adapted from Cisek and Kalaska, 2010).*

In a pop-out visual search task Shall's group (Thompson et al., 1996) has shown that an ideal observer can reliably differentiate the activity evoked by a target from that evoked by a distractor even earlier (30ms with respect to target onset). These results are consistent with the observations of Salinas group pointing out that decision biases for color based discrimination of target and distractor can also take place as early as 30ms (Stanford et al., 2010).

This perceptual detection latency is significantly earlier than in some other visual areas such as V2 and V4 further reinforcing the idea that the visual system neural activation does not necessarily comply with a serial activation sequence (Paradiso, 2002). Altogether, these results suggest that fast responses are not entirely perceptual because they reflect the *context* in which the stimuli are presented. For instance, in a reaching task in which the monkey expects to see one or two stimuli the PMd population is modulated by the presence of a familiar visual cue as early as 50ms after cue onset and the response is larger for one stimulus than for two stimuli (Cisek and Kalaska, 2005). This suggests that PMd activity can reflect anticipatory visual biases or priors (Coe et al., 2002; Takikawa et al., 2002) that need to be taken in consideration or not, depending on the contingencies of the task (Crammond and Kalaska, 2000). In summary the very *early wave of visual activity* in the dorsal stream represents the immediate environment in terms of *information about potential actions that are currently available* (Gibson, 1979; Milner and Goodale, 1995).

In addition, this initial wave of activity causes multiple *potential actions to be simultaneously encoded within effector-specific fronto-parietal systems* as distinct groups of active neurons within each local population (Cisek and Kalaska, 2005, Gharbawie et

al., 2011a, b). For example, visual targets for saccadic eye movements are represented in LIP and FEF (Schall and Bichot, 1998; Snyder et al., 1997, 2000b) while directions of reaching movements from the current hand location to graspable objects are represented in MIP and PMd (Alexander and Crutcher, 1990b, c; Buneo et al., 2002; Crutcher and Alexander, 1990; Ferraina and Bianchi, 1994; Kalaska and Crammond, 1995).

Within each cortical area multiple potential actions can be simultaneously encoded (Cisek and Kalaska, 2010). Hoshi and Tanji (2006) trained monkeys in a bimanual response-choice task in which the animals were first presented with a reach target location without specifying which arm to use and neural activity in the premotor cortex reflected the potential movements of *both hands* until the monkey was instructed about which hand to use (Hoshi and Tanji, 2006).

Moreover, simultaneous specification of multiple potential actions can occur even within the same effector system (Basso and Wurtz, 1998; Bastian et al., 1998, 2003; Baumann et al., 2009a; Cisek and Kalaska, 2005; Klaes et al., 2011; McPeek and Keller, 2002; Platt and Glimcher, 1997; Powell and Goldberg, 2000; Schall and Bichot, 1998; Scherberger and Andersen, 2007). For instance, when two potential reaching options are available the PMd population simultaneously reflects the impending reaching direction for both of them (Cisek and Kalaska, 2005). Even with a single target, the reach and anti-reach options can be simultaneously represented both in PMd and in the parietal reach region (PRR) (Klaes et al., 2011). In perceptual decision making tasks, Shadlen and Newsome (2001) have also shown that LIP cells can reflect a simultaneous representation of two alternative random-motion directions. There is substantial evidence of this notion in the oculomotor system in behavioral and neurophysiological data (Basso and Wurtz,

1998; ; McPeek et al., 2000; McPeek and Keller, 2002; Platt and Glimcher, 1997; Schall and Bichot, 1998).

McPeek and Keller (2002) suggest that the preparation of multiple sequential saccades can overlap in time. When two or more potential saccade targets are presented simultaneously, neural correlates for each of them can be observed in area LIP and even in the SC where they are modulated by selection probability (Basso and Wurtz, 1998; Kim and Basso, 2008; Platt and Glimcher 1997; Powell and Goldberg 2000).

According to the affordance competition hypothesis these simultaneously represented potential actions *compete* for release into overt execution through mutual inhibition in a similar way to the mechanism of selective attention (Boynton, 2005; Desimone and Duncan, 1995) consistent with earlier proposals suggesting parallel movement preparation (Erlhagen and Schoner, 2002; Fagg and Arbib, 1998; Tipper et al., 1998).

Action selection is mediated by a competition process that takes place across a distributed set of cortical areas, and it is biased by a variety of task-relevant factors. Action selection is a slow and gradual process that overlaps with the initial "visual detection process". For instance, FEF neurons respond to the onset of a stimulus as early as 50-30ms (Schmolesky et al., 1998) but discriminate the choice for prosaccades versus antisaccades in approximately 120ms (Sato and Schall, 2003). Moreover, neurons in PMd respond to the locations of the cues instructing two potential movements in around 70ms but start predicting the monkey's choice after 110ms (Cisek and Kalaska, 2005).

The biasing influences are conveyed by the second wave of visual activation that travels through the ventral stream (Milner and Goodale, 1995; Mishkin et al., 1983;

Pisella et al., 1998). This wave arrives from BG, PFC, and the limbic system, and within 50–100ms *after* the initial wave of visual activation, these biases become strong enough to cause a winning action to emerge and other potential actions to be suppressed, leaving activity throughout the fronto-parietal system to reflect a decision (Cisek and Kalaska, 2005; Ledberg et al., 2007; Thompson et al., 1996).

Ledberg et al. (2007) conducted a local field potential (LFP) study that is particularly relevant to the process discussed here. The group recorded LFPs from several regions simultaneously, meanwhile monkeys performed in a discrimination task. The group reported latency segregation between three types of neural events, namely visual responses at cue onset, discrimination of target features and prediction of the monkeys' choice (action selection). They observed a feedforward sweep of cue-onset related activity at around the same time (50-70ms) in all visual areas (striate/extra-striate cortex) as well as in FEF and premotor cortex, followed by a signal correlated with categorization 100ms after cue-onset in the visual areas, and 200ms in prefrontal sites.

Most interestingly, signals reflecting the animal's decision appeared around 150ms after cue-onset in all areas, somehow at an intermediate timing between the two previous processes. However, it is likely that the order in which the decision appears across the cerebral cortex is task dependent (Cisek, 2006). For instance, when monkeys perform in a pop-up visual search task, neural activity in LIP reflects the choice before FEF, but if the task requires conjunction search FEF reflects the choice before LIP (Buschman and Miller, 2007). In a GO/NO-GO task in which the animals are asked to make decisions on the basis of cognitive rules (i.e. matching task), PMd predicted the response even before PFC (Wallis and Miller, 2003b).

Although *action specification and action selection* appear as processes belonging to two distinct waves of activation, this may be consequence of the task design. It is likely that during continuous interaction with a natural environment these two *processes can be entirely overlapping with new actions being specified as others are being executed* allowing biasing information to dynamically redirect decisions from one behavioral option to another (***redirected actions, lion chasing prey from figure 1A***).

To summarize, the *affordance competition hypothesis suggests that visual information leads to the very rapid specification of potential actions across a diverse set of regions distributed within the fronto-parietal cortex at the same time that it receives biasing information to select an action for execution (simultaneous action selection and specification)*. PMd is an attractive candidate to test the predictions of this hypothesis because of a number of physiology and anatomy considerations (previously discussed) suggesting a role of this area both in action selection (decision making) and action specification.

16. A computational model for reaching decisions: achievements and predictions

Cisek developed in 2006 an "affordance competition model" focusing on visually guided actions. The model includes some of the main cortical regions involved in reaching behaviour, such as the PFC, PPC, PMd and M1 (**Figure 8A)**. The input to the model consists of visual information about the direction of the targets and a signal triggering movement onset (GO signal). The output of the model reflects the direction of the target selected and does not attempt to interpret overt kinematics.

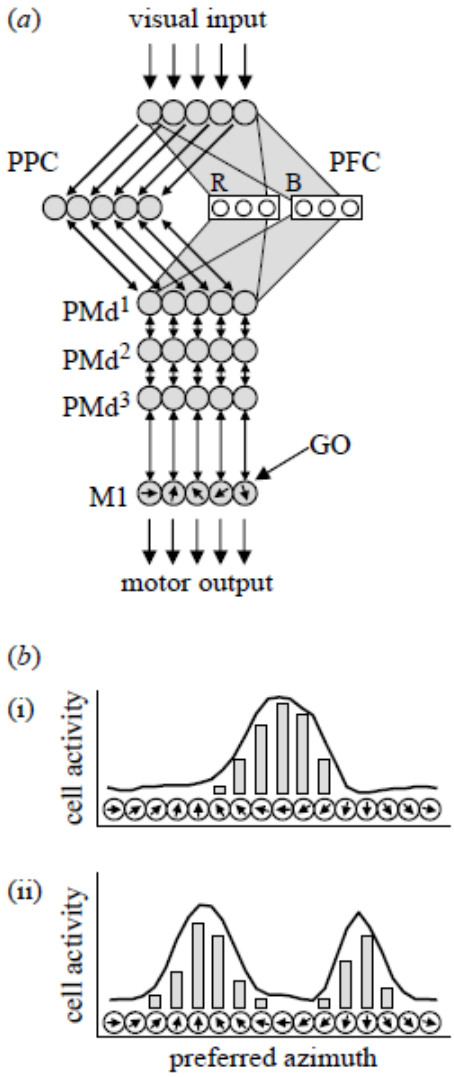

Figure 8. Computational model. A. Each neural layer is depicted by a set of circles representing cells with different preferences for a movement parameter (e.g. direction). Thin arrows represent topographic connections (in most cases reciprocal) between layers involved in action specification. Grey polygons represent the input to and from prefrontal cortex, which is divided into two subpopulations each preferring a different stimulus color (R:red, B:blue). These projections are also topographic, but with much lower spatial resolution. Visual inputs are presented to the input layer, and the GO signal gates activity in M1. Abbreviations: PPC, posterior parietal cortex; PFC, prefrontal cortex; PMd, dorsal premotor cortex; M1, primary motor cortex. **B.** Each population consists of cells with different preferred directions, and their pattern of activity can

represent one (i) or (ii) several potential directions simultaneously (*adapted from Cisek, 2007*).

The *neural populations in each cortical region* do not encode a unique value of a movement parameter such as a single movement direction in space but *represent* instead *an entire distribution of potential movement value parameters* allowing different movement directions to be represented simultaneously.

This defines a "parameter field" for the options (Cisek, 2006, 2007) that is related to the attention model of Tipper et al. (2000) and the "decision field" theory of Erlhagen and Schoner (2002). The model suggests that *a given population of cells, each with a preferred value of a particular movement parameter, behaves as something akin to a probability density function of potential values of that parameter.* This allows a single population to reflect two potential actions simultaneously by a bimodal distribution having distinct peaks of activity for each of the options when they are mutually exclusive *(i.e reaching to either of two diametrically opposed targets,* ***Figure 8B (ii))***, and by a single wide peak when the metrics of the competing actions is similar *(i.e. reach in-between targets for two close-by target locations,* ***Figure 8B (i))***.

In this situation the strength of the activity associated with a particular movement reflects its *likelihood of being selected that can be influenced by a variety of value biasing signals* such as salience, effort, reward magnitude, reward probability, expected value (EV) or any other decision-variable observed in frontal or parietal cortices (Gold and Shadlen, 2000; Kim and Lee, 2010; Platt and Glimcher, 1999).

In Cisek's model, potential actions are represented simultaneously within a single frontal or parietal region. Cells that have similar value preferences excite each other, while cells that have different value preferences compete with each other through

reciprocal inhibition. This biased competition mechanism is similar to recent models of visual attention (Boynton, 2005; Desimone, 1998) and can explain certain neural and behavioral results.

Most importantly the biased competition process assumes the existence of a *threshold* that emerges from the non-linear dynamics between competing populations of cells, namely the number, metrics and strength (relative or absolute) of the options (Cisek, 2006, 2007; Grossberg, 1973). The threshold prevents noise random fluctuations driving the decision process and is not hardwired (Carpenter and Williams, 1995; Mazurek et al., 2003; Smith and Ratcliff, 2004).

The model can reproduce qualitative features of neural activity in reach-decision tasks (Cisek and Kalaska, 2005). Notably, it can explain the inverse relationship between number of options and the firing rate for each of them (Basso and Wurtz, 1998; Cisek and Kalaska, 2005). It can also explain a relative coding between decision variables such as reward value and motivation (Roesch and Olson, 2004) and the narrowing of spatial tuning functions for multiple options (Cisek and Kalaska, 2005).

The model explains as well a number of psychophysical results on the spatial and temporal characteristics of motor decisions. For instance, it is consistent with the inverse relationship between RT and the quality of evidence for the options. It can also explain the direct relationship between RT and the number of options even if the spatial metrics is taken into account (Bock and Eversheim, 2000). For instance, Bock and Eversheim (2000) showed that the RT in a reaching task was not dependent on the number of targets (two or five) as long as the targets subtend the same spatial angle between them. It was

found instead that RT depended on the angular distance between the targets and was shorter when the targets were closer to each other.

In a timed response paradigm (Ghez et al., 1997), the model predicts correctly the different reach directions observed for close-by or far-apart targets. Ghez et al. (1997) showed that when subjects are forced to make choices quickly, they move to each of the targets randomly if they are spaced *farther than 60°* away, and move in-between them if the targets are close together. When two targets are far apart, the model (Cisek, 2006) predicts multiple competing peaks of activity in the PMd-PPC population and the decision is determined by the peak that happens to fluctuate higher when the GO signal is given. If the targets are close together, then their two corresponding peaks merge into a single one due to the positive feedback between cells with similar parameter preferences. The model presented here makes a number of general predictions that are examined in detail in the next section.

III. OBJECTIVE, HYPOTHESIS AND PREDICTIONS OF THE THESIS

Objective:

The present work examines how decisions among actions take place in premotor cortex. Specific interest is given to the interaction of spatial information and decisional biases such as expected value in the processes of action selection and specification.

Central hypothesis: affordance competition

Action selection and action specification involve a unified, parallel architecture that uses sensory information to simultaneously specify several potential actions while collecting information for selection among them through a biased competition process.

1. Specific hypothesis: action selection entails a biased competition process

Prediction 1A

Neural activity can represent multiple potential actions simultaneously

This has already been shown neurophysiologically for reach, grasp and saccade goal selection processes (Baumann et al., 2009; Cisek and Kalaska, 2005; Glimcher, 2003; McPeek and Keller, 2002; Scherberger and Andersen, 2007). Neurophysiology data in PMd suggests that two mutually exclusive potential reaching actions can be simultaneously represented until a choice can be made, at which time the activity corresponding to the non chosen option becomes suppressed. Simultaneous specification

of multiple potential actions is also supported by several behavioral studies of reaching movements made in presence of distractors (Song and Nakayama, 2006, 2008, Song et al., 2008; Tipper et al., 1992). Although a definitive assessment of the "simultaneity" aspect of this prediction could require multiple-unit recording using cell arrays (Shenoy et al., 2003), a simple cell population analysis of data collected through single electrode recordings can address indirectly this issue. The experimental and modeling results presented in *articles 1 and 2* support precisely this observation.

Prediction 1B

Neural activity in sensory-motor regions does not represent a single decision variable in isolation but integrates all factors that influence the choices

It has already been reported that sensory-motor areas such as LIP and ACC integrate value, cost and other factors affecting the subjective desirability of the options and constitute the "biases" of a decision (Kennerley et al., 2009; Platt and Glimcher, 1999). This prediction is tested explicitly for the interaction between spatial and value information in *articles 1 and 2*.

Prediction 1C

The variables that are associated with a given option are always expressed relative to the alternative actions

Neural correlates for relative value have been shown in the oculomotor system: FEF (Leon and Shadlen, 1999) and LIP (Louie et al., 2011). We test this prediction explicitly for the arm reaching system in *articles 1 and 2*.

2. Specific hypothesis: biasing information is incorporated gradually in the action specification process

Prediction 2A

The latency for biasing information (ventral stream) and spatial processing (dorsal stream) should be different.

Dorsal stream and ventral stream pathways can have typically different processing times. It is known that tasks that require prefrontal and ventral stream processing take more time than more perceptual tasks (e.g. categorization vs match/non-match) (Wallis and Miller, 2003a). *Articles 1 and 2* address this prediction by comparing the latency for relative value and spatial information in premotor cortex. *Article 2* compares additionally both variables within a learning context perspective.

3. Specific hypothesis: the strength of the competition between potential actions depends on the similarity between them.

Prediction 3A

Decisions among action are affected by the metrics of the options

In the natural environment, decisions between simultaneous options are usually associated with actions that have particular metrics (Figure 1, see introduction). The observation that decisions among actions are affected by the metrics of the actions is consistent with human psychometric data (Chapman et al., 2010; Favilla, 1997; Ghez et

al., 1997) and a growing body of evidence from oculomotor neurophysiology studies (Louie et al., 2011; Schall, 2004a, b). *Articles 1 and 2* examine this prediction.

4. Specific hypothesis: decisions are made in the same regions that guide the actions

Prediction 4A

Action selection and action specification are not two serial but parallel processes

This prediction can be rooted in ecological and interactive behaviour. Continuous interaction with the world does not often allow one to stop and collect indefinitely information about one's surroundings. Neurophysiology supports the notion that sensory information is continuously used to select and specify several currently available potential actions (Cisek and Kalaska, 2005; Glimcher, 2003; Gold and Shadlen, 2000; Kalaska et al., 1998; Kim and Shadlen, 1999; Platt, 2002). The same cells that guide initial decisions continue to update their activities after the animals change their mind. There is some evidence that this might be the case for the arm system (Archambault et al., 2009, 2011; Wise and Mauritz, 1985). *Article 3* addresses this particular issue.

IV. ARTICLE 1

NEURAL CORRELATES OF BIASED COMPETITION IN PREMOTOR CORTEX

by

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ABSTRACT

It has been proposed that whenever an animal faces several action choices, their neural representations are processed in parallel in fronto-parietal cortex and compete in a manner biased by any factor relevant to the decision. We tested this hypothesis by recording single-unit activity in dorsal premotor cortex (PMd) while a monkey performed two delayed center-out reaching tasks. In the one-target task, a single target was presented and its border style indicated its reward value. The two-target task was the same except two targets were presented and the value of each was varied. During the delay period of the one-target task, directionally-tuned PMd activity showed no modulation with value. In contrast, during the two-target task, the same neurons showed strong effects of the value associated with their preferred target, always in relation to the value of the other target. Furthermore, the competition between action choices was strongest when targets were furthest apart. This angular distance effect appeared in neural activity as soon as cells became tuned, while modulation by relative value appeared much later. All of these findings can be reproduced by a computational model which suggests that decisions between actions are made through a biased competition taking place within a sensorimotor map of potential actions.

INTRODUCTION

Classical theories (Tversky and Kahneman, 1981) consider decision-making to be separate from the sensorimotor processes that implement the chosen response (Fodor, 1983). However, recent neurophysiological studies have shown neural correlates of decision variables within brain regions implicated in sensorimotor control (for reviews, see Glimcher, 2003; Gold and Shadlen, 2007; Cisek and Kalaska, 2010). For example, neural correlates of decision variables have been found throughout the saccade system, including the lateral intraparietal area (Dorris and Glimcher, 2004; Platt and Glimcher, 1999; Sugrue et al., 2004; Yang and Shadlen, 2007), the frontal eye fields (Schall and Bichot, 1998; Coe et al., 2002) and the superior colliculus (Basso and Wurtz, 1998; Horwitz et al., 2004), raising the question of why a putatively cognitive process should involve the sensorimotor system.

Such results appear less surprising if we consider that many of our everyday decisions are decisions between actions, such as choosing a path through a crowd or the target for a reach. It has been proposed that in such situations, the brain specifies several potential actions in parallel, and selects between them through a process of biased competition within the sensorimotor system itself (Cisek, 2007; Cisek and Kalaska, 2010). Recent computational models have suggested how multiple potential movements can be simultaneously encoded in parietal and premotor cortex (Tipper et al., 2000; Erlhagen and Schoner, 2002; Cisek, 2006; Furman and Wang, 2008), and how a competition between them can be biased by decision variables (Cisek, 2006).

This hypothesis makes several predictions. First, it predicts that neural activity can simultaneously represent several potential actions, as shown in the reaching (Cisek and Kalaska, 2005; Scherberger and Andersen, 2007) and grasping systems (Baumann et al., 2009), as well as in the saccade system (McPeek and Keller, 2002; Glimcher, 2003) where the influence of decision variables is already well-established.

Second, neural activity in sensorimotor regions will not represent any single decision variable in isolation, but will integrate *all* factors that influence choices. This implies that the variables associated with a given action will always be expressed *relative* to those associated with alternative actions. Third, the strength of competition between potential actions *will depend on the similarity between them*. This is motivated by simple facts of geometry: when choosing between two nearby targets, their decision-signals can be mixed and one can start moving between the targets. However, choosing between two targets in opposite directions implies that the choice has to be all-or-none.

Here, we test these predictions through neural recordings in the dorsal premotor cortex (PMd) of a monkey performing a reach decision task, and compare the results to simulations of a biased competition model (Cisek, 2006). Some of these results have been presented previously in abstract form (Pastor-Bernier and Cisek, 2010).

MATERIALS AND METHODS

A male monkey (*Macaca mulatta*) performed a planar center-out reaching task illustrated in Fig 1A (see Supplemental methods). After a 350-650ms Center-Hold-Time (CHT), one or two cyan targets appeared, with border styles indicating their value in

drops of juice (See Fig 1A, inset). The reward was determined probabilistically to encourage the monkey to explore available options (Herrnstein, 1961). A "low-value" target (L, thick border) had a 60% chance of yielding 1 drop, 30% chance of yielding 2 and 10% chance of yielding 3 (Expected value, EV=1.5). A "medium-value" target (M, no border) was worth 2 (60%), 1 (20%) or 3 drops (20%) (EV=2). A "high-value" target (H, thin border) was worth 3 (60%), 2, (30%), or 1 drop (10%) (EV=2.5). The non-monotonic relationship between border thickness and value was used to dissociate motivational factors from physical properties of stimuli. The monkey held the cursor in the center for an instructed delay period (DELAY, 700-1300ms) until a GO signal was indicated by a change in target color and disappearance of the central circle. To receive the reward, the monkey had to move to a target within a maximum 550ms movement time (MT) and hold the cursor there (Target-Hold-Time, THT, 500ms).

When cells were isolated, we first ran a block of 90 trials in which only one target was presented (1T), to identify the DELAY-period preferred target (PT) of each cell. Next, we ran a block of 180 two-target trials (2T), including ones where the PT target was present and low, medium, or high-valued, while the other target (OT) appeared at 60°, 120°, or 180° away and was low, medium, or high-valued. Each block also included 30 trials in which the targets were 120° apart but neither was in the direction of the PT. These trials allowed us to analyze the activity of simultaneously recorded cells with different PTs. All analyses shown here use trials in which at least one of the targets presented was the cell's PT. In 67% of 2T trials (FREE), the monkey was free to move to either target after the GO signal. In 33% of 2T trials (FORCED), one of the targets disappeared at GO and the monkey had to move to the remaining one. FREE and

FORCED trials were randomly interleaved to encourage the animal to keep both options partially prepared.

To assess relative value effects we compared DELAY-period activity during trials with targets 120° apart in which the OT was medium-valued while the PT value varied ($N \geq 60$ trials), as well as those in which the PT was medium-valued while the OT value varied ($N \geq 60$). To assess distance effects we examined trials in which the PT was present and the OT was 60° ($N \geq 30$), 120° ($N \geq 120$) or 180° away ($N \geq 30$). Significance ($p < 0.05$) was assessed using two-tailed t-tests and ANOVA with post-hoc Tukey-Kramer tests. Latency of effects was calculated as the time when the difference in activity between compared conditions exceeded 2 standard deviations in a sliding window (size: 10ms; step: 2ms) beginning at cue onset (Sato and Schall, 2003).

To compare neural activity to model predictions (Cisek, 2006), we ran simulations of the same task and used similar analysis procedures. The model was identical to that previously described (see Cisek 2006), without any changes of parameters except that the model's "prefrontal" activity was scaled by a signal related to the *absolute* value of each target (low=0.3, medium=0.7, high=1.0).

RESULTS

Behavior

In 1T trials the monkey's success rate was 96%, in 2T FREE it was 96% and in 2T FORCED it was 94% (in all cases N>60,000). In 2T FREE trials the monkey selected

the more valuable target 85% of the time, indicating that he understood the meaning of the stimulus cues.

Reaction times (RTs) were similar across conditions due to the DELAY period. However, we observed a small but significant increase in movement speed to higher-valued targets: in the 1T task mean MT was 400ms to high-value and 416ms to low-value targets (KS-test, $p<0.01$).

Neural activity in PMd

Activity was recorded from 327 cells from the arm area of PMd (Supplemental Fig 1), of which 226 (69%) had significant directional tuning during at least one epoch (DELAY, MT, THT) and were considered task-related. Here, we focus on cells with DELAY-period tuning (112/226, 49%). About half of these (50/112, 45%) were isolated long enough to collect data across all angular distances ("*Distance-complete" cells*). Figures 1B-D show the neural activity of three example cells, from trials in which each cell's PT was one of the targets presented. During the 1T task (1st column), directionally-tuned DELAY period activity showed no effect of PT value. However, in the 2T task, when a second target was present and medium-valued (2nd column), the neural activity of all three cells now showed strong modulation with the *relative* value of the PT, firing more when their PT was more valuable than the OT (2nd column). This effect was also observed when the PT was medium-valued and the OT value was varied (3rd column). In this case the cell activity was lower when the OT was more valuable than the PT. This

suggests that the nature of the value effect is always *relative* to the other option presented.

Importantly, DELAY period activity was also modulated as a function of the angular distance between the targets (Figs 1B-D, 4th column). In most cases, activity was weaker when the targets were further apart (180°) than when they were closer to each other (60° or 120°). Another interesting finding is the difference in latency between relative value and angular distance effects. For example, the cell shown in Fig 1B exhibited effects of angular distance 102ms after target onset (4th column), while the effects of expected value emerged significantly later, at 220ms (3rd column).

Population analyses

The population of 112 DELAY-tuned cells was tested for relative value effects and "distance-complete" cells were additionally tested for distance effects. From the entire tuned population of 112 cells, 49 (44%) showed significant effects of relative value in the 2T task (t-test, $p<0.05$) with activity increasing with PT value and decreasing with OT value. Importantly, *no effects were ever observed in the 1T task* (t-test, $p>0.05$ for all comparisons). Across the group of distance-complete cells, 38/49 (78%) showed some effect of relative value or distance. Thirty-five cells (71%) showed relative value effects and 22 (45%) showed angular distance effects (Supplemental table 1). Congruent results were obtained with t-tests and ANOVA with post-hoc Tukey-Kramer tests ($p<0.05$, see Supplemental Materials).

Figure 2A compares the mean DELAY-period activity of individual cells (N=112) during the 1T task when the PT was low-valued (x-axis) versus when it was high-valued (y-axis). The means were not statistically different (Wilcoxon signed-rank test, p=1). In contrast, most cells had higher DELAY activity in the 2T task when the PT was more valuable than the OT (Fig 2B**,** Wilcoxon signed-rank test, $p<10^{-6}$) and lower when the OT was worth more than the PT (Fig 2C, $p<10^{-6}$). About half (19/35, 54%) of the distance-complete cells with relative value effects also had stronger activity when the targets were 60° apart than when they were 180° apart (Fig 1D, $p<10^{-3}$). Importantly, the same trends were observed across the entire population of cells with and without individually significant effects (p>0.9 in 1T; and $p<10^{-5}$ in 2T for all comparisons). No significant effects of overall target value were found for cells that were not tuned during the DELAY (p=1).

The latency of relative value and distance effects was calculated for all distance-complete cells with any effect (N=38). Figure 3A shows a cumulative distribution of the time at which a cell becomes tuned in the 1T task, the time at which it exhibits a distance effect in the 2T task, and the time at which it exhibits a relative value effect in the 2T task. Across the population, effects of angular distance appeared at approximately the same time as cells became tuned, while the effect of relative value appeared 50-200ms later. The relative-value and distance-effect distributions were statistically different (Kolmogorov-Smirnov test, p<0.024) as were the relative value and tuning-onset distributions (KS-test p<0.024). The difference between tuning-onset and distance effect distributions was not statistically significant (KS-test, p>0.98)

Gain effect of distance over relative value

Figure 3B shows the mean DELAY-period activity of three example cells (Fig 1B-D) as a function of OT value when the PT is medium-valued, separately for trials with targets 60°, 120° or 180° apart. Note that all slopes are negative and steeper when targets are further apart. This suggests an interaction between angular separation and relative value effects. Figure 3C compares the slopes of all distance-complete cells with any effect (N=38) when the targets are 60° (x-axis) versus 180° (y-axis) apart. The further apart the targets are, the more negative becomes the slope of activity versus relative value (t-test, $p<0.003$).

A biased competition model reproduces the results

Cisek (2006) described a model of action selection in which populations of cells along the dorsal stream form a distributed representation of potential actions, which compete against each other through lateral inhibition (Supplemental Fig 2). The same model can simulate our neural recording results without any changes of parameters, except the addition of an *absolute* value signal into the PFC layer. As shown in Fig 4A**,** the model chooses the more valuable target when values are unequal and chooses randomly when they are equal. When targets are 60° apart, the model often chooses the direction in-between the targets (Ghez et al., 1997). Figure 4B shows an example of a simulated PMd neuron. Just as real neurons, the simulated cell exhibits no sensitivity to value in the 1T task. This is because the model continuously re-normalizes activity across

the population, and with one target it always produces one hill of activity that is similar regardless of biasing. However, the cell shows strong sensitivity to *relative* value in the 2T task, in which the balance between two hills of activity can be influenced by biasing factors from PFC. The model also exhibits sensitivity to distance, with stronger activity when targets are 60° than 120° or 180° apart. Finally, as in the data, the effect of distance is evident in the model almost immediately but the effect of relative value takes longer to influence PMd activity due to the slow dynamics of model PFC (note arbitrary time units in Fig 4).

DISCUSSION

Recently, many studies have shown that decision variables influence neural activity throughout the sensorimotor system. These findings have sometimes been interpreted as the neural encoding of formal quantities such as uncertainty (Basso and Wurtz, 1998), expected gain (Platt and Glimcher, 1999), local income (Sugrue et al., 2004), or accumulated sensory evidence (Yang and Shadlen, 2007). We suggest that such findings do not necessarily imply that decision variables are explicitly *encoded* in neural activity (in the sense that they can be decoded), but may instead reflect their influence on a competition between potential actions taking place within the sensorimotor system. This predicts that any factor relevant for the monkey's choice will influence activity, including reward value, which was explicitly manipulated here. Importantly, however, our data shows that the effect of value was always *relative*, and therefore never appeared when there was no choice to make. Our PMd results are therefore more naturally

interpreted as motor-related activities that specify potential reach directions, which are modulated by relative subjective desirability (Dorris and Glimcher, 2004), a general term that includes all factors relevant to the choice.

While we found PMd activity to always reflect the *relative* values of actions, activity related to *absolute* values has been reported in the striatum (Samejima, 2005; Lau and Glimcher, 2008). It is possible that the basal ganglia are a major source of the biasing signal which influences premotor activity (Cisek, 2007; Leblois et al., 2006; Redgrave et al., 1999). In saccade tasks, activity related to absolute value has been reported in the parietal cortex (Platt and Glimcher, 1999; Seo et al. 2009) and in the ventral premotor cortex (PMv) (Roesch and Olson, 2003). The fact that we did not find reward-related modulations in PMd during our 1T task may be attributable to differences between eye versus arm control or to differences in recording locations. For example, since PMv has different response properties than PMd (Boussaoud and Wise, 1993; Hoshi and Tanji, 2007) as well as distinct anatomical connections (Rizzolatti and Luppino, 2001), it may be more involved in representing sensory and reward information than PMd, which is more concerned with motor information. An earlier study using a saccade task (Roesch and Olson, 2004) found that PMd activity increased when either the reward or the penalty for one of the targets was increased. Although it is difficult to directly compare our results with those of a saccade task, in which PMd cells were not strongly directionally tuned, it is plausible that the effect was also related to relative subjective desirability.

One could argue that our findings are related to selective attention, which has also been described as biased competition (Desimone and Duncan, 1995). From the traditional perspective of cognitive psychology, one may wish to dissociate processes related to

selective attention from those related to action selection. However, in our view (Cisek, 2007; Cisek and Kalaska, 2010) these may not be functionally distinct. It has been suggested that selective attention serves as an early mechanism for action selection (Allport, 1987; Neumann, 1990; Tipper et al., 1998), and that both are facets of the same biased competition occurring throughout the dorsal visuomotor stream (Duncan, 2006; Cisek, 2007). Indeed, it has been shown that microstimulation in a putatively motor region of frontal cortex can influence processing in visual cortex (Armstrong et al., 2006), demonstrating a strong link between attention and action selection.

Another important implication of our findings concerns the site of the competition that determines choices. Decision-related modulations in the sensorimotor system do not themselves necessarily imply that decisions are made within sensorimotor circuits. They could instead made "upstream" in regions such as PFC, which are clearly involved in decisions (Tanji and Hoshi, 2001; Wallis and Miller, 2003) and project into sensorimotor regions. However, our results argue against this traditional view. First, we found that the dynamics of the competition that determines decisions are dependent on spatial variables. These are irrelevant for the abstract economics of cognition, but are important for the motor system, which selects between physical actions where geometrical relationships matter. Second, these effects of distance appear in cell activity as soon as cells respond to the stimuli, implying that the competition between potential actions takes place all throughout the fast sensorimotor "dorsal" visual stream (Cisek, 2007; Cisek and Kalaska, 2010). All of these results are remarkably well captured by a simple computational model (Cisek, 2006) which suggests the following conclusion: that although decisions between

actions are influenced by variables supplied by higher cognitive regions, they are determined by a competition which takes place within sensorimotor circuits.

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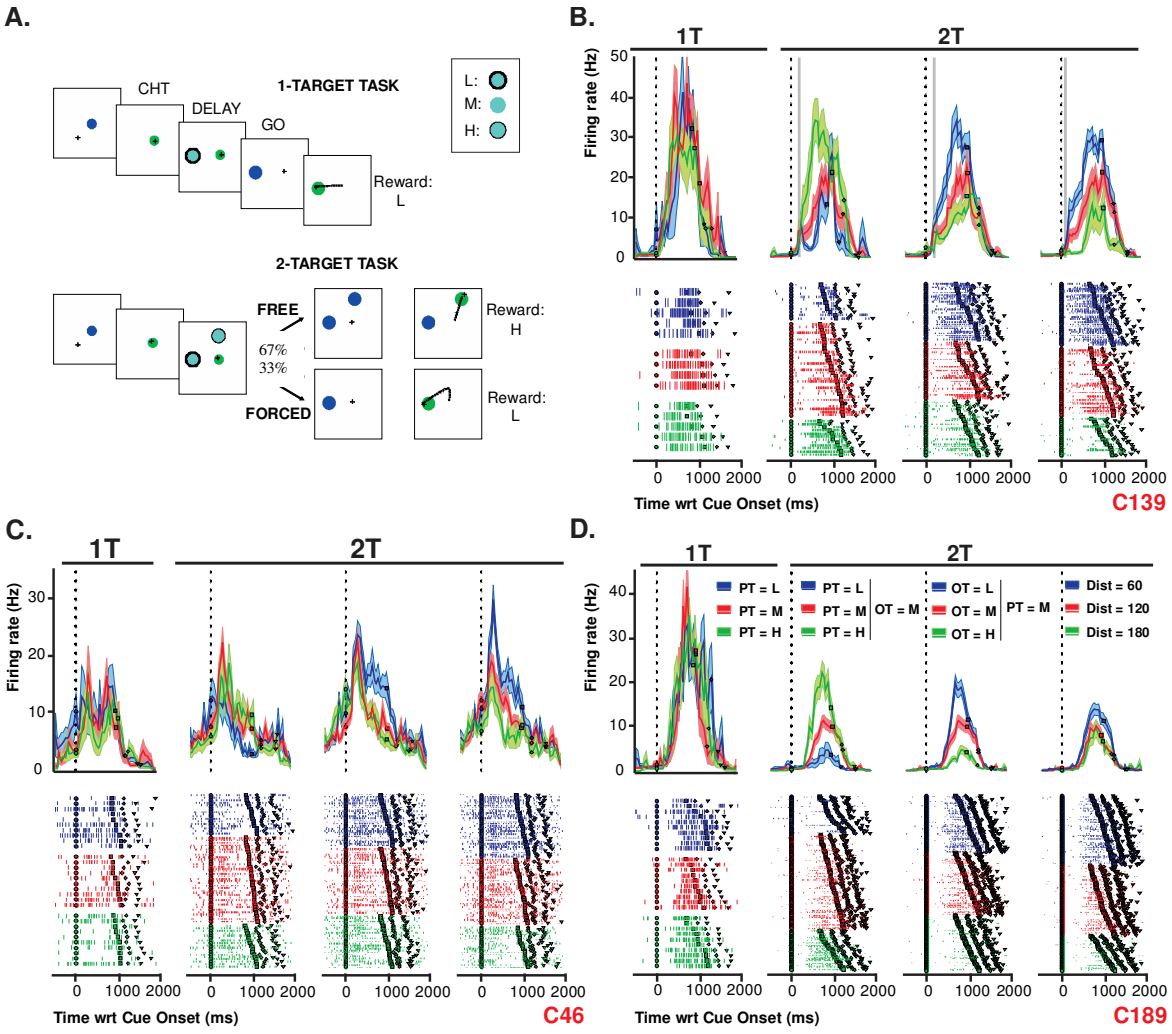

Figure 1. A. Behavioral task. **B-D.** Three individual cell examples. Each panel shows histograms and raster plots for 1T and 2T trials in which the cell's PT was present. Activity is aligned on cue onset. The GO signal, movement onset, and movement offset are indicated by thick squares, circles and triangles, respectively. In the 1st column (1T task), colors indicate whether the PT value was low (blue), medium (red), or high (green). In the 2nd column (2T) task, the PT values were low (blue), medium (red), or high (green) and there was also a medium-valued OT present. In the 3rd column, the PT was always medium-valued while the OT value was low (blue), medium (red), or high (green). In the 4th column, both the PT and OT were medium-valued but the OT was 60° (blue) 120° (red), or 180° (green) away from the PT.

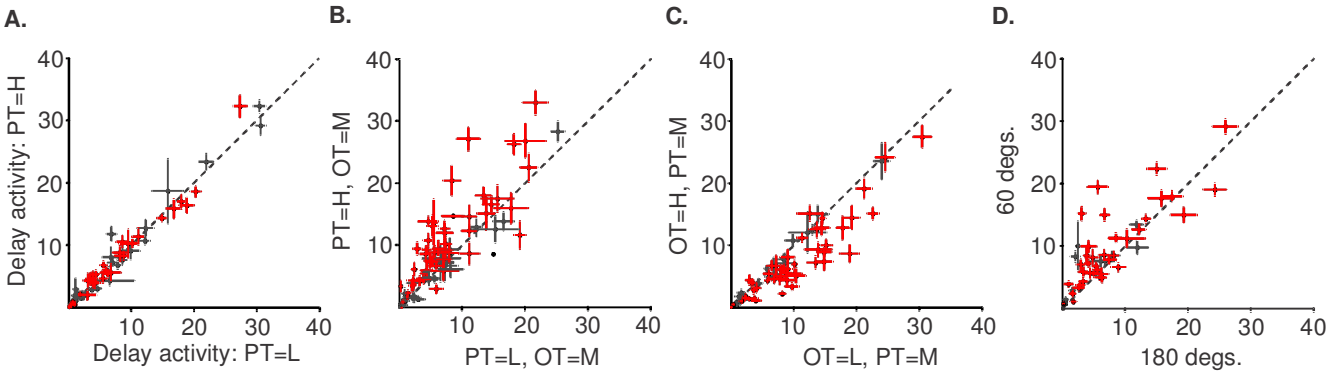

Figure 2. Population analyses. **A.** Mean firing rate of individual cells in the 1T task when the PT was low-valued (x-axis) versus high-valued (y-axis). Each cross indicates mean and standard error of the mean. **B.** Firing rates comparing 2T trials in which the OT is medium-valued and the PT is low-valued (x) versus high-valued (y). **C.** Comparison of 2T trials in which the PT is medium-valued and the OT is low-valued (x) versus high-valued (y). **D.** Comparison of 2T trials in which the PT and OT are medium-valued and are 60° (x) versus 180° apart (y). In all panels, black crosses indicate cells with statistically significant effects (N=52) along with the rest of the delay tuned population (N=60, grey).

