# Neuronal basis of goal-directed reach planning under reversed vision in the parietal and premotor cortices

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I hereby declare that this thesis has been written independently and with no other sources and aids than quoted.

(Shenbing Kuang)

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# Contents

# 1 Introduction

In our everyday life we can produce goal-directed movements precisely and effortlessly, for example to saccade towards a location that you are interested in, or to reach and grasp for a cup of coffee. Goal-directed behaviors are essential skills for survival when humans and higher animals interact with the environment. Correspondingly, a fundamental problem in system neuroscience is to determine how and where the central nervous system achieves the planning and control of these voluntary eye and hand movements. The aim of the current thesis was to use the visually-guided hand reaching movement as a model system to probe such sensorimotor functions in the brain, mostly at the levels of single neurons in the primate cerebral cortex.

To this end, I conducted extracellular single unit recordings in awake, behaving monkeys engaged in well controlled reaching tasks, and interpreted these cortical neural activities in relation to monkeys' behavior. Besides the studies using the method of monkey electrophysiology, I also employed psychophysical and modeling approaches to infer the properties of brain functions on motor planning and motor controls. The advantages of combining these different approaches are that they allowed converging understandings about the cortical sensorimotor functions at various levels, ranging from the theoretical to the behavioral and to the neuronal levels.

I will organize the thesis as follows: The first chapter will give a brief general introduction on the field of sensorimotor researches, with a focus on the evidences from the neurophysiologic studies. The second chapter will cover the main research results in the format of prepared manuscripts. This includes three manuscripts, two of which deal with data from the monkey electrophysiology project while the third one is based on data from human psychophysics. In the third chapter I will summarize the main findings and draw conclusions from the current thesis work, and meanwhile offer some outlooks on future studies which are necessary to further substantiate these conclusions.

## 1.1 Sensory-to-motor transformation

Even simple goal-directed movements such as reaching for a cup of coffee involve complex sensorimotor transformation process which integrates a sensory stimulus (the visual location of the cup) into a motor response (muscle activation to bring the hand toward the cup). Sensorimotor transformation requires solving a number of basic problems. From the sensory side, the location of visual target is coded in the retinal or eye-centered coordinates, whereas the location of the hand is either in the eye-centered (when hand is visible) or body-centered coordinates (hand invisible). From the motor side, target and hand locations must ultimately be translated into the coordinates of the muscles in order to execute the movements. Therefore, central questions in the sensorimotor research are to understand the issues of reference frames, which I will review the contemporary progress in the next section (1.1.2). Before that, in order to prepare for this topic, the following section will briefly introduce the basic cortical neuronal circuitry underlying sensorimotor functions.

### 1.1.1 Cortical reach-related sensorimotor areas

Neuropsychological studies have shown that parietal lesions in human patients often led to reach movement deficits such as inaccurate reaches to the peripheral targets (optic ataxia) or inability to perform smooth and skilled movements (apraxia) (Pisella et al., 2000a;Grea et al., 2002). Along the same lines, virtual lesions, using transcranial magnetic stimulation (TMS) over the posterior parietal cortex (PPC), interfere with the corrections of trajectories or adaptations to external perturbations (Della-Maggiore et al., 2004;Desmurget et al., 1999a). The involvement of PPC in the planning of reach movement is also evident from the neurophysiologic studies in both human and monkeys (Andersen and Buneo, 2002a;Buneo and Andersen, 2006;Vesia and Crawford, 2012). Note that, besides a role in the sensorimotor function, PPC has also been implicated in a number of other higher cognitive functions, among them are neural correlates of decision making (Gold and Shadlen, 2007a), reward expectation (Platt and Glimcher, 1999), rules (Stoet and Snyder, 2004), categories (Freedman and Assad, 2006;Swaminathan and

Freedman, 2012), associations (Fitzgerald et al., 2011), and numerical representations (Nieder et al., 2002). Here, the main focus of the current thesis is on the sensorimotor functions in PPC.

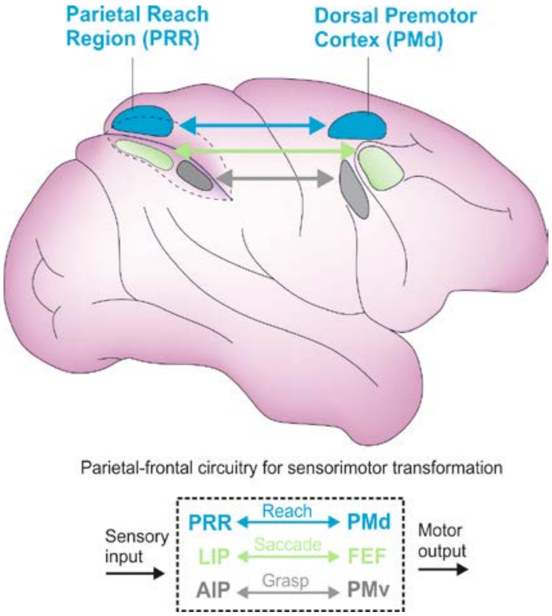

**Figure 1:** Sensorimotor reach-related areas in a lateral view of the macaque cortex. The diagram shows the inside of the intraparietal sulcus (IPS) within the posterior parietal cortex (PPC). The parietal reach region (PRR) occupies mainly the medial bank of IPS, neighboring with other PPC subareas specialized for eye saccade (lateral intraprietal area (LIP), left greenish zone) and hand grasp movement (anterior intraparietal area (AIP), left grey zone). These parietal areas reciprocally interconnected with areas in the frontal cortex, among them are dorsal premotor cortex (PMd) for reaches, frontal eye field (FEF, right greenish) for saccades, and ventral premotor cortex (PMv, right grey) for grasps. Figure adapted from Cohen and Andersen 2002.

PPC is anatomically located between the visual cortex in the occipital lobe and the somatosensory cortex in the post-central gyrus. Thus, it is well suited to receive both visual and somatosensory input and to send output to premotor and motor areas in frontal cortex. PPC contains both the superior parietal lobule (SPL) and inferior parietal lobule (IPL) segregated by the intraparietal sulcus (IPS). There is a mosaic of sensorimotor areas around the IPS (Fig. 1).

Various sub-regions within the IPS have been involved in the control of specific body effectors, including the eyes (lateral intraparietal area, LIP), arms (parietal reach region, PRR) and hand (anterior intraparietal area, AIP). Anatomically, PRR is located at the posterior end of the SPL, medial to the intraparietal sulcus, and it includes mainly portions of medial intraparietal area (MIP) and area V6A (situated between V6 and MIP within the SPL near the junction of the dorsal parietal-occipital sulcus (Andersen and Buneo, 2002a;Vesia and Crawford, 2012).

Furthermore, these parietal areas are reciprocally connected with frontal areas (Wise et al., 1997a): LIP to the frontal eye fields (FEF); PRR to the dorsal premotor cortex (PMd); and AIP to the ventral premotor cortex (PMv). Numerous studies have indicated that PMd is involved in the planning and control of visually guided reaches as well. Individual PMd neurons are active during the delay period preceding an instructed movement (memory-guided reach task), and are tuned for the direction (Scott et al., 1997a;Caminiti et al., 1991a) the distance (Messier and Kalaska, 2000a) and the speed (Churchland et al., 2006a) of reaches. Inactivation of PMd causes deficits in reaching, in particular for complex stimulus-response associations (Kurata and Hoffman, 1994a).

### 1.1.2 Multisensory integration and coordinate transformation

A reference frame means a set of axes that describes the location of an object. For instance, imagine that you are sitting at a table and looking at a cup of coffee on the table (Fig. 2a). The location of the coffee cup can be depicted in several different reference frames. The cup is straight ahead and below relative to the gaze direction, but it can meanwhile be described as to the left when relative to the right arm. The cup’s location can also be defined in a reference frame that depends on the external world (allocentric) rather than the location of your body (egocentric); for example, relative to its position on the table.

Early studies show that area PRR appears to have predominately eye-centred coding (Batista et al., 1999a;Buneo et al., 2002) with gain field modulations by eye and hand position signals (Chang et al., 2009). In contrast, PMd codes the targets in mainly the hand-centered reference

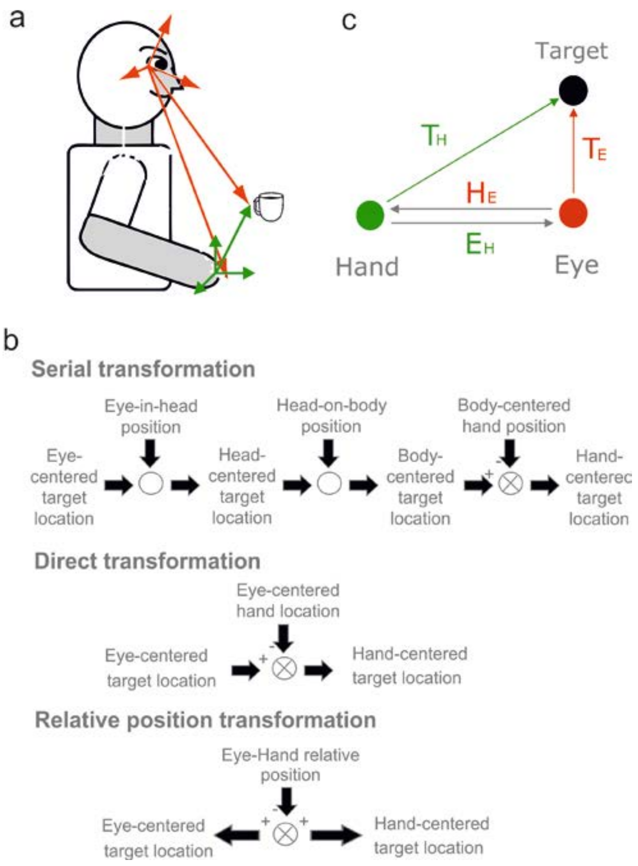

**Figure 2:** Visuomotor transformation Schemes. a, Example of reaching for a cup. The position of the cup is represented initially in the eye-centred coordinate (red axis). To reach for the cup, the cup position had to be defined with respect to initial hand position (green axis, movement vector pointing from hand to cup). b, such coordinate transformation can be achieved by gradually transforming the position of the target from eye- to body-, and finally to hand- centred coordinates (Serial transformation), or directly subtracting hand position from the target position in a common eye coordinates (Direct transformation). A third alternative is to have the invertible eye/hand centred target position by the relative eye in hand or hand in eye coding (Relative position transformation). c, Geometry of relative coding. Figure adapted from Buneo and Andersen 2006 (panel a), Pesaran et al 2006 (panel b) and Buneo et al 2002 (panel c).