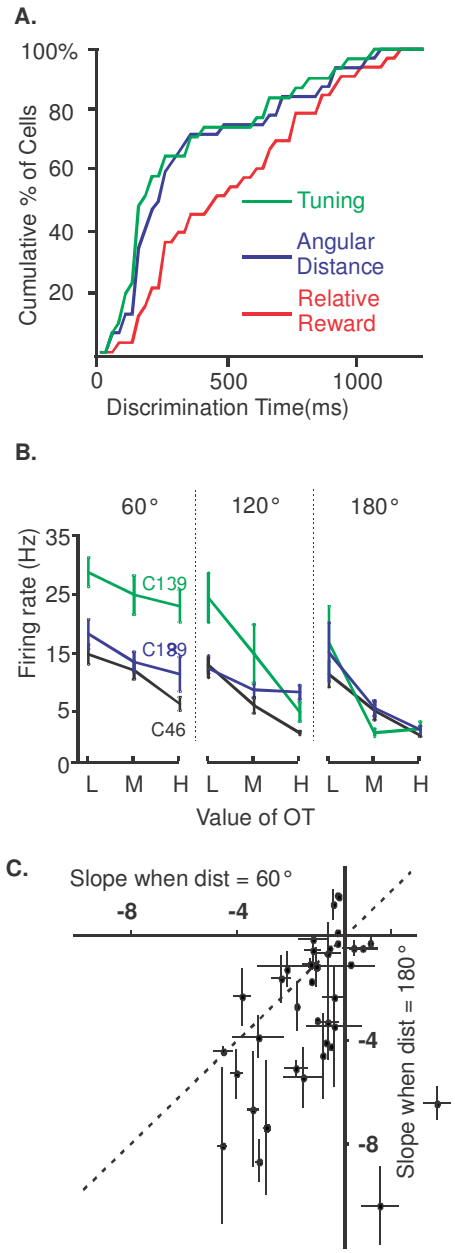

Figure 3. A. Cumulative distribution of latencies with which distance-complete cells (N=38) exhibit tuning in the 1T task (green), and discriminate angular distance (blue) and relative value (red) in the 2T task. **B.** Firing rates of three example cells (**Fig 1B-D**) as a function of OT value, when the PT was medium-valued. Each column shows trials with a different angular difference between targets (60°, 120°, 180°). Note that the slope is more negative for the 180° trials. **C.** Comparison of the mean (and s.e.m.) of the slopes in the 60° versus 180° conditions, for all distance-complete cells (N=38).

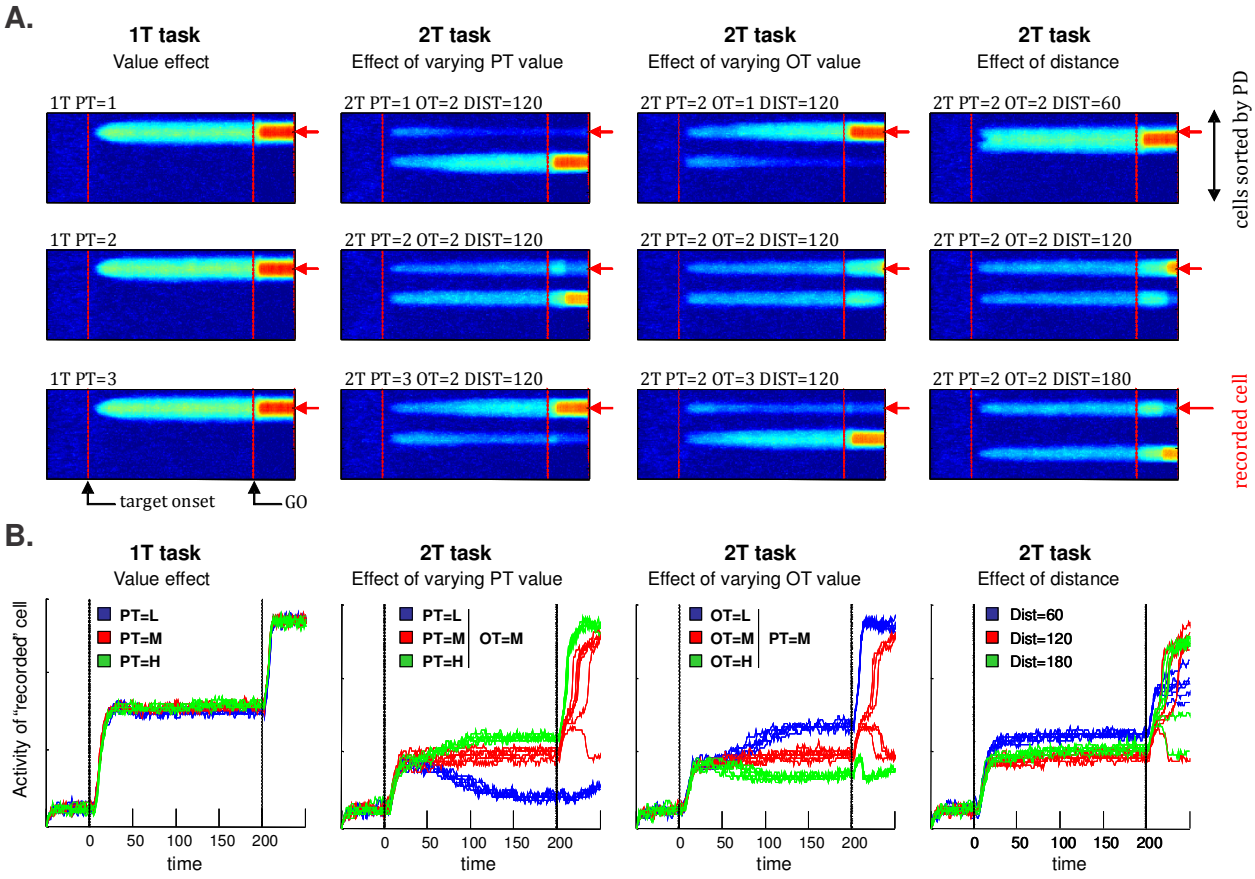

Figure 4. A. Activity from the model's caudal PMd population as color plots for 12 different conditions, as in the cell data. Each color plot shows activity evolving over the time-course of a single trial (x-axis), with cells sorted by their preferred direction (y-axis). Blue indicates low activity and red indicates high activity. **B.** Behavior of one cell from the caudal PMd population, comparing activity across conditions as in the neural data (**Fig 1B-D**).

NEURAL CORRELATES OF BIASED COMPETITION IN PREMOTOR CORTEX

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SUPPLEMENTAL MATERIALS

Task apparatus and recording sites

The task involved moving a cursor from a central circle (2cm radius) to one of six possible targets (2.4cm radius) spaced at 60° intervals around a 12.6cm radius circle. The monkey performed movements using a cordless stylus whose position was recorded (125Hz) by a digitizing tablet (*CalComp*). Target stimuli and continuous cursor feedback were projected onto a mirror suspended between the monkey's gaze and the tablet, creating the illusion that they are in the plane of the tablet. Oculomotor behavior was unconstrained as eye movements do not strongly influence arm-related PMd activity (Cisek and Kalaska, 2002). Neural activity was recorded with 3-4 independently moveable microelectrodes (*NAN microdrive*) and data acquisition was performed with AlphaLab (*Alpha-Omega*). On-line spike discrimination was used to estimate cell preferred directions for choosing target locations. All analog waveforms were stored on disk for offline sorting using principal components (*Plexon*). All task events, trajectory data and spike times were stored in a database (*Microsoft SQL Server 2005*) accessed through custom scripts for data analysis (*Matlab*). After completing training, the animal was implanted under general anesthesia with a titanium head post and a recording chamber placed using MRI images (*Brainsight primate*). The chamber was centered on the arm area of PMd, between the precentral dimple and the junction of the arcuate sulcus and spur (Supplemental Figure 1). All procedures followed university and national guidelines for animal care.

Calculation of directional tuning

We calculated directional tuning preferences of each cell during each behavioral epoch (DELAY, MT, and THT) in the 1T block, and assessed significance with a non-parametric bootstrap test (1000 shuffles, $p<0.05$; Cisek et al., 2003). The PT of each cell was based on its activity in the DELAY period. For cells that did not have trials in the 1T block (e.g. cells which were found while the monkey was performing the 2T block) the PT was based on the delay period activity for FREE trials in which a high-valued target (PT selected) and a low-value target (OT non-selected) was presented to the monkey, who selected the high-value target. The tuning obtained with this method was readily comparable with the tuning obtained in the 1T task, with very few exceptions (N=2 cells, which were not tuned in 1T and became tuned in the 2T task). A possible confound with this tuning method is that it assumes that cells have value effects in the 2T block. To investigate the impact of such an assumption, we calculated the tuning of DELAY cells with 1T trials (N=86/112, 77%) and DELAY cells without 1T trials (N=26/112, 23%) and treated them as two separate groups. Similar proportions of cells had statistically significant effects using t-tests ($p<0.05$): 42 out of 86 (49%) DELAY-tuned cells with 1T trials had value effects in 2T and 12 out of 26 (46%) DELAY-tuned cells without 1T trials had value effects in 2T. Comparable results were obtained using ANOVA and a post-hoc Tukey-Kramer test ($p<0.05$): 37 out of 86 (43%) DELAY tuned cells with 1T trials had value effects and 12 out of 26 (46%) DELAY tuned cells without 1T trials had value effects. A population analysis limited to cells with both 1T and 2T trials (Supplemental Figure 3) exhibited similar trends as an analysis of the total population

(including cells without 1T trials). As in the full data, no significant effects were found during the DELAY in the 1T task (Wilcoxon signed-rank test, p=1) and value and distance effects were observed in the 2T task ($p<10^{-4}$ in 2T for all comparisons). This suggests that both groups of cells (with and without 1T trials) belong to the same population and were therefore analyzed together in the main text.

Additional repetitions in single-cell recordings

A typical 2T block had 90 trials with targets 120° apart, and the PT of an isolated cell was one of the targets in 60 of these trials. In an additional 60 trials the PT appeared with an OT 60° away, and in 30 the PT appeared with an OT 180° away. Thus, in each 2T block the trials in which the targets are 180° apart were slightly under-represented with respect to trials with the other two angular distances (60° and 120°). For cells that were held isolated long enough (Distance-complete cells) a comparable number of trials across angular distances were obtained through block repetition.

Statistics for the assessment of value and distance effects

To assess the statistical significance of value and/or distance effects at the individual cell level, we compared the DELAY period activity of each cell using two-tailed t-tests ($p<0.05$) and an analysis of variance (ANOVA) with post-hoc Tukey-Kramer tests ($p<0.05$). For example, the delay period activity for trials in any of the three values tested in 1T (L, M or H) were compared using ANOVA to assess whether there

was a statistical difference within any value combination: low *vs.* high, low *vs.* medium and medium *vs.* high. Two-tailed t-tests and Tukey-Kramer tests were used to determine whether there was a statistically significant difference in a particular value combination (Criteria for a cell with value effects). In the 1T task there was no statistical significance for any cell with either of these two methods. In the 2T condition where the value in OT was varied (L, M, H) and the value in PT was held constant (M), the possible combinations were OT:low *vs.* OT:medium, OT:low *vs.* OT:high and OT:medium *vs.* OT:high. Both t-tests and ANOVA with Tukey-Kramer tests were in close agreement qualitatively and quantitatively (t-test: N=49 with $p<0.05$; ANOVA: N=42 with $p<0.05$). Similar numbers were obtained in the 2T condition in which the PT value was varied (L, M, H) and the OT value was held constant (M). The analysis of DELAY period activity for the three angular distances in 2T (60°, 120° and 180°) was performed with t-tests and ANOVA in a similar way as with value comparisons (t-test N=22 with $p<0.05$ and ANOVA N=18 with $p<0.05$). In general, both t-test and ANOVA methods were found to be in close agreement, yielding N=52 cells with reward or value effect with t-tests and 47 cells with ANOVA and Tukey-Kramer tests.

In addition, we performed 2-way ANOVAs to compare reward value in PT and angular distance as well as reward value in OT and angular distance. Fourteen out of 38 distance-complete cells (37%) showed a significant interaction between relative value and angular distance. This is in good agreement with the proportion of cells obtained with the t-test method 19/38 (50%). The interactions between relative value and angular distance were also quite similar for the distance-complete cells that had both 1T and 2T trials 12/31 (39%, 2-way ANOVAS) and 17/31 (54%, t-tests).

Determination of a unique value for latency of effects

The latency for relative reward or distance effects was taken as the earliest discrimination time for value effects. For example, in the 2T condition where the value in OT was varied (L, M, H) and the value in PT was held constant (M), the latency of relative value effects was chosen as the earliest among the combinations OT:L *vs*. OT:M, OT:L *vs.* OT:H and OT:M *vs*. OT:H. The earliest latency for angular distance was chosen among the earliest discrimination time among the following combinations: 60° *vs.* 120°, 60° *vs.* 180°, or 120° *vs.* 180°.

Supplemental Table 1.
Classification of delay activity according to observed effects

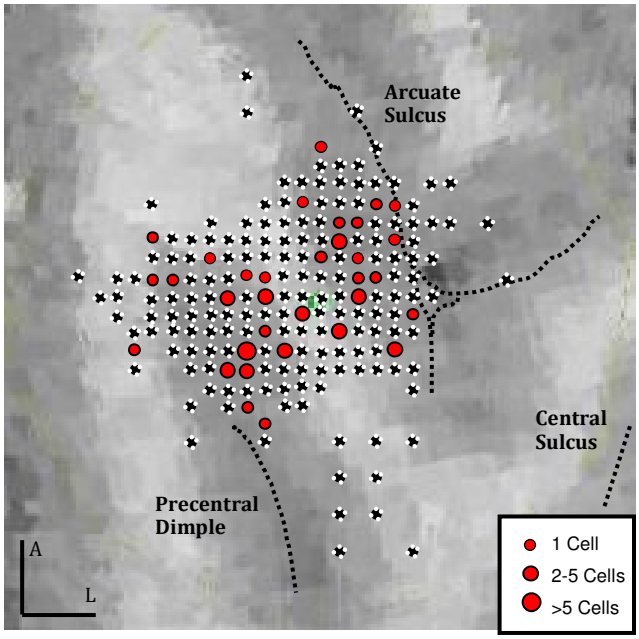
	N	N (1T & 2T)*
Cells tuned during delay (Delay-tuned)	**112[1]**	**89**
Delay-tuned with any effect of value or distance	**52[2]**	**41[2]**
Delay-tuned with value effect in 1T	0	0
Delay-tuned with value effect only (in 2T)	30	22
Delay-tuned with distance effect only	3	2
Delay-tuned with both value and distance effects	19	17
Delay-tuned with any value effect	49 (30+19)	39 (22+17)
Delay-tuned with any distance effect	22 (3+19)	19 (2+17)
Distance-complete delay-tuned cells	**50**	**41**
Distance-complete with any effect	**38[3]**	**31[3]**
Distance-complete with value effect in 1T	0	0
Distance-complete with value effect only (in 2T)	16	12
Distance-complete with distance effect only	3	2
Distance-complete with both value and distance effect	19	17
Distance-complete with any value effect	35 (16+19)	29 (12+17)
Distance-complete with any distance effect	22 (3+19)	19 (2+17)

(1T & 2T)* : Cells that have trials collected in both the 1T and 2T conditions
[1, 2] Cells used for general population analyses.
[3] Cells used for distance-and-value interaction effect (gain effect) and latency analyses.

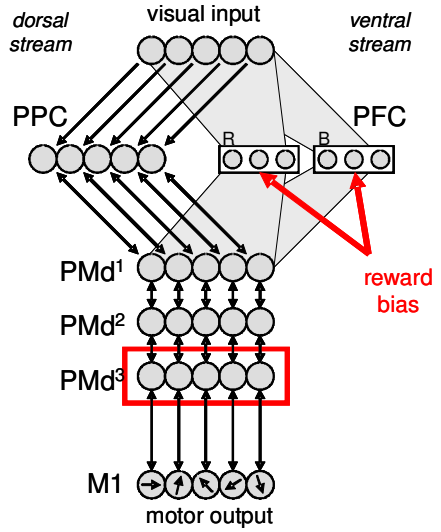
Supplemental References

Cisek P, Kalaska JF (2002) Modest gaze-related discharge modulation in monkey dorsal premotor cortex during a reaching task performed with free fixation. J Neurophysiol 88:1064-1072.

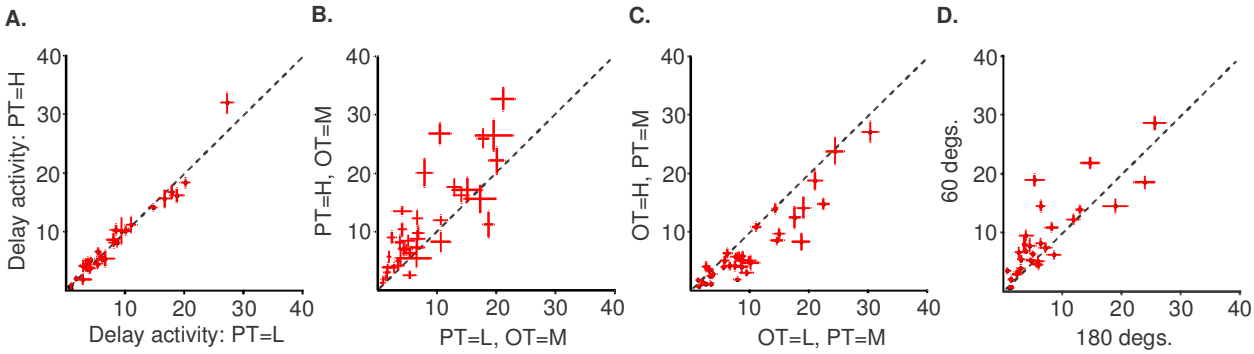
Cisek P, Crammond DJ, Kalaska JF (2003) Neural activity in primary motor and dorsal premotor cortex in reaching tasks with the contralateral versus ipsilateral arm. J Neurophysiol 89:922-942.



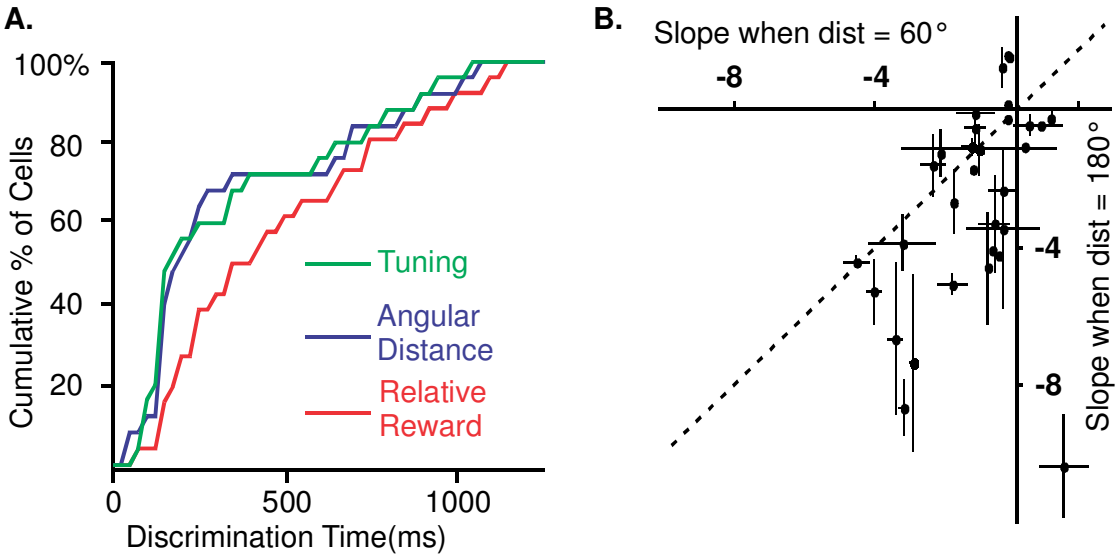
Supplemental Figure 1. Recording locations in PMd. Black crosses indicate recording sites. The locations for tuned cells with effects are shown with red circles (N = 52).



Supplemental Figure 2. Model of action selection, in which populations of cells along the dorsal stream implement a distributed representation of potential actions that compete against each other through lateral inhibition. Each population is modeled as a set of tuned neurons with "on-center-off-surround" recurrent connectivity. The model includes posterior parietal cortex (PPC), prefrontal cortex (PFC), three layers of PMd (rostral to caudal) and primary motor cortex (M1). Biasing signals related to absolute reward value enter as input to the PFC layer. Figure 4 in the main text shows activity from the caudal PMd population (red box).



Supplemental Figure 3. Population analyses limited to cells that had trials both in 1T and 2T blocks. **A.** Mean firing rate of individual cells in the 1T task when the PT was low-valued (x-axis) versus high-valued (y-axis). Each cross indicates mean and standard error of the mean. **B.** Firing rates comparing 2T trials in which the OT is medium-valued and the PT is low-valued (x) versus high-valued (y). **C.** Comparison of 2T trials in which the PT is medium-valued and the OT is low-valued (x) versus high-valued (y). **D.** Comparison of 2T trials in which both the PT and OT are medium-valued and are 60° (x) versus 180° apart (y).



Supplemental Figure 4. Latency and gain effect analysis limited to cells that had trials in both 1T and 2T. **A.** Cumulative distribution of latencies with which the cells (Distance-complete cells, N=31) exhibit tuning in the 1T task (green), and discriminate angular distance (blue) and relative value (red) in the 2T task. **B.** Comparison of the mean (and s.e.m.) of the slopes in the 60° versus 180° conditions, for all distance complete cells, N=31).

V. ARTICLE 2

SPACE MATTERS: TRADING ACTION METRIC AND VALUE REPRESENTATIONS IN PREMOTOR CORTEX

by

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ABSTRACT

Recent neuroeconomic theories suggest that decisions are made through comparisons of the costs and benefits of outcome values, prior to the preparation of actions. In contrast, ethologically-based theories propose that potential actions representations are prepared in parallel and interact with each other through a biased competition process. The latter view makes two key predictions: 1) that neural activity in sensorimotor regions is influenced by the relative, not absolute value of action choices; and 2) that the sensorimotor contingencies of potential actions influence the selection between them. We tested these predictions by recording neural activity in the dorsal and ventral premotor cortex (PMd and PMv) during a reach decision task in which the expected value (EV) of targets and the angular distance between them were independently manipulated. A significant fraction of cells in both regions (54% in PMd, 59% in PMv) were modulated by the relative value of targets, but no cell in either region was modulated by absolute value, consistent with a biased competition process that produces full divisive normalization. In addition, the gain of the value effect of many cells (42% in PMd and 20% in PMv) was modulated by the angular separation between targets, suggesting that the competition takes place within a sensorimotor map that respects the geometry of action space. The effect of angular separation appeared as soon as the cells became tuned (as early as 75ms after target onset), while modulation by relative value appeared 50-100ms later. To further examine how value and spatial information become integrated in the decision process, we also recorded activity in a task variant in which the mapping between cue stimuli and values had to be learned. We found that while spatial information is present even with novel cues, relative value

modulation only emerges after the animals learn the mapping. All of these results are consistent with a model in which the fast dorsal visual system specifies multiple potential actions in parallel, which then compete within a distributed sensorimotor map while other regions gradually bias that competition by modulatory decision variables such as expected value.

INTRODUCTION

When you go to the grocery store to buy a jar of peanut butter, your choice of product is influenced by a variety of factors, including subjective preference, cost, quality of ingredients, familiarity with the brand, etc. Economic theories suggest that humans make decisions by combining all of these factors into a unified estimate of the value of each choice, and then selecting the option with the highest value. While classic economic theories did not claim direct correspondence with neural processes (Von Neumann and Morgenstern, 1944), recent neurophysiological work has suggested that neural correlates of economic value do indeed exist in the brain. For example, neural activity in many cortical regions is modulated by a variety of decision variables such as expected gain (Platt and Glimcher, 1999), local income (Sugrue et al., 2004), and time-discounted rewards (Cai et al., 2011; Kim et al., 2008). In particular, neurons in the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) behave very much like what one would expect if they encoded the economic value of offered goods as well as the choice made (Padoa-Schioppa and Assad, 2006). These findings have led to proposals that the classical concepts

of economics correspond more or less directly to the actual brain processes that implement our choices (Padoa-Schioppa, 2011).

An important question concerns the kinds of mechanisms that determine our decisions: do we decide by comparing representations of the value of the potential outcomes of our choices, or do we decide through a competition between the courses of action available to us (Cisek, 2012)? The " model" (Padoa-Schioppa, 2011) suggests that choices are driven by explicit representations of offer value – a unified measure of the costs and benefits of each expected outcome. Importantly, it suggests that these decisions are independent of the sensorimotor contingencies associated with the required actions. The model suggests that decision-making is an executive function made in cognitive centers and does not involve the regions which plan and execute (Alexander and Crutcher, 1990; Andersen et al., 1997; Ferraina and Bianchi, 1994; Houk and Wise, 1995; Kalaska and Crammond, 1992; Kurata, 1989).

However, the activity in many fronto-parietal regions involved in sensorimotor control has been shown to be modulated by a variety of decision-variables (Croxson et al., 2009; Kennerley et al., 2009; Kim et al., 2008; Louie and Glimcher, 2010; Padoa-Schioppa and Assad, 2006, 2008; Platt and Glimcher, 1999; Roesch et al., 2006; Rushworth and Behrens, 2008; Schultz, 2010; Sugrue et al., 2004; Yang and Shadlen, 2007). This could have many implications. One possibility is that these modulations are not related to decision-making *per se*, but to processes that co-vary with decision variables, such as arousal (Roesch and Olson, 2004). Another possibility is that the regions in which these modulations are found are not in fact related to sensorimotor control, but are part of the cognitive system (Padoa-Schioppa, 2011). A third possibility

is that decision-related modulations of sensorimotor cells are simply the reflection of cognitive processes that actually occur upstream, but these cells do not themselves contribute to the process of selection. All of these proposals conform to a classic distinction in psychology, the distinction between cognitive and sensorimotor processes (Fodor, 1983; Pylyshyn, 1984).

A fourth possibility is that the brain does not respect this classic distinction, and that the neural mechanisms for decision-making and sensorimotor control are closely integrated (Cisek, 2006, 2007b; Cisek et al., 2002). While the model offers a promising account of economic choices, such as decisions between different brands of peanut butter, it does not address the larger context of ecological choices in which our decision-making capacities evolved. For our distant ancestors such as primitive vertebrates, whose behavioral needs determined the phylogenetic foundation of our brain's organization, nearly all decisions were about actions. This has an important implication: that for the kinds of decisions for which our brains originally evolved, sensorimotor contingencies were among the most important factors determining the correct choice at a given time (Cisek, 2012), in addition to factors such as value.

For example, consider the kind of decisions that a mouse must make as it is running away from a cat. Which escape route should it take? Should it continue along the present course or should it switch directions? Importantly, the mouse cannot stop to evaluate these questions but must perform the decision process during its ongoing locomotion. Furthermore, the options offered (escape routes), as well as their costs and benefits, are defined by the geometry of the environment and are constantly changing. An escape route

of putatively high value (big enough for the mouse but too small for the cat) may be less attractive if it requires a sharp turn. Furthermore, beyond the potential value of the options themselves, their geometric relationship to each other is also relevant. For example, a choice between two escape routes that are 180° apart has to be all-or-none and immediate, but two escape routes that are close together can be initially mixed and the choice between them made only at the last moment. In summary, for decisions between actions, sensorimotor contingencies matter.

For these reasons, a system that makes decisions between actions in real-time must integrate both cognitive and sensorimotor processes. This provides a straightforward explanation for why neural activity in sensorimotor regions is influenced by decision variables. It also predicts that sensorimotor contingencies such as the relationship between options should influence the process of deciding between them. Some behavioral evidence for this has already been reported. For example, the reaction time (RT) of a reaching movement is influenced not simply by the number of potential targets, but by the region of space they cover (Bock and Eversheim, 2000; Favilla, 1997). Target separation is also a critical determinant of whether guesses between targets are discrete (aimed randomly at one of two options placed far apart) or continuous (aimed in-between two options placed close together (Favilla, 1997; Ghez et al., 1997). Models aimed at explaining such results (Cisek, 2006; Erlhagen and Schoner, 2002; Tipper et al., 1998) suggest that the decision options themselves are defined within a continuous sensorimotor map of potential actions, and that it is competition within this map that determines the choice that is made. According to these models, such a competition receives many sources of bias, including input from regions that may represent classical economic variables such as offer value.

Interestingly, these models of action selection are mathematically closely related to models of attentional selection (Desimone and Duncan, 1995), which also involve a biased competition process.

The biased competition model (Cisek, 2006) proposes a distinction between the neural systems that compute the biases for influencing action competition and those that implement the competition itself. There may be many sources of bias, and they may not always be in agreement. Activity in biasing regions may be specialized for a given type of decision factor (e.g. discounted value, cost, probability of success) and it may represent that quantity on an *absolute* scale that preserves transitivity. In contrast, the competition itself should take place within a distributed but interconnected circuit, in which the constituent regions represent a sensorimotor map of potential movements that respects the geometric relationships between them. Activity in such regions should reflect all relevant biases, and always in a *relative* manner – i.e. the modulatory effect of the value of each option should always be relative to the other options simultaneously presented at a given moment.

Several testable predictions distinguish the biased competition model from a purely economic theory such as the model. The most critical of these is whether sensorimotor contingencies matter — for example, whether geometric relationships influence how decisions are made between actions. A second important prediction is that within the regions responsible for ultimately determining the choice, neural activity will be modulated by the *relative* and not the absolute values of currently available potential actions.

To test these predictions, we recorded neural activity in the premotor cortex of monkeys trained to perform a task in which they chose between two reaching targets whose values and locations were varied from trial to trial (Figure 1A). The angular separation

between the targets was 60°, 120°, or 180°, but they were always at the same distance from the central starting circle and always required approximately the same level of effort. Importantly, the angle between the targets did not change the value or the cost of either choice. Thus, for a model that makes decisions based on cost/benefit analyses of offers, angular separation has no bearing upon the decision process. However, for the biased competition model in which the decision evolves as a competition within a sensorimotor map, the angular separation influences how strong the competition between options should be. For targets far apart it predicts strong competition but for targets close together it predicts weaker competition and partial mixing of options, resulting in many movements initiated in-between the targets. Furthermore, the biased competition model predicts that in all cases, neural activity in the sensorimotor system will be related to the relative, not the absolute value of the potential rewards. Some of these results have previously appeared in preliminary form (Pastor-Bernier and Cisek, 2010, 2011).

MATERIALS AND METHODS

Two male monkeys (*Macaca mulatta*) performed a planar center-out reaching task illustrated in Figure 1A. After a 350-650ms Center-Hold-Time (CHT), one or two cyan targets appeared, with border styles indicating their value in drops of juice (See Figure 1A, inset). The reward was determined probabilistically to encourage the monkeys to explore available options (Herrnstein, 1961). A “low-value” target (L, thick border) had a 60% chance of yielding 1 drop, 30% chance of yielding 2 and 10% chance of yielding 3 (Expected value, EV=1.5). A “medium-value” target (M, no border) was worth

2 (60%), 1 (20%) or 3 drops (20%) (EV=2). A "high-value" target (H, thin border) was worth 3 (60%), 2, (30%), or 1 drop (10%) (EV=2.5). The non-monotonic relationship between border thickness and value was used to dissociate motivational factors from physical properties of stimuli. The monkeys held the cursor in the center for an instructed delay period (DELAY, 700-1300ms) until a GO signal was indicated by a change in target color and disappearance of the central circle. To receive the reward, the monkeys had to move to a target within a maximum 550ms movement time (MT) and hold the cursor there (Target-Hold-Time, THT, 500ms).

When cells were isolated, we first ran a block of 90 trials in which only one target was presented (1T), to identify the DELAY-period preferred target (PT) of each cell. Next, we ran a block of 180 two-target trials (2T), including ones where the PT target was present and low, medium, or high-valued, while the other target (OT) appeared at 60°, 120°, or 180° away and was low, medium, or high-valued. Each block also included 30 trials in which the targets were 120° apart but neither was in the direction of the PT. These trials allowed us to analyze the activity of simultaneously recorded cells with different PTs. All analyses shown here use trials in which at least one of the targets presented was the cell's PT. In 67 % of 2T trials (FREE), the monkey was free to move to either target after the GO signal. In 33 % of 2T trials (FORCED), one of the targets disappeared at GO and the monkey had to move to the remaining one. FREE and FORCED trials were randomly interleaved to encourage the animal to keep both options partially prepared.

To assess relative value effects we compared DELAY-period activity during trials with targets 120° apart in which the OT was medium-valued while the PT value varied

(N≥60 trials), as well as those in which the PT was medium-valued while the OT value varied (N≥60). To assess distance effects we examined trials in which the PT was present and the OT was 60° (N≥30), 120° (N≥120) or 180° away (N≥30). Significance ($p<0.05$) was assessed using ANOVA with post-hoc Tukey-Kramer tests.

In most sessions, the monkeys were presented with targets for which the mapping between border style and expected value was very familiar (see Figure 1A inset). However, in some cases, we held cells long enough to also record activity in a block of 2T NOVEL trials, in which the border styles presented to the monkey had never been seen before (different colors, dotted vs. dashed lines, multiple borders nested within each other, etc.). Thus, the monkey had to learn, through trial and error, the value indicated by each novel border style. We kept the mapping stable for the entire block of NOVEL trials, and only presented the monkey with FREE choice trials, but we continued to vary the value of both targets as well as the angular distance between the targets, as in the familiar condition.

Task apparatus and recording sites

The task involved moving a cursor from a central circle (2cm radius) to one of six possible targets (2.4cm radius) spaced at 60° intervals around a 12.6cm radius circle. The monkey performed movements using a cordless stylus whose position was recorded (125Hz) by a digitizing tablet (*CalComp*). Target stimuli and continuous cursor feedback were projected onto a mirror suspended between the monkey's gaze and the tablet, creating the illusion that they are in the plane of the tablet. Oculomotor behavior was

unconstrained as eye movements do not strongly influence arm-related PMd activity (Cisek and Kalaska, 2002), but in some sessions eye position was recorded (120Hz) with an infrared oculometer (*Applied Science Laboratories*). Neural activity was recorded with 3-4 independently moveable microelectrodes (*NAN microdrive*) and data acquisition was performed with AlphaLab (*Alpha-Omega*). On-line spike discrimination was used to estimate cell preferred directions for choosing target locations. All analog waveforms were stored on disk for offline sorting using principal components (*Plexon*). All task events, trajectory data and spike times were stored in a database (*Microsoft SQL Server 2005*) accessed through custom scripts for data analysis (*Matlab*). After completing training, the animal was implanted under general anesthesia with a titanium head post and a recording chamber placed using MRI images (*Brainsight primate*). The chambers were centered on the arm area of PMd, between the precentral dimple and the junction of the arcuate sulcus and spur (Figure 1B). All procedures followed university and national guidelines for animal care.

Data analysis

We calculated directional tuning preferences of each cell during each behavioral epoch (DELAY, MT, and THT) in the 1T block, and assessed significance with a non-parametric bootstrap test (1000 shuffles, $p<0.05$; Cisek et al., 2003). We classified cells as DELAY cells if they were significantly tuned during the DELAY epoch and as MT cells if they were significantly tuned during the MT epoch. A given cell could appear in both groups and thus to contribute data to analyses of activity in both epochs. For

analyses of DELAY activity, the preferred direction of each cell was based on its activity in the DELAY period, and for analyses of MT activity, it was based on MT activity. For each analysis, the target closest to a cell's preferred direction was denoted as the preferred target (PT) and any other target that appeared was called the other target (OT).

The latency of effects was calculated as the time when the difference in activity between compared conditions exceeded 2 standard deviations in a sliding window (size: 10ms; step: 2ms) beginning at cue onset (Sato and Schall, 2003). The latency for relative reward or angular distance effects was taken as the earliest discrimination time for each effect separately. For example, in the 2T condition where the value in OT was varied (L, M, H) and the value in PT was held constant (M), the latency for relative value effects was chosen as the earliest point in time at which activity for OT:L and OT:H segregated. The latency for the angular distance effect was chosen as the earliest time at which activity for 60° and 180° segregated.

To evaluate the monkey's learning performance we compared the cumulative number of trials (correct and incorrect) for the Low value and High value choices made by the monkey chronologically for each given pair association. We estimated a *pair-behavioral criterion* for each pair of associations (H vs L, M vs L and H vs M) and defined it as the 6th consecutive trial for which a high value choice was made on a given pair. Given that a correct choice represents a 0.5 probability of occurring by chance, six consecutive trials have a probability of 1.6%. This is close to what has been reported previously for a behavioral criterion in conditional visuomotor-learning (Mitz et al., 1991) where three consecutive responses with 0.25 probability of correct choice implied 2% chance of choosing by chance the same target. A global behavioral criterion represent the

time point (trial) at which all three paired-behavioral criterions have been reached (*complete learning*). We define as *incomplete learning* cases in which only certain pair associations have been learned and as *no learning* the situations in which none of them has been learned.

RESULTS

Behavioral results

Two monkeys participated in this study (M and K). In 1T trials the success rate was 98% for monkey M and 95% for monkey K. In 2T FREE trials the success rate was 99% (M) and 97% (K) and in 2T FORCED it was 96% (M) and 95% (K) (in all cases N>60,000). All incorrectly performed trials are excluded in the forthcoming analysis. In 2T FREE trials both monkeys selected the more valuable target 95% of the time, indicating that they understood the meaning of the stimulus cues. We found that movement times (MTs) were shorter to higher-valued targets in 1T trials (400ms to high-value and 416ms to low-value targets). Although the difference was small, it was significant for both animals (Kolmogorov-Smirnov test (KS), $p<0.05$). However, the reaction times (RTs) in 1T trials did not depend on target value for either animal (KS-test $p>0.05$ for all comparisons).

Figure 2A shows the average trajectories in different kinds of 2T trials, with the selected target oriented to the right. As expected, in the FORCED LOW trials (3rd column), when monkeys initiated movements quickly (short RT), they started toward the higher-valued target (which disappears at GO) and then turned around toward the remaining lower-valued target. The distributions of the initial directions are shown in Figure 2B. Note

that when targets are far apart (120° or 180°), the distribution for FORCED LOW trials is primarily oriented toward the high-value target if the RT is short, then is bimodal for medium RTs, and then is primarily oriented to the selected target for long RTs. However, when targets are closer together (60°), the peak of the distribution shifts gradually between the targets as RTs are longer. A straightforward explanation is that when targets are far apart, two separate groups of tuned cells are active, with cells tuned to the higher-valued target gradually becoming less active while cells tuned to the lower-valued target increasing in activity. When the targets are close together, these two groups of cells overlap, resulting in initial directions that gradually shift from the high to the low-valued target. This is reminiscent of the results of Ghez et al. (1997) in a timed-response task with human subjects, for which similar explanations have been proposed (Cisek, 2006; Erlhagen and Schoner, 2002).

Neural results

We recorded spiking data from 696 isolated neurons in the arm area of PMd, 596 from monkey M and 100 from monkey K (Table 1). Of these, 316 (45%) had significant directional tuning during at least one epoch (DELAY, MT, THT) and were considered task-related. From these we distinguish a group of 194 units with statistically significant tuning during DELAY (non-parametric bootstrap test, 1000 shuffles, $p<0.05$; (Cisek et al., 2003), of which 177 increased their activity with respect to baseline and 17 decreased their activity (the latter are not discussed further except in the Supplemental Materials). Of the 177 excited cells tuned during DELAY, 112 were also tuned during movement time (MT).

Finally, 69 cells were tuned only during MT. We also recorded 50 cells in PMv (4 in M and 46 in K) and analyzed these using the same convention (Table 2). Some PMd cells (N=113, all belonging to monkey M) were held long enough to be recorded in the learning variant of the task (Table 5).

PMd activity predicts free choices

When the monkeys were presented with two equal-valued targets and allowed to choose between them (FREE EQUAL trials), they made choices randomly. As shown in Figure 3A, these random choices were predicted by the neural activity in PMd just prior to the GO signal. On trials when a monkey chose a cell's preferred target (PT), pre-GO neural activity was higher than on trials in which the other target was chosen. This is shown for three example cells collected with enough trials to reach statistical significance (ANOVA with post-hoc Tukey-Kramer test, $p<0.05$) as well as for the entire population of DELAY-tuned cells (N=177).

PMd activity reflects the *relative* value of potential actions

The biased competition model predicts that PMd neurons reflect the value of their preferred target relative to the value of the other target that is simultaneously presented. This predicts that when only a single target is present, neural activity in PMd will be completely insensitive to its value. This prediction was strongly and very consistently confirmed. As shown for three example cells in Figure 3B-D (1st column), when a single

target was presented in a cell's PT the discharge rate was not dependent on the reward value for reaching that target (ANOVA with post-hoc Tukey-Kramer test, $p>0.05$ for all comparisons: L vs. M, M vs. H, and L vs. H). This was true for all PMd cells we recorded.

Despite the absence of value-related modulation when a single target was presented, when the same target in the cell's PT was accompanied by a second target that was medium-valued, neural activity was now strongly modulated by the value of the PT, increasing as the PT value increased from L to H (Figure 3B-D, 2nd column). Conversely, if the PT value was held constant then neural activity was inversely modulated by the value of the other target (OT), *decreasing* as the OT value increased from L to H (Figure 3B-D, 3rd column). Interestingly, in some cells (e.g. Figure 3C-D) these effects were seen not only during DELAY but also persisted during the reaction time and movement epochs.

It is possible that the absence of effects in 1T trials could be due to the fact that these were performed in a separate block than the 2T trials. However, among the 2T trials we also interleaved trials where both targets were equal-valued, and varied from low to high. In these 2T EQUAL trials, as it 1T trials, PMd activity was also not modulated by value (Figure 3B-D, 4th column). All of these results are consistent with the hypothesis that neural activity in PMd reflects the relative value of potential targets, in agreement with the biased competition model.

The trends shown in Figure 3 were consistent across the entire PMd population. Figure 4A shows DELAY period activity of neurons that are tuned during DELAY (N=177), of which 96 (54%) showed significant effects of relative value in the 2T task (ANOVA with post-hoc Tukey-Kramer test, $p<0.05$) with activity increasing with PT value in 76/96 (79%) cells and decreasing with OT value in 81/96 (81%) cells. When the PT

target is more valuable than the OT target, the activity of some cells is stronger by a factor of 3 or more than when the converse is true. However, despite these strong effects in the 2T task, no value effects were ever observed in the 1T task (t-test, $p>0.05$ for all comparisons). Furthermore, they were never observed in the 2T EQUAL trials for any of the 39 cells tested with those value combinations. Figure 4B shows MT activity of cells tuned during that epoch (N=181, note that some cells are tuned in both epochs and contribute data to both analyses in Figure 4A,B). Of these, 96 (53%) showed significant effects of relative value in the 2T task (t-test, $p<0.05$) with activity increasing with PT value (76/96, 82%) and decreasing with OT value (75/96, 78%) cells. Again, no effect was seen in the 1T task or in the 2T EQUAL trials (14 cells tested). Finally, PMd cells were not sensitive to changes in value when both targets were away from their PT (ANOVA and Tukey tests $p>0.05$ for L vs H in 1T or in 2T EQUAL) in either the DELAY or MT epochs (data not shown).

PMd is modulated by the angular distance between potencial actions

The presence of relative value coding in PMd is one important prediction of the biased competition model. However, for dissociating whether decisions are made in the space of actions versus in the abstract space of goods, the more critical question is whether sensorimotor contingencies matter. For example, does the angular distance between potential reaching actions influence the dynamics of the competition between them?

Figure 5A shows how the activity of four example PMd cells changes as a function of the angular distance between the PT and the OT, in trials where both are medium-valued.

For all four cells, activity is strongest when the targets are close together (60°) and weakest when they are far apart (180°). This trend was observed across the PMd population (Figure 5B, C), reaching significance in 44 (23%) of cells during the DELAY and 46 (25%) of cells in the MT epoch. The difference in activity was strongest between 60° and 180° and relatively small between 120° and 180°. However, it was not found when neither target was the cell's PT (ANOVA and Tukey-Kramer test $p>0.05$ comparing targets 60° and 120° apart when neither was the PT). Interestingly, this effect of angular distance was evident very early during the DELAY period, as shown in the lower right panels in Figure 5B, C. Its latency was as short as 75ms and followed closely behind the latency at which cells first became directionally tuned (difference in latency of tuning and angular distance not significant, KS-test, $p>0.05$). In contrast, the effect of relative value appeared significantly later (KS-test, $p<0.05$), approximately 50-100ms after cells became tuned.

Finally, and most importantly, once cells became modulated by the relative value of their preferred target, that modulation was itself dependent upon the angular distance between the two targets. In particular, if we examine trials in which a cell's PT is medium valued and examine how that cell's activity changes as a function of the OT value, we see stronger modulation when the OT and PT are further apart. This is shown for three example cells in Figure 6A-C, and summarized in Figure 6D. In particular, we observed that the further apart the targets were (120° or 180°), the more negative was the slope representing the magnitude of the relative value effect. These results suggest that *distance has a gain effect over relative value* (t-test, $p<0.02$ for all comparisons in DELAY or MT groups), consistent with a mechanism of competition that is stronger between cells whose preferred directions are far apart. The population analysis conducted in DELAY or MT cell groups

separately (Figure 6E and F, respectively) suggests that both groups of cells are involved in this competition process.

Neural activity across premotor cortex follows similar trends

Although fewer cells in PMv were task-related than in PMd (17/50, 34%), those that were exhibited similar effects. Of the 17 task-related PMv cells, 10 had relative value effects (Figure 7), but none showed any effect of absolute value. Furthermore, 4 PMv cells showed statistically significant effects of angular distance (t-test, $p<0.05$ between 60° and 120°). However, the modulation by target distance was overall more modest in the PMv population (Figure 7G) than what we observed in PMd (Figure 4B, C).

Figure 8 shows the cortical locations of cells that exhibited modulation by relative value, angular distance, or both, in either the DELAY or MT cell groups. We observed a mixture of effects across the rostral bank of PMd although a larger proportion of cells having both effects seemed to cluster more medially, particularly around the pre-central dimple. We did not observe a particular segregation of effects along the anterior-posterior axis of the sampled premotor areas.

Relative value modulation for novel instructional cues can be acquired through learning

In order to further examine the origin of both value and spatial signals in PMd, we recorded 113 neurons in a 2T NOVEL condition, in which the mapping between target

stimulus features and expected values had to be acquired through trial-and error learning (See Figure 9 for examples of learning behavior). Of these cells, 54 were task related and 41 were tuned in DELAY (Table 5). In each session, we calculated when the monkey reached the behavioral criterion for each paired learned association using a similar algorithm to the employed by Mitz et al. (1991) as described in the Methods section. It is noteworthy to mention that learning of novel value associations took few trials and resembled the particular case of primary learning of familiar associations. In both cases the learning rate (slope for each given pair in Figure 9A-B) allows learning to take place within one recording session (800 trials on average). It is also worth mentioning that learning behavior gives us insights in the type of the assumptions the animals might be making. For example, are they learning the value of each target in isolation or are they learning which target to choose for each particular pair? In some cases (Figure 9) it appears that the animal made an assumption about the value of one of the targets, choosing correctly whenever it appeared (Figure 9B, upper left and lower left panels) while in other cases the monkey appears to be trapped in a false assumption (Figure 9B, upper right). Figures 10B-G shows single cell examples collected in this task variant.

From behavioral analysis conducted on individual sessions (Figure 10A) we observed that the monkey sometimes learned individual pair-wise associations as early as 10-15 trials (Figure 10A top). However, in other sessions the monkey failed to learn even when 700-800 trials were provided (Figure 10A bottom). Of our task-related cells, we recorded 29 cells during sessions in which the animal reached the behavioral criterion. Of these, only 9 cells (31%) showed relative value effects when the behavioral criterion was reached. However, distance effects were present even before criterion in all of these cells; as well as

in those cells (13 out of 54 task related cells, 24%) recorded in sessions when the monkey failed to learn. Figure 10B shows an example of a cell presenting relative value and distance effects in the familiar condition, but only distance effects in the novel condition, even before criterion (Figure 10C). These results suggest that distance information does not require learning. Figure 10D-G shows another example of a cell presenting relative value effects in the familiar condition (Figure 10D) which also shows relative value effects in the novel condition after the criterion is reached (Figure 10E). However, while this modulation is present early after criterion (Figure 10F), it eventually disappears with further learning as shown in Figure 10G. (Note that the cell had a consistent waveform throughout the experiment).

Figure 10H-K shows the analysis for all learning cells in which we could obtain data after criterion. In summary, we observed that the effects of relative value are present, but they are relatively modest, as compared to data in the familiar condition. On the other hand, angular distance effects are relatively clear throughout. The latency of the distance effect and relative value acquired though learning is also similar to what we found in the familiar condition and in both DELAY and MT cells (Figure 4). Namely, the distance effect and relative value latency distributions are different (Kolmogorov-Smirnov test, $p<0.05$) with the former appearing around 75ms after target onset and preceding the latter by 100ms on average.

DISCUSSION

The results reported here were aimed at testing several critical predictions of a biased competition model of action selection. In agreement with that model, we found that neural activity in premotor cortex is modulated by the relative subjective desirability of potential actions, and never their absolute value. This implicates premotor regions in the process of determining the decision rather than a process of evaluating options using classical economic variables. In addition, we found that the strength of the competition was greater when targets were further apart, further suggesting that decisions emerge within a sensorimotor map that respects the geometry of actions. We found that these two effects appeared in cell activity with very different latencies, and that while modulation by relative value only appeared after the monkeys learned the meaning of stimulus cues, spatial interaction effects were always present. Below, we discuss the implications of these findings for general theoretical views on the functional architecture of voluntary behavior.

Theoretical background

Classical models of behavior describe it as a serial process of constructing perceptual representations, building knowledge and making decisions, and implementing the choice by executing an action. In contrast, the affordance competition hypothesis (Cisek, 2007b; Cisek and Kalaska, 2010) suggests that during natural behavior the brain specifies in parallel the potential actions that are currently afforded by the environment and selects between them through a biased competition mechanism. In the context of visually-driven

behavior, the specification of potential actions involves the dorsal visual stream and a distributed system of action-specific fronto-parietal cortical circuits (Andersen et al., 1997; Cisek, 2007b, 2012; Cisek and Kalaska, 2010; Colby and Goldberg, 1999; Gold and Shadlen, 2007; Milner and Goodale, 1995; Rizzolatti and Luppino, 2001; Wise et al., 1997). Within each region, simultaneously encoded potential actions compete against each other while different regions coordinate their competition via reciprocal cortico-cortical connections. The resulting competition is distributed, and reflects biases that can arrive at any point in the system from a variety of sources. These may include regions involved in reward prediction, such as the basal ganglia (Schultz et al., 2000), outcome valuation, such as the orbitofrontal cortex (OFC) (Padoa-Schioppa and Assad, 2006), action value, such as the anterior cingulate cortex (ACC) (Kennerley et al., 2011), and abstract rules, such as the lateral prefrontal cortex (lPFC) (Miller, 2000; Tanji and Hoshi, 2001; Genovesio et al., 2005), all of which can receive inputs from regions involved in sensory processing, such as the ventral visual stream (Kravitz et al., 2011). Importantly, the circuits within which the competition takes place are not merely decision centers, but continue to be involved in the online control of ongoing actions. This implies that the system can represent new opportunities that may present themselves even during ongoing activity, and in some cases a new potential action can suppress a current act and result in a behavioral switch.

In the context of this general hypothesis, the biased competition process involved in selecting between actions is related to the biased competition process proposed for attentional selection among stimuli (Boynton, 2005; Desimone and Duncan, 1995; Reynolds and Heeger, 2009). Indeed, an influential view of attention is that it serves as more than merely a solution to a computational bottleneck (Broadbent, 1958) but amounts

to an early mechanism for orienting actions toward objects of interest (Allport, 1987; Neumann, 1990). In that sense, the concept of the parameter space within which actions compete is similar to the concepts of a "salience map" (Bisley and Goldberg, 2010), and an "attentional landscape" (Baldauf and Deubel, 2010).

The affordance competition hypothesis also motivates a distinction between the systems involved in making the decision (a distributed biased competition mechanism) and those involved in valuation of options to provide the biases that yield adaptive selection behavior. The relative role of these systems can vary with context (Cisek, 2012). For purely abstract economic decisions, such as deciding on a brand of peanut butter, the process of valuation is of paramount importance and dominates behavior. The bulk of the task is to represent the outcome values, and translating that into action may be secondary and downstream to where the decision is resolved (Padoa-Schioppa, 2011). However, in the context of situated real-time activity such as escape behavior, the candidate choices themselves are defined as actions, and selection between them must take place within a map that combines abstract values with the sensorimotor contingencies of the actions themselves. Selection between two similar actions does not demand the same competitive dynamics as selection between two very different actions, such as two oppositely oriented escape routes (Cisek, 2012). Furthermore, although animals can covertly alternate between options while evaluating them (especially when different biases are in conflict), once they begin to act the consequences begin to play out. Thus, commitment to a decision about action should be closely integrated with motor initiation.

Premotor activity is modulated by relative value with full normalisation

Here, we tested several key predictions of the affordance competition hypothesis, specifically focusing on the dynamics of the biased competition proposed to take place in the arm reaching system. We found strong evidence for biased competition in PMd and to a lesser extent in PMv. In particular, we confirmed earlier findings that simultaneous representations of multiple potential actions can co-exist in PMd (Cisek and Kalaska, 2005) and showed that such parallel representations are modulated by their relative subjective desirability (manipulated here by varying reward magnitude).

Importantly, the value representations we observed were always relative, and never absolute. No cell ever exhibited modulation with the expected value of a target when only one was present (1T task), or when the value of two targets was varied together (2T EQUAL trials). This is important because it is consistent with a competition mechanism that implements full normalization. Previous studies in the lateral intraparietal area (LIP) of the oculomotor control system showed divisive normalization (Louie et al., 2011), which can be modeled as

$$R = \alpha \frac{V_{in}}{\sigma + V_{in} + V_{out}} \quad (1)$$

where R is a cell's response above baseline, V_{in} is the value of targets in the response field, V_{out} is the value of targets outside the response field, and α and σ are free parameters (see Reynolds and Heeger, 2009). Equation (1) implies that neural activity increases with V_{in} and decreases with V_{out}, as in our PMd data. However, it also implies that as long as $\sigma > 0$ then activity will still increase with V_{in} if only a single target is present. This agrees with previous studies (Platt and Glimcher, 1999), which provided the first evidence for neural

modulation with absolute value. We refer to this as partial normalization. In contrast, we never saw absolute value modulation in PMd. Thus, our results are consistent with equation (1) if the parameters σ is zero, implying a full normalization process.

There are a number of possible explanations for this difference in findings. First, it is possible that the dynamics of decisions between eye movements are different than decisions between arm movements. Alternatively, it is possible that there is a difference between the degree of normalization between parietal representations and frontal ones. In particular, regions that are more closely related to the final motor output must make strong all-or-none decisions so that commands are sent unambiguously to the effectors. This may explain why frontal eye field (FEF) neurons did not exhibit reward related modulation when a single target was presented (Leon and Shadlen, 1999), but were modulated when a distractor was presented simultaneously (Roesch and Olson, 2003). As noted in the introduction, in the regions involved in making decisions (as opposed to regions involved in valuation) one expects a competition that yields fully normalized relative value representations (Cisek, 2006). Such normalization is a natural property of recurrent inhibitory networks (Cohen and Grossberg, 1983; Grossberg, 1973), which can be used to simulate all of our main results (Pastor-Bernier and Cisek, 2011).

Evidence that decisions between actions are made within sensorimotor circuits

A second question investigated here concerns whether decisions between actions are made in an abstract space of outcomes (Padoa-Schioppa, 2011) or in a space related to actions (Cisek, 2007b). As noted above, one way to test this is to determine whether

sensorimotor contingencies influence the decision process. It is not enough, however, to vary action costs, because these could be construed as part of the economic cost/benefit equation. Instead, here we varied the angular separation between candidate movements. Importantly, this manipulation does not change any aspect of the candidate movements themselves, not their expected value, their action cost, or their chance of success. From the perspective of purely economic choice, this parameter has nothing to do with the decision. Two drops of juice is always better than one, and the difference between them is unchanged whether reaching movements that yield those outcomes are 60° or 180° apart.

However, if decisions are made within a sensorimotor map that respects the geometry within which potential actions are themselves defined, then a choice between two nearby targets is very different than a choice between two diametrically opposed ones. In particular, the competition between movements should be stronger as the difference between them increases. In strong agreement with this prediction, we found that the gain of the suppressive effect that the value of a competing target had on the neural representation of a cell's preferred target was stronger when they were further apart (Figure 6), especially in PMd but also in PMv. A model (Padoa-Schioppa, 2011) does not account for this finding, but it logically follows from any model in which decisions are made within a sensorimotor map (Cisek, 2006, 2007a; Erlhagen and Schoner, 2002; Tipper et al., 2000).

If the competition that drives action decisions is indeed resolved within the sensorimotor system (for arm movements, in a frontoparietal circuit including PMd and MIP/PRR), then its influence should be seen even during movement execution. In agreement with this prediction, we found strong and consistent effects on reaching trajectories produced in trials in which the higher-valued of the two targets disappeared at

the time of the GO signal (2T FORCED LOW), forcing the monkey to move to a target that was presumably less desirable. Our trajectory data (Figure 2) can be easily explained in the context of a competition between movements represented in a sensorimotor map. Because the monkey did not know which trial would be forced and which would be free, neural activity prior to the GO signal always favored the higher-valued target (Figures 3 and 4). After that higher-valued target vanished at the time of the GO signal, if the monkey withheld his movement long enough, the activity of cells tuned to that target decreased while the activity of cells tuned to the other increased, and the movement was initiated directly to the remaining target. However, in short RT trials, the strong activity associated with the high-value target is still present at movement initiation, producing a trajectory that is initially oriented toward the location of that target. Importantly, if the two targets were close enough for the two groups of cells to overlap, then the movement was initiated in-between the target locations. This explanation is also consistent with numerous behavioral studies in humans, both in reaching movements made among distractors (Song and Nakayama, 2008; Tipper et al., 2000) as well as in tasks in which fast response choices were forced to be made close to movement onset (Chapman et al., 2010a, 2010b; Favilla, 1997; Ghez et al., 1997). Interestingly, effects of switches between movements have also been observed when reaching movements are used to report abstract cognitive decisions (McKinstry et al., 2008), allowing trajectory information to be used to infer the time-course of the deliberation process.

An additional prediction of our hypothesis is that the very same cells that are involved in the competition process during the DELAY period continue to be involved in the online guidance of movements. Although many DELAY-tuned PMd cells (65/177,

36%) become untuned as the movement begins (e.g. Figure 3B), many others (112/177, 63%) continue to discharge in a tuned manner and their activity continues to reflect relative value (e.g. Figure 3C). Furthermore, when we examined the activity of these cells during FORCED LOW trials, in which the more desirable target vanished at the time of the GO signal and the monkey had to switch plans, we found that the neural activity of these cells reflected the plan switch approximately 155ms after the GO signal (Pastor-Bernier et al., 2012), well before the time that the movement trajectory was corrected. Thus, these cells could still be causally involved in the plan switch.

Convergence of specification and selection systems in premotor cortecs

The distinction between the biased competition process and the selection influences that bias the choice lead us to ask where these processes may take place within the brain. Previous studies have strongly implicated the dorsal visual stream and the posterior parietal cortex as involved in the visual guidance of movements (Andersen et al., 1997; Cisek, 2007a; Cisek and Kalaska, 2010; Colby and Goldberg, 1999; Gold and Shadlen, 2007; Milner and Goodale, 1995; Wise et al., 1997), and thus suggest that these regions, together with closely interconnected premotor areas, implement the biased competition process. We thus predict that most of the results we have shown here will be recapitulated again within the parietal cortex, and in particular with the medial intraparietal area (MIP) and parietal reach region (PRR) that are closely interconnected with the PMd, as well as the anterior intraparietal area (AIP) which is connected with PMv (Johnson et al., 1996; Rizzolatti and

Luppino, 2001). Klaes et al. (2011) have already reported compatible results in PRR, and Baumann et al. (2009) confirmed parallel grasp representations in AIP.

The proposal that the biased competition process occurs within fronto-parietal circuits is further supported by our finding that the effect of distance between targets appears in PMd at approximately the same time as cells become tuned (Figure 5B, C). This can be explained by the hypothesis that as visual information proceeds along the dorsal stream, converting stimulus information into potential actions, a competition occurs throughout, and always takes place in topological maps of space (be it stimulus or action space). Indeed, it is plausible that the same intracortical inhibitory connections are responsible for both shaping cell tuning functions as well as mediating the competition between options. In particular, while mutually inhibitory connections may be quite short-range within extrastriate visual regions, allowing a large number of sharply defined peaks of activity, similar inhibitory connections may be more long-range as one proceeds to progressively more anterior representations of potential actions, which permit the presence of only a few peaks that are broadly tuned.

In contrast to the rapid effects of angular separation, the effects of relative value modulation were comparably slow. In PMd, they appeared approximately 100ms after tuning (50-70ms). This closely agrees with a wide variety of studies showing that while simple responses to the onset of stimuli are fast – as fast as 50ms in PMd (Cisek and Kalaska, 2005) – it takes approximately 150ms for the brain to discriminate non-target stimuli from targets (Sato and Schall, 2003; Song and McPeek, 2010) or to decide between potential actions (Cisek and Kalaska, 2005; Ledberg et al., 2007). This slower processing

implies a separate source of information, possibly involving sensory input processed along the ventral visual stream and relayed through prefrontal cortex or the basal ganglia.

The proposed distinction between a dorsal stream system for specifying actions and a separate source for selection biases is further supported by our findings in the NOVEL condition. In particular, when monkeys were first presented with targets whose mapping to expected value was unknown, cell activity was nevertheless still modulated by angular separation, and with the same fast latency as was observed with the familiar targets. In contrast, modulation by value obviously could not be present until the monkeys began to learn the mapping of targets to value. Once that mapping was known, two observations could be made. First, the effects of value were again always relative, and in no case did absolute value coding appear, even early in the learning process. This is again consistent with the distinction between competition and valuation – the newly learned values (possibly coming from the basal ganglia or from OFC via lPFC) immediately entered into a fully normalizing biased competition process in premotor cortex. Second, the latency with which a given cell reflected the relative value of targets was not significantly different in the familiar condition than in the novel condition after the behavioral criterion was reached. This suggests that whatever the source of biasing (lPFC or BG), there is no clear evidence of a shift from a system supporting newly learned mappings to a system for evaluating highly trained habits.

Is modulation of neural activity simply a result of motivational changes?

Previous studies of value-related modulation in sensorimotor regions have suggested that such modulation may not be related to a process of decision-making, but rather may simply reflect changes in the animal's motivational state (Roesch and Olson, 2004). In particular, those authors found that activity increased with both the reward for a success and with the penalty for an error, suggesting that both manipulations simply increased the animal's state of motivation for making the correct decision. Given those findings, it is important to consider whether the results shown here may be simply artifacts of changes in motivation.

We believe that in the case of our data, this alternative explanation can be rejected. First, while our monkeys were more motivated to reach to higher-valued targets in the 1T task (and made those movements more quickly), we never observed any modulation with reward size in any PMd or PMv cell during the 1T task. Second, the neural activity modulation we observed in the 2T task was not consistent with any plausible definition of how motivation would vary in those conditions. Consider first the possibility that motivation is related to the sum of the values of targets presented in a trial. This would predict that when the targets are both high-valued, there would be more activity than when they are both low-valued, but this was never observed (Figure 4 and Tables 3 and 4). It would also predict that activity in trials where the PT is high-valued and OT is low-valued would be the same as in trials where the converse is true (because the sum of expected values is 4 in both cases), but we found activity much stronger in the latter than in the former case. Alternatively, consider the possibility that motivation is related to the value of

the highest-value target. This would predict that activity is similar in trials where the targets are high and low, high and medium, and high and high. However, this was not observed. In 81/96 cells in PMd, and 10/17 cells in PMv, activity was inversely related to the value of the OT when the cell's preferred target value was held constant. Finally, it is unclear how changes in motivation could explain why there should be any effect of the angular separation between targets. Thus, we believe that the modulations we report here cannot be explained as effects of changes in motivation, and are more parsimoniously accounted for by a simple biased competition process.

Concluding remarks

The results described above were obtained in a highly constrained experimental study in which monkeys made thousands of repeated planar center-out reaching movements to one of two targets, for which they received variable amounts of juice rewards. While this is far from the natural environment for which primates have evolved, we believe the results nevertheless carry important implications for theories of the functional architecture of natural behavior. In particular, our findings support the view that decisions between actions are made within the same sensorimotor circuits that guide the execution of movements, and involve a biased competition between representations of potential actions. This proposal seems at odds with classical economic models of choice (Simon, 1947; Von Neumann and Morgenstern, 1944), which have dominated cognitive psychology and now strongly influence cognitive neuroscience (Padoa-Schioppa, 2011) . However from the point of view of everyday interactive behavior, it may be more plausible to consider that animals

have evolved to deal with a world full of demands and opportunities for action rather than to deal among abstract economic representations. These types of decisions require a functional architecture that is ready to act at any moment, even during ongoing behavior, and respects the sensorimotor contingencies implied by the geometry and physics of the environment. The brain can make abstract choices that are not defined by concrete actions, and neurophysiological studies of that condition can partially separate the processes of decision or perceptual judgments from mechanisms of action preparation (Bennur and Gold, 2011; Gold and Shadlen, 2003). Separate neural systems may be recruited for purely perceptual decisions or pure action selection in different contexts (Camille et al., 2011; Cisek, 2012). However, to understand the functional architecture underlying the kinds of behavior that dominated brain evolution and established its highly-conserved organization, it is useful to consider the brain's primary role in mediating real-time interaction with the environment.

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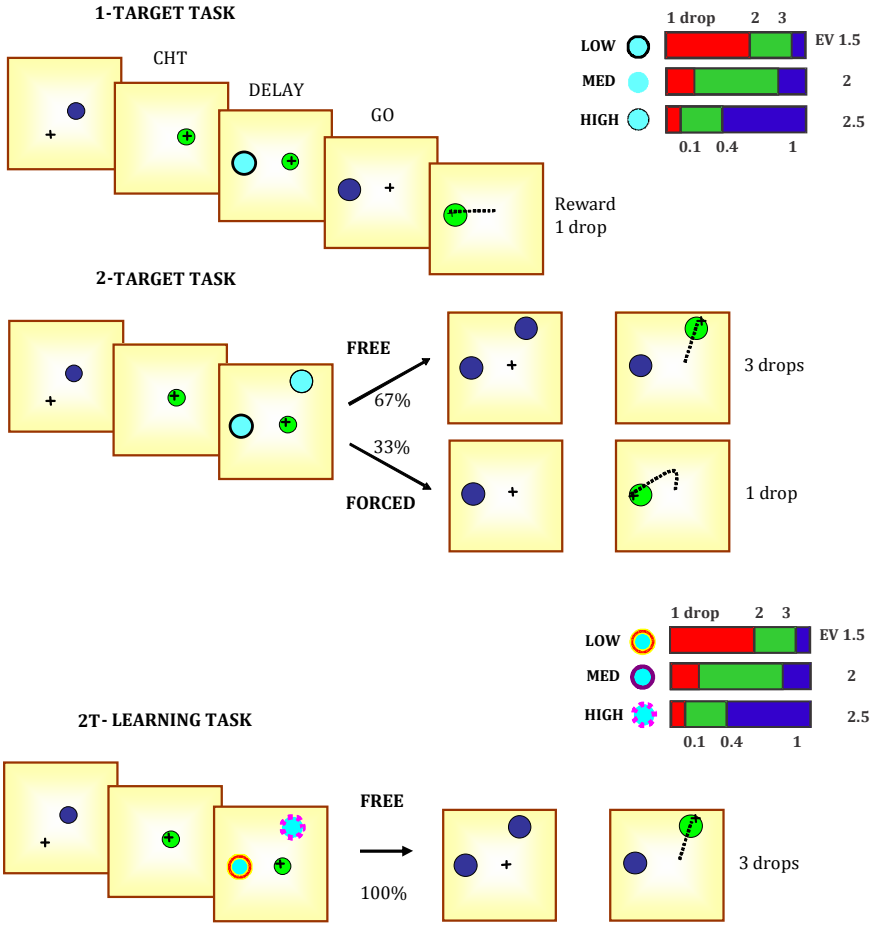
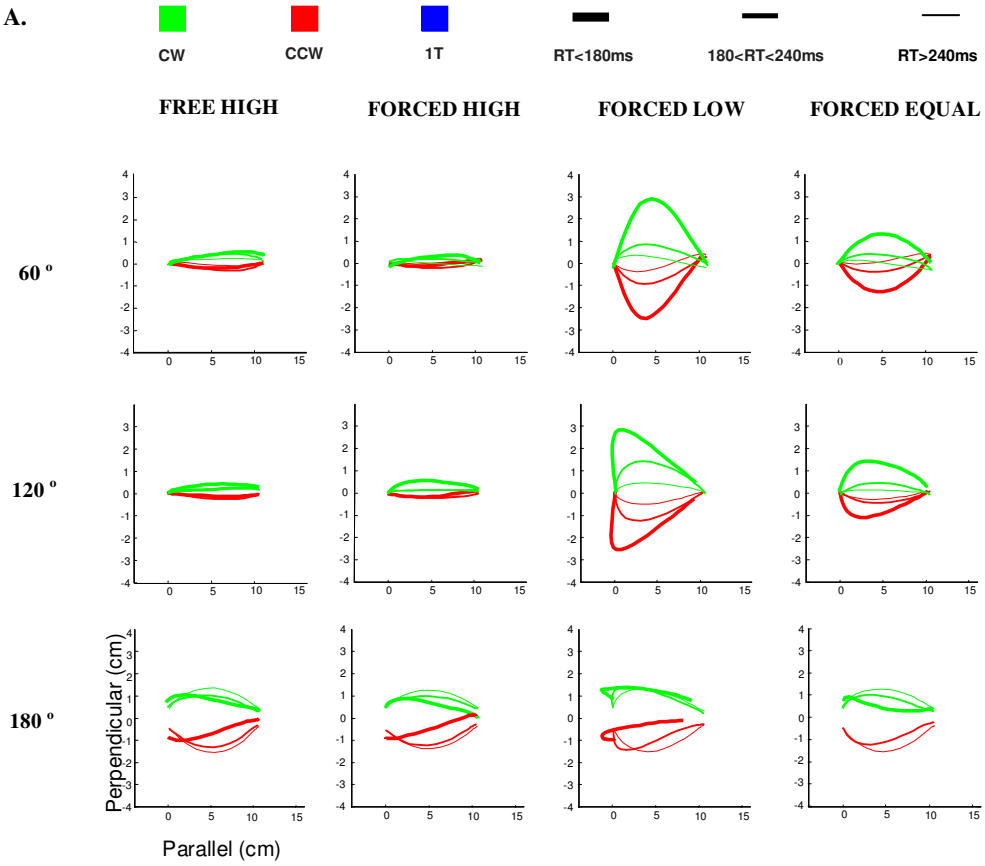


Figure 1. A. Behavioral tasks. The tasks involve moving a cursor from a central circle to one of six possible locations. At the beginning of each trial the monkey placed the cursor in the center and two targets appeared. Each target was associated with different rewards indicated by different border styles (legend shows the probability of receiving 1 (red), 2 (green) or 3 (blue) drops of juice for each border style). The monkey had to keep the cursor in the center until the targets changed color (GO signal). Then, it moved to one of the targets and held the cursor there to get a reward. In one variant of the task, the monkey was presented with only one target (1T). In a second variant two targets were presented (2T) and the monkey was either free to move to either of them after the GO signal (FREE trials), or one disappeared after GO leaving the monkey with only the remaining option (FORCED trials). In a third variant of the task (2T-Learning), two targets with randomly-generated border styles were presented to the monkey. In this variant all the trials were FREE.


A.
CW
CCW
1T
RT<180ms
180<RT<240ms
RT>240ms
FREE HIGH
FORCED HIGH
FORCED LOW
FORCED EQUAL
60 º
120 º
180 º
Perpendicular (cm)
Parallel (cm)

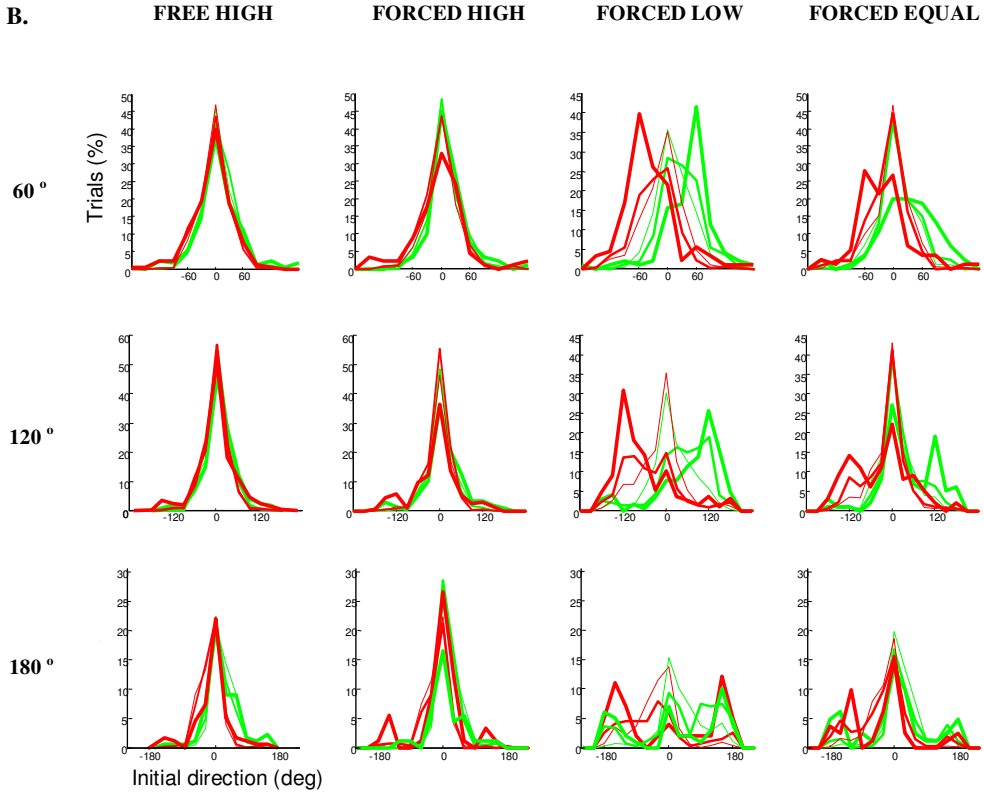

B.
FREE HIGH
FORCED HIGH
FORCED LOW
FORCED EQUAL
60 º
120 º
180 º
Trials (%)
Initial direction (deg)

Figure 2. Kinematic analysis. **A**. Average trajectories for 2T trials with the selected target oriented to the right and unselected targets located 60° or 120° clockwise (CW, red) or counterclockwise (CCW, green). In the 180° case red and green represent trajectories in the upper or lower half of the plane. The four panels from left to right represent FREE, FORCED HIGH, FORCED LOW and FORCED EQUAL trials. Thin lines show the average of long RT (>240ms) trials, medium lines show intermediate RT (between 180ms and 240ms) trials, and thick lines show the average of short RT (<180ms) trials. **B.** Distribution of initial launching directions with the selected target oriented at 0°. The color and line thickness code is the same as in A. Trial numbers range between 2300 to 6000 in all FORCED panels and 5000 to 14000 in the FREE panel.

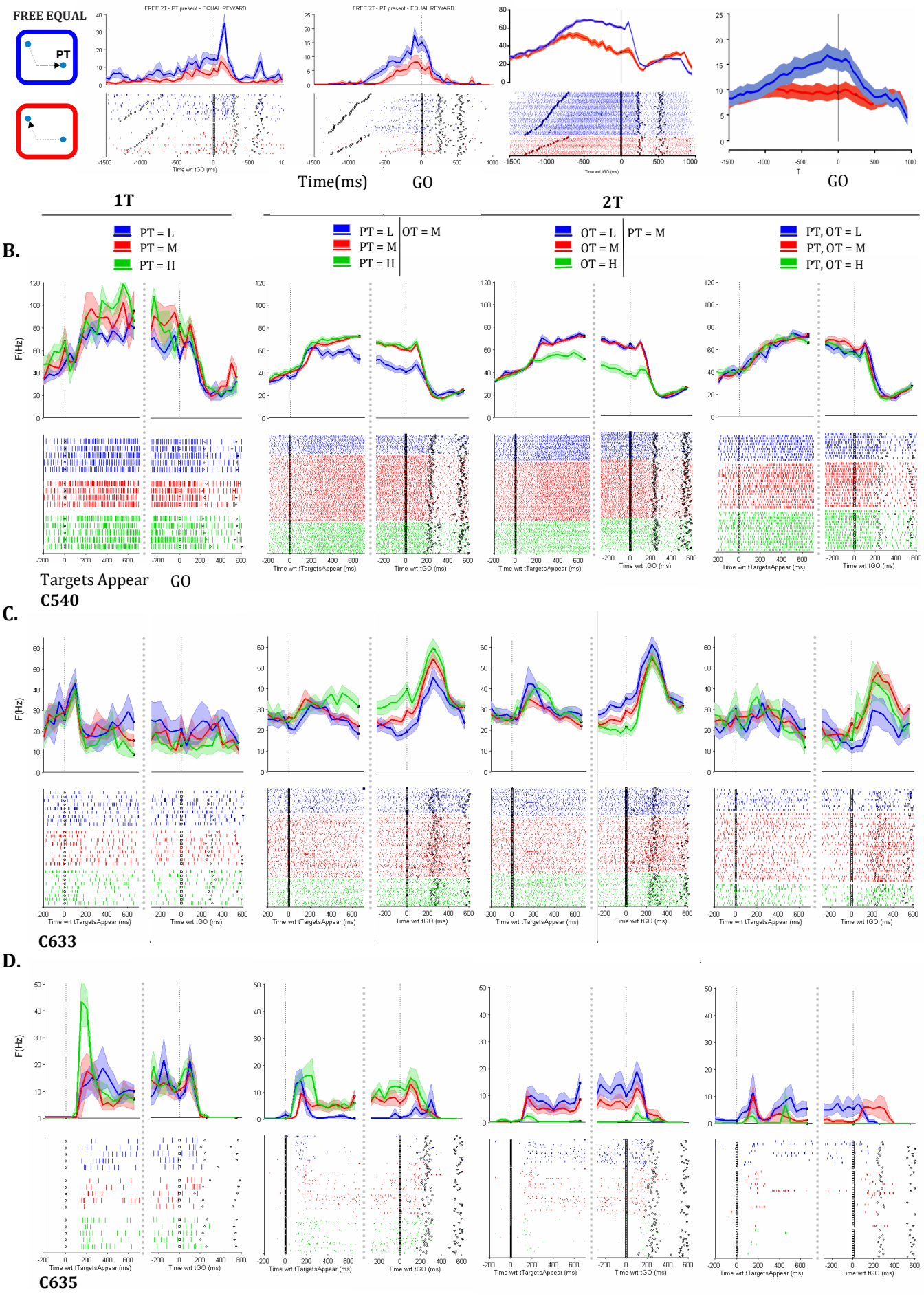

A.
FREE EQUAL
PT
FREE 2T - PT present - EQUAL REWARD
Time wrt tGO (ms)
Time(ms)
GO
1T
2T
B.
PT = L
PT = M
PT = H
OT = L
OT = M
OT = H
PT, OT = L
PT, OT = M
PT, OT = H
F(Hz)
Time wrt tTargetsAppear (ms)
Targets Appear
GO
C540
C.
C633
D.
C635

Figure 3. A. Neural activity (aligned on the GO signal) of three individual PMd cells during 2T FREE EQUAL trials in which two equal value targets were presented to the animal and one was in the PT of each cell. In blue are trials in which the monkey selected the PT and in red the trials when the monkey selected the OT. The rightmost panel in A illustrates the mean activity of the PMd DELAY population (N=177) comparing choices to the PT (blue) or to the OT (red) in the FREE condition. **B-D.** Examples of activity of individual PMd cells assessed for the presence of absolute and relative value effects. Each row represents a cell and each column a different condition. The first column shows activity in 1T trials in which the PT was presented alone and was either low (blue), medium (red) or high valued (green). In the second column we show 2T trials in which the PT value varied from low (blue) to high (green) and OT was always medium valued. The third column shows 2T trials in which the PT was medium valued and the OT value varying from low (blue) to high (green). The fourth column examines 2T EQUAL trials where both the PT and OT are low (green), medium (red), or high valued (green). Data in each split panel is aligned on target onset and on the GO signal. Marks in the rasters indicate the time of target onset, GO signal, movement onset, and movement offset.