frames (Caminiti et al., 1991a;Crammond and Kalaska, 1994;Pesaran et al., 2006a). Corresponding to this simple single reference frame- oriented view, sensorimotor transformation is traditionally viewed as a feed-forward spatial transformations converting visual information, which enters the brain in eye-centred coordinates, into hand-centred coordinates, and finally muscle commands for the arm and hand. This feed-forward transformation can be done either serially or directly (Fig. 2c). Recent studies reveal that representations in both the parietal and frontal cortices are not simply in a single reference frame. Responses are heterogeneous and seem to have mixed or intermediate eye/hand centered coding (Pesaran et al., 2006a;Chang and Snyder, 2010a;McGuire and Sabes, 2011a). Neurons are found that code the target of a reach relative to the eye (eye-centered, $T_E$), the target relative to the hand (hand-centered, $T_H$), the eye relative to the hand (eye-in-hand, $E_H$ or equivalently hand-in-eye, $H_E$), as well as combinations of two or even all three. These results indicate that, in some neurons, a unique relative spatial relation of all three variables will produce the same activity for different absolute positions in space. This form of relative encoding has an advantage for hand-eye coordination in defining a coordinate frame based on the ‘‘work space’’ of the hand, eyes, and reach target (Fig. 2c).

### 1.1.3 Context dependent motor goal encoding

Not all reach movements would go towards a visible target (pro-reach).  For instance, one might reach away from a visual object that he or she wishes to avoid. In the scenario, the visual stimulus and the goal of the movement are not congruent. This discordance has been used to separate sensory perceptions from movement plans in anti saccade and anti reach tasks. In some studies, monkeys have been trained to move in the opposite direction to the appearance of a stimulus (anti-reach, Fig. 3a). If a neuron codes the stimulus location, it is considered sensory; if it encodes the movement direction, it is considered movement-related. In memory-guided reach tasks, neurons in both PRR and PMd often exhibit brief activations during the visual cue presentation, followed by the sustained activity during the delay period when visual stimulus is not available any longer and the movement is not yet executed (Fig. 3b). The sustained activity is typically highly directional selective (spatially tuned). Contrasting the activity between pro and anti reaches indicates that sustained planning activity is correlated with the intended direction of the reach movement (Crammond and Kalaska, 1994;Gail and Andersen, 2006), rather than the memories of sensory stimuli (PRR area as an example, Fig. 3d). The movement goal tuning often persists throughout the delay period and shows very similar properties in both areas except some differences in the magnitude of gain modulations (Gail et al., 2009).

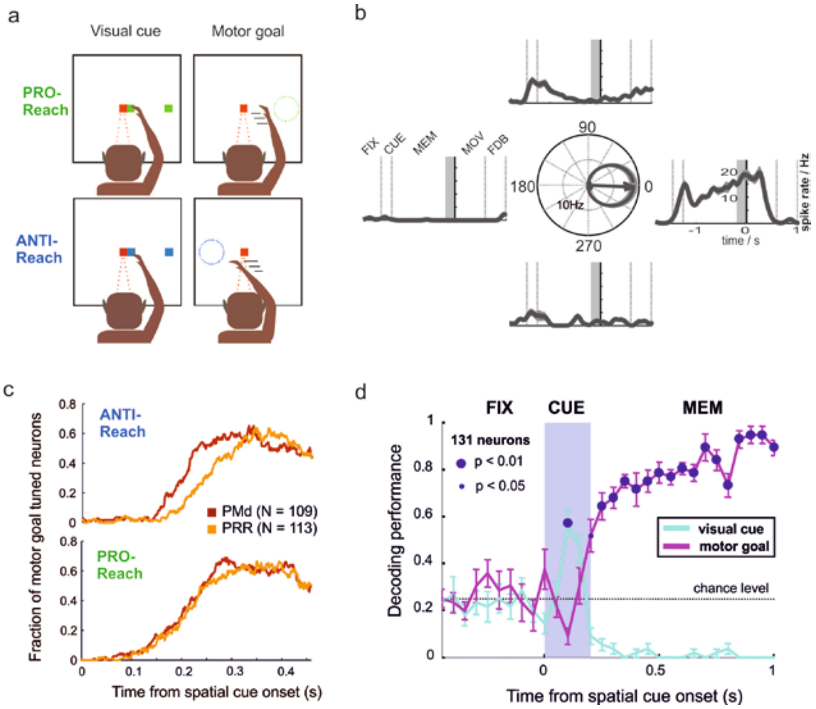

**Figure 3:** Context dependent motor goal representations in the frontoparietal reach areas. a, Task design with reaching movement towards (pro) or away from (anti) a visual stimulus dissociates sensory (stimulus related) and motor (reach related) representations. b, Spike rates in single PRR/PMd neuron is strongly direction selective during the memory guided reaches. c, The fractions of motor-related neurons as a function of time for both PRR and PMd. d, Decoding performance of visual cue versus motor goal in a population of PRR neurons. Figure adapted from Gail and Andersen 2006 and Westendorff et al 2010.

Timings within the parietal-frontal reach network provide some insights into which areas may encode the movement goal earlier. Simultaneous recordings from the fronto-parietal reach areas shows that neural representations of motor goal appears first in PMd and later in PRR (Fig. 3c).

Similar results of frontal areas leading parietal areas have been found when monkeys were engaged in decision-related reach task  (Pesaran et al., 2008). Spike-field coherence suggests that the link from PMd to PRR is activated first, followed by motor goal signals from PRR to PMd in a "hand-shake" fashion within a few milliseconds. However, the timing within this circuit may depend on the task contexts. For instance, the more natural pro-reach task produces approximately simultaneous motor goal representations in PRR and PMd (Fig. 3c). PMd leads PRR only in the case of anti reaches when a spatial remapping is required. These motor goal latencies are interpreted as reflecting a dynamic reorganization of network activity in PRR, and the reorganization is contingent on fronto-parietal projections from PMd (Brozovic et al., 2007a;Westendorff et al., 2010a). The functional relevance of this top-down projection is speculated to be related to prospective forward model estimations, which are essential elements in several motor cognition concepts (see below section for detailed elaborations).

## 1.2 Motor-to-sensory transformation

To date, there are emerging speculations that the pure feed-forward sensory-to-motor integration needs to be accompanied by feedback motor-to-sensory mechanisms which allow updating of motor goals and movement corrections based on an on-line state estimations and motor error signals (Buneo and Andersen, 2006;Andersen et al., 2010a;Shadmehr et al., 2010a;Wolpert, 1997). The term "motor-to-sensory" means a reverse transformation from the motor response to its associated sensory consequence and highlights a bidirectional link between intended action and sensory outcome based on learned associations (Desmurget and Sirigu, 2009;Waszak et al., 2012).

### 1.2.1 Sensory prediction during movement execution

Forward sensory prediction during motor execution is one of the core concepts in adaptive motor control theory (Wolpert, 1997;Desmurget and Grafton, 2000a).  According to this theory (Fig. 4), to monitor the execution of a reach movement, the brain needs to predict the consequences of its motor commands. Further, visual and proprioceptive feedback signals need to be integrated with efference copies of on-going motor commands (also termed as corollary discharges), as well as information about limb dynamics and visual feedback of the hand, to generate an estimate of the current state of the limb as the movement unfolds (Desmurget and Grafton, 2000a).

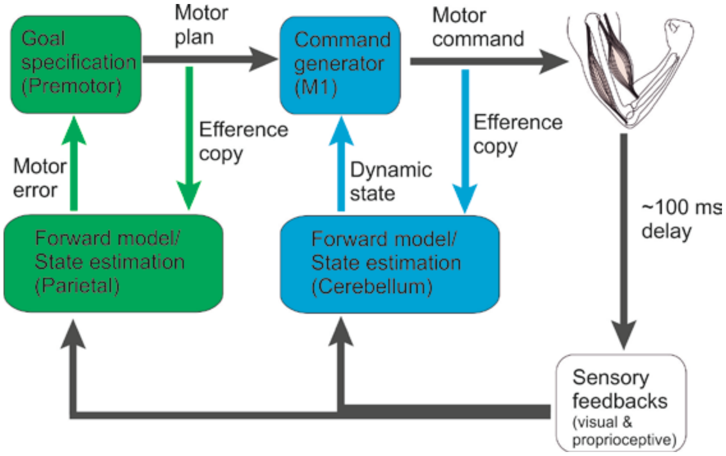

**Figure 4:** Schematic diagrams of motor planning and motor control for voluntary movements. Motor commands, formulated from the current and desired states of the arm via inverse computation in controller. In parallel to being sent to motor periphery for execution, efference copies of command signals are also used to predict the sensory consequences of a movement, which is then integrated with delayed sensory feedback signals to form the belief about the current hand positions (blue loop). A similar internal loop also exists during movement planning to allow predicting the sensory consequences of motor intentions (green loop) prior to movement onset, which is important for motor cognitive functions.