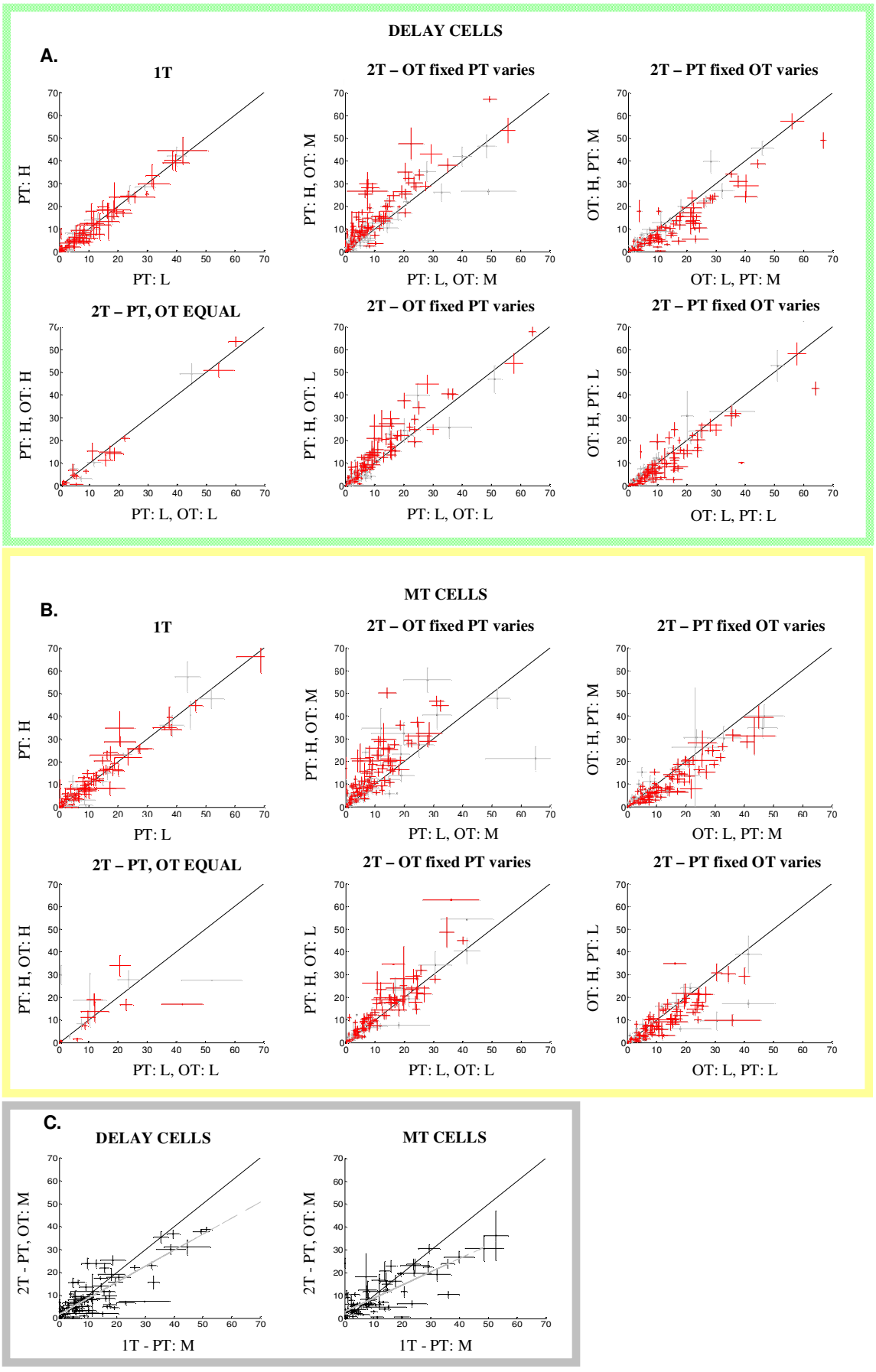

DELAY CELLS
A.
1T
PT: H
PT: L
2T – OT fixed PT varies
PT: H, OT: M
PT: L, OT: M
2T – PT fixed OT varies
OT: H, PT: M
OT: L, PT: M
2T – PT, OT EQUAL
PT: H, OT: H
PT: L, OT: L
2T – OT fixed PT varies
PT: H, OT: L
PT: L, OT: L
2T – PT fixed OT varies
OT: H, PT: L
OT: L, PT: L
MT CELLS
B.
1T
PT: H
PT: L
2T – OT fixed PT varies
PT: H, OT: M
PT: L, OT: M
2T – PT fixed OT varies
OT: H, PT: M
OT: L, PT: M
2T – PT, OT EQUAL
PT: H, OT: H
PT: L, OT: L
2T – OT fixed PT varies
PT: H, OT: L
PT: L, OT: L
2T – PT fixed OT varies
OT: H, PT: L
OT: L, PT: L
C.
DELAY CELLS
2T - PT, OT: M
1T - PT: M
MT CELLS
2T - PT, OT: M
1T - PT: M

Figure 4. Population analysis assessing absolute and relative value modulation. Each panel shows the mean firing rate during DELAY of the DELAY cell group (**A**) or during MT of the MT cell group (**B**) for all conditions. In all panels red crosses indicate cells with statistically significant effects in each cell group (N=102 in DELAY and N=105 in MT) along with the rest of delay or movement tuned population (grey crosses). Each cross indicates mean firing rate and SEM. **A.** The upper left panel compares the mean firing rate of cells in the 1T task when PT was low valued (x-axis) versus high-valued (y-axis). The bottom left panel compares the mean firing rates for 2T trials in which the PT and OT are equally low valued (x-axis) versus equally high valued (y-axis). The upper central panel compares the firing rates for 2T trials in which the OT has a fixed medium-value and the PT is either low-valued (x-axis) or high-valued (y-axis). The bottom central panel does a similar comparison with OT having a fixed low-value. The upper right panel compares the mean firing rates for trials in which the PT is fixed and medium-valued and the OT is either low-valued (x) or high-valued (y). The bottom right panel repeats this analysis for trials when the PT has fixed low-value. **B** has a similar convention to A but shows the MT cell group. **C** illustrates the target number effects. The left panel compares the mean firing rate for DELAY cells in 2T trials in which both PT and OT are medium valued with the mean firing rate in 1T trials in which the PT is medium valued. The right panel repeats this analysis for the MT cell group. The right panel repeats this analysis for the MT cell group. Grey dotted lines show regression slopes: -35deg, R2: 0.79 for DELAY and -30 deg, R2:0.62 for MT.

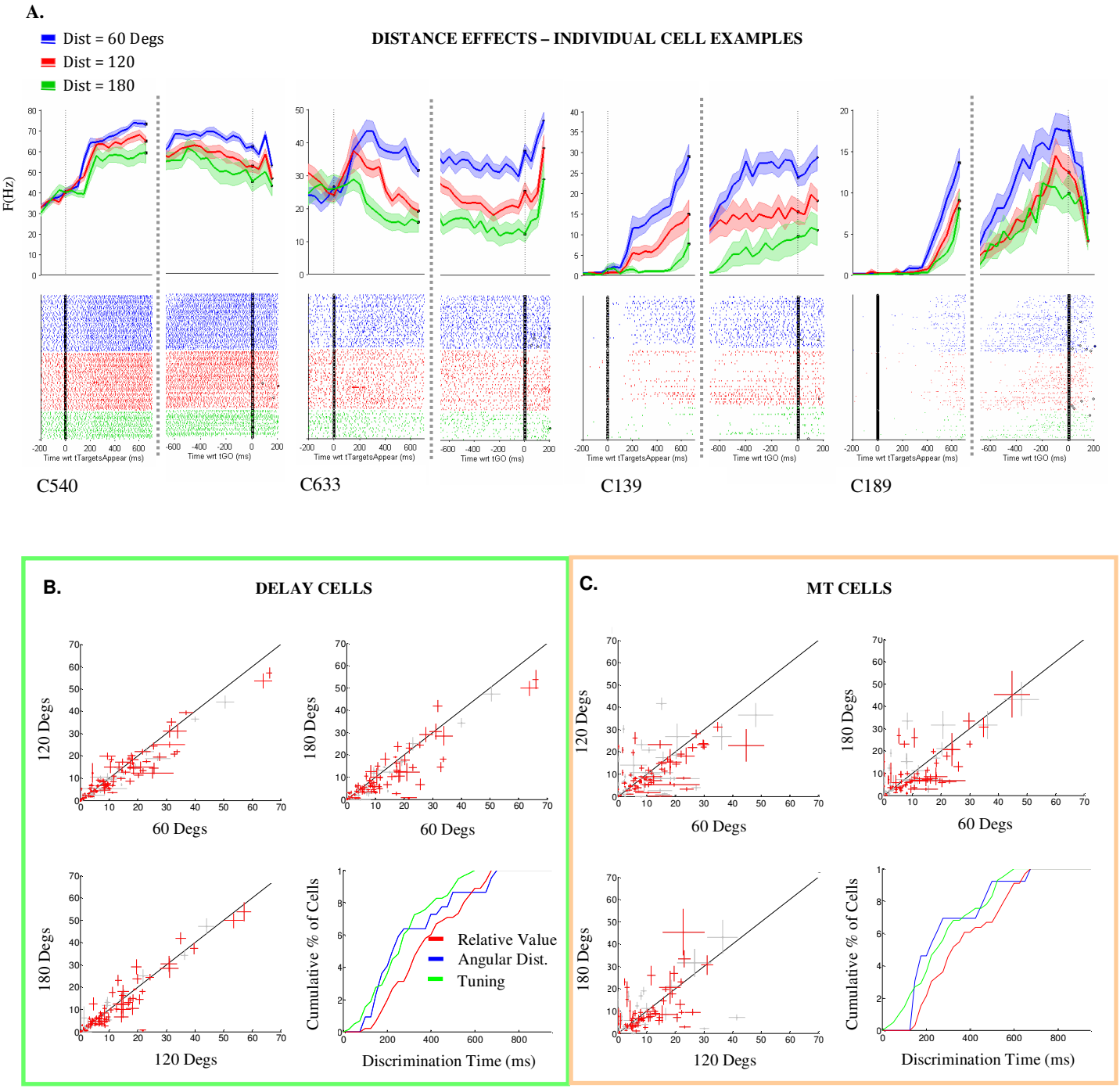

A.
DISTANCE EFFECTS – INDIVIDUAL CELL EXAMPLES
Dist = 60 Degs
Dist = 120
Dist = 180
F(Hz)
Time wrt tTargetsAppear (ms)
Time wrt tGO (ms)
C540
C633
C139
C189
B.
DELAY CELLS
120 Degs
60 Degs
180 Degs
60 Degs
180 Degs
120 Degs
Cumulative % of Cells
Relative Value
Angular Dist.
Tuning
Discrimination Time (ms)
C.
MT CELLS
120 Degs
60 Degs
180 Degs
60 Degs
180 Degs
120 Degs
Cumulative % of Cells
Discrimination Time (ms)

Figure 5. A. Examples of the activity of individual PMd cells illustrating angular distance effects for equally valued trials in which both PT and OT are medium-valued. Each column compares the activity of a cell when PT and OT are 60, 120 or 180 degrees apart. **B** Analysis of angular distance effect across the population of DELAY cells (N=177). Each panel shows the mean firing rates of the cells during DELAY and compares 2T trials in which the PT and OT are medium-valued and are 60^o (x) versus 120^o apart (y) (upper left), 60^o (x) versus 180^o apart (y) (upper right) or 180^o (x) versus 120^o apart (y) (bottom left). The bottom right panel illustrates the cumulative distribution of latencies for relative-value, angular distance and tuning effects. **C** uses the same convention than B but shows activity of MT cells during the MT epoch.

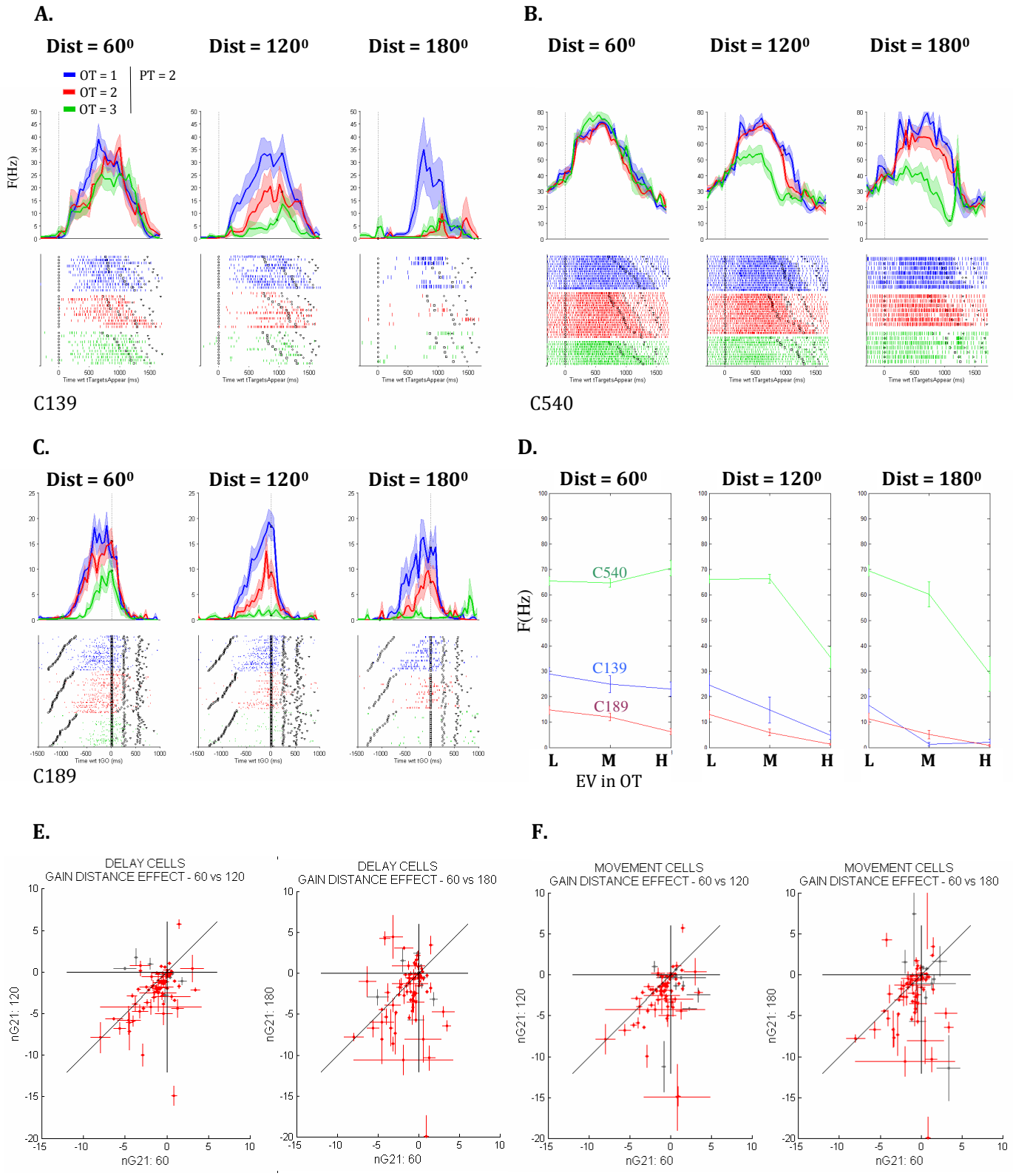

A.
Dist = 60⁰
Dist = 120⁰
Dist = 180⁰
OT = 1
OT = 2
OT = 3
PT = 2
F(Hz)
Time wrt tTargetsAppear (ms)
C139
B.
Dist = 60⁰
Dist = 120⁰
Dist = 180⁰
Time wrt tTargetsAppear (ms)
C540
C.
Dist = 60⁰
Dist = 120⁰
Dist = 180⁰
Time wrt tGO (ms)
C189
D.
Dist = 60⁰
Dist = 120⁰
Dist = 180⁰
C540
C139
C189
F(Hz)
L
M
H
EV in OT
E.
DELAY CELLS
GAIN DISTANCE EFFECT - 60 vs 120
DELAY CELLS
GAIN DISTANCE EFFECT - 60 vs 180
nG21: 120
nG21: 180
nG21: 60
F.
MOVEMENT CELLS
GAIN DISTANCE EFFECT - 60 vs 120
MOVEMENT CELLS
GAIN DISTANCE EFFECT - 60 vs 180
nG21: 120
nG21: 180
nG21: 60

Figure 6. Gain effect of angular distance on relative value. **A-C** Firing rates of three example PMd cells illustrating the relative value effects when PT is fixed (medium value) and OT varies (low, medium and high). The columns in each panel show trials with different angular distance between the targets (60°, 120°, 180°). Note that the slope is more negative for larger angular distances **D.** Comparison of the mean (and s.e.m.) of the activity of these three example cells in the 60°, 120°, and 180° angular distances. **E.** Means (and SEM) for relative-value slopes in the 60° versus 120° angular conditions (left) and 60° versus 180° angular conditions (right) for all DELAY cells. **F** shows the same for MT cells. Red crosses represent units with any statistical value or angular distance effects, while grey crosses represent the rest of the tuned population in each group.

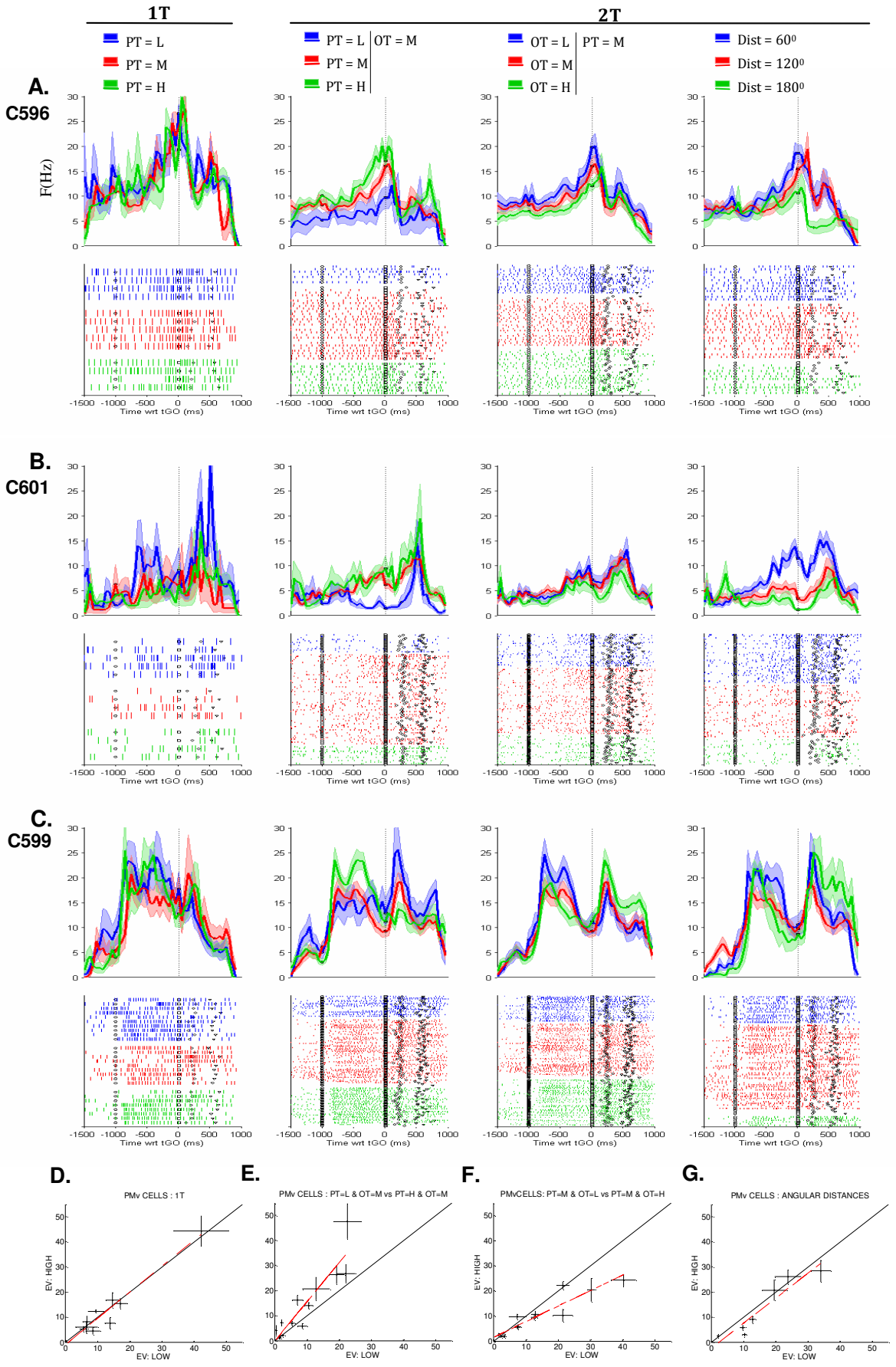

1T
2T
PT = L
PT = M
PT = H
OT = L
OT = M
OT = H
Dist = 60⁰
Dist = 120⁰
Dist = 180⁰
A.
C596
B.
C601
C.
C599
F(Hz)
Time wrt tGO (ms)
D.
PMv CELLS : 1T
E.
PMv CELLS : PT=L & OT=M vs PT=H & OT=M
F.
PMvCELLS: PT=M & OT=L vs PT=M & OT=H
G.
PMv CELLS : ANGULAR DISTANCES
EV: HIGH
EV: LOW

Figure 7. A-C Single cell examples in PMv assessed for the presence of relative value and distance effects. Each row represents a cell and each column a different condition. The first column shows 1T trials, second and third columns assess relative value effects in 2T trials, and the third column shows angular distance effects. All conventions are as described in previous figures. Trial alignment is done on GO. **D-G** Value and distance effect population analysis. **D**. Mean firing rates in PMv cells comparing 1T trials in which the PT is low-valued (x) versus high-valued (y). **E.** Mean firing rates in PMv cells comparing 2T trials in which the OT is medium-valued and the PT is low-valued (x-axis) versus high-valued (y-axis). **F.** Mean firing rates in PMv cells comparing 2T trials in which the PT is medium valued and the OT is low-valued (x) versus high-valued (y). **G.** Mean firing rates in PMv cells comparing equally valued targets that are 60° (x) or 180° apart (y).

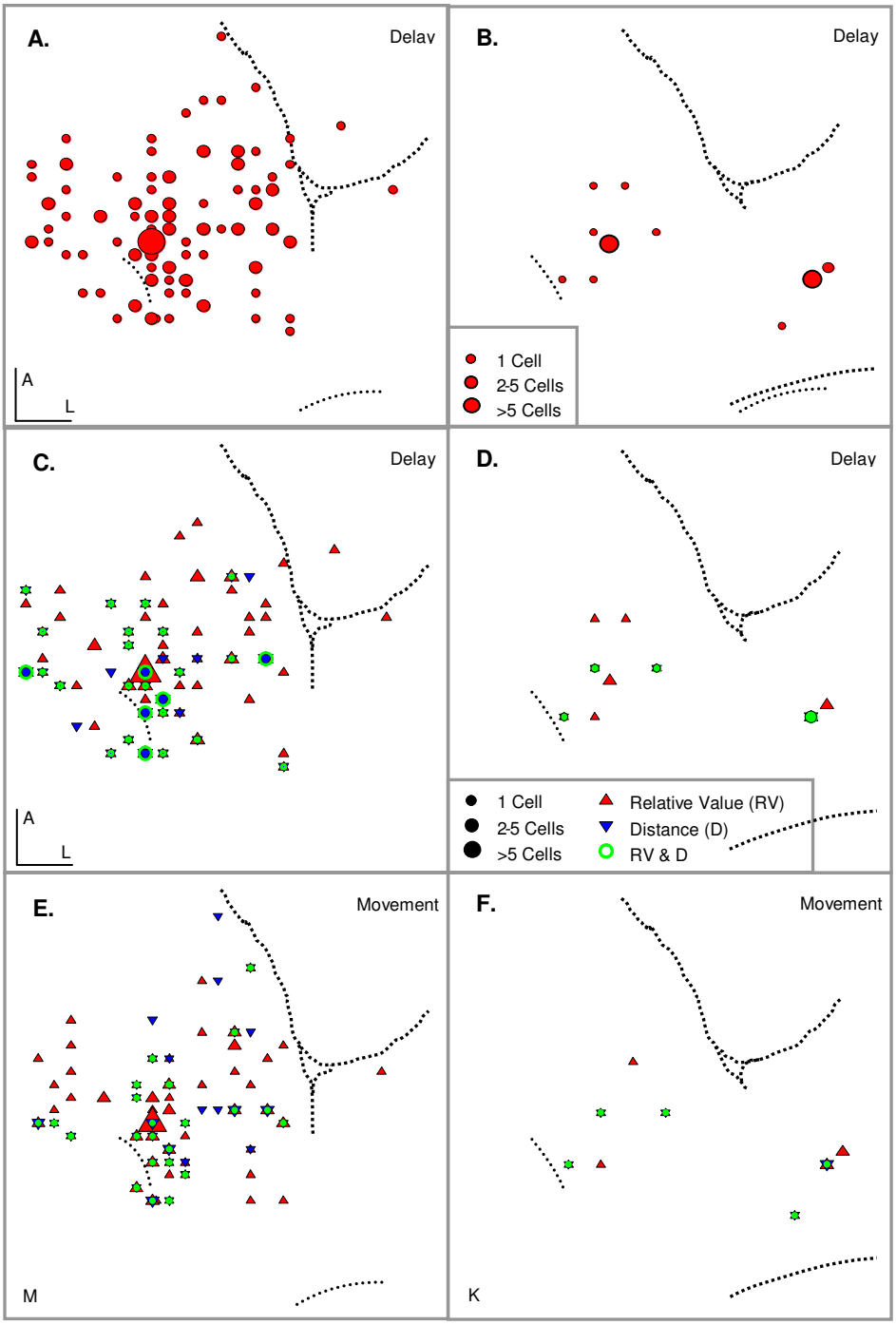
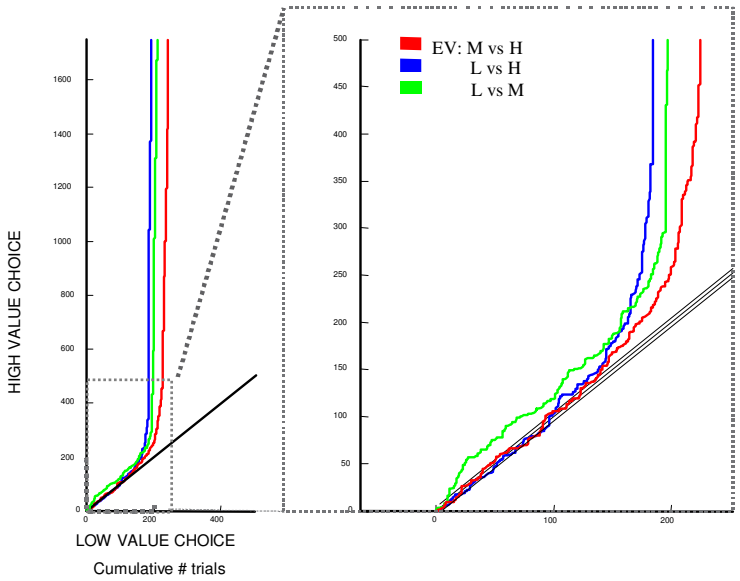


Figure 8. A. Recording locations in premotor cortex for monkey M (left) and monkey K (right). **C-F.** Location of effects during delay (C-D) and movement (E-F). The locations of cells with relative value effects are shown as upward red triangles, those with distance effects as downward blue triangles, and those with both effects as green circles. The number of cells with effects is represented as the size of the symbols in each location

A. LEARNING FAMILIAR VALUE MAPPINGS : FREE TRIALS



B. LEARNING NOVEL VALUE MAPPINGS : FREE TRIALS

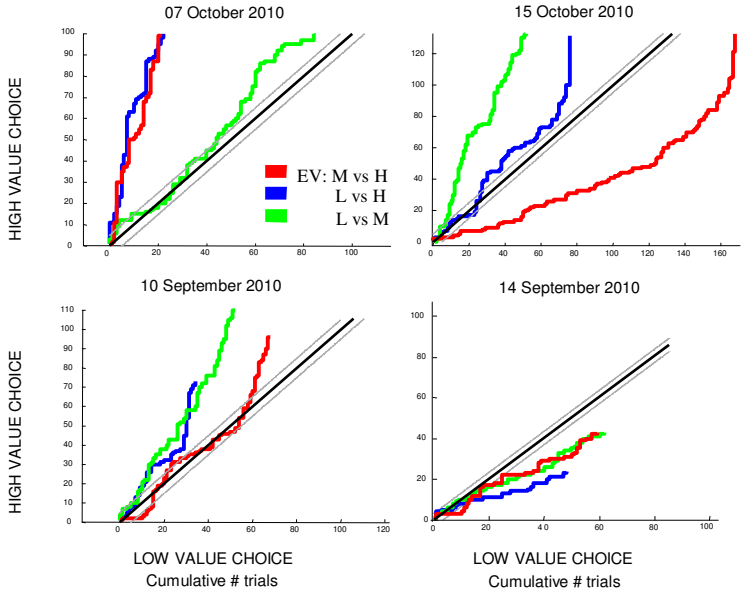


Figure 9. Behavioral characterization of learning. In each panel, we plot the cumulative number of trials in which the higher-valued target was chosen (y-axis) against the cumulative number of trials in which the lower-valued target was chosen (x-axis), for each pair of values: medium and high (red), low and high (blue), and low and medium (green). **A.** The behavioral session when monkey M was first presented with the standard border styles. The inset expands the region where the learning first took place. The diagonal line represents chance and the grey dotted lines above and beneath it represent 5 consecutive choices of the higher or lower value. **B.** Four examples of sessions when the monkey was learning NOVEL mappings. For example, in the upper left session the monkey quickly learned the high-value target but took longer to learn the others. In the lower left session the monkey quickly learned the low-value target but only later discriminated the others. In the upper right session the monkey first appeared to choose the medium-value target the most, and only later reversed this initial mistake. In the lower right panel the monkey never learned the values of the targets.

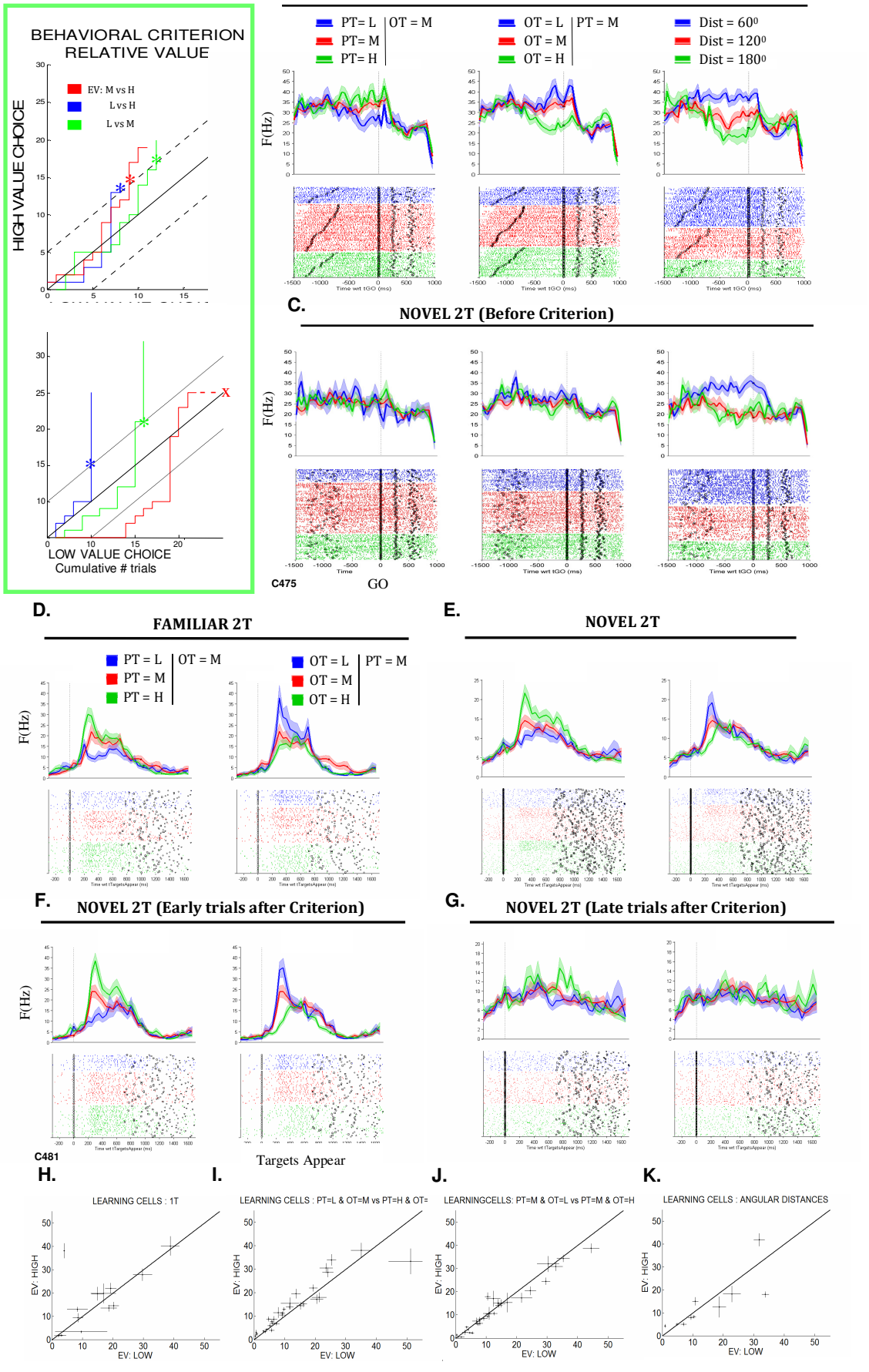

A.
BEHAVIORAL CRITERION
RELATIVE VALUE
HIGH VALUE CHOICE
EV: M vs H
L vs H
L vs M
LOW VALUE CHOICE
Cumulative # trials
B.
FAMILIAR 2T
PT= L
PT= M
PT= H
OT = M
OT = L
OT = M
OT = H
PT = M
Dist = 60⁰
Dist = 120⁰
Dist = 180⁰
F(Hz)
Time wrt tGO (ms)
C.
NOVEL 2T (Before Criterion)
F(Hz)
Time
Time wrt tGO (ms)
C475
GO
D.
FAMILIAR 2T
PT = L
PT = M
PT = H
OT = M
OT = L
OT = M
OT = H
PT = M
F(Hz)
E.
NOVEL 2T
F.
NOVEL 2T (Early trials after Criterion)
F(Hz)
C481
Targets Appear
G.
NOVEL 2T (Late trials after Criterion)
H.
LEARNING CELLS : 1T
EV: HIGH
EV: LOW
I.
LEARNING CELLS : PT=L & OT=M vs PT=H & OT=
EV: HIGH
EV: LOW
J.
LEARNINGCELLS: PT=M & OT=L vs PT=M & OT=H
EV: HIGH
EV: LOW
K.
LEARNING CELLS : ANGULAR DISTANCES
EV: HIGH
EV: LOW

Figure 10. A. Identification of the behavioral criterion for two different sessions. The top row represents a case in which the animal achieved behavioral criterion (*Complete learning*) and the bottom row a case where it did not. On each row three learning pair conditions M vs H (red) L vs H (blue) and L vs M (green) are compared, showing the cumulative number of High value (y-axis) versus Low value choices (x-axis). The diagonal line represents random choices and the diagonal dashed line represents the limit of 6 consecutive trials that are considered the threshold for each paired behavioral criterion (red, blue or green asterisk). Note that in these two panels the animal learned two pair associations within 10-15 trials except for one pair in the lower panel, which the animal failed to learn (shown as x). Panels **B-G** illustrates individual cell examples**. B** shows three panels illustrating relative-value and angular distance effects of a cell collected in the familiar condition. **C.** Shows the trials for this cell before criterion. This cell was recorded in the session corresponding to the lower panel in A. Note that angular distance effects are already present despite the fact that learning has not been completed. **D-G** shows an example of a cell that presents relative value effects in the familiar condition (D) and also in the novel condition (E). Notice that the value effects acquired through learning are stronger in the early trials after criterion (**F**) but gradually disappear later during the session (**G**). **H-K** illustrate the value and distance effect across the PMd population, in all learning cells after criterion (regardless of whether these cells had statistically significant effects or not). The conventions for these figures are the same as in Figures 4 and 5. **H**. Mean firing rates in PMd cells comparing 1T trials in which the PT is low-valued (x) versus high-valued (y). **I.** Mean firing rates in cells comparing 2T trials in which the OT is medium-valued and the PT is low-valued (x-axis) versus high-valued (y-axis). **J.** Mean firing rates in PMd cells comparing 2T trials in which the PT is medium valued and the OT is low-valued (x) versus high-valued (y). **K.** Mean firing rates in PMd cells comparing equally valued targets that are 60° apart (x) or 180° apart (y).

Table 1
Classification of recorded neurons in dorso-lateral PMd
The recorded population is subdivided according to the alignment in a particular epoch (Delay, Movement or Reward). Task related neurons are all those cells for which there is directional tuning in any epoch. In grey is outlined the group of cells that is used in further analysis in the study.

	Number of neurons
Total recorded	696
Task related	316
Delay or Movement	263
Delay tuned cells	194
Selective excitations	177
Selective inhibitions	17
Cells with any movement related activity *	181
Delay only *	65
Delay and movement *	112
Movement only *	69

*Cells with movement related activity and cell split by tuning epoch refer exclusively to selective excitations

Table 2
Classification of recorded neurons in PMv
The recorded population is subdivided according to the alignment in a particular epoch (Delay, Movement or Reward). Task related neurons are all those cells for which there is directional tuning in any epoch. In brown is outlined the group of cells that is used in further analysis in the study.

	Number of neurons
Total recorded	50
Delay or Movement	17
Delay tuned cells	6
Cells with any movement related activity *	4
Delay only *	0
Delay and movement *	6
Movement only *	4

Table 3
Classification of cell activity in PMd according to observed effects

Cells with any tuning during Delay	**177**
Delay-tuned with any effect of value or distance[1]	**102**
Delay-tuned with absolute value effect in 1T	0
Delay-tuned with absolute value effect in 2T EQ*	0
Delay-tuned with any relative value effect (RV)	96
Delay-tuned with any distance effect (D)	44
Delay-tuned with both RVand D	38
Delay-tuned with RV only	58
Delay-tuned with D only	6

Cells with any tuning during Movement[2]	**181**
Delay-tuned with any effect of value or distance	**105**
Delay-tuned with absolute value effect in 1T	0
Delay-tuned with absolute value effect in 2T EQ*	0
Delay-tuned with any relative value effect (RV)	96
Delay-tuned with any distance effect (D)	46
Delay-tuned with both RVand D	37
Delay-tuned with RV only	59
Delay-tuned with D only	9

[1] wherein effects were analyzed during DELAY
[2] wherein effects were analyzed during MT
* n=39 cells (8 MM, 31 MK) were collected in this condition; they split up as 25 in DELAY and 14 in MT.

Table 4
Classification of cell activity in PMd
Effects split by tuning epoch

Delay Only cells [1]	**65**
Delay-tuned with any effect of value or distance	**24**
Delay-tuned with absolute value effect in 1T	0
Delay-tuned with absolute value effect in 2T EQ	0
Delay-tuned with any relative value effect (RV)	21
Delay-tuned with any distance effect (D)	7
Delay-tuned with both RVand D	4
Delay-tuned with RV only	17
Delay-tuned with D only	3

Delay & Movement cells [2]	**112**
Delay-tuned with any effect of value or distance	**72**
Delay-tuned with absolute value effect in 1T	0
Delay-tuned with absolute value effect in 2T EQ	0
Delay-tuned with any relative value effect (RV)	69
Delay-tuned with any distance effect (D)	34
Delay-tuned with both RVand D	31
Delay-tuned with RV only	38
Delay-tuned with D only	3

Movement Only cells [3]	**69**
Delay-tuned with any effect of value or distance	**33**
Delay-tuned with absolute value effect in 1T	0
Delay-tuned with absolute value effect in 2T EQ	0
Delay-tuned with any relative value effect (RV)	27
Delay-tuned with any distance effect (D)	12
Delay-tuned with both RVand D	6
Delay-tuned with RV only	21
Delay-tuned with D only	6

[1, 2] wherein effects were analyzed during DELAY
[3] wherein effects were analyzed during MT

Table 5.
Classification of PMd neurons collected in the learning condition

	Number of neurons
Total recorded	113
Task related Cells: Delay or Movement	54
Delay tuned cells	41
Cells with any movement related activity *	25
Task related cells that have a behavioral criterion (BC)	29
Task related cells with effects in familiar condition and have BC	16
Task related cells with effects in familiar condition without BC	13
Task related cells with effects in the familiar condition that have BC and effects in the learning condition	9

Table 6.
Predicted firing rates for relative value effects according to a completely divisive normalization model

	Value in OT fixed (RM combinations)			Value in PT fixed (RM combinations)		
PT	1	2	3		2	
OT		2		1	2	3
F	0.33	0.50	0.60	0.67	0.50	0.40
Δ	Δ12	Δ23	Δ13	Δ12	Δ23	Δ13
	0.17	0.10	0.27*	0.17	0.10	0.27

	Value in OT fixed (RL combinations)			Value in PT fixed (RL combinations)		
PT	1	2	3		1	
OT		1		1	2	3
F	0.50	0.67	0.75	0.5	0.33	0.25
Δ	Δ12	Δ23	Δ13	Δ12	Δ23	Δ13
	0.17	0.08	0.25	0.17	0.08	0.25

The predicted firing rate in the cells PT can be described as a function of F: $V_{PT}/(V_{PT}+ V_{OT})$. PT and OT rows represent expected value in two groups (value in OT fixed and PT varies, or value in PT fixed and OT varies) and two combinations (RM or RL). RM stands for *reference medium*, and represents the case in which the value of the target that is fixed (reference) has a medium value (2). RL follows a similar convention and has a low value. The F row indicates the predicted firing rate according to a fully divisive normalization model taking account of the values in PT and OT rows. The values displayed are integers: 1 (Low), 2 (Medium), 3 (High). The delta row (Δ) shows pair-wise differences between particular F values (Eg. The delta row on the top left panel, Δ13 = $F_{PT:3OT:2}$ - $F_{PT:1OT:2}$ = 0.60 - 0.33 = 0.27*). The delta values in dark shades represent the largest differences between F values (Δ13).

- Note that Δ13 in RM combinations are greater than Δ13 in RL combinations for all groups. This predicts stronger effects in the former case. We tested the model predictions by conducting linear regressions analysis in population scatterplots comparing the same values presented in the table and shown in **Figure 4**:

1) For cells recorded in the RM combination where the value in OT is fixed and PT varies we obtain a 49° linear regression slope with R2 statistic 0.8 meanwhile the RL combination has 47° slope (R2: 0.9).
2) For cells recorded in the RM combination where the value in PT is fixed and OT varies we have a -38° linear regression slope with R2 statistic 0.8 meanwhile the RL combination has -37° slope (R2: 0.8). In all cases the error of the variance for the slopes is 0.9°. The linear regressions in DELAY and MT cell group yield comparable results.

These results suggest that cells in PMd display larger modulations in RM than RL combinations. Although the difference is very modest (2°), a complete divisive normalization model complies well with experimental data as described previously (Pastor-Bernier and Cisek, 2011; Pastor-Bernier et al., 2012).

SPACE MATTERS: TRADING ACTION METRIC AND VALUE REPRESENTATIONS IN PREMOTOR CORTEX.

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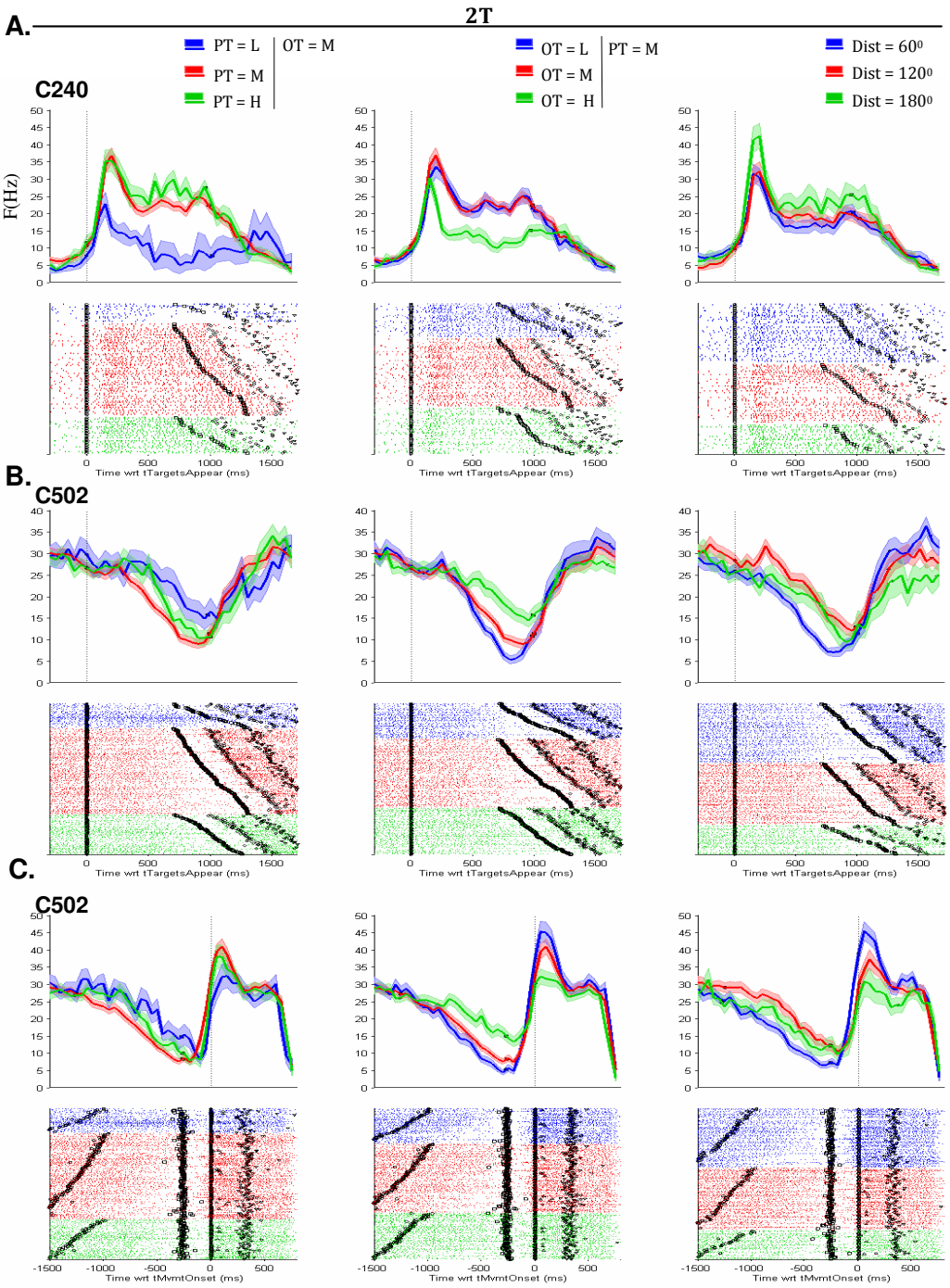
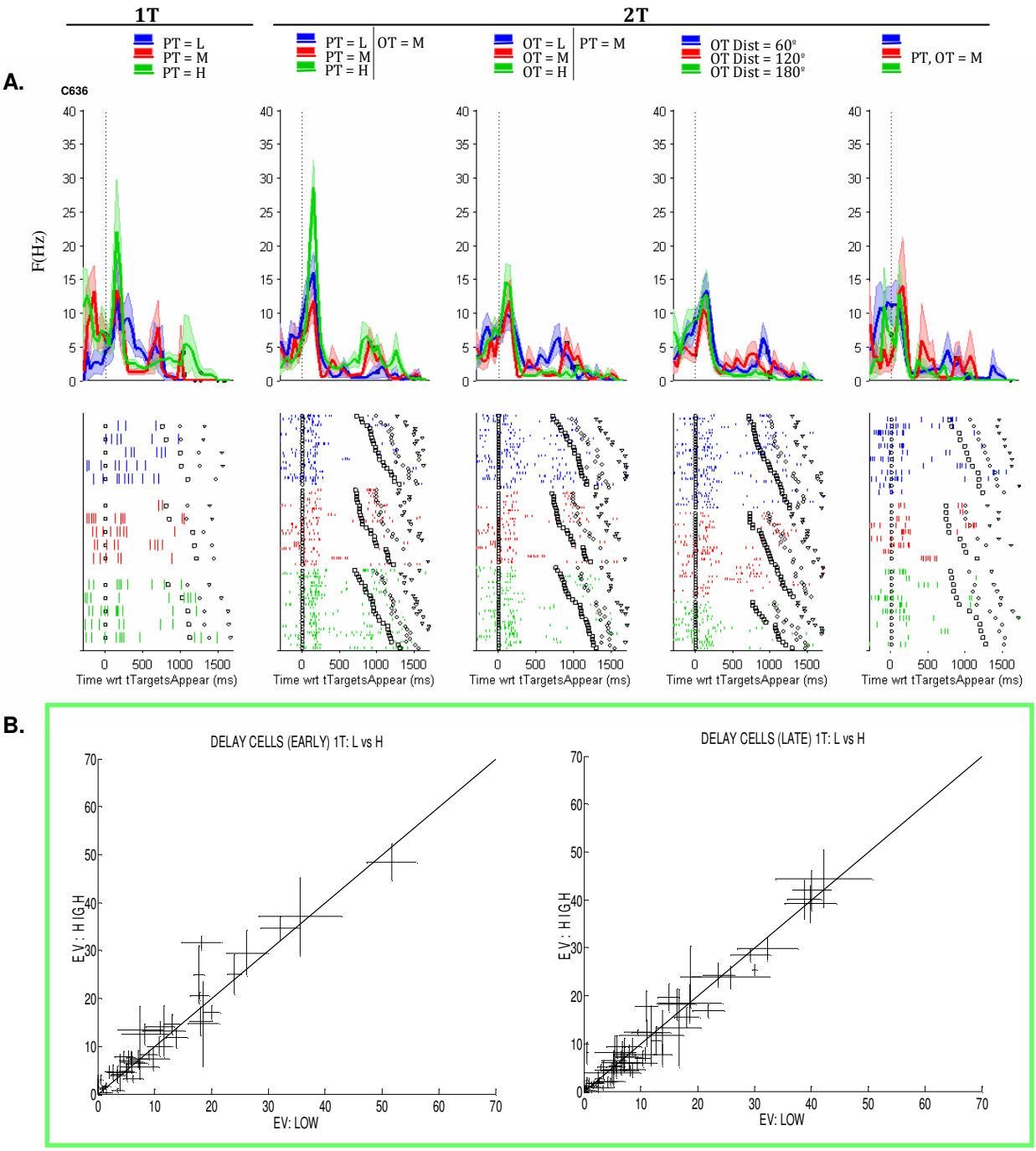
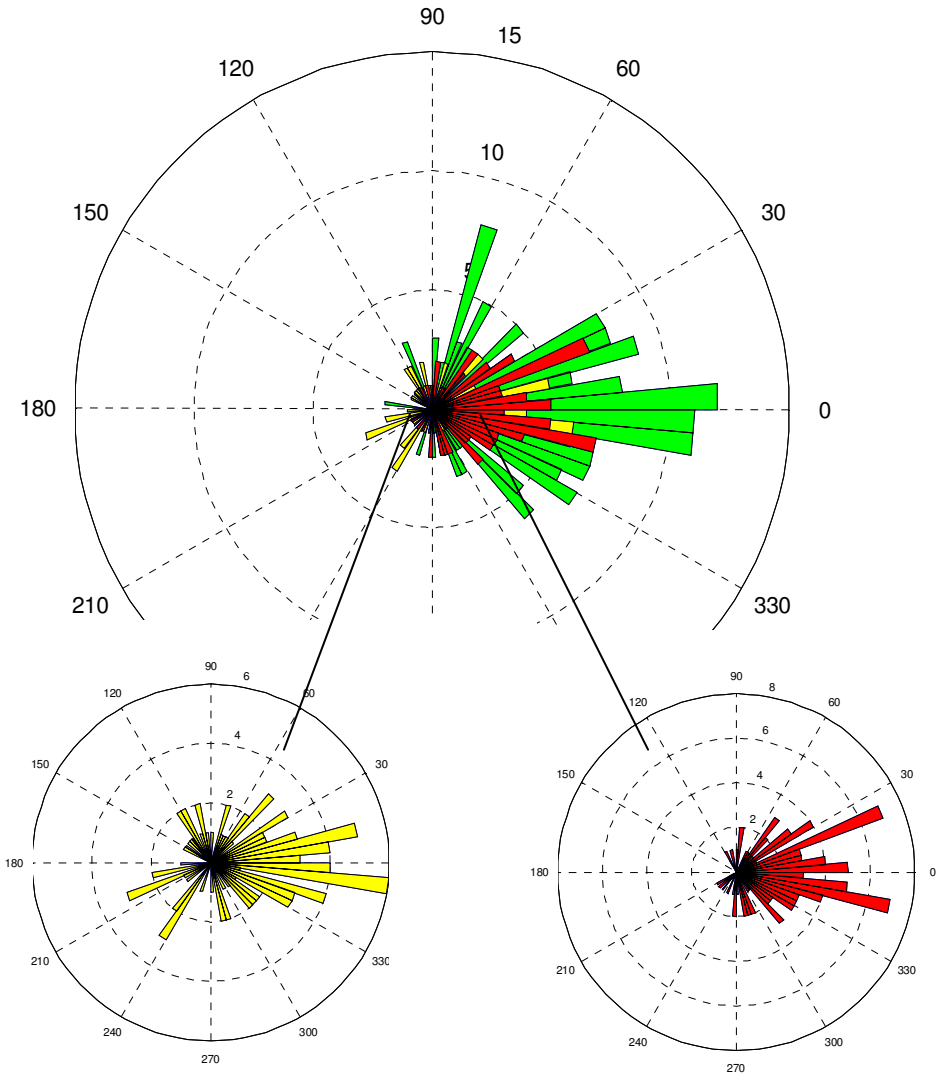
SUPPLEMENTAL MATERIALS



Supplemental Figure 1. Additional single cell examples in PMd. Cells were recorded in three conditions and assessed for the presence of relative value and distance effects. Each row represents a cell and each column a different condition. The first and second columns assess relative value effects and the third column distance effects. The convention is similar as described in previous figures. In **A** and **B** the trial alignment is done on Cue onset. In **C** the alignment is done on Movement onset.



Supplemental Figure 2. Early transient responses are generally not modulated by value. **A.** Single cell example displaying early visual responses in all 1T and 2T conditions. **B.** Population scatterplots comparing DELAY responses in 1T for cells during EARLY tuning (first 200ms, *left panel*) and LATE tuning (last 200ms, *right panel*). Note that PMd cells do not show transient value responses in the EARLY group. A single outlier (C635) can be observed but does not represent the population.

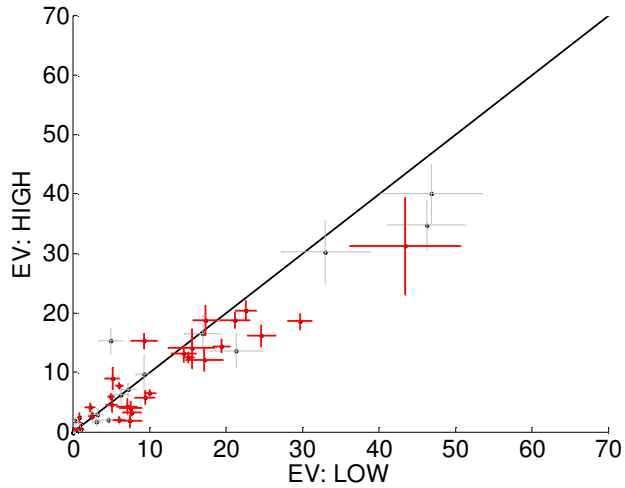


Supplemental Figure 3. Rose plots illustrating the angular difference between the cells preferred direction during DELAY and during MT: *PD(Delay)-PD(MT)*. Rose plots in green represent the totality of cells with relative value effects. Rose plots in yellow represent cells that are directly modulated by value magnitude during DELAY but are inversely modulated (inverted effect) during MT. Rose plots in red represent cells that are inversely modulated during DELAY and not during MT. We do not observe a clear clustering of cells with inverted effects with respect to inverted tuning. Cells with inversions have in general the same tuning properties in both DELAY and MT epochs. All histograms have 10°/bin.

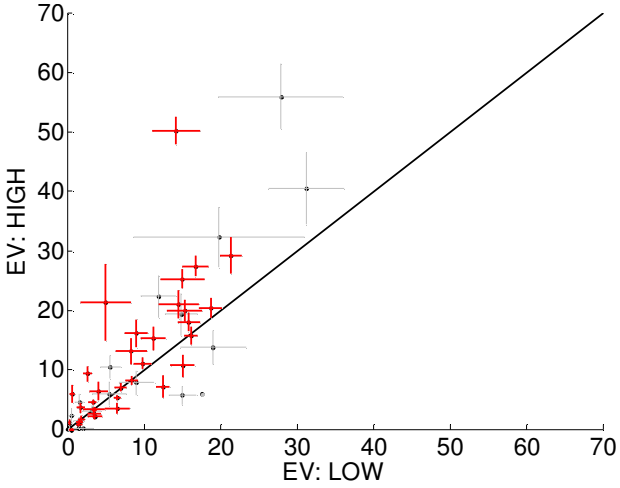
2T – PT fixed OT varies

2T – OT fixed PT varies

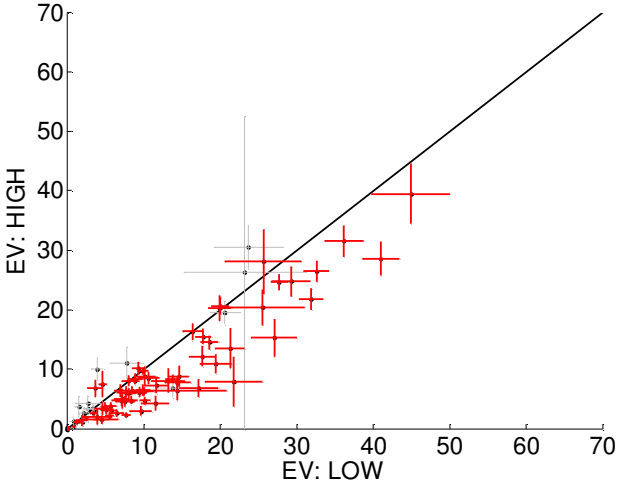
A. **MT ONLY**



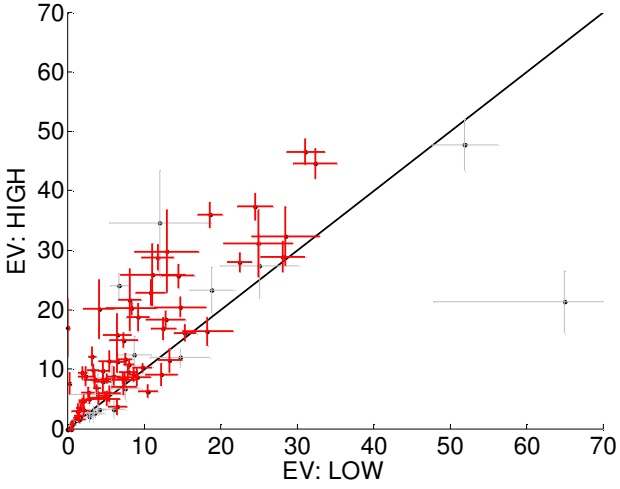
B. **MT ONLY**



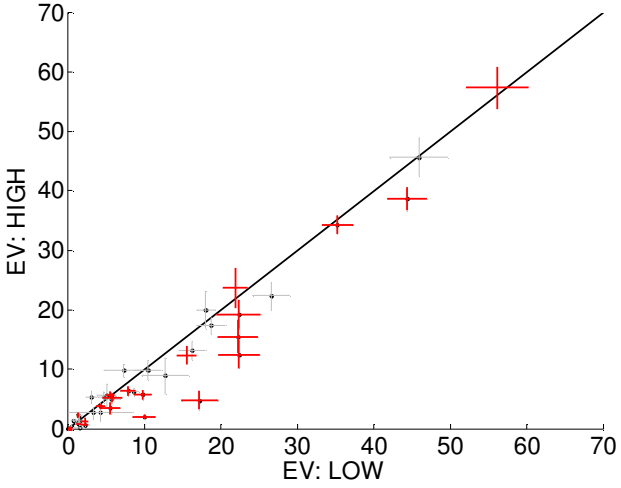
C. **MT AND DELAY**



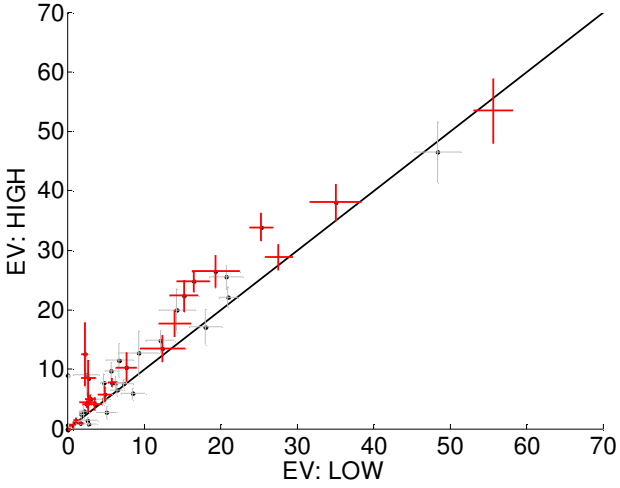
D. **MT AND DELAY**



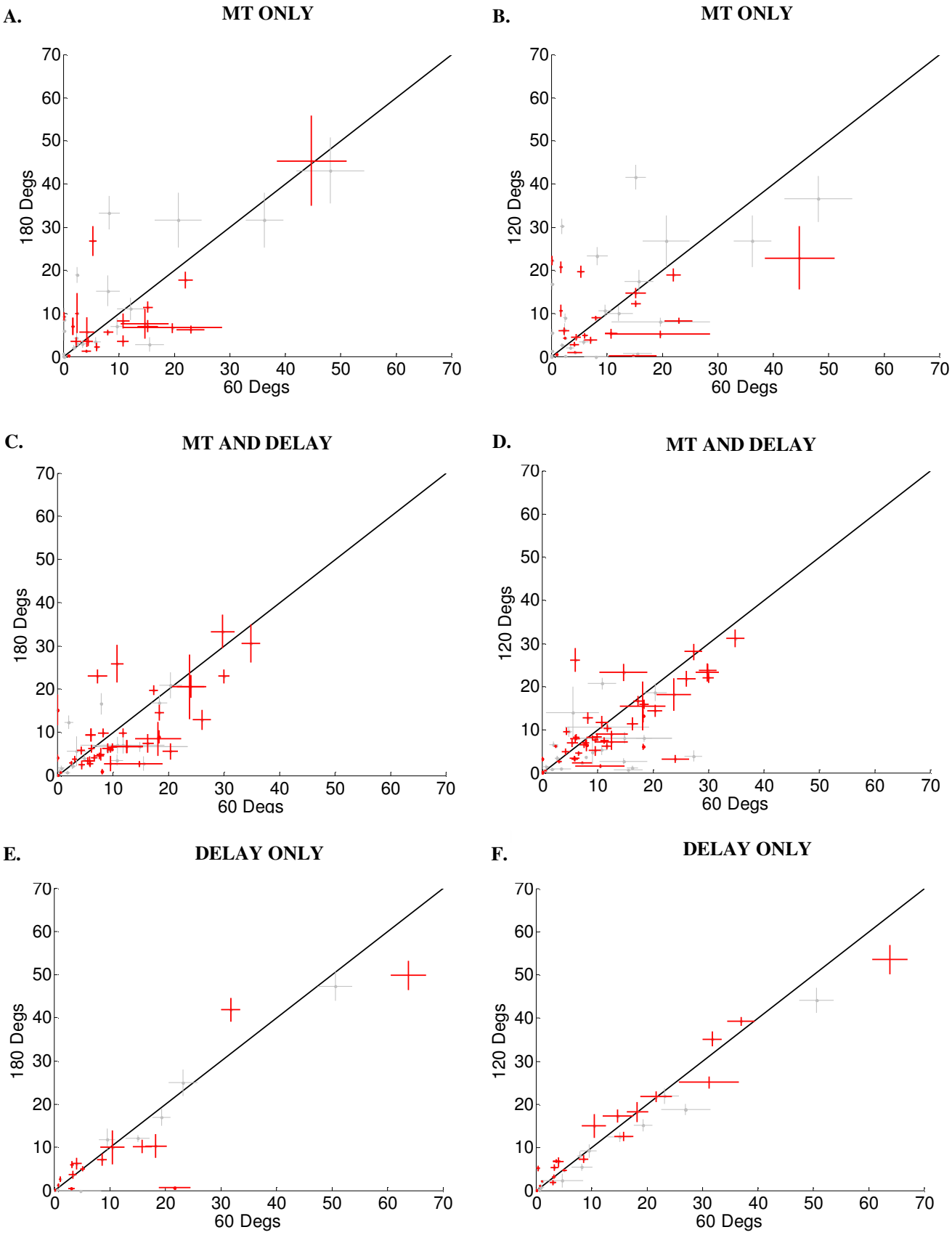
E. **DELAY ONLY**



F. **DELAY ONLY**



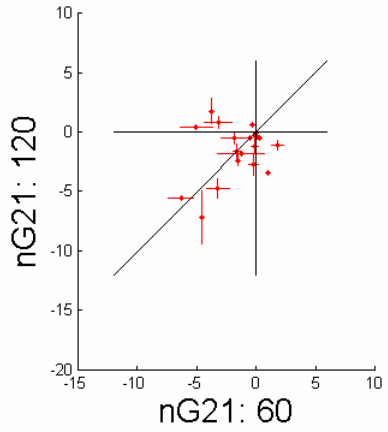
Supplemental Figure 4. Relative-value population analyses split by epoch tuning exclusivity **A.** Mean firing rates in MT ONLY cells comparing 2T trials in which the PT is medium-valued and the OT is low-valued (x-axis) versus high-valued (y-axis). **B.** Mean firing rates in MT ONLY cells comparing 2T trials in which the OT is medium valued and the PT is low-valued (x) versus high-valued (y). **C** and **D** have same convention than A and B but present modulation during delay of cells with strongest tuning during both DELAY and MT epochs. **E** and **F** have same convention than A and B but represent cells with tuning during DELAY only.


A.
MT ONLY
180 Degs
60 Degs
B.
MT ONLY
120 Degs
60 Degs
C.
MT AND DELAY
180 Degs
60 Degs
D.
MT AND DELAY
120 Degs
60 Degs
E.
DELAY ONLY
180 Degs
60 Degs
F.
DELAY ONLY
120 Degs
60 Degs

Supplemental Figure 5. Distance effect population analyses split by epoch tuning exclusivity **A.** Mean firing rates during MT for MT ONLY cells comparing 2T trials in which the PT and the OT is equally valued (EV:2) and 60° (x-axis) versus 180° apart (y-axis). **B.** Same convention as in A but for targets that are 60° (x) versus 120° apart(y). **C** and **D** have same convention than A and B but represent mean firing rates in DELAY for cells with tuning during both DELAY and MT. **E** and **F** have the same convention than C and D but represent cells with tuning during DELAY only.

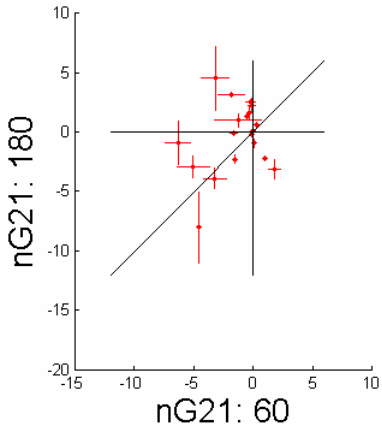
A.

DELAY ONLY



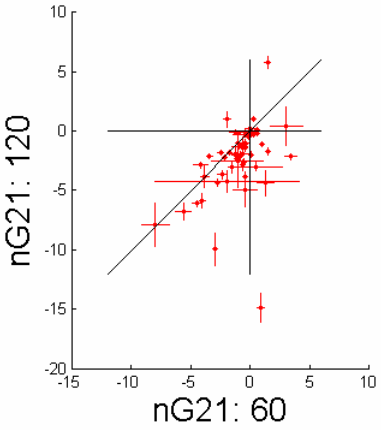
B.

DELAY ONLY



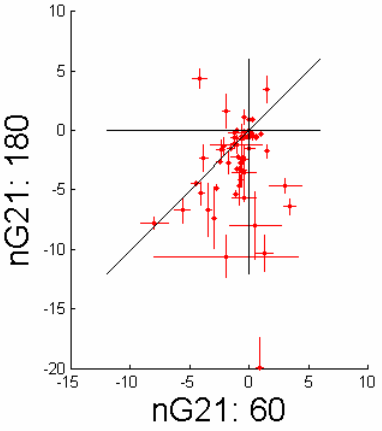
C.

MT AND DELAY



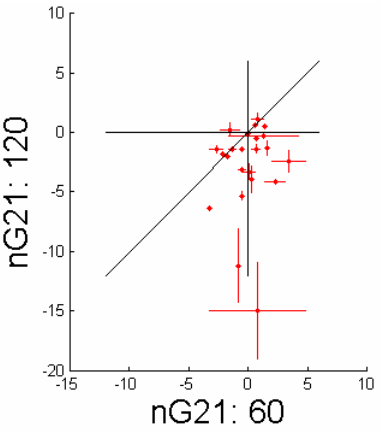
D.

MT AND DELAY



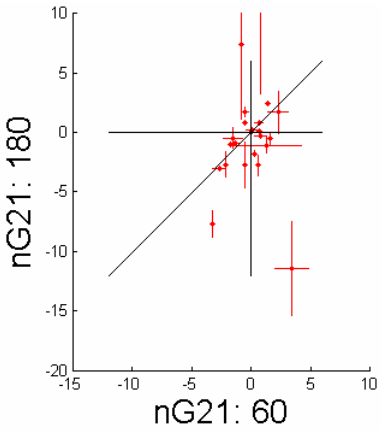
E.

MT ONLY



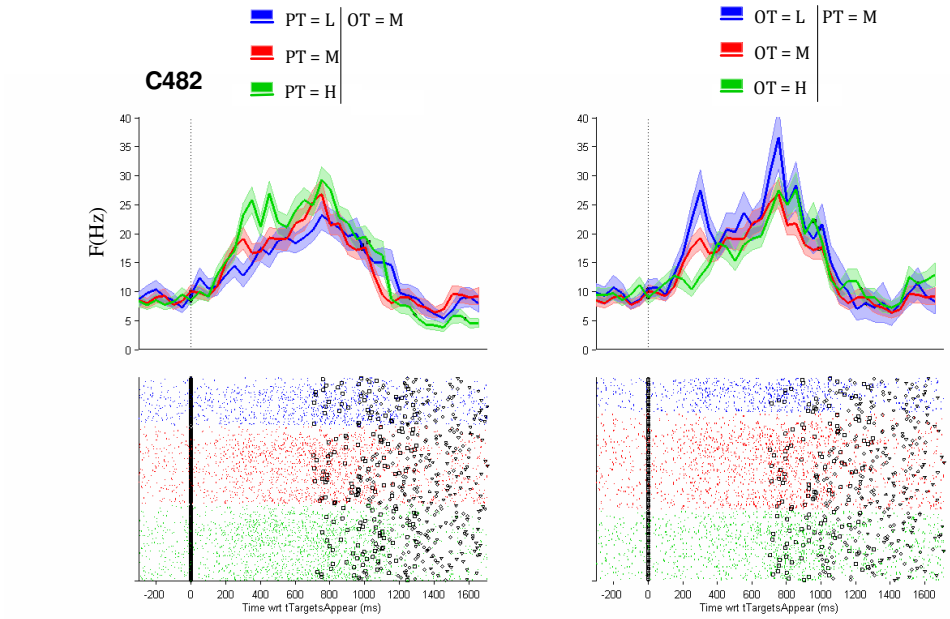
F.

MT ONLY

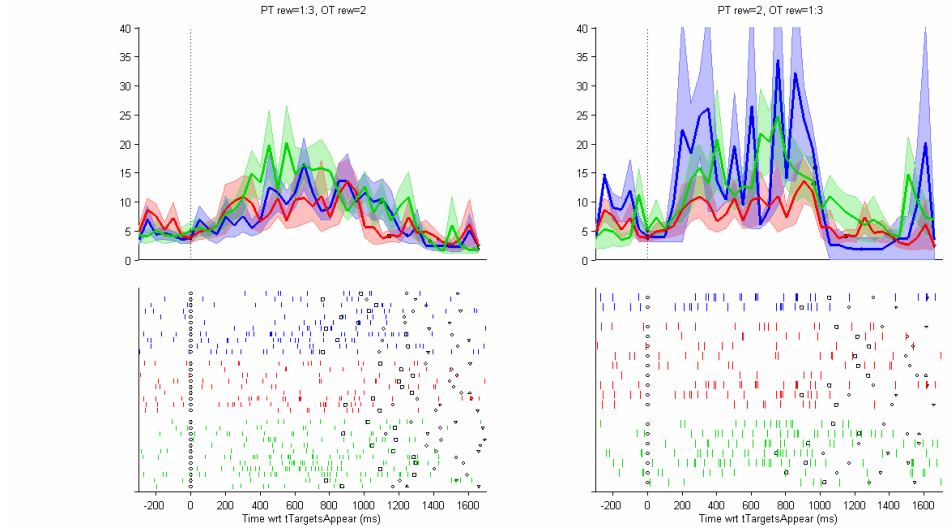


Supplemental Figure 6. Mean and standard error of the mean (SEM) for relative-value slopes in different angular conditions for DELAY-only cells (A, B), DELAY and MT cells (C-D) and MT-only cells (E-F). The compared angular distances follow the same conventions as figure 16. Red crosses represent units with any statistical value or distance effect.

A. **NOVEL 2T (Unsorted)**

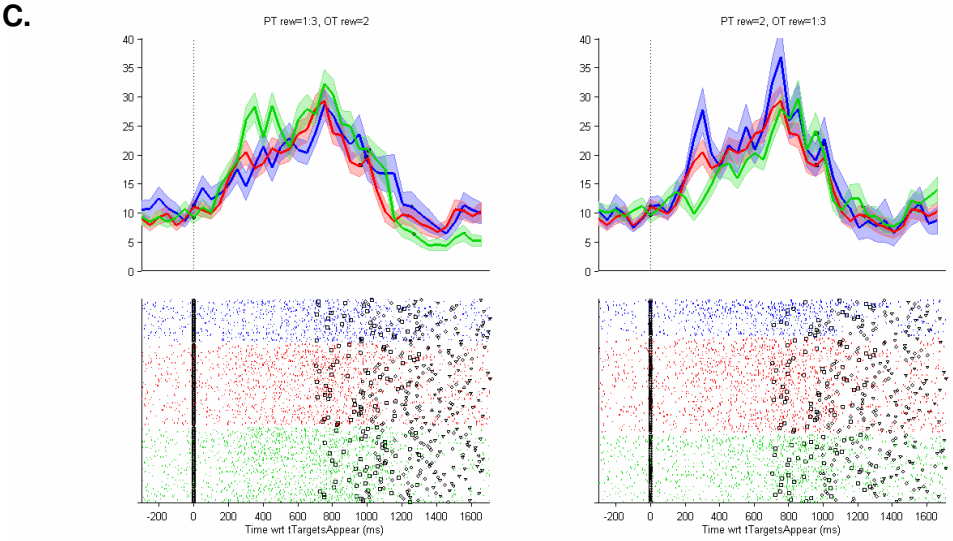


B. **NOVEL 2T (Before Criterion)**

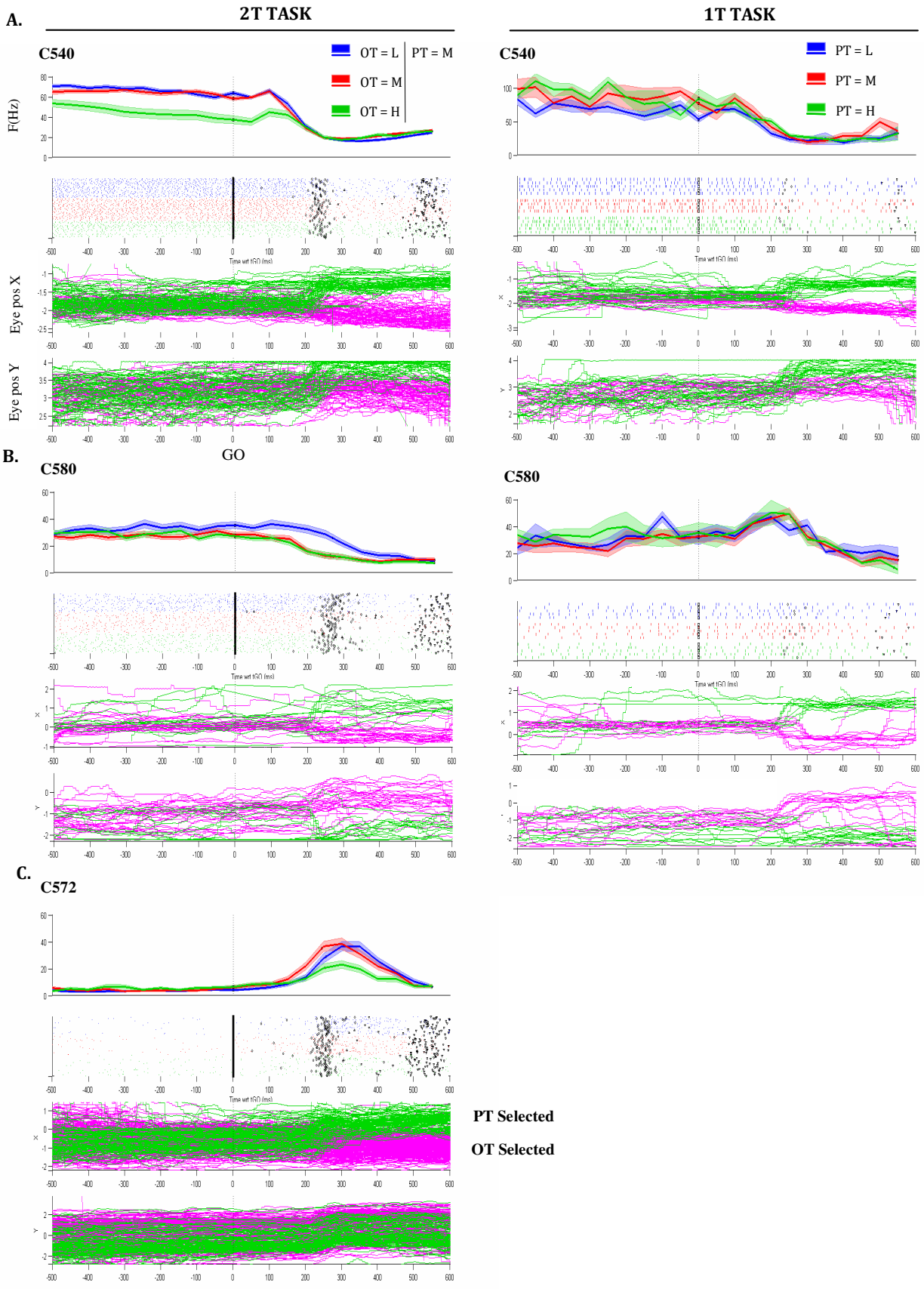


NOVEL 2T (After Criterion)

C.