Forward sensory prediction is advantageous over the sensory feedback signals for motor control purpose because, it is instantaneous, therefore does not suffer from the problem of time delays that normally lead to overcompensation and instability. For example, the execution of a goal directed arm movement will result in visual signals that will take approximately 90ms (Raiguel et al., 1999) and somatosensory signals that will take 20 to 40ms (Allison et al., 1991) to reach sensorimotor cortex. Subsequent processing delays for sensorimotor integration, motor command generation, and execution result in delays of more than 100ms for somatosensory control and over 200ms for visuomotor control (Cordo and Flanders, 1989;Flanders and Cordo, 1989). However, by monitoring the movement commands through an efference copy of the command, the current state of the arm can be estimated internally well in advance of the late-arriving sensory information. Neuropsychological studies have suggested that the function of motor control relies on the integrity of PPC. Transcranial magnetic stimulation (TMS) over the PPC at the onset of movement, disrupt online correction of trajectories (Desmurget et al., 1999a;Pisella et al., 2000a) or adaptation to novel force- fields (Della-Maggiore et al., 2004).

The concepts of motor-to-sensory transformation are prominent in a number of aspects of motor researches. During motor execution, the motor-to-sensory transformation is equivalent to the ideas of internal forward model where predicting the sensory consequences for the sense of agency (Jeannerod, 2003a) or for fast motor control (Wolpert, 1997;Wolpert and Kawato, 1998a;Franklin and Wolpert, 2011;Shadmehr et al., 2010a). During motor planning, the motor-to-sensory transformation refers to as anticipating sensory consequences of intended action prior to its onset. Action effect anticipation could serve the purpose of action selection and planning (James, 1890a;Waszak et al., 2012), and relates to several modern concepts of motor cognition (Jeannerod, 2001a;Jeannerod, 2003a;Desmurget et al., 2009;Desmurget and Sirigu, 2009).

### 1.2.2 Sensory prediction during movement planning

The idea of predicting the sensory consequences of intended movement, independent of immediate movement execution but as part of the prospective planning process, originates in German psychology of the mid-19th century (Lotze, 1852;Stock and Stock, 2004). Action effect anticipation prior to movement onset could serve the purpose of action selection and planning as postulated within the 19th century ideomotor concept (Lotze, 1852;James, 1890a). Psychophysical findings support this idea. The presence of task irrelevant but contingently experienced action effects (e.g. a tone)  led to faster reaction times or biased choices in subjects' motor responses (Elsner and Hommel, 2001;Hommel et al., 2001a;Ziessler et al., 2004;Waszak et al., 2012). So far, direct evidence is lacking that motor goal signals at the neuronal level encode anticipated sensory effects of an intended movement (Desmurget and Sirigu, 2009;Waszak et al., 2012). This is the main research question that we are going to ask in the thesis work. Specifically, we will test whether single neurons in the parietal and frontal sensorimotor areas will exhibit directional selectivity during the delay period that is correlated with the future visual feedback about the hand once the movement is executed. Moreover, we will further ask whether and how these spatial representations differ across parietal and frontal areas.

In this thesis, we are going to use the reversing-prism ("Dove" prism) as a tool to separate the physical movement from its associated visual feedback. Firstly, we will incorporate this into the typical memory-guided pro and anti reach tasks. We will conduct single unit recordings in both the parietal and premotor areas of behaving primates, and correlate the neuronal selectivity of single neurons with either the physical movement direction or the anticipated visual consequences of that movement. With this approach, we will be able to test whether visual sensory predictive representations can be found in the parietal and frontal sensorimotor areas. In addition, we will compare these spatial representations between these two sensorimotor areas. The details of these findings can be found in the chapter 2.1 and 2.2. Secondly, we will employ the reversing-prism into the human psychophysical study where we ask healthy subjects to perform visually-guided hand reach movements under the reversed vision. Since the reversing-prism dissociates the visual sensory feedback from the actual movement, we wonder if subjects could flexibly adapt their movements to this special viewing context. If so, what would be the mechanisms underlying such adaptations with reversed feedback. This part of the work is going to be described in the chapter 2.3.

# 2 Original manuscripts

This chapter contains the following three first-authorship manuscripts:

1. Kuang, S, Gail, A. Predicting sensory consequences of intended movement in monkey posterior parietal cortex. Submitted.
2. Kuang, S, Gail, A. Differential encodings of anticipated visual sensory consequences during reach planning in the premotor cortex compared to the posterior parietal cortex. Prepared for submission.
3. Kuang, S, Gail, A. When adaptive control fails: Slow recovery of reduced rapid online control during reaching under reversed vision. Submitted.

Some computational modelling work, which has been done in collaboration with the lab colleagues, is not included in this current thesis.

4. Westendorff, S; Kuang, S; Taghizadeh, B; Schwarz, I; Donchin, O; Gail, A Asymmetric generalization in adaptation to target displacement errors. Submitted.

Author's contributions:

1. S.K. and A.G. designed the experiment. S.K. collected the data. S.K. and A.G. performed the analysis, wrote and edited the manuscript.
2. S.K. and A.G. designed the experiment. S.K. collected the data. S.K. and A.G. performed the analysis, wrote and edited the manuscript.
3. S.K. and A.G. designed the experiment. S.K. collected the data. S.K. and A.G. performed the analysis, wrote and edited the manuscript.
4. S.W. and A.G. designed the experiment; S.K., S.W., I. S. and A.G. designed the model. S.W. and B.T. collected the empirical data; S.K. and S.W. ran the model simulation. S.W. did the analysis and wrote the manuscript. A.G., S.W. and O.D. edited the manuscript.

## 2.1 Predicting sensory consequences of intended movement in monkey posterior parietal cortex

Predicting sensory consequences of pending actions is essential for controlling goal-directed movements and for selecting among action alternatives. The idea of predicting the sensory consequences of a movement goes beyond a pure feed-forward view of sensory-to-motor transformations. In the context of motor planning, such sensory predictions emphasize a bidirectional link between intended action and sensory outcome based on learned associations. So far, direct evidence is lacking that motor goal signals at the neuronal level in PPC encode anticipated sensory effects of an intended movement.

We directly tested the idea of sensory predictions with a novel reversing-prism anti-reach task, in which rhesus monkeys planned two movements with identical visual instructions and identical motor responses, yet opposite anticipated visual feedback about the movement. We found that a substantial fraction of neurons in PRR were selective for the anticipated visual feedback, rather than the planned physical movement or anticipated proprioceptive feedback. These results provide direct evidence for the notion that motor planning evokes sustained neuronal representations linked not only to a planned action per se, but also to its anticipated perceivable sensory consequences.

# Predicting sensory consequences of intended movements in monkey posterior parietal cortex

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## Abstract

A longstanding idea in psychology postulates that intended actions are planned and selected with respect to their perceptual consequences. Accordingly, neural encoding of the anticipated sensory consequences of action should be inherent to motor planning. Yet, neurophysiological evidence of such sensory predictive representations during motor planning is lacking, despite supportive behavioural data. We tested this sensory prediction hypothesis with a novel reversing-prism anti-reach task. Monkeys planned movements with identical preceding visual instructions and identical future physical motor responses, yet opposite anticipated visual feedback about the future movement. We report neurons in the posterior parietal cortex the activity of which correlates with the visual consequences of upcoming actions. These neurons could serve as a basis for sensory predictions during motor planning, which are a necessary prerequisite for actions to be planned based on the desired sensory outcome, rather than required motor commands. This view on cortical sensorimotor representations is fundamentally different and complementary to the canonical feed-forward perspective of sensory-to-motor integration.

## Introduction

Being able to predict the sensory consequences of a movement is essential during goal-directed behaviour, both, for controlling movements (Shadmehr et al., 2010b;Franklin and Wolpert, 2011) and for selecting among potential action alternatives (James, 1890b;Prinz, 1987;Waszak et al., 2012). The idea that we predict the sensory consequences of a movement during motor preparation goes beyond pure feed-forward sensory-to-motor transformations. In the context of motor planning, such sensory predictions emphasize a bidirectional link between the intended action and the anticipated sensory outcome. It has been suggested that this link is based on learned associations established during sensorimotor learning and that these associations become effective during subsequent motor planning prior to movement onset (Lotze, 1852;James, 1890b;Prinz, 1987;Hommel et al., 2001b;Waszak et al., 2012). The idea of sensory predictions about an impending movement, independent of immediate movement execution, but as part of the prospective motor planning process, originated in German psychology of the mid-19th century (Lotze, 1852;Stock and Stock, 2004) and is still prominent in modern concepts of motor cognition, including motor imagery (Crammond, 1997;Jeannerod, 2001b) and motor awareness (Desmurget et al., 2009;Desmurget and Sirigu, 2009). Yet, direct evidence for sustained encoding of anticipated sensory effects of planned action at the single neuron level is lacking. Here we tested if the posterior parietal cortex (PPC), which is strongly associated with motor planning, contains signals that correlate with the to-be-anticipated visual sensory consequences of planned action.