Supplemental Figure 7. Example of learning cells. **A** shows all unsorted trials in for a cell collected in the novel condition. This cell has a modest but significant relative value effect in DELAY. **B** illustrates the cell responses before criterion (last trials for each color raster). **C.** Activity after behavioral criterion. Note that the cell has a modest increase of cell activity in B and this activity becomes sustained in C.


A.
2T TASK
1T TASK
C540
OT = L
OT = M
OT = H
PT = M
PT = L
PT = M
PT = H
F(Hz)
Eye pos X
Eye pos Y
GO
B.
C580
C580
C.
C572
PT Selected
OT Selected

Supplemental Figure 8. A-C Three single cell examples (rows) displaying relative value effects in the 2T task (EV in OT: L-H and PT: M) (left column) and value effects in the 1T task (EV in PT: L-H, right column). The cell shown in **C** did not have a complete 1T set and data for the 1T block is not available. All alignments shown are done with respect to GO. The upper section on each panel illustrates firing rate histograms and raster plots as shown in previous figures. The lower section on each panel represents oculomotor behavior. Notice that in all three examples, the animals looked at the center most of the time and started to look at the targets shortly after the GO signal, stabilizing the gaze upon them during the movement epoch. The cell in **A** has relative value effects only during DELAY. During this period the monkey looks towards the preferred target (OT or PT depending on the relative value). Note that one could interpret the presence of relative value effects in A on the basis of oculomotor behavior. **B and C** are late-DELAY and MT cells that also display the same relative value effects. We do not observe alternating saccade behavior between PT and OT after the GO signal since the animals are already looking at the targets. Note that for these cells oculomotor behaviour cannot be interpreted as causal for the observation of relative value. Also notice that exploratory saccades outside the single target appearing in the 1T block are present in cells A and B while this behavior does not seem affect cell activity.

VI. ARTICLE 3

DORSAL PREMOTOR CORTEX IS INVOLVED IN SWITCHING MOTOR PLANS

By

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Body:	9192
Figure legends	1529
Total	11060

ABSTRACT

Previous studies have shown that neural activity in primate dorsal premotor cortex (PMd) can simultaneously represent multiple potential movement plans, and that activity related to these movement options is modulated by their relative subjective desirability. These findings support the hypothesis that decisions about actions are made through a competition within the same circuits that guide the actions themselves. This hypothesis further predicts that the very same cells that guide initial decisions will continue to update their activities if an animal changes its mind. For example, if a previously selected movement option suddenly becomes unavailable, the correction will be performed by the same cells that selected the initial movement, as opposed to some different group of cells responsible for online guidance.

We tested this prediction by recording neural activity in the PMd of a monkey performing an instructed-delay reach selection task. In the task, two targets were simultaneously presented and their border styles indicated whether each would be worth 1, 2 or 3 juice drops. In a random subset of trials (FREE), the monkey was allowed a choice while in the remaining trials (FORCED) one of the targets disappeared at the time of the GO signal. In FORCED-LOW trials the monkey was forced to move to the less valuable target and started moving either toward the new target (Direct) or toward the target that vanished and then curved to reach the remaining one (Curved). Prior to the GO signal, PMd activity clearly reflected the monkey's subjective preference, predicting his choices in FREE trials even with equally valued options. In FORCED-LOW trials, PMd

activity reflected the switch of the monkey's plan as early as 100ms after the GO signal, well before movement onset. This confirms that the activity is not related to feedback from the movement itself, and suggests that PMd continues to participate in action selection even when the animal changes its mind on-line. These findings were reproduced by a computational model suggesting that switches between action plans can be explained by the same competition process responsible for initial decisions.

INTRODUCTION

Natural behavior requires animals to make many kinds of decisions. For example, an animal is often faced with selecting between different movements that accomplish the same behavioral goal, such as different directions to run to escape a predator. At a higher level of selection, the same animal may decide between different types of activity, such as running away versus turning around to fight. Still other kinds of decisions may involve purely abstract choices, which are not (at least immediately) associated with any specific action. In human behavior, such decisions may be extremely abstract, such as choosing what kind of career to pursue in life. Because the brain was built through continuous evolutionary refinement, we expect that the neural mechanisms of decisions at different levels of abstraction share many aspects of their architecture, and that consideration of simple spatial decisions between movement options may yield insights into decision-making in general (Cisek and Kalaska, 2010).

Recent work has suggested that, at least in the case of selecting between actions, decision-making is intimately integrated with sensorimotor control (Basso and Wurtz,

1998; Cisek and Kalaska, 2005; Gold and Shadlen, 2007; Platt and Glimcher, 1999; Romo, 2004). This has led to the proposal that while an animal is deciding between actions, neural activity in the sensorimotor system represents several movements simultaneously and the decision is made by selecting between these parallel representations (Cisek 2007; Cisek and Kalaska, 2010; Kim and Shadlen, 1999). For example, Cisek and Kalaska (2005) found that while a monkey is deciding between two different potential reaching movements, neural activity in dorsal premotor cortex (PMd) represents both options simultaneously and reflects the selection of one over the other when the monkey makes his choice. This is consistent with earlier proposals suggesting parallel movement preparation (Erlhagen and Schoner, 2002; Fagg and Arbib, 1998; Tipper, 1998), and with the hypothesis that action selection is accomplished through a biased competition within a sensorimotor map of potential actions (Cisek, 2006).

This "affordance competition" hypothesis (Cisek, 2007) stands in contrast to the classical serial model, in which decisions are made in higher cognitive centers and the resulting choice passed down to the sensorimotor system for execution. Instead, it suggests that decisions are determined when a competition between actions is resolved *within* the sensorimotor system – e.g. for reaching, within the fronto-parietal cortex and associated corticostriatal loops. This means that although the biases that influence the decision may come from many sources, including the activity of higher cognitive regions, it is in the sensorimotor system that the final decision is taken. For selecting between actions, this makes good sense from an ecological perspective: The systems most sensitive to the spatial and dynamic attributes of the candidate actions are best qualified to make the final selection that takes all of these factors into account. For example, when

choosing between actions, the spatial layout of the immediate environment directly specifies the options and is of critical importance for evaluating what is the best choice in terms of payoffs and costs. Indeed, all else being equal, humans select the action that is least demanding from a biomechanical perspective (Cos et al., 2011), suggesting that the same "forward models" (Shadmehr et al., 2010) useful for predicting the consequences of motor commands may also play a role in selecting the actions themselves by biasing activity in sensorimotor cortices.

Decision making within a sensorimotor map is particularly useful for spatial choices, such as selecting among different ways to escape a predator through an environment filled with obstacles. If two escape routes are close together, then you should not waste time deciding but instead run between them and choose in flight. In contrast, if you are up against a wall then a clear "winner-take-all" decision is critical, even if it takes a little more time to resolve. Finally, even during ongoing escape, you must continuously evaluate and update the options presented by the environment in case what appeared as an escape route turns out to be a dead end and/or if a new and better option presents itself. If that new option is already partially represented in sensorimotor maps of potential actions, then switching to it will be very fast.

In an analogy to the above scenario, here we consider selection between reaching movements to different spatially specified targets. The affordance competition hypothesis predicts that if we present a monkey with multiple reaching options associated with different rewards, neural activity in PMd will be modulated by the *relative* value of those rewards. However, if a single option is present, then its value will not influence PMd activity because there is no competition. A recent study in our lab (Pastor-Bernier and

Cisek, 2011) confirmed both of these predictions, showing relative value modulation when two targets were presented but no value modulation with one target. Furthermore, it was found that the competition between options was strongest when they were furthest apart – just as predicted in the prey escape example described above. All of these results are consistent with the idea that the competition unfolds within a sensorimotor map that respects the pragmatic issues of selecting actions in space, and all of them could be simulated with a simple model of biased competition among populations of tuned cells (Cisek, 2006).

In summary, previous studies have shown that the process of deciding between actions involves the very same brain regions that are implicated in sensorimotor guidance of actions, consistent with the affordance competition hypothesis (Cisek, 2007). However, the hypothesis also makes a complementary prediction: that the same cells involved in selecting the initial action will continue to be involved in adjusting and even switching between actions during overt behavior. In other words, if the environment changes and old opportunities are lost or new ones become available, the same integrated selection and sensorimotor guidance system should reflect the switch of the plan. Here, we investigate this issue by examining neural activity in PMd after a monkey has chosen one of two actions, but the selected option becomes unavailable. We examined the same cells whose delay period activity showed relative value modulation in our previous work (Pastor-Bernier and Cisek, 2011) but extended our analysis to the activity after the GO signal, with particular interest in trials in which the option with highest payoff becomes unavailable. Some of these results have been previously presented in abstract form (Pastor-Bernier et al., 2011).

MATERIALS AND METHODS

Instrumentation and technical procedures

A male monkey (*Macaca mulatta*) performed a planar center-out reaching task illustrated in **Figure 1A**. The task involved moving a cursor from a central circle (2cm radius) to one of six possible targets (2.4cm radius) spaced at 60° intervals around a 12.6cm radius circle. The monkey performed movements using a cordless stylus whose position was recorded (125Hz) by a digitizing tablet (*CalComp*). Target stimuli and continuous cursor feedback were projected onto a mirror suspended between the monkey's gaze and the tablet, creating the illusion that they are in the plane of the tablet. Oculomotor behavior was unconstrained, as eye movements do not strongly influence arm-related PMd activity (Cisek and Kalaska, 2002), but was monitored with an infrared oculometer (ASL). Neural activity was recorded with 3-4 independently moveable microelectrodes (*NAN microdrive*) and data acquisition was performed with AlphaLab (*Alpha-Omega*). On-line spike discrimination was used to estimate cell preferred directions for choosing target locations. All analog waveforms were stored on disk for offline sorting using principal components (*Plexon*). All task events, trajectory data and spike times were stored in a database (*Microsoft SQL Server 2005*) accessed through custom scripts for data analysis (*Matlab*). After completing training, the animal was implanted under general anesthesia with a titanium head post and a recording chamber placed using MRI images (*Brainsight primate*). The chamber was centered on the arm area of PMd, between the precentral dimple and the junction of the arcuate sulcus and

spur (**Figure 1B)**. All procedures followed university and national guidelines for animal care.

Behavioral task

The monkey began each trial by placing the cursor in the central circle for a 350-650ms Center-Hold-Time (CHT). Next, one or two cyan targets appeared, with border styles indicating the amount of juice that the monkey was likely to receive for reaching to that target (See **Figure 1A**, inset). The reward was determined probabilistically to encourage the monkey to explore available options (Herrnstein, 1961). A "low-value" target (L, thick border) had a 60% chance of yielding 1 drop, 30% chance of yielding 2 and 10% chance of yielding 3 (Expected value, EV=1.5). A "medium-value" target (M, no border) was worth 2 (60%), 1 (20%) or 3 drops (20%) (EV=2). A "high-value" target (H, thin border) was worth 3 (60%), 2, (30%), or 1 drop (10%) (EV=2.5). The non-monotonic relationship between border thickness and value was used to dissociate motivational factors from physical properties of stimuli. In particular, the most visually salient cue with a thick border style is deliberately chosen to have a small payoff ("low value") to dissociate saliency from value effects. The monkey held the cursor in the center for an instructed delay period (DELAY, 700-1300ms) until a GO signal was indicated by a change in target color and the disappearance of the central circle. After the GO signal, the monkey had to initiate the movement within a 550ms reaction time (RT) (which had to be at least 100ms, to discourage anticipation). To receive a reward, the monkey had to move to a target within a maximum 550ms movement time (MT) and

hold the cursor there for 500ms (Target-Hold-Time, THT). When cells were isolated, we first ran a block of 90 trials in which only one target was presented (1T), to identify the DELAY-period preferred target (PT) of each cell. Next, we ran a block of 180 two-target trials (2T), including ones where the PT target was present and low, medium, or high-valued, while the other target (OT) appeared at 60°, 120°, or 180° away and was low, medium, or high-valued. Each block also included 30 trials in which the targets were 120° apart but neither was in the direction of the PT. In this paper we focus only on trials in which the targets are 120° apart (90 trials per 2T block) and at least one of the presented targets was the cell's PT. In 67% of 2T trials (FREE), the monkey was free to move to either target after the GO signal. In 33% of 2T trials (FORCED), one of the targets disappeared at GO and the monkey had to move to the remaining one. FREE and FORCED trials were randomly interleaved to encourage the animal to keep both options partially prepared. FORCED trials were classified according to the value of the target that disappears after the GO signal. In FORCED LOW trials the target with the higher expected value disappears (inset in Figure 1A bottom), while the opposite is true in FORCED HIGH trials. In a FORCED EQUAL trial both the target that disappears and the target that remains have the same value.

Kinematic analysis

Movement trajectories were re-sampled at a constant rate (200Hz) and filtered using a two-way butterworth filter (0 phase lag, 4^{th} order, norm. cutoff 0.05 (~20Hz)) using Matlab functions *butter* and *filtfilt* (Mathworks). The initial direction vector (**IDV**)

was calculated as the X and Y coordinate cartesian arctangent (*atan2*) between the position at movement onset and the position 100ms later. Trials were sorted by short RT (<180ms), medium RT (between 180ms and 240ms) or long RT (>240ms). The mean trajectory profiles and mean initial direction vectors were calculated for each RT group independently. To determine whether the **IDV** was pointing to a given target in space, we calculated the mean **IDV** in the 1T condition for each target individually. Then, 2T trials were classified as "*direct*" to the selected target if their **IDV** fell within 120° of that target's mean **IDV** in the 1T condition. Trials whose **IDV** pointed away from the ultimately acquired target were classified as "*curved*".

Cell tuning and relative value discrimination

We investigated only cells that had both spatial tuning and relative value discrimination (see Pastor-Bernier and Cisek, 2011) during DELAY. We calculated directional tuning preferences for the cells during each behavioral epoch (DELAY, MT, and THT) and assessed significance with a non-parametric bootstrap test (1000 shuffles, $p<0.05$; Cisek et al., 2003). To assess whether a cell discriminated relative value during DELAY, we examined whether the cell showed statistically significant differences in firing rate between a "HIGH" value condition (value in PT was larger than OT) and a "LOW" value condition (value in OT larger than PT) for the last 300ms prior to the GO signal (1-way ANOVA, $p<0.05$). This was done to verify whether the same cells that are involved in the initial decision continue to reflect plan switches after the GO signal. Cells satisfying both requirements were used for post-GO analyses. Discrimination latencies

were obtained using a sliding ANOVA method adapted from Peng et al. 2008 (window: 50ms, step: 5ms, $p<0.05$) to perform a statistical temporal analysis between the HIGH and LOW value conditions. We obtained latencies for relative value discrimination with respect to the GO signal by aligning the neural activity on GO and parsing each trial backwards for 700ms (shortest variable DELAY duration). This chosen interval ensured that all trials had a similar time range for firing rate comparisons. The latency of relative-value discrimination was obtained as the last 80ms sliding time-window for which a statistical difference could be observed. The cells that satisfied both the 1-way ANOVA and sliding-ANOVA requirements were called relative value discriminating cells (**RV cells**, N: 52). This population is identical to the data set described previously (Pastor-Bernier and Cisek, 2011) in which relative-value effects were assessed for particular value combinations (PTvsOT: 3vs1, 2vs1, 3vs2) using paired ANOVA and Tukey-Kramer tests.

Plan-switch analysis

FORCED LOW trials were of particular interest for plan-switching analysis because they represent conflict situations in which the more desirable option must be replaced by the less desirable option. In these "plan-switch" cases, DELAY activity prior to GO (pre-GO plan) was compared with activity after GO (post-GO plan). We further distinguished cases where the target that disappears is located in the cell's PT or in the OT, giving rise to two different kinds of FORCED LOW trials. In FORCED LOW PT2OT trials the pre-GO DELAY activity reflects an initial plan to PT and the post-GO

activity a final plan to OT. In FORCED LOW OT2PT trials the pre-GO DELAY activity reflects a movement plan to OT and the post-GO activity a final plan to PT. To obtain plan-switch latencies FORCED LOW trials were compared with trials belonging to the FREE condition in which the animal naturally chose the high valued option (FORCED-FREE comparison). To obtain the switch latency from an initial plan to PT to a final plan to OT (**SwitchPT2OT**) the activity of FORCED LOW PT2OT trials was compared with FREE trials in which PT was the plan selected (FREE HIGH PT). This type of switch is illustrated in **Figure 3A.** The plan-switch latency was obtained by parsing the neural activity for both types of trials from GO to movement offset using a sliding ANOVA method (window: 50ms, step: 5ms, $p<0.05$) and calculated as the first moment in time in which they were significantly different for at least 80ms *after* the GO signal. For the plan-switch latency to be valid we also required that there be no significant difference between the FORCED LOW PT2OT and the FREE HIGH PT types of trial for at least 300ms *before* the GO signal (1-way ANOVA, $p<0.05$ms). To calculate the switch latency from an initial OT plan to a final PT plan (**SwitchOT2PT**) the activity of FORCED LOW OT2PT trials was compared to FREE HIGH OT trials in which OT was selected. **Figure 3B** illustrates an example of this type of switch. We define as "convergence" the situation in which the pre-GO DELAY activity for two types of trials represents different movement plans, while the post-GO activity represents the same plan. The time of convergence to a plan in the PT direction (**CONV**) is found by comparing FORCED LOW OT2PT trials with FREE HIGH PT trials (**Figure 3C**). Convergence to an OT plan cannot be determined from the activity of cells because activity to OT is generally low. To obtain **CONV** latency a similar sliding ANOVA method was used, although the time

of convergence was defined as the first moment after the GO signal in which the difference between the two types of trial was *not significant* ($p>0.05$) for at least 80ms. We also required the pre-GO DELAY activity between FORCED LOW OT2PT and FREE HIGH PT to be different for at least 300ms (1-way ANOVA, $p<0.05$). In a variant of the plan-switch latency study we used FORCED HIGH trials instead of FREE HIGH trials for the calculation of plan-switch latencies (FORCED-FORCED comparison). This allowed us to address whether differences in visual input after the GO signal (the number of remaining targets) could have an effect on the plan-switching process.

The population's mean switch latencies (ms) were calculated using the sliding-ANOVA method mentioned above. The confidence intervals (CI) at 95 % probability ($p<0.05$) were obtained as $\pm Z^*\sqrt{E}$, where Z represents the critical area for the distribution of mean switch latencies across trials. Z can be approximated to ±1.96 assuming by the central limit theorem (Polya, 1920) that the mean distribution tends to normality with large sample sizes. The variable E represents the error variance of the mean and was calculated using the expression correcting for overlapping intervals described in Müller (1993) (*eq. 3.7*) and cited elsewhere (Dacorogna et al., 2001; Hansen and Lunde, 2006).

$$E = r/N^2 * (rR - (r^2-1)/3),$$

where $r = \min(m,N)$, $R = \max(m,N)$ and where m is the overlap between intervals and N is the number of samples per time interval.

In our case we have a 50ms window sliding by 5ms bins. Therefore $m = 45$ and $N = 10$. Because $m>N$, then $r = N$ and $R = m$, and the previous expression takes the form:

$$E = m - N/3 - 1/3N$$

Solving numerically with $m = 45$ and $N=10$, we obtain $E = 41.7$ and therefore

$$CI = \pm 1.96\sqrt{41.7} = \pm 12.6 \approx \pm 13ms$$

With no overlap m=0, r=0, R =1, N=1 and the error of overlap E = 0.

Computational modeling

The model (Cisek, 2006) is aimed at explaining and predicting systems-level phenomena such as response patterns over large population of neurons. It is implemented with a set of equations describing the activity of several populations of neurons that correspond to specific cortical regions. Each population is organized as a layer of neurons that are tuned to spatial directions of potential actions. Each neuron in a layer behaves according to an expression that defines how its activity changes over time as a function of four terms: passive decay, excitation toward saturation, inhibition and noise. This expression can also be called "mean-rate leaky integrator" (Grossberg, 1973) and takes the following form:

$$dX/dt = -\alpha X + (\beta - X)\gamma \cdot E - X \cdot I + \theta, \quad (1)$$

where X is the mean firing rate of a given neuron, dX/dt is the change in rate over time, E is the excitatory input, I is the inhibitory input, α is a decay rate, β is the maximum activity of a neuron, γ is the excitatory gain and θ is the Gaussian noise. The connections between each layer are hardwired and organized to respect basic neuroanatomical connection patterns. Further details concerning connectivity patterns and model behavior have been described previously elsewhere (Cisek, 2006). For purposes of the present task the model's "prefrontal" activity was scaled by a signal related to the absolute value of each target (low=0.3, medium=0.7, high=1.0). To simulate plan switches, we removed

one of the two presented targets (high valued target in FORCED LOW trials) at the beginning of the GO epoch. All parameter settings were identical to Cisek (2006), except that we used a gradual GO signal that allows the activity in PMd to gradually spill into the M1 layer. The gradual GO signal is defined as a multiplicative factor that scales the input from PMd to M1 and is zero before the GO instruction. After the GO instruction, it grows as $2.5 \cdot t$ where t is the time since the GO instruction.

Note that the model in its present form is not intended to simulate the movement itself. Activity in the model M1 population simply indicates the initial direction of movement, computed as the preferred direction of the first M1 cell that crosses a threshold of activity equal to 1.75.

BEHAVIORAL RESULTS

In 1T trials the monkey's success rate was 98%, in 2T FREE it was 99% and in 2T FORCED it was 96% (in all cases $N>60{,}000$). In 2T FREE trials the monkey selected the more valuable target 90% of the time, indicating that he understood the meaning of the stimulus cues. We found that movement times (MT) were shorter to higher-valued targets in 1T trials (400ms to high-value and 416ms to low-value targets). Although the difference was small, it was significant (Kolmogorov-Smirnov test (KS), $p<0.01$). Reaction times (RTs) in 1T trials did not depend on target value (KS-test $p>0.05$ for all comparisons).

We observed an interaction effect between RT and trajectory kinematics in 2T trials. Trajectories belonging to short RT trials were generally more curved than

trajectories belonging to medium or long RT trials (**Figure 2A**). This effect was accentuated by the value of the unselected target with respect to the value of the selected target in the FORCED condition. Trajectories in the FORCED LOW condition (**Figure 2A,** rightmost panel) were generally more curved than the ones in the FORCED HIGH or FREE HIGH conditions (**Figure 2A,** left and middle panels). These curved movements have an initial launching direction towards the target that vanishes and are corrected later to the remaining target. To quantify this we obtained the mean trajectory initial direction vector (**IDV**) across all conditions (**Figure 2B**). We observed that a great deal of the curvature in FORCED LOW trials was due to movements launching to the target that becomes unavailable after GO (High value). This effect was particularly strong for short RT trials and moderate for intermediate RT trials. Long RT trials were essentially straight toward the remaining target (**Figure 2B,** rightmost panel). We did not see this effect when the monkey was forced to move to the high value target or when the monkey was free to choose among the two targets, because in either situation the preferred and available target were the same. We further investigated the interaction between RT, relative value and initial launching direction by comparing raw RT distributions. The mean RTs in FREE HIGH (266ms, light-brown dashed histogram), FORCED HIGH (271ms, dark-brown dashed histogram) and FORCED LOW (279ms, black dashed histogram), were very similar **(Figure 2D)** with only small differences between the mean RTs in FREE HIGH and FORCED LOW distributions (KS test, $p<0.01$). This could be due to the contribution of a higher proportion of correct trials in FREE HIGH than in FORCED LOW trials (3% difference). Most importantly we observed that the mean RT in FORCED LOW trials with “direct” trajectories (red histogram, 291ms) was

significantly longer *(21ms difference, KS Test, p<0.01)* than the mean RT in FORCED LOW trials with "curved" trajectories (blue histogram, 270ms). In comparison, FORCED LOW "curved" trials and FORCED HIGH trials did not show RT differences (KS Test, p>0.05) **(Figure 2D)**.

NEURAL RESULTS

PMd activity predicts switching of motor plans ahead of movement onset

Activity was recorded from 327 cells from the arm area of PMd (**Figure 1B)** of which 226 (69%) had significant directional tuning during at least one epoch (DELAY, MT, THT) and were considered task-related. Here, we focus on cells with DELAY-period tuning (181/226, 80%), 52 of which (29%) were modulated by relative value combinations during DELAY (1-way ANOVA, p<0.05) and were considered further for the plan-switch analyses (relative value, **RV cells**). In the first variant of this analysis we compared neural activity in FORCED LOW versus FREE HIGH conditions (FORCED-FREE). **Figure 3A-C** shows three individual cells illustrating the different types of plan-switch analyses. In a **SwitchPT2OT** (**Figure 3A)** we compare trials that had a pre-GO plan to PT and a post-GO plan to OT (FORCED LOW PT2OT, green trace) with trials that had both a pre-GO and post-GO plan to PT (FREE HIGH PT, red trace). In a **SwitchOT2PT (Figure 3B)** we compare trials with a pre-GO plan to OT and a post-GO plan to PT (FORCED LOW OT2PT, blue trace) with trials that had both a pre-GO and post-GO plan to OT (FREE HIGH OT, pink trace). In a convergence (**CONV**) the pre-GO plan is different for two types of trials (FORCED LOW OT2PT and FREE HIGH PT)

but is the same (movement plant to PT) after the GO signal (**Figure 3C**). **Figure 3D-G** show additional examples that had statistically significant plan switches at the individual cell level. Thirty-seven of the 52 (71%) **RV cells** showed statistically significant modulation (sliding ANOVA $p<0.05$) in at least one plan-switch analysis in the FORCED-FREE latency comparison and are referred to as **Switch cells**. Switches of activity of the other cells did not reach statistical significance, often because those cells were recorded during only a few trials of each type.

To address the role of visual input (the number of targets remaining after GO) on the plan-switching process, we also compared FORCED LOW versus FORCED HIGH conditions (FORCED-FORCED comparison). **Figure 3F-G** illustrates a single cell example in which plan switches were obtained both for the FORCED-FREE comparison (**Figure 3F**) and for the FORCED-FORCED comparison (**Figure 3G**). Twenty-eight out of 52 (54%) **RV cells** showed statistically significant modulation to plan switches in the FORCED-FORCED comparison. **Table 1** summarizes the cell counts for the different types of switch in both comparisons.

To test whether the plan-switch pattern observed at the individual cell level also held at the population level, we obtained the population profile for plan-switching in **Switch Cells** and all **RV** cells separately and for both FORCED-FREE **(Figure 4A-B)** and FORCED-FORCED **(Figure 4C-D)** comparisons. We observed that the latency of SwitchPT2OT and SwitchOT2PT for **Switch Cells** was 155 ± 13ms (95% CI) after the GO signal and therefore well before movement onset (300 ± 50ms) in both FORCED-FREE and FORCED-FORCED comparisons (**Figure 4E-F**). Convergence to a plan occurred later, 190ms ± 13ms after the GO signal, but still well-ahead of movement onset.

These results held for both the **Switch cell** or **RV cell** populations, although we observed that switch latencies in the larger **RV cell** population were later than in the **Switch cell** population by about 15-20ms (this difference did not reach statistical significance, ANOVA $p>0.05$), and was presumably due to the presence, in the RV population, of cells with very few trials resulting in a larger standard error. **Table 2** summarizes the latency results for each cell population and comparison.

PMd contribution to kinematics prior to movement onset (initial direction) is observed in situations where there is no relative value bias

We examined the cell responses in the plan-switch paradigm taking into account the initial direction of the reach movements in each trial. By doing so we classified trajectories as initially aiming to the selected target ("direct", to PT or OT) or initially aiming to the unselected target ("curved"). We compared both direct and curved movements in the conditions that were more likely to provoke curvatures due to plan-switches, namely the FORCED LOW and FORCED EQUAL conditions. **Figure 5A-C** shows population histograms for **Switch cells** and **RV cells**, comparing FORCED LOW direct and curved trials. We observed that curvature is not predicted by DELAY activity in the FORCED LOW condition. We did not observe statistically significant differences either between activity in the FORCED LOW PT2OT direct trials and FORCED LOW PT2OT curved trials, or between FORCED LOW OT2PT direct and FORCED LOW PT2OT curved (ANOVA, $p>0.05$ in both cases). However, DELAY activity in the FORCED EQUAL conditions does predict whether a trial will be curved or straight.

During the 600ms prior to the GO signal, we observed statistically significant differences (ANOVA, $p<0.05$) between FORCED EQUAL direct and FORCED EQUAL curved trials, for both **Switch cell** and **RV cell** populations (**Figure 5D-F**). It is noteworthy to mention that these differences take place only during DELAY prior to the monkey's knowledge of which target will disappear (GO), and reflect pre-GO selection biases. That is, among the FORCED EQUAL trials there are some in which the pre-GO activity happens to be strongly biased toward one target, and when that target disappears, the bias is likely to cause a curved movement (green and blue traces).

Note that, as shown in **Figure 5B, E**, when we align activity on the movement onset (MO) we can see that the switch of the plan (computed at the population level) occurs approximately 150ms before movement onset. This is interesting because in the curved trials the monkey still launches to the now nonexistent target.

A biased competition model can reproduce the dynamics of the plan-switch

Cisek (2006) described a "biased competition" model of action selection, in which populations of cells along the dorsal stream implement a distributed representation of potential actions that compete against each other through lateral inhibition (**Figure 6A**, see methods). The model simulates relative value effects reported previously when reward-related biasing signals are introduced into PFC (Pastor-Bernier and Cisek, 2011). Here, we used the same model to simulate plan switches by removing one of the two presented targets at the beginning of the GO epoch and by letting the activity in PMd to gradually spill into the M1 layer (see Methods). **Figure 6D** shows the activity of a

simulated neuron illustrating plan switches from OT2PT, PT2OT and convergence to PT. Note that the timing of the PT2OT and OT2PT plan switches occur simultaneously and prior to movement onset. This is also the case for convergence to PT. These results are compatible with the experimental data and suggest that PMd contains all the information concerning the final action plan before movement onset. **Figure 6B** shows RT distributions from FORCED LOW simulations for trials in which the model launched toward the target that vanished (blue) or the remaining target (red). We observe that RTs are shorter for trials initiated toward the vanishing target, in agreement with behavioral data (Figure 2D). **Figure 6C** shows the distribution of initial launching directions. Note that the blue distribution (which comprises the majority of early RT trials) is aimed toward the target that vanished, predicting that if the model were equipped with online feedback during the movement itself, it would produce curved trajectories as in the behavioral data. **Figure 6E** shows the model's Parietal, PFC (rostral and caudal), PMd (rostral to caudal) and M1 population patterns of activity during a FORCED LOW trial where we observe a plan switch that is completed before movement onset. In contrast, in the trial shown in **Figure 6F**, the model launches the movement before the plan switch is complete. We observe that the timing of plan switches in all PMd layers is before movement onset, in agreement with our experimental results.

DISCUSSION

Recent studies have shown that while a monkey is deciding between two potential reaching movements, neural activity in the dorsal premotor cortex (PMd) can specify

both movements simultaneously (Cisek and Kalaska, 2002, 2005; Klaes et al., 2011), and the neural representations of these movements are modulated by their relative subjective desirability (Pastor-Bernier and Cisek, 2011). These findings suggest that decisions between reaching actions are made within the same brain regions involved in the execution of the actions themselves, in agreement with research on reaching (Cisek, 2007; Cisek and Kalaska, 2010; Pesaran et al., 2008) and oculomotor control (for reviews, see Glimcher, 2003; Gold & Shadlen, 2007). In fact, decisions about eye movements appear to involve even the superior colliculus, a brainstem structure that is just two synapses away from the motor neurons that move the eye (Basso and Wurtz, 1998; Carello and Krauzlis, 2004; Horwitz et al., 2004; Ignashenkova et al., 2004; Thevarajah et al., 2009).

However, the finding that decision variables (such as relative value) influence neural activity in sensorimotor regions does not necessarily imply that these same cells continue to be involved in the on-line guidance of movement. It is plausible that once a decision is made and an action is launched toward a given target, the decision-related cells fall silent while a separate circuit becomes responsible for guiding movement toward the selected target. The results presented here suggest that this is not the case. We found that the very same PMd cells previously shown to reflect relative value during a delay period continue to update their activity to reflect when the monkey changes its plan during situations in which a previously selected action becomes unavailable. This argues against the distinction between regions responsible for choosing an action and those responsible for its guidance through on-line feedback, and in favor of the hypothesis that decisions emerge through a competition within the same circuit that guides movement execution (Cisek, 2007).

A number of earlier studies provide converging evidence consistent with this integrated view. For example, it has been shown that humans and monkeys can quickly and smoothly update their movement plans when the location of the reach target suddenly and unpredictably changes (Archambault et al. 2009, 2011; Day and Lyon, 2000; Desmurget et al., 1999, Georgopoulos et al., 1981, 1983; Gritsenko et al., 2011; Prablanc and Martin, 1992), even when they are not consciously aware of the change. During these "target jump" experiments, neural activity in fronto-parietal cortex smoothly transitions between the original and final motor plan (Archambault et al., 2009, 2011), without any "refractory period" for aborting the previous plan before preparing a new one. Among the regions tested, the earliest changes in neural activity were found in PMd, in which 50% of cells reflected the new plan about 140ms after a target jump, followed by M1 at 180ms and dorsal area 5 at 200ms (Archambault et al., 2011). This is comparable to the latency of responses to target jumps in earlier studies by Georgopoulos et al. (1983), who observed latencies of about 130-150ms in the rostral part of M1.

Interestingly, the neural latencies to target jumps are comparable to the latencies of plan switches observed in PMd in our study – about 155ms for both increases (SwitchOT2PT) and decreases of activity (SwitchPT2OT). They are also comparable to the latencies reported by Wise and Mauritz (1985) in a study in which the stimulus that instructed the plan switches was presented during the delay period, well before the GO signal. In that study, it was found that PMd cells reflected the switch with a median latency of 140-150ms. In other words, the latency with which neural activity in PMd reflects a plan change is approximately 140-150ms after the sensory stimulus which instructs that plan change. This holds true regardless of whether that stimulus is the

change of a target from one location to another during the delay period (Wise and Mauritz, 1985), the displacement of a target during reaction time or movement (Archambault et al., 2009, 2011; Georgopoulos et al., 1983), or the offset of a preferred target that leaves only a less-desirable one available (present study). Furthermore, we found that the latency at which cells became suppressed when their preferred target disappeared (SwitchPT2OT) was not statistically different than the latency with which their discharge increased when their preferred target, which was initially less desirable, suddenly became the only remaining option (SwitchOT2PT). The similarity of these neural latencies across different experimental conditions demonstrates that in all cases, neural activity in PMd remains sensitive to new information pertinent to available actions and their values. This suggests a view whereby sensory information continuously flows into the motor system (Cisek 2007; Coles et al., 1985), as opposed to a view of separate computational stages involved in canceling one motor program and computing a new one.

The neural processes of canceling a planned movement have been studied in the frontal eye fields (Hanes, 1998), superior colliculus (Pare and Hanes, 2003) and for arm-reaching studies in the supplementary motor area (SMA), pre-SMA (Scangos and Stuphorn, 2010) and PMd (Mirabella et al., 2011) using the countermanding task (Logan et al., 1984). In this task, subjects are asked to make a saccade or reach to a target, but to inhibit the movement if an infrequent STOP-signal is presented after a variable delay following the GO signal. As the delay increases, it becomes increasingly difficult to successfully inhibit the movement, making it possible to estimate a given subject's "stop-signal reaction time" (SSRT). Although many cortical areas such as motor cortex (M1) and supplemental motor areas (pre-SMA and SMA) harbor neurons with DELAY activity

related to movement planning (Okano and Tanji, 1987) it is unlikely that these areas are involved in processes causally related to movement cancellation because their responses to a stop signal take place *after* the SSRT (Scangos and Stuphorn, 2010). In contrast, Mirabella et al. (2011) found that during successful STOP trials, neurons in PMd show activity changes *prior* to the SSRT, making it possible that this region is involved in inhibiting the movement. This is consistent with the findings reported here that the suppression of PMd activity tuned to the target which vanished (SwitchPT2OT) occurs well before movement onset.

Our behavioral results are compatible with the proposal that at the end of the DELAY period, the movement to the higher-valued target is more strongly prepared than the movement to the lower-valued target. When the higher target disappears in a FORCED LOW trial, then one of two things can happen. If the RT is short, then the movement initiates toward the location of the unavailable target and the monkey must later turn around (curved trials, Figure 2D blue). If the RT is long, then the monkey completes his plan switch and initiates directly to the remaining target (direct trials, Figure 1F red). Nevertheless, what is surprising is that in both cases, neural activity in PMd already clearly reflects the change of plan more than 150ms before the movement onset. This can be seen in Figure 5A and B. For example, the green traces illustrate trials in which the monkey initiated the movement toward the PT of recorded cells, which was the more valuable of the targets present during the DELAY. However, that target vanished and so the monkey curved its movement trajectory and arrived at the remaining target. Although the neural activity becomes suppressed within 200ms of the GO signal, reflecting the change of plan away from the PT, the initial movement some 100ms later is

still launched in the direction of the original plan. This happens most often during trials with short reaction times (Figure 1C, F) suggesting that the motor system has a certain "inertia" that cannot be easily overcome. That is, movement initiation and muscle contraction could be starting to take place shortly after the GO signal despite the possibility that the more desirable choice will become unavailable. In this sense, the short-RT curved movements would be a natural consequence of the monkey's impulsivity and a strategy of reaching quickly and correcting the trajectory when necessary. In FORCED LOW trials, we found no significant difference in PMd activity between curved versus direct trials (Figure 5A-C), suggesting that other regions (presumably M1) may be more strongly responsible for determining whether the movement launches toward the initially selected or not. In FORCED EQUAL trials, we did observe differences in PMd activity when comparing curved versus direct movements (Figure 5D-F), but we believe this is simply due to selection bias: Curved movements (dark blue and green traces) are more likely to occur when the monkey happens to be strongly biased during DELAY toward the target that vanished, while direct movements could result equally from trials in which DELAY activity is biased to the PT, the OT, or neither, and the average DELAY activity of these three groups of trials will lie somewhere in the middle (red and cyan traces).

Cisek (2006) described a model of biased competition between action plans, which was originally designed to capture neural data on the simultaneous specification of multiple movements (Cisek and Kalaska, 2005) and behavioral data on the distributions of initial directions in short-RT pointing tasks (Favilla, 1997; Ghez et al., 1997). That same model, without any changes in parameters, was able to simulate more recent data on

the modulation of PMd activity by relative subjective desirability (Pastor-Bernier and Cisek, 2011). In the model, potential actions are encoded as hills of activity in populations of directionally tuned neurons with short-range mutual excitation between similarly tuned cells and long-range lateral inhibition among cells with different tuning. The distance dependence of these lateral interactions is responsible for producing both the distance-dependent distributions of initial reach directions (Favilla, 1997; Ghez et al. 1997) and the distance-dependent influence of the value of one target on the PMd activity related to another (Pastor-Bernier and Cisek, 2011). That same model, only slightly modified with a gradual GO signal, is also able to reproduce our current results on plan switches (Figure 6D) and the distributions and timing of initial launching directions (Figure 6B, C). Note, however, that the model makes no attempt whatsoever to explain activity after movement onset – it includes no dynamics for producing or guiding movement, and its M1 activity should only be interpreted as capturing the initial pattern around the time of movement onset. Nevertheless, despite the absence of any movement production mechanisms in the present form of the model, it is consistent with models in which the movement trajectory is generated through continuous feedback via proprioceptive and visual signals (Bullock and Grossberg, 1988, 1998; Burnod et al., 1999; McIntyre and Bizzi, 1993; Shadmehr and Wise, 2005) and through internal forward models (Bullock et al., 1993; Miall and Wolpert, 1996; Shadmehr et al., 2010). The model is compatible with general theories proposing that movements unfold as a dynamical system that is guided by the continuously updated pattern of activity within a distributed sensorimotor map. These patterns of activity can be shaped by a variety of processes, including attention (Baldauf and Deubel, 2010; Tipper et al., 1998), decision-

variables (Cisek, 2007), and continuous spatial information from the dorsal visual stream (Day and Lyon 2000; Desmurget et al., 1999; Goodale and Milner, 1992; Milner and Goodale, 1995).