Neurophysiological research on sensorimotor processing in PPC (Batista et al., 1999b;Buneo et al., 2002) has mostly focussed on the integration of sensory information from different modalities for the purpose of defining action goals. It is well-established that multimodal sensory integration leads to spatial representations in PPC which correlate with intended movement goals in different spatial frames of reference (Batista et al., 1999b;Buneo et al., 2002;Chang and Snyder, 2010b;McGuire and Sabes, 2011b) (for reviews, see (Cohen and Andersen, 2002;Crawford et al., 2011)). Moreover, such motor goal representations can be sustained while movement execution is voluntarily withheld, and hence are considered signatures of motor planning (Snyder et al., 1997;Andersen et al., 2010b;Kalaska, 1996) and action selection (Klaes et al., 2011;Platt and Glimcher, 1999;Scherberger and Andersen, 2007;Cui and Andersen, 2007;Gold and Shadlen, 2007b;Iyer et al., 2010). It is this sustained motor-related activity in PPC, prior to movement initiation and independent of motor execution, for which we ask if it contains information about the sensory consequences of the future movement.

There is emerging consensus that the described feed-forward integration in PPC needs to be accompanied by feedback mechanisms. Such feedback mechanisms would allow updating of motor goals and corrections of on-going movements based on on-line state estimations and motor error signals (Kalaska et al., 1997;Andersen et al., 2010b;Shadmehr et al., 2010b;Wolpert, 1997;Lalazar and Vaadia, 2008). Predicting sensory consequences of on-going movements is inherent to adaptive motor control theories (Shadmehr et al., 2010b;Franklin and Wolpert, 2011). PPC has been suggested to produce or use such immediate, internal–model based sensory predictions to compute motor error during motor execution for the purpose of adaptive motor control. The observations that PPC is highly active during adaptation of visually guided movements (Clower et al., 1996), that PPC inactivation (Desmurget et al., 1999b) or lesion (Grea et al., 2002) impairs on-line updating of reaching movements, and that PPC activity during reach movement can be used to estimate hand position without time-lag (Mulliken et al., 2008), have been taken as support for the existence of forward predictions in PPC during motor execution. Also, immediately prior to movement onset (~50ms) the existence of predictive sensory signals has been inferred from an observed predictive remapping of visual receptive fields during saccade initiation (Duhamel et al., 1992). Yet, for the purpose of motor planning, such sensory predictions would have to occur in a sustained fashion independently of immediate motor execution, and would have to contain sensory predictive information about the impending movement as such. “Action effect anticipation”, as such anticipated sensory effects of planed movements are often referred to in psychology (Waszak et al., 2012), are known to affect behaviour. For example, the presence of task irrelevant but contingently experienced sensory action effects (e.g. a tone) during motor planning led to faster reaction times or biased choices in subjects’ motor responses (Elsner and Hommel, 2001;Ziessler et al., 2004;Waszak et al., 2012).

It is not known, though, if the sustained activity in PPC which is prominent during movement planning contains information about anticipated sensory consequences of a planned action (Desmurget and Sirigu, 2009;Waszak et al., 2012). Here we address this sensory prediction hypothesis at the single neuron level in the parietal reach region.

We directly tested the sensory predictions hypothesis with a novel reversing-prism anti-reach task. The idea was to create situations during the planning of a reach movement, in which all preceding sensory inputs and pending motor parameters of the task are identical, except for the to-be-anticipated visual sensory feedback about the later hand movement. For this we combined the benefits of the anti-reach paradigm (Gail and Andersen, 2006;Gail et al., 2009) with those of sensory feedback manipulation (Fernandez-Ruiz et al., 2007;Eskandar and Assad, 1999;Shen and Alexander, 1997;Ochiai et al., 2002). In our reversing-prism anti-reach task, the monkey planned two movements which were characterized by identical spatial sensory input (visual instructions, seen and felt initial hand endpoint position) during movement planning, and by identical physical motor responses during later movement execution, yet were associated with opposite to-be-anticipated visual feedback about the movement. If the neural activity during motor planning co-varied with the variable sensory consequences of the planned movement, despite the monkey having experienced the same sensory input, and despite planning the same motor output, then this would provide evidence for an impact of sensory effect anticipation on spatial encoding in PPC. We found that a substantial fraction of neurons in the parietal reach region (PRR) were selective for the to-be-anticipated visual feedback about an intended reach movement, while others encoded the planned physical movement or to-be-anticipated proprioceptive feedback during movement planning. These results provide direct evidence for the notion that motor planning evokes sustained neuronal representations linked not only to a planned action per se, but also to its associated perceivable sensory consequences.

## Results

### *Spatial dissociations with the reversing-prism anti-reach tasks*

We designed a combined reversing-prism anti-reach task to directly test the sensory prediction hypothesis (**Fig. 1**). The task spatially dissociates the sensory-mnemonic, motor-intentional, and sensory-predictive aspects of arm reaching movements. In the main experiment, a monkey was trained to perform visually-instructed memory-guided reaches from the centre of a touch screen to peripheral goal positions. The task for the monkey was to move its visually perceived hand either towards the visually cued location (pro trial) or to the location symmetrically opposite to the cue (anti trial) (Gail and Andersen, 2006;Westendorff et al., 2010b;Klaes et al., 2011). Pro and anti trials were carried out under either a normal (no prism) viewing context, or under a prism viewing context. In the latter, the visual input was left-right reversed by a dove prism (**Fig. 1A**). An instructed delay between the visual instruction and the 'go'-signal ensured that the sensory input during the extended motor planning did not contain spatial information about the reach goal and was essentially identical in all task conditions (**Fig. 1B**). A simplified version of the task was conducted in two animals, confirming the conclusions from the one animal that performed the combined task design (see below and **Materials and Methods**).

The pro vs. anti comparisons dissociated the visual spatial memory of the cue from the spatial motor goal, since the same cue position instructed opposite-side movement goals in pro and anti reaches. For example, the same right-side cue was associated with either a left-side (anti) or right-side (pro) reach goal (**Fig. 1C** top panels), and vice versa. Hence, the pro-anti comparison (further referred to as "anti dissociation") is well suited to identify spatial neural representation of an intended motor goal, as compared to representations of the visual memory of the cue. Yet, this anti dissociation alone does not allow deciding if such motor goal representations indicate the preparation of the intended physical hand movement (physical intention, dark orange hand symbol) or the to-be-anticipated visual feedback about this movement (visual prediction, light orange hand symbol). During the normal viewing context (as is the case for everyday movements without perturbation of the sensory feedback) both the physical hand movement and the visual feedback about this movement are congruent. To dissociate physical intentions from visual predictions, we asked the monkey to conduct the pro and anti reaches in the two different viewing contexts, the no-prism context (**Fig. 1C** top panels) and the prism context (**Fig. 1C** bottom panels). The comparisons between prism and no-prism trials (further referred to as "prism dissociation") helped dissociating the future physical movement from the associated visual movement since the same physical movement can lead to opposite-side visual hand movements, and vice versa. The prism dissociation could be achieved in the pro (**Fig. 1C** left panels) and the anti reaches (**Fig. 1C** right panels).

Most importantly, the combined prism and anti task created two pairs of conditions where the preceding sensory cue and the impending physical reach directions were identical, but the to-be-anticipated visual feedback during planning was opposite (**Fig. 1C**, both diagonals). For example, if one compares the two diagonal conditions "non-prism pro" and "prism anti", then the monkey received the same right-side visual instruction and had to conduct the same right-side physical movement, but with opposite visual feedbacks of the hand (further referred to as "prism-anti dissociation"). This means, only by combining the anti and the prism dissociation one is able to separate predictive sensory signals from visual memory and from physical intention signals. This is because, as a result of the anti dissociation, one can rule out that the seeming visual encoding is independent of the memory of the visual cue, hence is movement-related (**Fig. 1D**, top panel). And further, as a result of the prism dissociation, one can confirm that the so identified movement-related signals reflect properties of the pending movement which correlate with the predictable sensory feedback (**Fig. 1D**, middle panel).

Our task design allowed anticipation of the different sensory consequences of movement, but did the monkeys actually anticipate these differences during movement planning? The analysis of the behavioural data in the following paragraph suggests that this was the case.

### ***Behavioral performance in the combined reversing-prism anti-reach task***

The monkey had become well acquainted to the task conditions and performed pro and anti trials in both viewing conditions with high performance. The overall success rates (counting trials with ocular/hand fixation breaks, belated responses or erroneous choices as incorrect) were above 80% in each task condition (non-prism pro: 83%, non-prism anti: 82%; prism pro: 81%; prism anti: 81%) and were not significantly different across task conditions (two-way ANOVA, p = 0.94 for factor “rule”, 0.26 for factor “context”, and 0.52 for rule-context interactions). Most error trials were attributable to the early trial abortions (because of ocular/hand fixation breaks before the “go” signal), rather than confusions of the reach directions. For example, the overall task performance in the first 5-8 trials after switching the viewing context was significantly reduced compared to later trials in the same viewing context, and this was true for the switching from no-prism to prism context and for the reverse switching (**Supporting Information Fig. S1**). While this indicates that the monkey needed at least in some way to repeatedly ‘adapt’ to the switching viewing contexts, these errors where mainly due to early trial abortions. On average, in only 2% of the non-aborted trials the monkey reached to the wrong targets (correct choice trial percentage; normal pro: 98%; normal anti: 97%; prism pro: 98%; prism anti: 99%). This means that in terms of selecting the correct goal direction the monkey switched back and forth between both viewing contexts quickly.