That a relatively simple "biased competition" model can explain this fairly large set of data is particularly interesting given that the same mechanism is often used to explain the neural mechanisms of spatial attention (Boynton, 2005; Desimone and Duncan, 1995). This supports the conjecture (Allport, 1987; Cisek, 2007; Duncan, 2006; Neumann, 1990; Rizzolatti et al., 1987) that both attention and decision-making are related aspects of a general process of selection necessary to arbitrate between the many demands and opportunities for action that animals are continuously faced with in their natural environment. In this view, sensory information is continuously winnowed along the dorsal stream as it is converted into information specifying potential actions and ultimately guiding their execution. In all cases, this winnowing process involves a biased competition, but the specific dynamics of the process may be somewhat different in different brain regions.

For example, Louie et al. (2011) showed that activity in LIP was best described as

$$R = R_{\max} \frac{V_{in} + \beta}{\sigma + V_{in} + V_{out}}, \tag{2}$$

where R is the firing rate, R_{max} is the maximum firing rate, V_{in} is the value of targets in the , V_{out} is the total value of targets outside the , and β and σ are the baseline activity and semi-saturation terms, respectively (see Reynolds and Heeger, 2009). Note that, as shown by Grossberg (1973), the normalization computation described by equation (2) can be produced by the steady-state solution of equation (1) if the excitation term E is equal to V_{in} and the inhibition term I is equal to V_{out} (see Cohen and Grossberg, 1983, for a proof

of Lyapunov stability for a general class of such networks). In other words, divisive normalization may result from the competitive interactions within neural populations.

Louie et al. (2011) found that to explain their LIP data, the parameter σ had to be large, implying incomplete normalization such that LIP cells exhibited value-related modulation even with a single target. In contrast, our results suggest that PMd exhibits complete or nearly complete divisive normalization, because in the 1T task we found no value-related modulation whatsoever (Pastor-Bernier and Cisek, 2011), as if the σ parameter is zero. This raises the intriguing question of whether partial divisive normalization is the trend in parietal cortex, which is still far from overt execution, while activity is more fully normalized in regions closer to motor output, such as PMd. This would make good sense if PMd is most closely related to the process of final arbitration between potential actions, but a deeper understanding of these differences between LIP and PMd require further investigation.

To summarize, we found evidence that PMd neurons, which appear to be involved in the competition determining the initial selection of action, continue to take part in action selection after movement onset, reflecting a change of plan when a selected target becomes unavailable. This finding is compatible with previous studies of plan changes during the delay period (Wise and Mauritz, 1985) and during target jump paradigms (Archambault et al., 2009, 2011; Georgopoulos et al., 1983), as well as with the suggestion that PMd activity may be causally involved in the voluntary inhibition of movement (Mirabella et al., 2011). Taken together, these results provide support for the general hypothesis that the brain mechanisms for selecting between actions involve the same circuits that guide the execution of the actions during overt behavior.

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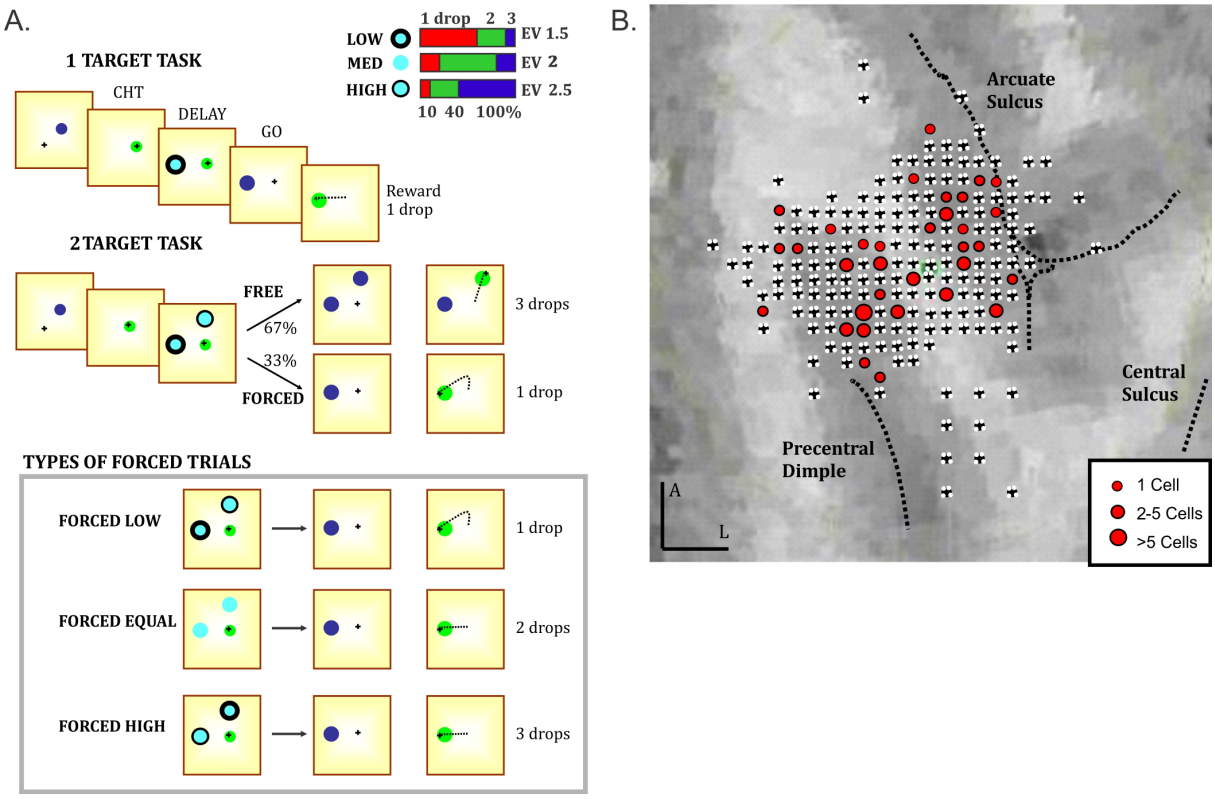

Figure 1. A. Behavioral task. The task involves moving a cursor from a central circle to one of six possible target locations. At the beginning of each trial the monkey placed the cursor in the center and two targets appeared. Each target was associated with different rewards indicated by different border styles (legend shows the probability of receiving 1 (red), 2 (green) or 3 (blue) drops of juice for each border style). The monkey had to keep the cursor in the center until the targets changed color (GO signal). Then, it moved to one of the targets and held the cursor there to get a reward. In one variant of the task, the monkey was presented with only one target (1T). In a second variant two targets were presented, and the monkey was either free to move to either of them after the GO signal (FREE trials), or one disappeared after GO leaving the monkey with only the remaining option (FORCED trials). **B.** The recording locations in PMd. Black crosses indicate recording sites. The locations for cells modulated by relative value (RV cells) are shown with red circles (N = 52).

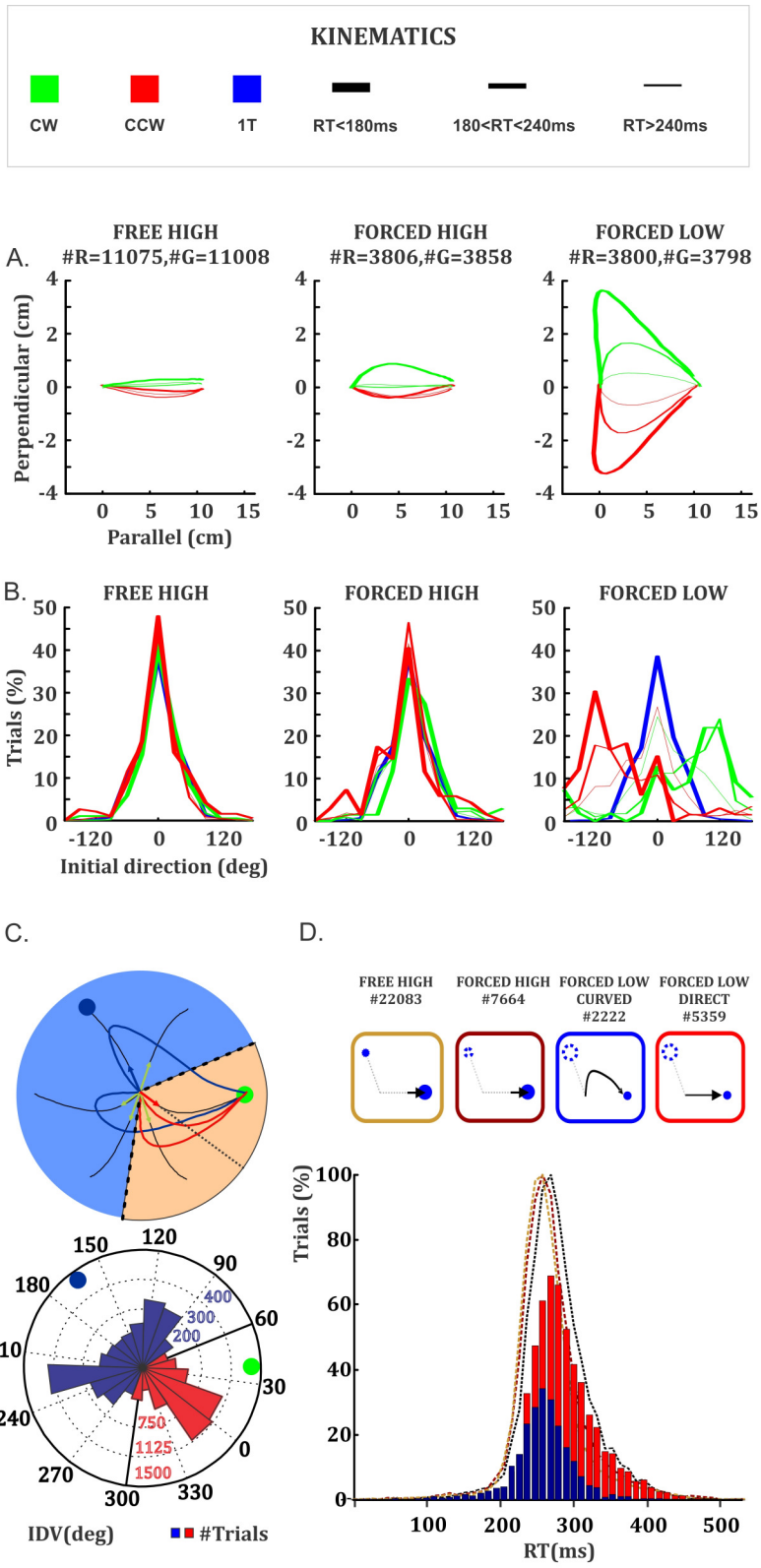
KINEMATICS
CW
CCW
1T
RT<180ms
180<RT<240ms
RT>240ms
A.
FREE HIGH
#R=11075,#G=11008
FORCED HIGH
#R=3806,#G=3858
FORCED LOW
#R=3800,#G=3798
Perpendicular (cm)
Parallel (cm)
B.
FREE HIGH
FORCED HIGH
FORCED LOW
Trials (%)
Initial direction (deg)
C.
D.
FREE HIGH
#22083
FORCED HIGH
#7664
FORCED LOW
CURVED
#2222
FORCED LOW
DIRECT
#5359
Trials (%)
RT(ms)
IDV(deg)
#Trials

Figure 2. A. Average trajectories for 2T trials with the unselected target located 120 degrees clockwise (red) or counterclockwise (green) to the selected target (always on the right). The three panels from left to right represent FREE, FORCED HIGH and FORCED LOW trials. The line thickness represents trials classified by their RT. Thick lines correspond to long RT (>240ms), medium sized lines to intermediate RT (between 180 and 240ms) and thin lines short RT (<180ms) (See Method sections for details). **B.** Distribution of initial launching directions, with selected target at 0°. The color and line thickness code is the same as in Figure 2A. Blue histograms represent 1T trials to the selected target. **C.** Method used to classify trials as direct (red) or curved (blue). The top panel shows individual FORCED LOW trials when the remaining target is to the right and the vanished target is to the upper left. Small arrows indicate the initial direction vectors and the red region indicates the 120° angle around the average, within which trials were considered to be "direct". The bottom panel shows a rose plot of the distribution of individual initial direction vectors. **D.** The RT distributions of FORCED LOW (black dash) trials, including FORCED LOW "*direct*" (red solid) and "*curved*" (blue solid) trials along with the RT distributions of FREE HIGH (light brown dash) and FORCED HIGH (dark brown dash).

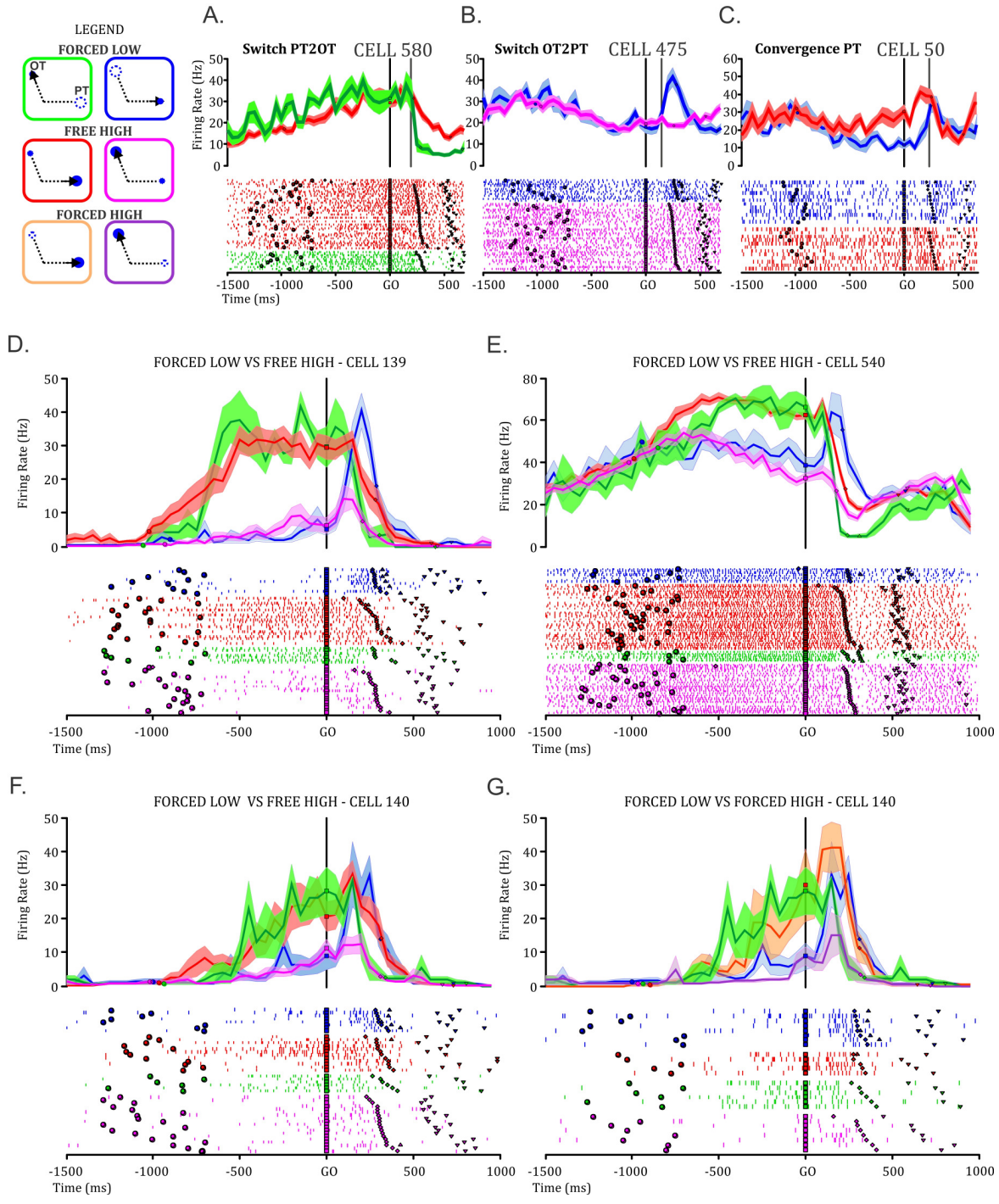
LEGEND
FORCED LOW
OT
PT
FREE HIGH
FORCED HIGH
A.
Switch PT2OT
CELL 580
B.
Switch OT2PT
CELL 475
C.
Convergence PT
CELL 50
Firing Rate (Hz)
Time (ms)
GO
D.
FORCED LOW VS FREE HIGH - CELL 139
E.
FORCED LOW VS FREE HIGH - CELL 540
F.
FORCED LOW VS FREE HIGH - CELL 140
G.
FORCED LOW VS FORCED HIGH - CELL 140

Figure 3. Top-left: The different types of trials are represented in color boxes. Target position is indicated by a blue circle in PT or in OT. The target value is indicated by circle size. In a "FORCED LOW" condition the most valuable option disappears after the GO signal (dashed circles) giving rise to two possibilities: whether the target with the larger value (big circle) was the cell's PT (green box) or the other target (blue box). In both cases the monkey is forced to move to the remaining option (small circle). We compare these trials with "FREE HIGH" trials, in which the monkey is free to choose the target located either in PT or OT (red or pink) and selects the option with higher value (FORCED-FREE comparison). We also separately compare FORCED LOW trials with "FORCED HIGH" trials in which the target that disappeared after the GO signal was the less valuable one (orange and violet) (FORCED-FORCED comparison). In all panels bold black arrowheads indicate the selected option. **A-G.** Examples of the activity of individual cells illustrating the switching of movement plans observed between the pre-GO and the post-GO period. Cell activity is depicted as firing-rate histograms, with mean±s.t.e., and rasters in which black marks indicate cue onset, go signal, movement onset and offset, with trials sorted by RT. A switch from PT to OT (**SwitchPT2OT**) is seen by comparing trials that have a pre-GO plan to PT and a post-GO plan to OT (green) with trials that have both a pre-GO and post-GO plan to PT (red). The time of the switch is indicated by a grey vertical bar (only in Figure 1A-C for simplicity). The alignment of activity on the GO signal for rasters and firing rate histograms is indicated by a black vertical bar in all panels. A switch from OT to PT (**SwitchOT2PT**) is seen by comparing trials that have a pre-GO plan to OT and a post-GO plan to PT (blue) with trials that have both a pre-GO and post-GO plan to OT (pink). The time of convergence to a plan in the PT direction (**CONV**) is found by comparing trials with a pre-GO and post-GO plan to PT (red) with trials with a pre-GO plan to OT but a post-GO plan to PT (blue). Convergence to an OT plan cannot be determined from the activity of cells because activity to OT is generally low.

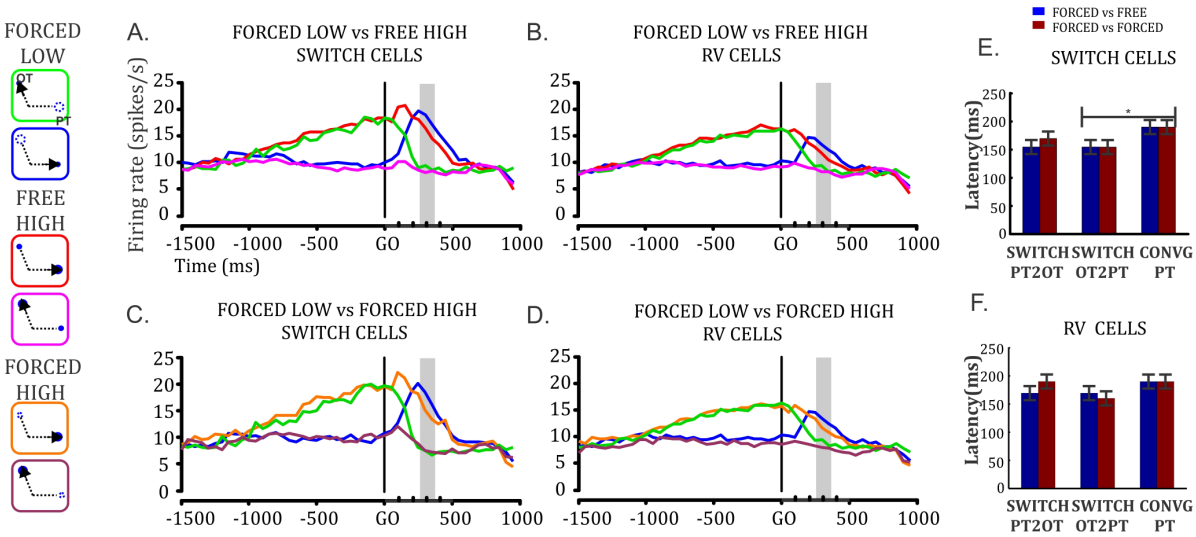

Figure 4. Population activity. Cells with statistically significant plan switches (**Switch Cells**, N=37) and all cells discriminating relative values (**RV Cells**, N=52) were examined separately for switch latencies in the FORCED vs. FREE (**A-B**) and FORCED vs. FORCED comparisons (**C-D**). The grey bar indicates the time range of movement onset. The legend has the same color code as in **Figure 3**. **E-F.** Comparison of the latencies of SwitchPT2OT, SwitchOT2PT and CONV in these two groups of cells in FORCED-FREE (blue bars) and FORCED-FORCED comparisons (brown bars). The horizontal line above the histograms represent comparisons that were statistically significant (ANOVA, $p<0.05$).

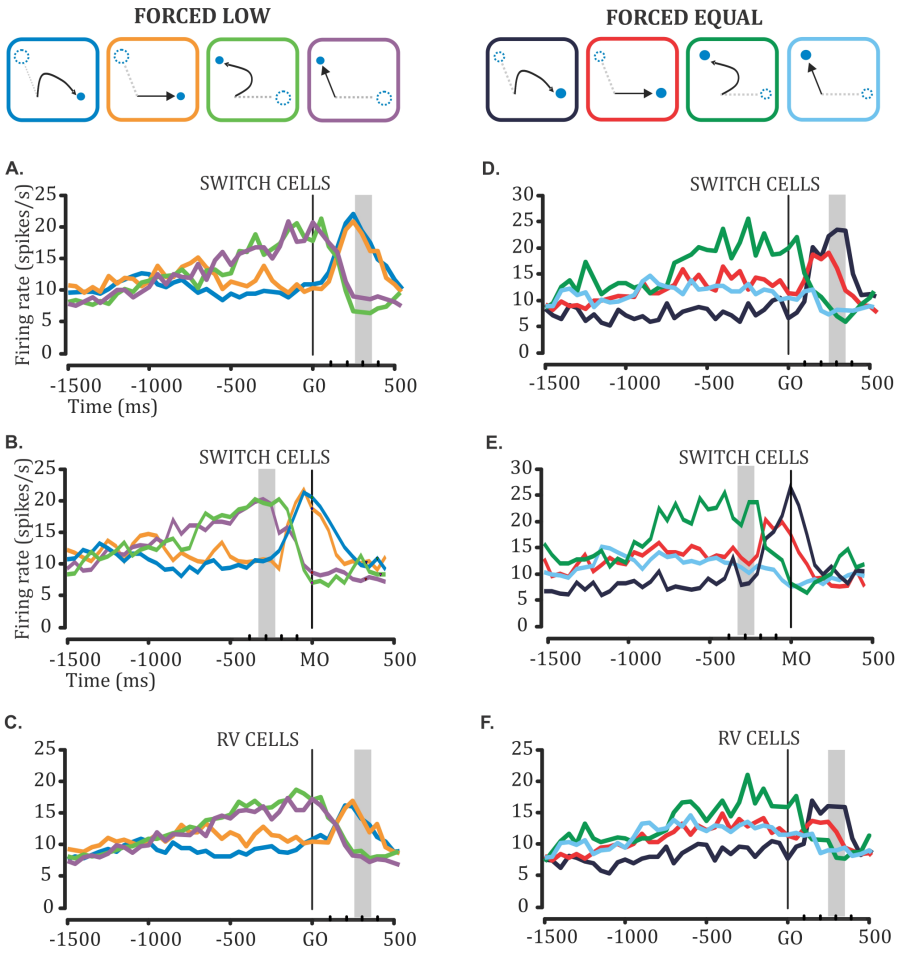

Figure 5. Cell responses in the plan switch paradigm taking into account the initial direction of the reach movements in each trial. **A-C.** Comparison of direct and curved movements in the FORCED LOW condition for **Switch Cells** (**A-B**) and **RV Cells** (**C**). Trajectories are classified as curved to PT (blue box), curved to OT (green box), direct to PT (orange) or direct to OT (violet). **D-F.** Comparison of straight and curved movements in the FORCED EQUAL condition for **Switch Cells** (**D-E**) and **RV Cells** (**F**). Trajectories are classified as curved to PT (dark blue box), curved to OT (dark green box), direct to PT (magenta) or direct to OT (cyan). In panels A, C, D and F the data is aligned on GO and the grey bar represents the time range of movement onset. Panels B and E replot the data in A and D, respectively, with alignment on movement onset (MO), and the grey bar indicates the time range of the GO signal.

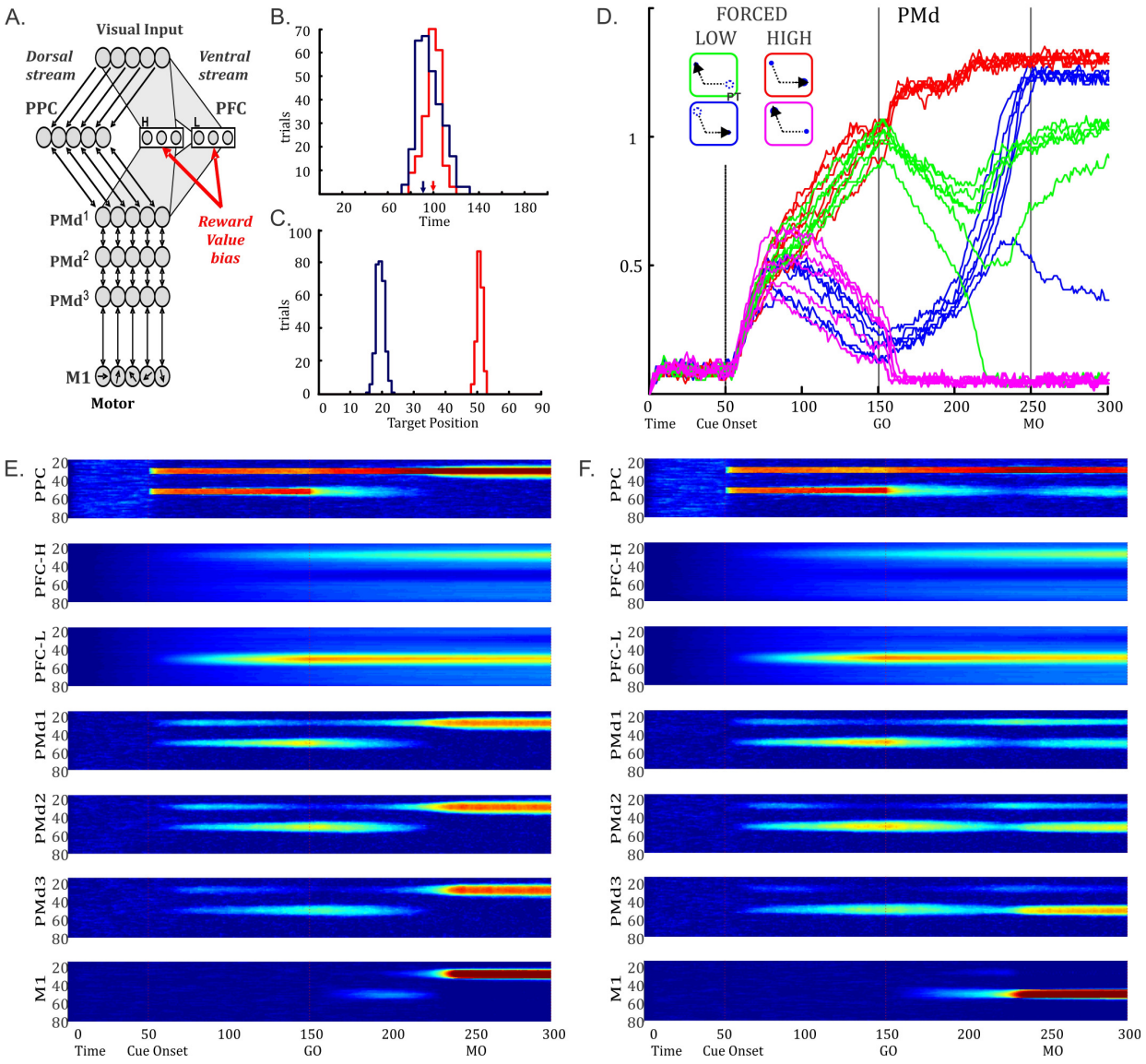
A.
Visual Input
Dorsal stream
Ventral stream
PPC
PFC
H
L
PMd1
PMd2
PMd3
M1
Motor
Reward Value bias
B.
trials
Time
C.
trials
Target Position
D.
FORCED
LOW
HIGH
PMd
PT
Time
Cue Onset
GO
MO
E.
F.
PPC
PFC-H
PFC-L
PMd1
PMd2
PMd3
M1
Time
Cue Onset
GO
MO

Figure 6. A. Model of action selection, in which populations of cells along the dorsal stream implement a distributed representation of potential actions that compete against each other through lateral inhibition. Each population is modeled as a set of tuned neurons with "on-center-off-surround" recurrent connectivity. The model includes posterior parietal cortex (PPC), prefrontal cortex (PFC), three regions of PMd (rostral to caudal) and primary motor cortex (M1). Biasing signals related to absolute reward value (High, H or Low, L) enter as independent inputs to particular PFC layers (PFC-H, PFC-L). **B.** RT distributions for trials in which the model launched to the target that vanished (blue) or to the remaining target (red). **C.** Initial launching directions toward the vanishing target (blue, at position 20) or remaining target (red, at position 50). **D.** A simulated neuron showing activity during four compared conditions: FORCED LOW OT2PT (blue), FORCED HIGH OT (purple), FORCED LOW PT2OT (green) and FORCED HIGH PT (red). Individual lines represent individual simulated trials. **E.** Patterns of activity in the model's Parietal, PFC, PMd (rostral to caudal) and M1 populations, during a FORCED LOW trial in which the target at position 50 was more valuable but vanished at the time of the GO signal, and the plan switch was completed prior to movement onset (MO). **F**. Patterns of activity in another FORCED LOW trial, but in which the movement was launched before the plan switch was complete, initiating to the target at position 50.

Table 1. Classification of cells

PMd Cell counts	**N**
Cells with any delay activity	**181**
Delay activity only	77
Movement and Delay activity	104
Discrimination of relative value (RV)	**52**
Delay and Movement	30
Delay only	22
Switch Cells *FORCED vs FREE	**37**
Switch OT2PT	31
Switch PT2OT	22
Convergence PT	15
Switch **FORCED vs FORCED	28
Switch OT2PT	24
Switch PT2OT	17
Convergence PT	13

* FORCED LOW vs FREE HIGH

** FORCED LOW vs FORCED HIGH

Table 2. Population latencies obtained with sliding ANOVA

	SwitchPT2OT	SwitchOT2PT	Convergence PT
N:37 POP ANOVA			
FORCED-FREE	155±13*	155	190
FORCED-FORCED	170	155	190
N:52 POP ANOVA			
FORCED-FREE	170	170	190
FORCED-FORCED	190	160	190

Table 2. Plan switch latencies in PMd cells that discriminate relative values (RV cells, N=52) and in a cell subset with individually statistically significant switches (Switch cells, N=37). The mean activity for each individual cell was calculated prior to pooling the cells together in order to obtain a balanced contribution of each cell. Latency values were obtained by a sliding ANOVA on the population profile.
*CI = 95% confidence interval for latency values at $p<0.05$.

VII. GENERAL DISCUSSION

1. Recapitulation of results

The work presented in this thesis confirms a number of important predictions suggested by the *affordance competition hypothesis* (Cisek, 2006, 2007) focusing on decision making and action planning in PMd during visual guidance of arm movements. *This hypothesis reads as follows:* **action selection and specification in PMd involve a unified, parallel architecture that uses sensory information to simultaneously specify several potential actions while collecting information for selecting among them through a biased competition process.** This general hypothesis consists of several specific hypotheses. The first proposes that **action selection entails a biased competition process.** This hypothesis makes three main predictions.

The first prediction states that neural activity can represent multiple potential actions simultaneously (***prediction 1A***)**.** *Articles 1 and 2* confirmed indirectly that neural activity in PMd can simultaneously represent several potential actions in agreement with previous studies conducted by the same group (Cisek and Kalaska, 2005). In addition, population activity in PMd behaves in agreement with the biased-competition model proposed by Cisek in 2006.

The second prediction states that neural activity in PMd does not represent a single decision variable in isolation but integrates all factors that influence choices such as expected value and spatial information (angular distance) of the targets **(*prediction 1B*).** This prediction is consistent with the "subjective desirability" concept proposed by

Dorris and Glimcher (2004) for oculomotor decisions in LIP. *Articles 1 and 2* showed that PMd reflects both EV and the spatial parameters of the actions. Moreover, these two studies suggest an interaction between the metrics of the actions and the value representations (spatial gain effect).

The third prediction states that the variables that are associated with a given option are always expressed relative to the alternative actions (***Prediction 1C***). *Articles 1 and 2* show this for PMd and PMv. The results presented in *article 2* suggest in particular that PMd reflects relative value according to a fully divisive normalization model (Louie and Glimcher, 2011), which is a requirement for a structure involved in a decision process as opposed to a valuation process (Padoa-Schioppa, 2011). The first two articles emphasize the interaction of value and spatial information and substantiate the notion that the action metrics can be taken into account in the process of action selection.

Similar observations are raised for area PMv which is also close to the motor output for grasping (*article 2*). It is important to mention here the absence of absolute value representation in the arm system in contrast with the oculomotor system in PMv or LIP (Platt and Glimcher, 1999; Roesch and Olson, 2003, 2004). This difference can be interpreted from the point of view of functional differences that exist among these two systems. It seems more plausible to represent absolute value in the oculomotor system because its role may be more fundamentally related to help find and identify items of value (attentional search function) rather than obtaining them as it is the case with reaches among two or several edible items.

The second hypothesis states that biasing information is incorporated gradually in the action specification process. This hypothesis predicts that the latency

for biasing and spatial information will be different (***Prediction 2***). In all three articles we observed that spatial information in PMd was conveyed to the action specification process as early as 75ms after cue onset, presumably through the fast dorsal visual stream, meanwhile biasing information such as relative value was incorporated gradually and slightly later (starting from 150ms after cue onset). *Article 2* addresses the *prediction 2* from a learning perspective. In a novel environment the spatial metrics of the actions seem to be already present in PMd. Spatial information is present even in the situation in which the animal did not learn the novel associations. However, relative-value appears only when the animals start to make behaviorally informed decisions about the value of the available options. Both in familiar and novel conditions the value information is delayed with respect to spatial information by 75-100ms. These results suggest that the fast visual pathways of the dorsal stream provide PMd with all the spatial information required for specifying the metrics of actions, while slower learning-dependent ventral stream processing is required for the mapping from target feature to abstract value representations.

The third hypothesis states that the strength of the competition between potential actions depends on the similarity between them, and predicts that decisions among actions are affected by the metrics of the options (***Prediction 3***). This prediction is verified in *articles 1 and 2*. Cells show an increased gain in value effects when the targets are farther apart than when they are close to each other. This statement may be particular to the interaction kernel of PMd cells involved in reach planning as differences have been observed between the arm and eye system (Louie et al., 2011). The results for the reach system can be interpreted from the point of view of an affordance competition

mechanism. When choosing to *reach* between two nearby targets, the nervous system can mix their neural representation and start moving between them. However, when the targets are located in diametrically opposed locations the choice has to be all or none. For the oculomotor system no such effect can be observed and this can interpreted taking account of the following consideration. There may be little value in saccades that land in between targets and saccades cannot be smoothly adjusted if a target jumps. Instead one might require two or several saccades. However, it is known that the location of distractors can affect saccade trajectory (McPeek et al., 2003) so one cannot completely rule out the possibility that the arm and oculomotor system might reflect similar features.

The fourth hypothesis states that decisions are made in the same regions that guide the actions. This hypothesis predicts that action selection and action specification are not two serial but parallel processes (***Prediction 4***). *Article 3* addresses this particular prediction and shows that the same cells that guide initial decisions continue to update their activities after animals change their mind, further substantiating the notion that decisions are made in the same regions that guide the actions. All major findings could be reproduced by a computational model (Cisek, 2006). Altogether, these results suggest that, **although decisions between actions are influenced by variables supplied by higher cognitive regions, they are determined by a competition which takes place within the sensorimotor circuits themselves.**

2. Deciding among actions in PMd

Recent neurophysiological studies have shown that when decisions are made between actions, the process of action selection involves areas implicated in sensorimotor control (Glimcher, 2003; Gold and Shadlen, 2007; Schall et al., 2004b; Schall and Bichot; 1998). Action selection is a distributed process that takes place in parallel within many sensorimotor areas (Cisek, 2007a, b, 2012). Our first article suggests that decision variables such as EV influence the outcome of the decisions and this process might be the result of a competition between alternative action representations in PMd. Our data shows that the effect of EV is always relative and never appeared when there is no choice to be made.

It is however, known that activity reflecting the absolute value of actions has been reported in PMv for oculomotor tasks (Roesch and Olson, 2003). The discrepancy between our and Olson's results may be attributed to the well known differences between visual guidance of eye and arm movements in these two distinct areas (Boussaoud and Wise, 1993; Hoshi and Tanji, 2007). PMd is mainly concerned with goal selection and specification processes for arm reaching, meanwhile PMv seems to be involved in sensory processes (extrinsic and intrinsic space representations), complex object manipulation (grasping) and action-observation representations ("mirror" neurons) altogether requiring a different treatment of sensory and value information than PMd (Kakei et al., 2001; Rizzolatti et al., 1981, 1988; Rizzolatti and Luppino, 2001). This view is substantiated by the distinct pattern of anatomical connections between the two areas (Rizzolatti and Luppino, 2001).

Absolute value representations could arise from prefrontal areas such as DLPFC (Kalenscher et al., 2010; Leon and Shadlen, 1999). In particular DLPFC projects heavily

to PMv but not to PMd (Carmichael and Price, 1995b; Lu et al., 1994) with exception of subregion F7. Despite the compelling anatomical connectivity between DLPFC with area F7 and PMv we did not observe absolute value representations in either of the two. Alternatively, the absolute value signal present in PMv could be differentially conveyed through BG loops, since there is good evidence that both areas receive partially segregated projections from the thalamus (Morel et al., 2005; Stepniewska et al., 2007). Absolute value representations could also be conveyed indirectly through parietal projections since these signals are present in some particular regions such as LIP (Louie et al., 2011).

3. Decisions among actions in basal ganglia

It has been proposed that BG might contribute to action selection through a competition process between action representations originating from different motor systems. According to this idea, the competition is resolved by selectively inhibiting unwanted actions through feedback loop projections (Brown et al., 2004; Leblois et al., 2006; Mink, 1996; Redgrave et al., 1999).

Leblois et al. (2006) have proposed a model in which information traveling through the direct- and the hyperdirect BG pathway interacts via diffuse subthalamic-pallidal connections, and a competition between action representations takes place across these loops. It has been suggested that the dynamics of this competition can explain both normal and pathological motor behavior. This is supported by latency studies in the non-human primate suggesting that action selection can take place earlier in BG than in motor

structures (20ms for virtual action plans; Arimura et al., 2010; Yamagata et al., 2010), and earlier in SC than in PMd, for arm related tasks (Song et al., 2008).

Notably, focal inactivation of SC, an area involved in eye-movement target selection and execution, causes target selection deficits for reaching movements but no deficits for action specification (Song et al., 2011). This is not surprising since the circuitry from cortex to SC through BG is shorter than the cortico-basal loop through the thalamus (Shires et al., 2010).