Importantly, though, different short-latency movement kinematics in the prism compared to the no-prism viewing context suggested that the monkey prepared for different sensorimotor control situations in the two different viewing contexts prior to movement onset. The monkey conducted stereotyped hand reaching movements with smooth velocity profiles in each task condition and each direction (see the raw trial-by-trial trajectories and the averaged velocity traces from a typical recording session in **Fig. 2A, B**). However, the horizontal peak velocities were different between prism trials and non-prism trials in each direction and in each task rule (pro/anti) (**Fig. 2B**). Across the recording sessions, the horizontal peak velocities were smaller in the prism trials compared to the non-prism trials, with a main effect of directions (ipsi vs. contra, $p<10^{-5}$, three-way ANOVA) and viewing contexts ($p<10^{-4}$), but no main effect of the task rule ($p>0.05$), and no interactions ($p>0.05$) (**Fig. 2C**). The peak velocities occurred around 50ms after the monkey’s reach movement onset (**Fig. 2B**), i.e., before the actual visual sensory feedback about the movement can affect the ongoing movement (min. 80-100ms (Desmurget and Grafton, 2000b)).

Hence, the difference in the peak velocities indicates that the monkey initiated reaches with different kinematics between the prism and the no-prism viewing contexts independent of an immediate movement-induced visual feedback, but based on a context-specific planning.

In summary, while the monkey's choice of the reach direction appeared to be a highly trained conditioned response, the monkey not only conducted but also prepared the movements differently between the prism and no-prism viewing contexts, apparently being affected by the to-be-anticipated reversed visual feedback during planning and later by the actually reversed visual feedback during execution.

### ***Visuospatial neural selectivity in the combined reversing-prism anti-reach task***

We asked if motor planning activity in PRR reflected spatial parameters of the to-be-anticipated sensory feedback of the planned movement. For this, we correlated the neuronal activity of each neuron during the instructed delay period with three task parameters: the location of the preceding visual instruction (visual memory), the direction of the impending physical reach (physical intention) and the to-be-anticipated visual hand feedback (visual prediction). We compared the preferred direction of each neuron across these task conditions and quantified it with a signed left-right directional selectivity index (DSI) (see **Material and Methods**). The example in **Fig. 3A** shows a neuron which was selective for the to-be-anticipated visual feedback rather than the physical intention. This visual prediction neuron was characterized by the following response pattern. First, the directional selectivity reversed between pro and anti trials, and this was true in both the no-prism and the prism contexts. The reversal of the directional selectivity was indicated by opposite-signed DSIs. The DSI reversal in the anti-dissociation shows that the neuron was selective for the direction of the intended movement (motor intention) rather than the visual memory, since a right-side cue in pro reaches elicited similarly strong responses as a left-side cue in anti reaches, and vice versa (**Fig. 3C** for the raw spike events and spike density curves). Second, the DSIs had the same sign in the no-prism and the prism contexts, and this was true in both pro and anti trials. This indicated that the neuron was selective for the to-be-anticipated visual feedback of the movement, but not the intended physical movement, since a right-side physical movement during normal viewing elicited similarly strong responses as a left-side physical movement in the prism viewing condition **(Fig. 3C)**. Other neurons, from the same monkey, showed response patterns with opposite-signed DSIs in the anti-dissociation, and opposite-signed DSIs in the prism dissociation. Hence, these neurons were selective for the direction of the intended physical reach (physical intention neuron; **Fig. 3B, D**).

We classified all task-related neurons (significant DSIs in at least one of task conditions; 71/81 = 88% of all recorded neurons) according to their directional selectivity in both the anti dissociation and the prism dissociation (see **Fig. 4**, detailed descriptions in **Materials and Methods**). In brief, visual memory neurons would have significant left-right selectivity with same-signed DSIs in the pro and anti trials. Motor intention neurons, instead, were characterized by significant but opposite-signed DSIs in the pro and anti trials. The motor intention neurons, in a second step, were further classified as visual prediction or physical intention neurons. Visual prediction neurons had significant same-signed DSIs in the prism and non-prism trials. Physical intention neurons showed significant opposite-signed DSIs in the prism and no-prism trials. Note, the fact that we quantified our results via such classification approach does not imply that the underlying distribution of neural selectivity is necessarily categorical (see **Material and Methods**).

A significant fraction of neurons was selective for the to-be-anticipated visual prediction of the hand movement during the late delay period (800ms prior to the “go” cue), hence were classified as visual prediction neurons (**Fig. 5**). As in previous studies (Gail and Andersen, 2006;Westendorff et al., 2010b;Klaes et al., 2011), task-related neurons were in general motor intention related during the instructed delay, most of which significantly (53/71, 75%), many others with a non-significant trend (**Fig. 5A, B**). In contrast, a sustained encoding of the visual cue memory was basically absent (1/71, 1%). Accordingly, the DSIs in the pro compared to the anti trials were strongly negatively correlated across the population of neurons, in both no-prism (**Fig. 5A**) and prism trials (**Fig. 5B**). Of the 53 neurons which were classified as motor intention neurons, seven neurons (13%; 7/71=10% of all task related neurons) were further classified as visual prediction neurons, and 29 (55%; 29/71=41% of all) as physical intention neurons (**Fig. 5C, D**). The remaining 17 neurons (32%; 17/71=24% of all neurons) were undefined motor intention neurons since their DSIs did not reach significance simultaneously in both the prism and no-prism conditions in either pro or anti trials. Note that a considerable fraction of neurons were non-classifiable in the anti dissociation (17/71=24%), or were undefined motor intention neurons according to the prism dissociation (17/71=24%) because they had close-to-vertical preferred directions which did not match well with our left-right task design (see **Materials and Methods**).

To illustrate the spatial encoding of each neuron across all conditions, i.e. in the anti dissociation and in the prism dissociation in combination, we plotted their DSI ratio from the anti dissociations (average across prism and no-prism contexts) against the DSI ratio from the prism dissociations (average across pro and anti rules) (**Fig. 5E,** see also **Material and Methods**). In this ratio plot two out of four quadrants were populated with significantly selective neurons. These are the two left quadrants which correspond to the motor intention encoding (negative DSI ratio for anti-dissociation). Importantly, the upper left quadrant contains a substantial fraction of neurons. This quadrant corresponds to visual prediction encoding (positive DSI ratio for prism dissociation). The ratio plot shows that the selectivity of the motor intention related neurons spreads widely between visual prediction encoding (positive DSI ratio in prism dissociation, top left quadrant) and physical intention encoding (negative DSI ratio in prism dissociation, bottom left quadrant). Note, we analyze DSI ratios rather than DSI differences in Fig. 5E since the definition of visual prediction or physical intention encoding is independent of the strength of the left-right selectivity (absolute DSI value). Rather, the question was how the left-right selectivity (the DSI) keeps or inverses its sign across conditions. Supplemental Information (Text & Fig. S2) shows a neuron with weak but significant left-right selectivity (small absolute DSI), yet a directional selectivity across the different conditions which was highly consistent with the visual prediction hypothesis.

The left-right selectivity pattern of individual neurons that led to their classification as visual prediction or physical intention neurons did not just reflect random variation of directional selectivity. We confirmed this in three independent ways. Firstly, when analyzing the spatial selectivity of individual neurons, the criterions of the neuron classification into visual prediction or motor intention categories was conservative and required a simultaneous statistical significance of left-right firing rate differences in at least three task conditions Each difference was tested with a t-test at $p=0.05$, which means for a random process with independent spike rate fluctuations in each of the conditions the chance level for a neuron to become significant was at $0.5^3 = 1.25*10^{-4}$. Secondly, an additional non-parametric randomization test at the level of individual neurons, which assumed as a null hypothesis that there would be no selectivity at all, confirmed the classification (see **Materials and Methods**). This alternative significance criterion gave rise to the identical number of visual prediction neurons, and five less physical intention neurons (data not shown). Thirdly, rather than testing against the null hypothesis of not being spatially selective at all, we used a non-parametric randomization test and tested against the null hypothesis that all task related neurons are physical intention selective. This means, in this third test we asked if it was possible that all task-related neurons actually were encoding the physical motor goal, but due to random fluctuations could have been miss-classified as visual prediction neurons. For this, we shuffled task conditions such that directional selectivity and general motor intention encoding were preserved. Otherwise trials were randomized such that the resulting surrogate data complies with the null-hypothesis of pure physical intention encoding, but not with visual prediction encoding (see **Materials and Methods**). The dashed ellipses in **Figure 5A-D** show the 99% confidence limits of the shuffle prediction**.** As a result, the intention encoding observed in the pro/anti comparison of the real data fitted very well with this null hypothesis. Almost all neurons which were classified as motor intention related fell into the 99% confidence limit of the shuffle prediction (**Fig. 5A, B**). This was not surprising since motor intention encoding according to this definition had been shown in several previous studies (Gail and Andersen, 2006;Gail et al., 2009;Westendorff et al., 2010b). Yet, more importantly, the observed DSI values of many neurons in the prism/no-prism comparisons fell outside the 99% confidence limits of the shuffle prediction (**Fig. 5A-D**), and thereby did not comply with the null hypothesis. This was especially true for neurons which were classified as visual prediction neurons in our other testing procedures. The result of this third test strongly indicated that the existence of our visual prediction neurons cannot be explained by inherent random variability of left-right directional selectivity under the null-assumption of pure physical intention encoding. Equivalently to the randomization data shown in **Fig. 5**, the existence of the physical intention neurons cannot be explained by random variability under the null-assumption of pure visual prediction encoding (data not shown).

In summary, even though the total number of neurons which could be recorded with the complete prism- and anti-dissociation paradigm and which showed visual prediction selectivity was small, their existence marked a highly significant deviation from the expectations of our null hypotheses. Below, we will further confirm the presence of visual prediction encoding during movement planning with two additional data sets, one from the same animal and the other from an independent animal.