Since somatotopy and space representations are also well represented in the motor regions of the basal structures, one would lean towards the idea that biased competition between actions can take place in BG rather than in PMd and that that information is merely relayed to premotor cortex subsequently. The latency results have to be taken with caution. It is noteworthy that modulation by CVML has been reported in frontal lobe structures such as PMd, SEF as well as in BG but little difference has been observed in latency of the effects across these structures (Brasted and Wise, 2004; Buch et al., 2006; Chen and Wise, 1995a, 1995b, 1996; Hadj-Bouziane and Boussaoud, 2003).

Furthermore, Miller's group has shown that the latency of information processing between sensory-motor and prefrontal structures might largely depend on task design. For instance, activity related to action-selection might be reflected earlier in PMd than in PFC in a match-non-match task (Cromer et al., 2011), and earlier in FEF than in LIP in a search conjunction task (Buschman and Miller, 2007). Antzoulatos and Miller (2011) recorded neuronal activity in the prefrontal cortex and caudate nucleus as monkeys learned to map visual categories to either a left or right goal for a saccade. They confirmed an earlier finding from Pasupathy and Miller (2005), as monkeys learn to map

exemplar stimuli to a goal, striatal activity encoded the goal earlier than did cortical activity. However, as the monkeys learned to classify many exemplars in each category, cortical activity that encoded category-to-goal mappings developed earlier than did striatal activity. It is important to mention that this task or feature dependent variability is in agreement with the idea that action-selection takes place through a distributed network (Cisek, 2007a, b).

4. Representations of value or probability of choice: LIP vs PMd

Platt and Glimcher (1999) were among the first to show that LIP neurons could be modulated by the magnitude of expected gain in either forced or free choice trials. In their task they presented animals with delay cued saccade trials in which a change in the color of a centrally located fixation stimulus instructed the animals to choose among two possible eye-movement responses in order to obtain reward. In any given block the animals could obtain either a fixed gain for a correct saccade or no reward.

In their study the value probabilities were manipulated across blocks and not across trials, and thus it is hard to tell here if the neural activity changes reflected local income or EV. The forced task did not compare RF activity in LIP cells with respect to changes in expected gain outside of the RF, since there was only one correct choice available so it is also hard to conclude if the expected gain representation was absolute or relative. A “free choice” variant in which the animals were not cued the spatial location of the correct response was also conducted. In this situation the animals had to figure out the expected gain of each of the options by trial and error.

The monkey's choice in the cell's RF was directly proportional to the value of the target in the RF demonstrating good agreement with Herrnstein's "matching law" (Herrnstein, 1961), which implied LIP in value-guided decision making. However, this variant also did not address whether LIP could be modulated by different gains between target options because there was only one possible "correct" option (i.e reward vs no reward) to choose among.

Later on, Dorris and Glimcher (2004) trained monkeys in a free-choice paradigm in which the monkeys were asked to choose between a "safe" target, consistently delivering a small reward, and an alternative "risky" target, probabilistically delivering a large reward. This type of task is also called inspection game (Kreps, 1990), and has no single correct action. Free to choose, rational subjects adopt a *mixed strategy* in which they devote a certain portion of responses to each action (Fudenberg, 1994) leading to a Nash equilibrium (Nash, 1950, 1951) in which the "subjective desirability" of each of the available actions becomes equivalent. The subjective desirability was estimated by the expected utility of each of the actions in the gamble. The expected utility is a function of the probability, magnitude and delay of reward (Kreps, 1990).

Dorris and Glimcher (2004) showed that macaque monkeys performed this task using a mixed strategy and reached the Nash equilibrium for each of the gambles. Most importantly, LIP activity was correlated with the *relative subjective desirability* of the options as opposed to *absolute subjective desirability*. Relative subjective desirability is the subjective estimate of desirability associated with the saccade in the neurons RF divided by the sum of the subjective desirability associated with all saccades. The

absolute subjective desirability would have LIP activity correlating with the value of the targets appearing in the neurons RF without any dependency on the value of targets appearing elsewhere. In a sense, Dorris and Glimcher's result is similar to our study in PMd in which delay period activity in PMd reflects the *relative expected-value* of the options and not absolute EV.

Dorris and Glimcher (2004) also addressed whether the correlate of subjective desirability was absolute or relative by doubling the gain equally for both options (safe and risky) across different blocks. This is similar to our 2T-EQUAL task variant.

However, the group failed to see any evidence of absolute value in LIP, although these results have to be considered carefully. Simple and double gain trials were not interleaved but presented in different blocks and a normalization process within each block could explain the lack of modulation across them. This is different in our case, in which we had interleaved reward-equal trials of different absolute magnitudes within the same block, so this limitation could be safely ruled out.

5. Absolute and relative value representations: LIP vs PMd

Newsome's group (Rorie et al., 2010) conducted follow-up experiments on Glimcher's work addressing whether or not LIP contains absolute value representations. In their experiments, the animals were presented with two spatial cues followed by a delay period after which the cues change color according to the reward magnitude associated with each of them (red high, blue low). Subsequently, a dot motion discrimination stimulus was presented, and after a variable delay (250-500ms) two

decision cues appeared. The animals could be presented with targets with equal high value (high-high, HH), equal low value (low-low, LL) or with targets having different relative values (high-low, HL, low-high, LH). The absolute and relative value trials were randomly interleaved, potentially encouraging a more dynamic representation of value, as in our 2T task.

In this experiment, Rorie et al. (2010) did observe absolute value effects. *This is in contrast with our results because we did not observe absolute value differences between equal-valued targets of different overall magnitudes in PMd or PMv (i.e. between LL, medium-medium, MM and HH).* However, Rorie's results are consistent with previous work (Sugrue et al., 2004) suggesting that *LIP neurons simultaneously represent relative value, absolute value and motion coherence*.

Furthermore, Rorie et al. (2010) reported interesting latency differences between the observed relative and absolute value effects. LIP neurons initially respond with a representation of absolute value (about 100ms after color cue onset), which is then modulated by the value of the target outside the response field, and comes to represent the target's relative value (about 150-200ms after color cue onset). Both relative and absolute value effects could be detected both at an individual cell and population level. Moreover, these relative and absolute value representations fade after the movement motion instruction and become modulated only by the monkey's forthcoming choice.

The representation of choice quickly dominates the LIP response and is modulated by the specific coherence of the motion stimulus. As the motion epoch ends, the representation of relative value is largely gone, but the representation of *absolute*

value remains. The group concludes that throughout the entire delay epoch, LIP activity represents the absolute value of the target in the response field and predominantly represents choice of that target, irrespective of the coherence or relative value supporting it (Rorie et al., 2010).

It is important to mention here that the latency for relative value effects is very similar to the one we observed in PMd. This observation substantiates the notion of a distributed network for value representation through the parieto-frontal cortex. However, in Rorie's experiment relative value representations fade during action selection and argue against a simultaneous action selection and planning process for oculomotor decision in LIP, although it is important to mention that in Rorie's task we have matching behavior and not free choice behavior.

Assuming that relative value representations play a role in biased competition between options, it is natural that Rorie et al. (2010) would not see any at movement time (GO signal), as there is no longer a competition taking place at this point. Rorie's task is different than ours in this respect. In our task the animals were encouraged to keep both plans available at the time the GO signal appears, since one of the options might randomly disappear 1/3rd of the time (FORCED trials). Accordingly, we observed relative value modulation extending well beyond the movement instruction and specifying alternative plans, in particular when the best pay off option is gone (FORCED LOW trials, *article 3*).

A more recent experiment with oculomotor perceptual decision making in free choice conditions comes from Glimcher's lab (Louie et al., 2011). In close agreement with our results their work supports the notion that LIP harbors relative value

representations that influence the process of action selection. However, in agreement with Rorie's results and in contrast with ours, Louie et al. (2011) reports the existence of absolute value signals in LIP and suggests uncomplete value normalization. For example, Louie et al. (2011) showed that activity in LIP was best described as

$$R = R_{\max} \frac{V_{in} + \beta}{\sigma + V_{in} + V_{out}},$$

where R is the firing rate, R_{max} is the maximum firing rate, V_{in} is the value of targets in the , V_{out} is the total value of targets outside the , and β and σ are the baseline activity and semi-saturation terms, respectively (see Reynolds and Heeger, 2009). Our results can be explained by a similar expression, except that σ is equal to 0 and normalization is therefore *complete*.

We can naturally ask what could be the role of absolute value signals. Absolute value signals comply with rational, context independent behavior, such as it has been claimed in prescriptive neuroeconomics (Von Neumann and Morgenstern, 1944). Relative value signals are instead important for adaptative and context-dependent choice behavior as it has been proposed in prospect economic theory (Kahneman and Tversky, 1979, 1982).

Louie et al. (2011) showed that modeling activity in LIP was best described by an algorithmic expression implying *incomplete divisive normalization* in order to take account of both absolute and relative value representations. In our case, neural activity in PMd is best described using a computational model where the activity in PMd is reflected as the result of a dynamic interaction between cell populations. In Cisek's model (Cisek, 2006) absolute value signals are inputs to PMd, although the outcome of

the decision, a dynamic interaction process, reflects only relative value signals. The cell population interaction process can be described as follows:

Potential action plans are encoded in hills of activity for populations of directionally tuned neurons. Short-range mutual excitation interactions take place between similarly tuned cells and long range lateral inhibitions take place among cells with different tuning.

A biased competition between action plans can lead to a steady-state solution (Cohen and Grossberg, 1983) in which PMd activity reflects *complete divisive normalization*. The difference between LIP and PMd raises an intriguing hypothesis. Partial divisive normalization is the trend for parietal cortex, which is still far from overt execution, while activity is more fully normalized in regions close to the motor output such as PMd. This would make good sense if PMd is more closely related to the process of final arbitration between potential actions, and predict similar behavior in closely related areas for eye movements such as FEF (Roesch and Olson, 2003).

6. Absolute and relative value representations: FEF vs PMd

Studies in area FEF provide different insights to the process of valuation and decision than area LIP. For instance, Leon and Shadlen (1999) trained animals in an oculomotor working memory task in which the animals were required to remember the location of a briefly lit target and to shift their gaze to its location upon extinction of the fixation point. During the task a change in the color of the fixation point indicated whether the animals would receive a small or a large reward at the end of the trial.

Although this is not a decision task, since the animals are forced to saccade to a single location in space, the task is similar to the 1T condition we explored in our articles.

Leon and Shadlen (1999) recorded in area FEF and DLPFC, and observed that cells in FEF were not sensitive to the magnitude of the reward. This observation is in agreement with our finding that no absolute value was observed in PMd in the 1T task. The results in FEF could still be confounded by the block design as normalization could take across trials in the 1T block since the experimenters did not attempt to randomize 1T trials with choice trials as in our task, in which this confound could be ruled out.

Despite this problem, there is some confidence that normalization due to task design was not taking place, or if it was the case it would be only locally since the same group reported absolute value modulation in the nearby area 46 of DLPFC. We can interpret these results in reference to the properties of area FEF. The FEF like PMd is an area that is relatively closer to the motor output than DLPFC and LIP. Based on the anatomy and physiology one would expect these two areas to be more involved in taking part in decision rather than in valuation processes. It is possible that despite receiving absolute value signals the network dynamics reflects exclusively relative and not absolute value information, as it is only the former that is required for decisions.

7. Distribution of effects in PMd and comparison with human tasks

Comparatively little is known about differences within subregions of PMd in action selection in species other than rhesus macaques. It is known for instance, that the rostral and caudal portion of PMd, namely areas F7 and F2 described in macaques, have

functional and anatomical homologues in humans (Abe and Hanakawa, 2009; Boussaoud, 2001; Geyer et al., 2000; Rizzolatti et al., 1998; Wise and Murray, 2000). Area F7 is called *pre-PMd* and area F2, *PMd-proper* (Picard and Strick, 2001) and both areas share the connectivity pattern of the prefrontal-premotor-parietal network identified in monkeys (Tomassini et al., 2007). Furthermore, rostro-caudal gradients for cognitive to executive functions have also been reported within PMd in both monkeys and humans (Boussaoud, 2001; Simon et al., 2002).

In fMRI studies conducted by Toni et al. (1999) and Hanakawa et al. (2006) humans were tested with instructed delay visuo-motor tasks involving choice within a single limb (index or middle finger flexion) or across different limbs (right or left hand). In both cases pre-PMd and PMd-proper were modulated after cue onset by the instruction specifying the type of movement. However, pre-PMd seemed to be more active during the early delay period meanwhile PMd proper was more active after GO instruction and movement epoch. In particular, PMd-proper was the only area among the two that reflected choice effector (right or left hand) during execution. These results could be to some extent task-dependent, since it is known that in monkeys the difference in cell tuning properties for left and right arm reaches is modest at best in PMd, in contrast with M1 which shows clear contralateral preferences during the movement epoch (Cisek et al., 2003).

Hanakawa's results (2006) could be seen in light of the observed differences between humans and other primates concerning laterality or handedness (Zhao et al., 2012). It is plausible that functional differences between human and macaque PMd could be attributed to the different role of the forelimb in the two species (Annett, 2002; Porac

and Coren, 1981). It is also plausible that laterality effects might have been overlooked in monkeys since those subtle effects are normally larger in complex bimanual coordinated tasks compared to less demanding unimanual tasks (Fagot and Vauclair, 1991).

Studies in a number of primate species are providing evidence in support of the task complexity view of primate hand preference, although there might be other factors at play such as variability of these effects across primates species such as *Cebus abella* (Lilak and Phillips, 2008; Spinozzi, 1998; Westergaard and Suomi, 1996), *Gorilla gorilla* (Byrne and Byrne, 1991) and *Pan troglodytes* (Colell et al., 1995).

In summary, human experimental studies suggest that pre-PMd plays a more important role in visual attention and memory aspects of action planning and selection meanwhile PMd-proper is more involved in the executive aspects of action planning and selection. In our study however, we observed no differences in the distribution of effects between the analog area of pre-PMd (F7) and PMd-proper (F2).

8. Competition among action representations takes place in the same areas involved in guidance of movements

Another important implication of our findings is that the site where the competition takes place is also the site that specifies and executes the chosen actions. Traditionally, it has been accepted that decision-related modulations are made in "upstream" regions (OFC, DLPFC) which are clearly involved in decisions among abstract goods (Padoa-Schioppa, 2012; Wallis and Miller, 2003a, b). However, our results argue against this traditional view. Namely, we found that the dynamics of

competition that determines decision among actions appears to be done in the sensorimotor system because it takes account of the geometry of the environment and the effector used. These spatial effects appear in PMd cell activity as soon as the cells respond to visual stimuli, further implying that the competition between actions take place throughout the fast sensorimotor dorsal visual stream (Cisek, 2007; Cisek and Kalaska, 2010).

9. Simultaneous action and specification extends beyond the time a movement is instructed

In agreement with previous studies, our results suggest that decisions between reaching actions are made within the same brain regions involved in the execution of the actions themselves (Cisek, 2007; Cisek and Kalaska, 2010; Glimcher, 2003; Gold and Shadlen, 2007; Pesaran et al., 2008). Our results suggest that once a decision is made, the decision related population in PMd continues to be involved in the on-line guidance of movement.

This argues against the traditional cognitive view where action selection, specification and execution are serially connected and non-overlapping processes. The alternative view proposes that decisions among actions emerge through a competition process within the same circuit that guides movement execution, implying that these processes are integrated and can largely overlap (Cisek, 2007).

A growing body of evidence suggests that such integrated processes are best suited to deal with dynamic changes of the environment, allowing us to quickly and

smoothly update movement plans and even change decisions in-flight (Archambault et al., 2009, 2011; Day and Lyon, 2000; Desmurget, 1999; Georgopoulos et al., 1981, 1983; Gritsenko et al., 2011; Mirabella et al., 2011; Prablanc, 1992; Scangos and Stuphorn, 2010; Wise and Mauritz, 1985). In our case, PMd neurons that are involved in the competition determining the initial selection of an action continue to take part in action selection, and start to reflect a plan toward an alternative action once the previous one becomes unavailable.

These findings are in agreement with previous PMd studies of switch of plans during the delay period (Wise and Mauritz, 1985), during target jump paradigms (Archambault et al., 2009, 2011; Georgopoulos et al., 1983) and voluntary inhibition of movements (countermanding task; Mirabella et al., 2011). Moreover, the same model that was used to simulate neural data on simultaneous specification of alternative action plans and subjective desirability of the options during the delay period (Cisek and Kalaska, 2005; Pastor-Bernier and Cisek, 2011b; Pastor-Bernier et al., 2012) could be used without major parameter changes in order to reproduce the results of plan switches. Altogether, this data substantiate the notion that the brain mechanisms involved in decisions among actions involve the same circuits that guide the execution of the actions during overt behavior.

VIII. FUTURE PERSPECTIVES

1. Action cost during action selection: interaction between context and value

When choosing between actions, the spatial layout of the environment directly specifies the options and is of critical importance for evaluation what is the best choice in terms of payoff and cost. If the value of the options is equal, humans select the actions that are least demanding biomechanically (Cos et al., 2011). Concerning the spatial effects described in our studies, it could be thought that choosing among distant targets is intrinsically more effortful than choosing among two close ones. This is because it takes a larger amount of commitment to move to either of the far targets than it does when the targets are close by, because in the latter case one can start moving between them and determine the concrete decision later.

Animals choose the course of an action not simply on the basis of the expected value but also on the potential action costs (Charnov, 1976; Croxson et al., 2009; Hull, 1943; Stephens and Krebs, 1986). In terms of foraging, this may involve deciding between harvesting *now* an impoverished source of food nearby, or travel further to reach a better source and harvest *later* (*spatio-temporal choice*). For instance, South African baboons (*Papio ursinus*) walk by less desirable food patches in order to get more desirable food further (Noser and Byrne, 2007). Action costs might also imply choosing between a high or a low energy mode for locomotion, such as flying or walking, depending on the value of the expected reward (Bautista et al., 2001; Janson, 1998; Kacelnik, 1997; Tinbergen, 1951; Stevens, 2005).

Several subjective representations of action costs have been proposed, namely biomechanical, emotional or ultimate metabolic cost. However, all these representations have in common the willingness that the animal has to trade off the commodity and effort in order to obtain reward. Therefore, it is still unclear today if cost has a common neurobiological currency. For instance, decision making in birds reflects an estimation of both the value and the metabolic cost of an action (Bautista et al., 2001). Rats and monkeys maximize the reward rate by taking account of both the reward magnitude and the effort entailed by repetitive number of lever presses required for each of the options (Walton et al., 2006). Humans take account of the biomechanical context of potential actions when choosing among them (Cos et al., 2011).

It is also common to observe a trade off between the cost of an action and its temporally discounted value. However, *temporal discounting* has been traditionally studied in isolation within the framework of very particular inter-temporal choice tasks. Within this context, both rats, pigeons, monkeys and humans typically prefer smaller rewards that occur earlier over larger rewards occurring later (Ainslie, 1974; Richards et al., 1997; Rodriguez and Logue, 1988). However, animals often employ ecologically rational decision strategies (Todd and Gigerenzer, 2007), and take account of the actions costs depending on the environment (spatial context). For instance, Stevens et al. (2005) has shown that spatio-temporal choice and temporal discounting can be dissociated behaviorally across different primate species. Tamarins *(Saguinus oedipus)* travel farther for large rewards than marmosets *(Callithrix jacchus),* and attend more to the ratio of reward differences between the options rather than their absolute values. The converse can be observed in a temporal task for these two species. When the spatial context is not

important, marmosets are normally more patient than tamarins for large rewards indicating that they discount the temporal delay less steeply than tamarins.

These results are in agreement with a number of pharmacological, lesion and imaging studies (Aoki et al., 2006a, b; Denk et al., 2005; Prevost et al., 2010; Rudebeck et al., 2006) indicating that temporal discounting and spatio-temporal cost decisions depend on partially separable neural systems. For instance, dorsal ACC lesions in rats lead to impairments in cost decisions and not temporal discounting meanwhile lesions in OFC explicitly impair the ability to sustain reward expectations across a delay (discounted value) but does not affect effort-based decisions (Kennerley et al., 2011; Roesch et al., 2006; Rudebeck et al., 2006; Schoenbaum and Roesch, 2005).

2. Neural encoding of action costs

2.1. Basal ganglia

The BG's dopaminergic system, which is implicated in the modulation of goal-directed behavior, motivation and reward expectation (Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Salamone and Correa, 2002; Schultz et al., 1992, 1993; Wise and Rompre, 1989) also seems to mediate effort-related behavior in the rat (Salamone et al., 1994, 2003).

Salamone's group (1994) presented animals with two different reward-cost options in a T-maze barrier paradigm. One of the options consisted in scaling a wall in one of the arms of the T-maze in order to obtain a large reward (High reward - High effort). The other option was to follow the alternative unobstructed arm of the T-maze

and obtain a low reward (Low reward - Low effort). Salamone et al. (1994, 2003) showed that dopamine depletion in nucleus accumbens biased rats away from choosing the high reward high effort option, leading them to prefer instead the low reward in the unobstructed arm of the T-maze.

In a further study (Cousins et al., 1996) Salomone injected rats systemically with haloperidol (a dopamine receptor antagonist) and tested them on a similar T-maze barrier task where identical large barriers were present in both the high-reward and low reward T-maze arms. In this situation there was a small but significant switch away from choosing the high reward arm, even though selecting the low reward arm entailed the same cost as for the high-reward arm but with half the concomitant reward.

This suggests that dopamine could be involved in the motivation aspects of the action options rather than the comparative cost among them. Since the dopaminergic system is fundamentally related to motivation (Evenden and Robbins, 1984; Horvitz and Ettenberg, 1988; Liao and Fowler, 1990; Ungerstedt, 1971), anti-psychotic drugs targeting the dopaminergic system might influence primarily the motivational aspect of the options (Ho et al., 1999; Mobini et al., 2000a, b; Wise and Rompre, 1989) .

2.2. Anterior cingulate cortex

There is a growing body of evidence suggesting ACC as an important region involved in cost-based decisions (Kennerley et al., 2011; Walton et al., 2002, 2003). This area is also known to be implicated in action selection (Picard and Strick, 2001) and is connected to other areas involved in action selection such as premotor cortex (Beckmann

et al., 2009). Of particular interest are the series of recent studies conducted by the groups of Wallis, Kennerley and Walton (Kennerley et al., 2009; Kennerley and Wallis, 2009; Wallis and Kennerley, 2011; Walton et al., 2002, 2003). To investigate directly the role of rat ACC in effort-related decision making, Walton et al. (2002, 2003) started by comparing the choice performance of rats in the T-maze barrier task both before and after lesions to this region. As described in Salamone's studies (1994, 2003), the animals typically chose to do more work for an increased quantity of food (High reward - High cost). However, following lesions to ACC there was a complete reversal in behavior and the animals always selected the response involving less work and smaller reward (Low reward - Low cost).

However, the biases obtained as a result of the lesions were still contingent on the magnitude of the cost (barrier height) and the animals would start choosing the high reward option when the effort was equated by addition of an identical barrier on the low reward and low cost maze arm (Walton et al., 2003). This suggests that the animals were not impaired on the perception of (absolute) cost itself but had maybe *altered a relative cost representation*, thus changing the decision criterion and making them less willing to overcome the work constraints to gain a high reward.

Complementary electrophysiological and imaging studies suggest that ACC reflects the interaction of both expected reward and effort costs in decision making tasks both in humans (Croxon et al., 2009) and monkeys (Kennerley et al., 2011) pointing further towards a specific role of this structure in comparative cost evaluation. Although action cost representations in decision making seem to be emerging in ACC, action cost is still hard to dissociate from motivation in humans. Patients with bilateral ACC lesions

result in akinetic mutism, a wakeful state characterized by prominent apathy, indifference to painful stimulation, lack of motor and psychological initiative (Tekin and Cummings, 2002). Apathy (and depression) for instance, is often present in patients with subcortical brain lesions (involving BG and dopaminergic system) but it is more commonly found in those with prefrontal, mainly ACC lesions (Kurniawan et al., 2011; Van Reekum et al., 2005). It is therefore, plausible that both ACC and the dopaminergic system participate in the mechanisms underlying evaluation of cost in overt behavior.

2.3. Premotor cortex

It could be plausible to observe effort signals in other structures than ACC or BG. For instance, effort signals could be relayed from either of these two areas to PMd given the existent connectivity between them (Arikuni et al., 1994; Beckmann et al., 2009; Kelly and Strick, 2004). From a theoretical point of view it is also plausible for these effort signals to be involved in action selection processes.

The affordance competition hypothesis predicts that *neural activity in PMd does not represent a single decision variable in isolation but integrates all factors that influence the choices.* This observation is in agreement with observations in which other sensory-motor areas such as LIP and ACC integrate value, cost and other factors affecting the subjective desirability of the options and constitute the "biases" of a decision (Kennerley et al., 2009; Platt and Glimcher, 1999). The generality of this assumption predicts that we will see effort-biases in PMd in a similar way we already observed value biases.

It could be plausible to oberve effort biases in other premotor areas such as in PMv, in particular concerning actions involving tool usage or different types of grasp. It has been shown that non human primates such as chimpanzees (*Pan troglodytes*) represent the cost associated with tool usage in potential future actions (Frey and Povinelli, 2012). Area PMv (F5) is particularly known for treating hand-tool information during action execution and observation (Gallese et al., 1996; Rizzolatti et al., 1988, 1996; Rochat et al., 2010) and context-specific grasping (Fluet et al., 2010; Fogassi et al., 2001; Gentilucci et al., 1983; Murata et al., 1997). These cost representations could also participate in action selection since PMv has also been related to action selection in perceptual decision tasks such as tactile stimuli discrimination (Acuna and Pardo-Vazquez, 2011; Pardo-Vazquez et al., 2011; Romo et al., 2004).

Based on these observations it could be reasonable to expect some degree of involvement of PMv in cost-based action selection mechanisms, particularly in cases in which the actions involve different types of graps or grasping-specific tools. In general, one could examine these effort signals in either PMd during reaching tasks or PMv during grasping tasks in order to further assess the valididty of predictions made by the affordance competition hypothesis.

3. The cognitive debate in neuroeconomics

The debate for the allocation of cognitive functions to specific areas continues until today. It has been proposed that *economic choice* and compliant decision variables such as *economic value* are found in particular cortical areas (Padoa-Schioppa, 2011).

Economic choice is the behavior observed when individuals make choices solely on the basis of subjective preferences and is closely related to decision making, as originally conceived by the *prescriptive economic theory*, a branch in economics that addresses rational decision making (Simon, 1947, 1983).

Prescriptive economic theories have initially proposed that humans tend to maximize "utility" in rational choice behavior, although it has been shown that humans can display irrational behavior as well (Allais, 1953; Ellsberg, 1961) and maximize utility only in certain circumstances (Simon, 1997), just as other simpler organisms are also able to do (Harper's mallard duck forage experiment; Harper, 1982).

Human non-transitive behavior (Kahneman and Tversky, 1979, 1982; Güth et al., 1982) supports the notion that decisions are not made according to the classic economic choice, but through a combination of utility (economic value) and other variables representing the desirability of the options (subjective relative desirability) such as risk and cost (Glimcher et al., 2005). This general framework for decision making is predicted by the *prospect theory of economics* (Kahneman, 1979).

Neural correlates of utility (economic value) have been found in the OFC of non-human primates (Padoa-Schioppa, 2011). Padoa-Schioppa and Assad (2006) presented animals with a free-choice task in which it was encouraged to trade between commodity (taste) and reward amount. The experimenters observed that OFC contained three main types of task related neurons: *offer value* cells, *taste* cells *and chosen value* cells.

Offer value cells encode the subjective value of only one of the options presented, irrespectively of whether either of the options is actually chosen or not. Conversely, *taste*

cells encode the binary result of the choice process and reflect the outcome of the decision (Padoa-Schioppa and Assad, 2006).

The *chosen value* cells reflect the combined subjective value of the two options. These cells had a typical U-shaped response pattern as a function of value for two given option gambles, and do not reflect the process of selection itself but the subjective value of the gambles themselves. *Chosen value* cells are particularly interesting because they also reflect transitivity (Padoa-Schioppa and Assad, 2008) and encode the value of a gamble *per-se* independently of the physical property of each of the offers (type of juice).

Subsequent studies showed that cells in OFC comply with the "rationality" axioms proposed by the prescriptive economic theory: *the Von Neumann–Morgenstern utility theorem* (Von Neumann and Morgenstern, 1944). In fact, OFC neurons encode the *absolute* value of an outcome, not the *relative* value, thus respecting value transitivity (Padoa-Schioppa and Assad, 2008). OFC neurons adjust their gain to reflect the full range of values on a given block of trials (range adaptation; Padoa-Schioppa, 2009) and are independent of the sensory-motor contingencies of the task (Kennerley et al., 2009; Kennerley and Wallis, 2009; Padoa-Schioppa, 2007, 2009; Padoa-Schioppa and Assad, 2006, 2008).

It is also known that OFC represents other economic variables as well, such as *risk* (O'Neill and Schultz, 2010), *economic cost* (Sloan et al., 2010) *and social reward* (Watson and Platt, 2008). In addition, different cortical areas share some of the economic variables found in OFC. For instance, ACC is modulated by the *economic value* of the options (Cai and Padoa-Schioppa, 2012; Kennerley et al., 2011; Wallis and Kennerley,

2011) and the dopaminergic system reflects both *risk (uncertainty) and range adaptation* (Fiorillo et al., 2003; Tobler et al., 2005).

In a recent study conducted by Kennerley et al. (2011) neural activity was recorded in area ACC and OFC in a task paradigm in which monkeys were asked to choose between pairs of stimuli associated with different risk (probability of reward), payoff (reward amount), or action cost (effort represented as the number of lever presses needed to obtain reward). ACC neurons primarily integrated several decision parameters (effort, cost and reward amount) in contrast with OFC in which this was not prevalent. In addition, neurons in ACC that integrated all the decision parameters also encoded reward prediction errors. In contrast, OFC did not encode reward prediction errors but reflected the chosen value relative to the recent trial history.

The complementarity between OFC and ACC extends beyond economic valuation. For instance, the groups of Platt (Chang et al., 2012) and Duhamel (Azzi et al., 2012) have recently shown a differential coding of egocentric and allocentric reward outcomes during social interaction in the primate ACC and OFC. ACC neurons reflect predominantly the outcome for reward delivered to other monkeys (allocentric), whereas OFC neurons reflect self-delivered reward (egocentric).

Together, these results suggest *a complementary interaction between OFC and ACC both in valuation and decision processes*. The comparison of OFC with ACC is particularly interesting because the latter structure supports economic choice in a *task-dependent* manner. A recent study by the group of Padoa-Schioppa (Cai and Padoa-Schioppa, 2012) has shown that ACC contain *chosen-value* and *taste-value* cells with

identical properties as reported in OFC, including *range adaptation,* thus reflecting economic value.

However, in another context in which the options have different action-cost requirements, decisions in ACC seem to violate the Von-Neumann prescriptive economic axioms. In fact, ACC cells are spatially selective and can be also modulated by movement direction and physical effort (Amiez et al., 2006; Hayden and Platt, 2010; Hillman and Bilkey, 2010; Kennerley et al., 2009; Kennerley and Wallis, 2009). Thus, ACC harbors both *absolute and relative value* representations substantiating either transitive or non-transitive behavior in a situation of uncertainty, risk or conflict (Cai and Padoa-Schioppa, 2012; Coricelli et al., 2005; Fujiwara et al., 2009; Hayden et al., 2011a).

Decision making in a risky or uncertain environment can be dependent on context (Kacelnik, 1997) and influence foraging behavior (Charnov, 1976). For instance, Hayden et al. (2011b) trained primates in a oculomotor *stay-or-switch* task that contains elements of foraging theory (Charnov, 1976; Stephens and Krebs, 1986). In this type of task the animals were encouraged to select consistently one of the targets (stay and harvest a food resource, also called "patch") and obtain reward within a short intertrial delay or select an alternative target obtaining no reward and suffering a long delay (switch or leave a patch). After a given choice on a given target, the monkey received a constant amount of water. However, on subsequent choice on the same target ("stay" target) the reward decreased by 19µl. If the monkey continued to choose the 'stay' option, its value would eventually reach 0 and remain 0 thereafter. This setting encouraged the animals to switch to the alternative target once the stay target was "depleted". The alternative target does not yield reward and imposes a long time delay (proportional to the size of the target) but it resets

the value of the depleted one. This setting introduces a trade off between staying and obtaining a gradually decreasing reward, or switching and resetting the value of the options with an associated effort (traveling time in foraging theories).

Hayden et al. (2011b) found that neurons in ACC encoded a decision variable signaling the *relative value of leaving a depleting resource for a new one*. In fact, neurons fired during each sequential decision to stay in a patch and, for each travel time, these responses reached a fixed threshold for patch-leaving. Longer travel times reduced the gain of neural responses for choosing to stay in a patch and increased the firing rate threshold mandating patch-leaving. These modulations closely matched the behavioral decisions.

All these results lead to the following observations: decisions are highly affected by context (action cost, uncertainty, risk and social weight of the options). Several predictions can be derived from this observation: first, decisions are better explained by a prospect economic theory (Kahneman, 1979) and an affordance competition mechanism (Cisek, 2007a) than by prescriptive economy axioms (Von Neumann and Morgenstern, 1944) addressing exclusively rational behavior. Second, the affordance competition mechanism can take account of all variables that explain adaptative behaviour including action costs. In fact, an affordance competition mechanism includes all factors that affect the subjective desirability of the options and influence the choices (Dorris and Glimcher, 2004).

4. Recent models for decision making

Padoa-Schioppa (2011) has recently proposed a “” model for decisions. In this model, all of the factors relevant for a decision are integrated in the OFC producing a unified representation of the economic value of potential offers. These values are compared and once the larger one is chosen, the appropriate action plan is released for execution. This model predicts that sensorimotor regions begin to prepare movements only after decisions are made (Padoa-Schioppa, 2012). However, many studies have shown that neurons in both parietal and frontal cortices can represent multiple potential targets and/or actions long before the animal decides between them (Baumann et al., 2009; Cisek and Kalaska, 2005; Cui and Andersen, 2007; Hoshi and Tanji, 2007; Klaes et al., 2011; Pastor-Bernier and Cisek, 2011a; Platt and Glimcher, 1997; Scherberger et al., 2007).

A claim that these are not true motor representations is difficult to reconcile with behavioral results. In particular, the trajectories observed in a variety of reach (Chapman et al., 2010; Ghez, 1997; Tipper, 2000; Song and Nakayama, 2008b; Welsh et al., 1999) and saccade tasks (McPeek et al., 2003) strongly suggest simultaneous processing of multiple actions in parallel. For instance in McPeek’s study saccadic eye movements are made in a search task that requires selecting a target from distractors and the movements show greater curvature in their trajectories than similar saccades made to single stimuli. The group performed single-unit recording and microstimulation experiments in the superior colliculus (SC). They found that saccades that ended near the target but curved toward a distractor were accompanied by increased presaccadic activity of SC neurons coding the distractor site. The magnitude of increased activity at the distractor site was correlated with

the amount of curvature toward the distractor. In contrast, neurons coding the target location did not show any significant difference in discharge for curved versus straight saccades. The stimulation in SC location where the distractor was presented mimicked the activity recorded for curved saccades in search, and the subsequent saccades to the visual target showed curvature toward the location coded by the stimulation site. These results support the hypothesis that the increased saccade curvature observed in search arises from competitive interaction between two simultaneously attended options.

Additionally, it is unclear how the brain could compute action costs without having at least some representation of the potential actions. Cos et al. (2011) showed that when faced with two equal-valued actions, humans strongly preferred the one that is biomechanically easier. Because the biomechanical costs are similar at the beginning of the movement the subjects had to take account of the future biomechanical properties of both choices in order to select the easier one. Moreover, OFC cannot explain economic choice when *action cost* takes part in the decision of the process (eg. climb a small or large obstacle in order to obtain a reward). Growing evidence suggests in fact that ACC may have a specialized role in influencing effort-based decision making. Lesions in ACC bias animals toward actions that are associated with less effort even when a more rewarding option is available (Floresco and Ghods-Sharifi, 2007; Schweimer et al., 2005; Walton et al., 2002, 2003). In contrast, OFC lesions impair delay-based decision making, but not effort-based decision making (Rudebeck et al., 2006).

A model does not explain why neural activities in sensorimotor regions are modulated by decision variables. Such modulation has now been consistently observed in

parietal, frontal, and subcortical components of both the oculomotor and skeletomotor systems (Cisek and Kalaska, 2010; Gold and Shadlen, 2007; Hernandez et al., 2010; Kable and Glimcher, 2009; Kim and Basso, 2008; Sugrue et al., 2005; Thevarajah et al., 2010), including M1 (Michelet et al., 2010). There is good evidence that subjective values are being represented in sensorimotor areas that are modulated by attentional percepts or impending actions such as PMd, LIP, SMA, SEF, SC and even M1 (Amador et al., 2000; Bestmann et al., 2012; Ikeda and Hikosaka, 2003; Louie and Glimcher, 2010; Pastor-Bernier and Cisek, 2011b; Roesch and Olson, 2003; Sugrue et al., 2004; Thevarajah et al., 2010). It has even been demonstrated that the gain of mid-latency reflexes is modulated by the sensory evidence used to make perceptual judgements, suggesting that the decision process could very well change the limb preparatory state at the corticospinal level (Selen et al., 2012).

As an answer to the "goods-based" model, Cisek (2012) has proposed an alternative framework for the decision process that addresses some of the issues of the goods model for decisions that are made among actions. In Cisek's proposal the decision is the result of a competition process (affordance competition) that takes place at multiple levels in parallel. Assuming these processing levels are reciprocally connected, biases that may arrive from a variety of sources are shared among them and encourage decision through a "distributed consensus". For example, when choosing between two ways to obtain the same piece of fruit, the decision is determined at a lower level due to the influence of action cost biases. In contrast, when deciding between exploiting nearby resources versus exploring other parts of the environment, the particular actions are not explicitly specified and the decision is resolved at a higher level. Finally, when choosing between two prey one must

weigh abstract factors such as their value (e.g. amount of food) as well as concrete sensorimotor contingencies (e.g. distance to target). In this situation the decision taken is the outcome of a weighted competition between the different biases (Cisek, 2012).

IX. CONCLUSIONS

The work presented in this thesis confirms a number of important predictions suggested by the *affordance competition hypothesis* (Cisek, 2006, 2007), focusing on decision making and action planning of the PMd in visual guidance of arm movements. This hypothesis reads as follows: *action selection and specification in PMd involve a unified, parallel architecture that uses sensory information to simultaneously specify several potential actions while collecting information for selection among them through a biased competition process.*

We confirmed that neural activity can simultaneously represent several potential actions in agreement with previous studies conducted in the same group (Cisek and Kalaska, 2005). We showed more specifically (Pastor-Bernier and Cisek, 2011b) that neural activity in PMd does not represent a single decision variable in isolation but integrates all factors that influence choices such as expected value and spatial information (angular distance) of the options and this observation is consistent with the "subjective desirability" concept proposed by Dorris and Glimcher (2004) for oculomotor decisions in LIP. The spatial information in PMd was conveyed to the action specification process relatively early (75ms after cue onset), presumably through the fast dorsal visual stream, meanwhile biasing information such as relative value was incorporated gradually and slightly later (150ms after cue onset).

We also found evidence that the strength of the competition between potential actions depends on the similarity between them. Two spatially dissimilar targets affect both the behavioral (initial movement directions) and neural correlates (cell modulation)

of a decision more than two close-by targets. Namely, when choosing to reach between two nearby targets the nervous system can mix their neural representation and start moving between them. However, when the targets are located in diametrically opposed locations the choice has to be all or none. The same cells that guide initial decisions continue to update their activities after the animals change their mind, further substantiating the notion that decisions are made in the same regions that guide the actions (Pastor-Bernier et al., 2012).

This observation implies that action selection and action specification are not two serial processes but they occur in parallel. These findings could be reproduced by a computational model (Cisek, 2006; Pastor-Bernier and Cisek, 2011b; Pastor-Bernier et al., 2012) further substantiating these notions. Altogether these results suggest that, *although decisions between actions are influenced by variables supplied by higher cognitive regions, they are determined by a competition which takes place within the sensorimotor circuits themselves.*

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