### *Visual prediction neurons in the reversing prism task alone*

In retrospect, our classification of visual prediction and physical intention neurons could be achieved purely based on the prism dissociation, without making the anti dissociation beforehand. The anti dissociation in our main experiment was essential to rule out that neurons encode a spatial cue memory, which could have been confounded with the visual prediction encoding when testing prism reversal with only pro reaches (**Fig. 1C**). But the anti dissociation almost exclusively revealed motor related neural selectivity during movement planning (75% motor selective neurons vs. 1% visual memory selective neurons in the delay period, see above). This means, visual memory encoding is not a confounding factor in our data, and, hence, we could by-pass the anti dissociation due to the strong dominance of motor intention encoding during the instructed delay (**Fig. 5A, B**). To quantitatively test this consideration, we used the same data as above of monkey S during the reversing-prism anti-reach task, and ignored the anti dissociation. Instead, we classified the neurons as visual prediction neurons (same-sign DSI in prism and no-prism trials) or physical intention neurons (opposite-sign DSI in prism and no-prism trials) based on the prism dissociation alone. In this case only one additional neuron was classified as physical intention neuron, while the group of visual prediction neurons stayed the same as in the complete analysis. This means that for our data set (single neuron data from monkey PRR) we can test the visual prediction hypothesis directly with the reversing prism task. Note, though, that the combined reversing-prism anti-reach task and the pure reversing prism-task only led to identical conclusions for data from individual neurons, not for more global signals of neural population activity, as we can show for local field potentials (**Supporting Information Text S3**). This means, whether such by-passing of the combined task is also possible for other species, other brain areas, or other signal types would first have to be tested explicitly (Fernandez-Ruiz et al., 2007;Ochiai et al., 2002;Shen and Alexander, 1997).

Given that the anti dissociation in PRR is not mandatory for our type of classification of single neurons, we were able to expand our tests to two additional data sets from two monkeys (including the same monkey S shown with the combined task) involved in the prism dissociation tasks with only pro trials. Additional data sets comprised 362 recorded neurons (monkey F: 199; S: 163). Of those, 76% (151/199, F) and 73% (119/163, S) were task-related. 35% (53/151, F) and 39% (47/119, S) of the task-related neurons were significantly directional selective in the prism and no-prism task condition, i.e., eligible for further neuron classification and testing of our main hypothesis. Of these eligible neurons, 39 (74%; 39/151=26% of all task related neurons; monkey F) and 37 (79%; 37/119=31% of all neurons; monkey S) were classified as physical intention neurons, while 14 (26%; 14/151=9% of all; F) and 10 (21%; 10/119=8% of all; S) were classified as visual prediction neurons (**Fig. 6A, B**).

This means, the percentages of visual prediction and physical intention neurons were comparable across monkeys and data sets. They lay close to 10% for visual prediction neurons and in the range 26-41% for physical intention neurons, when calculated relative to the total number of neurons (**Fig. 6C**). This is a very conservative estimate in two senses. First, a large fraction of neurons in the pure reversing-prism task drop out of the analysis because of the sub-optimal match of their preferred directional selectivity to our left-right task design, as it was the case for the full reversing-prism anti-reach task. Relative to the number of neurons which were directional tuned in enough conditions to be fully eligible for testing the visual prediction hypothesis, between 19% and 26% (7/36=19% combined task S, 10/47=21% prism task S, 14/53=26% prism task F) of neurons showed visual prediction encoding during the late memory period (**Fig. 6C**). Second, the fraction of visual prediction neurons depends on the choice of the time window within the delay period (**Fig. 6D**). Above we focused on the late delay period as conservative approach, since the neural encoding typically becomes more "motor-like" towards the time of the movement. In fact, the fraction of visual prediction neurons during the early delay period is higher than during the late delay period. During the early delay 12%, 16%, and 17% of all task-related neurons were visual prediction neurons in the combined data set, and the prism-only data sets of monkey S and F, respectively, as compared to the late delay where the numbers were 10%, 8%, and 9% (**Fig. 6C, D**).

### ***Visual prediction encoding versus visual input encoding***

We tested if the neurons that were classified as visual prediction neurons during the delay period would also be sensitive to actual visual input. For this we tested the influence of the visual cue on their neural tuning during the cue period, as well as the influence of the actual visual hand feedback during the movement period.

Previous studies showed that part of the neurons that developed motor intention related selectivity during the delay period encoded the position of the visual instruction stimulus during the preceding cue period ("visuomotor neurons"), while others were only directionally selective after the cue presentation when the monkeys knew already about the pending motor goal ("motor-goal neurons") (Gail and Andersen, 2006). If the visual prediction neurons were identical to the neurons which are sensitive to the actual visual input, then the visual prediction neurons should be largely overlapping with the visuomotor neurons. We tested this possibility by analyzing the spatial selectivity of visual prediction neurons during the cue period for the data set with the combined reversing-prism anti-reach task. Note, the other two data sets are not eligible for this analysis, since the definition of visuomotor tuning depends on the anti dissociation (Gail and Andersen, 2006). Overall, directional selectivity was much less frequent in the cue period than in the delay period (cue period: 37% = 30/81, late delay period: 88% = 71/81 of all recorded neurons showed significant directional selectivity in any of the four task conditions). Specifically, of the seven visual prediction neurons, only one (1/7, 14%) showed a visual related tuning during the cue period (**Fig. 7, dashed arrows**). Most visual prediction neurons (6/7, 86%) were not directional selective during the cue period, as can be seen from the example neuron in Fig. 3A. This means, visual prediction neurons are not identical to visuomotor neurons.

Are visual prediction neurons selective for the actual visual feedback during the movement period when the spatial visual input about the hand is available? For this we examined the spatial selectivity of visual prediction neurons during the movement period in all three data sets. Visual prediction neurons overlapped poorly with the group of neurons that showed visual movement related tuning during the reach period. Of the total 31 visual prediction neurons, only 16% (5/31) showed significant directional tuning that was selective for the visual movement during movement execution, while others were either not significantly directional tuned (55%, 17/31) or significant directional tuned but selective for the physical movement direction (29%, 9/31) during the reach movement period (**Fig. 7, solid arrows**). This indicates that visual prediction neurons are not necessarily sensitive to the visual input during the movement when visual hand feedback is available.

In summary, there was little overlap between the visual prediction encoding during the delay period and the visual input encoding during both the cue period and the reach period. This shows that visual prediction neurons do not represent direct sensory or perceptual parameters, but rather show activity related to motor-planning which correlates with spatial parameters of the predictable visual sensory consequences of upcoming movements.

## Discussions

To identify neural signals of sensory action-effect anticipation one needs to achieve at least three goals. First, the task design needs to vary exclusively the sensory consequences of an impending movement with all other spatial parameters being equal. Second, the subjects need to behaviorally anticipate the sensory consequences. And third, the neural activity needs to correlate with these anticipated sensory consequences. We could show that the sustained activity in monkey PRR during the planning of a hand movement contains information about the anticipated visual sensory consequences of this movement. A minimum of close to 10% (up to more than 20% in less conservative estimates) of single neurons in PRR showed visual prediction encoding in a reversing-prism reach task in which monkeys prepared movements in two different anticipated visuomotor feedback conditions. The observed visual prediction encoding was not related to visual memory, but related to motor planning, as the combination of the reversing-prism task with an anti-reach task revealed. The visual predictions neurons were not in general sensitive to direct visual input, which additionally emphasizes their relatedness to motor planning.

### *Identifying sensory anticipation signals with the reversing-prism anti-reach task*

The double-dissociation of our reversing-prism anti-reach task allowed identifying signals of sensory action-effect anticipation. Our combined task design spatially double-dissociated the visual memory of an instructive cue, the intended physical movement response, and the associated visual feedback about the movement. Previous studies which used the pro/anti-reach paradigm reported that neurons in monkey PRR (Gail and Andersen, 2006;Westendorff et al., 2010b;Klaes et al., 2011) and parts of human PPC (Medendorp et al., 2005;Van Der Werf et al., 2008;Vesia and Crawford, 2012) encode the spatial parameters of planned movements (“motor intention”) rather than the visual memory of a spatial input during sustained planning. However, the encoding of movement intention in anti-reach studies remained ambiguous, since motor-related activity in a pro/anti reach task could have reflected either the intended physical hand movement, or the to-be-anticipated sensory feedback of that movement. Other studies dissociated neural activity related to the physical movement of the hand from spatial visual parameters of the task by manipulating the visual representation of the hand. These studies used either a computer cursor or a video image to represent hand position and to manipulate the spatial mapping between seen and actual hand position (Ochiai et al., 2002;Ochiai et al., 2005;Schwartz et al., 2004;Eskandar and Assad, 1999), or a reversing prism (Fernandez-Ruiz et al., 2007). The previous studies did not allow testing the visual prediction hypothesis, though, since they lacked an instructed delay period to investigate sustained movement planning activity (Eskandar and Assad, 1999;Schwartz et al., 2004), or did not spatially dissociate the visual target information (spatial instruction stimulus) from the visual representation of the planned movement (Eskandar and Assad, 1999;Ochiai et al., 2002;Ochiai et al., 2005;Fernandez-Ruiz et al., 2007). Neural encoding of visuo-spatial task parameters, therefore, in previous studies could have been related to the immediate visual input during movement execution, or a mnemonic representation of preceding visual instructions, and, consequently, were not interpreted as sensory predictive signals (see also the discussion section on “motor goal” below) . In the light of the current results it is intriguing to speculate that these previous findings could have partly contained predictive sensory encoding. This re-interpretation remains speculative, though, since the double-dissociation which characterizes our combined task was not applied in previous experiments, and the instead used single-dissociation which characterizes tasks with only visual feedback manipulation (like our prism-only task) does not necessarily lead to the same conclusions. This was shown by the analysis of our LFP data which revealed different result than the analysis of the single unit data (Supporting Information Text S3).

In summary, using the prism-only task as a substitute of the combined prism-anti task is potentially misleading, and in our case was only justified for single unit data, but not for LFP data. For single units in PRR, the combined task revealed the existence of spatial selectivity which correlated with the impending sensory visual feedback of a planned movement.

### *Behavioral indications for sensory action-effect anticipation*

Our behavioral analysis showed that the monkeys not only quickly adapted their target choices but also their movement kinematics to the two visuomotor contexts. Importantly, the viewing context, and hence the impending visuomotor feedback (being reversed or not), behaviorally affected the movement planning, not just the motor execution, as indicated by two findings. First, the monkeys showed kinematic differences for movements to the same targets when they were conducted in either prism or no-prism trials, and these differences could be observed with latencies (max. 50ms) which were too small to be explained by differences in the actual visual feedback during motor execution (Desmurget and Grafton, 2000b). Second, posture differences between the prism and no-prism trial during movement planning could be ruled out as an explanation for the differences in movement kinematics (see Material and Methods) (Kritikos et al., 1998;Timmann et al., 1996). This means that the monkeys, for the same selected reach targets, apparently prepared different movements for visuomotor environments in the prism and no-prism trials. Corresponding differences in the short-delay reach kinematics between pro and anti trials were not found. This indicates that the behavioral difference between the two reversing-prism viewing contexts had a different quality than the difference between a pro and anti reach. Memory-guided pro and anti reaches could be learned by conditional stimulus-response associations and did not differ with respect to the anticipated visual sensory feedback. The proper target in prism and no-prism reaches might have been selected based on conditioned stimulus-response associations as well. But the movement itself then had to be conducted (hence controlled) under different visuomotor feedback controls under the reversed vision (Gritsenko and Kalaska, 2010a). This required an association of the intended movement with the context-dependent feedback during movement planning in order for the movement to be conducted properly right from the start.

In short, differences in the short-latency reach kinematics for different viewing contexts indicate that the monkeys were adapted to the different contexts not only with respect to proper target selection, but also to account for the different visuomotor environments associated with the two viewing contexts. In this sense, at least an implicit anticipation of the impending visual feedback must have been available during movement planning, and the left/right selectivity of the visual prediction neurons correlated with this visual feedback.

### *What is a motor goal?*

We labelled the two ends of the otherwise continuous range of observed encoding schemes ‘visual prediction’ encoding versus ‘physical intention’ encoding to emphasize the fact that the corresponding neurons correlate best with these two immediate parameters of our task design. Yet, the labelling implied two very distinct functional roles for the two types of encoding. While visual prediction encoding refers to a sensory representation of an impending movement, physical intention encoding refers to a precursor of an impending motor command. One interpretation of our data is that both encoding schemes can be found in PRR because the role of the PPC is to learn the associations between movements and their sensory consequences. This idea of such association is reminiscent of internal models for the purpose of optimal motor control, a function that PPC has been associated with before (Mulliken et al., 2008;Shadmehr et al., 2010b;Franklin and Wolpert, 2011). The intriguing finding here would be that PPC co-represents the intended physical movement and its associated sensory consequences already during motor planning (see below for a putative functional relevance).

But a different interpretation of the co-existence of the two encoding schemes is possible. The use of the term ‘physical intention’ was motivated by pre-existing concepts of intention encoding in the sensorimotor cortex (Andersen and Buneo, 2002b;Cohen and Andersen, 2002;Kalaska, 1996) and is associated with the preparation of a physical motor command. But the physical intention (left or right hand movement) in our task co-varied with the to-be-anticipated proprioceptive feedback about this movement, and, in contrast to the visual feedback, could not be dissociated from each other. Hence, we could interpret the selectivity of all neurons as sensory anticipation signals, the visual prediction neurons being dominated by the visual anticipation, the ‘physical intention’ neurons being dominated by the proprioceptive anticipation. This would provide a parsimonious interpretation for which we would not have to assume different functional roles but only one common role, namely sensory prediction encoding.

Previous studies including our own, interpreted spatial selectivity during motor planning in PPC as ‘motor goal’ encoding (Gail and Andersen, 2006;Snyder et al., 1997;Kalaska, 1996;Snyder et al., 1998;Crawford et al., 2011;Medendorp et al., 2005) (but see an alternative view in Supporting Information Text S4). In our current task, motor goals were defined by a combination of the desired visual feedback about the movement (‘Where do I want my hand to visually be at the end of the trial?’) and the required physical movement itself (‘Which movement is needed to achieve this?’), which co-varied with the desired proprioceptive feedback (‘Where do I want my hand to be felt at the end of the trial’). During movement planning, the to-be-anticipated visual feedback for the impending movement was the only parameter of our task that was directly manipulated with the reversing prism. This means, the desired sensory feedback defined the motor goal in our task. This leads us to postulate that spatial motor goal representations might more generally include modality-specific sensory action effect anticipation signals, rather than merely reflecting precursors of motor command in different spatial reference frames (see also Supporting Information Text S5).

In this context it should be noted that the single neuron resolution of our approach turned out to be critical for distinguishing our data from previous interpretations of PPC spatial encoding during a reversing-prism task as motor goals in the visual coordinate (Fernandez-Ruiz et al., 2007). Our single neuron data reflected a substantial diversity of encodings ranging from visual prediction to physical intention/proprioceptive prediction encoding, with a predominance of the latter. Brain signals based on a superposition of large populations of neurons wash out such individual differences. More than this, our LFP data counter-intuitively suggested ‘pure’ visual encoding (**Supporting Information Fig. S3**), as was the case for fMRI signals in part of human PPC in a previous study[39]. As argued above, we think that the diversity of encoding, comprising physical intention neurons and visual predictions neurons within the same area prohibits a simple interpretation of the spatial selectivity in PRR as “visual motor goals” (Fernandez-Ruiz et al., 2007).

In summary, our findings help refining the concept of a motor goal. We argue that motor goals, at least in the posterior parietal cortex, but maybe in cortical sensorimotor areas more generally (Ochiai et al., 2002;Ochiai et al., 2005), are defined with respect to the different sensory dimensions of a given task, not just or not at all with respect to the required motor command. This task space for motor goals is constructed by the anticipated sensory feedback in different sensory modalities, especially those modalities in which one intends to achieve the required task (here: visual and proprioceptive), and to a lesser extent in which modality subjects were instructed (McGuire and Sabes, 2011b). A motor goal representation in the parietal sensorimotor cortex would then be defined by the desired sensory feedback in different modalities and at different levels of abstraction ("hand seen left", "hand felt right", etc.), rather than by a representation of the required physical implementations of the underlying movements.

### ***Functional relevance and related concepts***

Our study provides direct neurophysiological evidence for action effect anticipation during motor planning. Motor-related sensory prediction signals play a role in various concepts of motor cognition, like the ideomotor concept (James, 1890b;Prinz, 1987), motor imagery and rehearsal (Jeannerod, 2001b;Crammond, 1997), motor awareness (Haggard, 2005;Desmurget et al., 2009;Desmurget and Sirigu, 2009), the mirror neuron system (Rizzolatti and Sinigaglia, 2010),sense of agency (Jeannerod, 2003b), perceptual stability (Duhamel et al., 1992) and concepts of motor control (Franklin and Wolpert, 2011;Shadmehr et al., 2010b).

A major functional relevance of anticipatory encoding of action effects during motor planning lies in its potential to contribute to action selection (James, 1890b;Prinz, 1987). This marks a conceptual difference to sensory forward predictions during control of motor execution (Shadmehr et al., 2010b;Franklin and Wolpert, 2011;Mulliken et al., 2008). Immediate sensory predictions during on-going movements can serve in the detection of motor errors as a basis for fast and feedback-independent on-line corrections of movements and for sensorimotor adaptation. This function is assumed to be mediated by cerebro-cerebellar loops including the PPC (Miall et al., 2007;Blakemore and Sirigu, 2003;Shadmehr et al., 2010b;Franklin and Wolpert, 2011;Clower et al., 1996;Desmurget et al., 1999b;Mulliken et al., 2008;Izawa et al., 2012;Blakemore et al., 1998). Prospective sensory prediction signals during movement planning, which are sustained while execution of an already selected motor plan is withheld, might be mediated by fronto-parietal loops (Blakemore and Sirigu, 2003;Desmurget and Sirigu, 2009) and suggest a different function. According to the longstanding ideomotor concept, a bidirectional link between action and anticipated effect is acquired automatically during early stages of sensorimotor learning (Prinz, 1987;Shin et al., 2010). An intended motor plan then is initiated by invoking these sensory "images" of the movement (Lotze, 1852;James, 1890b). The frontoparietal sensorimotor loops, including PRR and dorsal premotor (PMd) area, would be highly suited to support this associative function. In a stronger version of the concept, choice of action includes invoking multiple such sensorimotor representations (Waszak et al., 2012). PRR and PMd can encode two mutually exclusive movement plans in parallel prior to action selection (Klaes et al., 2011;Cisek and Kalaska, 2010). Given our current result, such representations of multiple potential motor goals in the frontoparietal sensorimotor areas should contain sensory prediction signals. Such parallel representation of sensory prediction signals for multiple potential movements would provide a neural basis for selecting actions based on their anticipated sensory outcomes.

## Conclusion

Our results add a new perspective to the current understanding of spatial representations in the PPC of primates. The visual prediction neurons observed in our experiment highlight the role of action effect anticipation during movement planning. They shed a new light on the concept of ‘motor goal’ in that they suggest that the formation of a motor goal implies the prediction of the visuo-spatial consequences of the intended action, not just the preparation of a proper physical motor command and its representation in different spatial reference frames. We speculate that such anticipatory signals could mark the very nature of spatial motor-goal representations in PPC, the idea being that sensory action effect anticipation is inherent to motor planning across different sensory modalities. Such neural representations of anticipated sensory effects of movement could provide a basis for a general motor cognitive principle according to which intended actions are planned and likely also selected with respect to their perceptual consequences, very much in line with a more than 150 year old core principle of the ideomotor concept (James, 1890b).

## Materials and Methods:

Except for the reversing prism optics and the optical motion tracking, the technical details of the apparatus and procedures were described previously (Westendorff et al., 2010b). All experimental procedures were conducted in accordance with European and German laws governing animal welfare.

### *Apparatus*

Two rhesus monkeys participated in the experiments. Both monkeys performed memory-guided center-out reaches in the fronto-parallel touch-screen plane with monocular reversed vision (Dove prism PS992, Thorlabs, Germany) in a dimly lit room. The monkeys looked through a square aperture with their left eye (**Fig. 1A**), while the view of the hand and screen for the right eye was occluded by a piece of cardboard. The distance between the screen and monkeys' viewing eye was about 40cm, and this large distance helped on the one hand to maximize the visual workspace on the screen (10 x 10cm square) and on the other hand to minimize the variability in arm postures across trials and conditions (see below). Through the aperture the monkeys had a direct vision of only the fingertips of their own hand during fixation and movement. The aperture contained either nothing (no-prism trials) or the Dove prism (prism trials), but provided the same field of view in either case. Gaze direction was monitored via the right eye. The monkeys had to keep ocular fixation (224 Hz infrared CCD camera, ET-49B, Thomas Recording, Germany) and initial hand fixation within a tolerance of 2 cm (2.9° visual angle). Reach trajectories were recorded as raw 3D position data at 200 Hz sampling frequency with an infrared optical motion tracking system (VZ 4000, PTI, Canada) for which an LED was attached to the monkeys' fingertips. In two of our datasets in which we recorded the prism task without the pro/anti comparison (see below), in a subset of trials, only reach endpoints could be registered. For this we used a transparent touch sensitive panel (IntelliTouch, ELO Systems, CA, USA) in front of the display screen (LCD VX922, ViewSonic). The technical resolution of both recording systems is in the sub-millimeter range. The monkeys had to reach to the targets with an endpoint tolerance of 2 cm with either recording method.

### *Behavioural tasks*

Each trial started with a variable-length fixation period, followed by 0.2 s of the visual cue presentation, and then 1-2 s variable delay period when the visual cue were absent (**Fig. 1B**). During these time periods the monkeys had to keep both eye and hand fixation in the centre of the screen. Centre-out reaches (5 cm = 7.1° visual angle eccentricity) were conducted in response to the disappearance of the central hand fixation spot ('go' signal). The monkeys received acoustic feedback about their performance in each trial and liquid reward for correct trials. Finger-tip movements were continuously optically tracked to rule out on-line movement reversals. The monkeys had to keep ocular fixation on a small central spot throughout the trial.

There were only two possible visual cue locations (either to the left or to the right of the central fixation spots) at constant positions over all experimental sessions. (Note that this means that the reach targets were not always centered on the response fields of the recorded neurons, which in multi-channel recordings is anyhow not possible). There were two task rules (pro and anti) and two viewing contexts (non-prism and prism). The pro/anti task rules were instructed to the monkey by the colors of the central frames (green: pro rule; blue: anti rule). The pro rule required the monkey to reach towards the visual cue position whereas the anti rule to the opposite of the visual cue location. Pro and anti trials were conducted either under the normal (non-prism) or the prismatic (prism) viewing contexts. Monkeys could distinguish prism and non-prism contexts either by visually noticing when the prism was in the aperture, by noticing the reversed feedback about his hand movements during acquisition of the fixation spot at the beginning of the trial, or by the oppositely slightly tilted fingertips during fixation in the reversed viewing context. Importantly, despite the reversed vision of the finger tips the monkeys had the same arm postures during the planning phase between the prism and non-prism viewing contexts. This was due to the large screen-body distance that monkeys had to keep the arm stretched to reach the screen (i.e., little freedom on the elbow angles to allow different arm postures). To confirm this, we video-recorded over several sessions the arm of the monkey from below on the background of a measuring tape (The motion tracking device could not be used for this purpose since the arm was occluded for the cameras). The standard deviation of the horizontal lower arm position near the elbow was 0.24 cm during prism-reaches, and 0.17 cm during no-prism reaches, and the difference of 0.1 cm between the mean positions in prism and no-prism trials was not significant ($p>0.1$ t-test, data not shown).

The reach task was defined in the visual coordinate in all task conditions. This means that, in the prism context, for instance, with a perceived right side visual cue, monkeys would need to physically reach to the left in order to bring the visual hand toward the visual cue location (prism pro condition, lower left panel in **Fig. 1C**). In the prism anti trials (lower right panel in **Fig. 1C**), a perceived right side visual cue would be associated with a physical rightward movement in order to bring the visual hand to the left (away from the perceived visual cue). Left and right cues and pro and anti trials were randomly interleaved from trial to trial. Prism and no-prism trials were alternated by manually switching between the prism and the empty boxes in the aperture in a block of 40 trials (most recording sessions had four blocks, with two in each context). The precise visual field alignment with and without prism was confirmed by constant central gaze direction across both conditions.

The combined reversing-prism anti-reach task (2 contexts (prism/non-prism) x 2 rules (pro/anti)) was performed by one monkey (S). In a simplified version of the task (prism/non-prism contexts in pro rule only), two monkeys (S and F) participated in the experiments. We recorded three independent datasets from two monkeys in this study.

### *Neural data acquisition*

We simultaneously recorded extracellular spikes and local field potentials (LFPs) with a five-channel microdrive (“mini-matrix”; Thomas Recording, Germany) from PRR area of two rhesus monkeys. Pre- and post-surgical structural magnetic resonance imaging guided chamber and electrode placement contra-lateral to the handedness (monkey S: 6mm lateral, 10mm posterior; F: 7 mm lateral, 13 mm posterior). The raw signals were pre-amplified (20x; Thomas Recording), band-pass filtered into broad-band data (154 Hz to 8.8 kHz) and LFPs (0.7 Hz to 300 Hz). The band-pass filtered LFPs were digitized and sample at 1000 Hz. Broad-band signals were further amplified (400–800x; Plexon, Dallas, TX), before online spike-sorting was conducted (Sort Client; Plexon). Additional to spike times the spike waveforms were recorded, sampled at 40 kHz, and later subjected to offline sorting for the control of sorting quality (Offline Sorter; Plexon). All recorded and sufficiently well isolated single spiking units, regardless of task-relatedness or direction tuning properties, were included in the neural data analyses. Only LFPs from those channels which also contained isolated single unit data were included in the LFP analysis **(Supporting Information Fig. S3)**.

### *Neural data analysis*

Neural spiking responses were quantified by the average spike rate across trials in the last 800ms before the “go” signal (the delay period) to capture the sustained planning activity. The direction selectivity index (DSI) was defined as contrast in spike rate (r) between left (L) - and right (R) -side cued trials:

$$DSI = \frac{r_L - r_R}{r_L + r_R}$$

The cue position was defined in the subject’s visual field (i.e., viewed through the prism if present). The left-right direction selectivity was considered significant at $p<0.05$ (t-test).

As schematized in **Fig. 4**, cells that were significant in neither task conditions dropped out of the further analysis because of not being considered task-related. As a first step, we compared the directional selectivity between pro and anti trials (anti-dissociation). If DSIs did not reach significance simultaneously for both the pro and anti trials, this neuron was defined as unclassifiable. In case that significant DSIs were present in both pro and anti trials, the DSIs could have either the same signs (classified as visual memory neuron), or the opposite signs (motor response neuron). Note that the anti-dissociation could be done in either the non-prism or the prism context. The classifications (based on anti-dissociation) from these two viewing contexts were not in contradiction with each other except for one neuron (significant visual memory-related in non-prism context but meanwhile significant motor intention-related in the prism context). For this specific neuron, we labeled it as unclassifiable because of its “confusing” characteristic. As a second step, for those motor intention-related neurons, depending on their DSIs in the prism and non-prism trials (prism-dissociation), we could further classify them into visual prediction related neurons (significant DSIs in both contexts, same signs), physical intention neurons (significant DSIs in both, opposite signs), or undefined motor intention neurons (significant in only one or neither of the two contexts). Similarly, the prism-dissociation could be done in either the pro or the anti rule, and neuron classifications from these two task rules did not yield contradictory neuron membership. Note that, firstly, this two-step neuron classification protocol was applied to the dataset with the combined reversing-prism anti-reach task. For the two datasets with the reversing-prism task in the pro rule only, we skipped the first anti-dissociation and used the prism-dissociation to label the neurons. Secondly, the membership of almost all neurons did not depend on the order of this two-step procedure. For example, applying the prism-dissociation without the anti-dissociation would yield similar neuron counts (see Results).

To examine the spatial selectivity of the same neuron across anti dissociations and prism dissociations, for each neuron we computed their DSI ratios in the anti dissociations and in the prism dissociations separately as the following:

$$DSI\ \mathrm{ratio}_{anti\ dissociation,\ non-prism} = \frac{sign\,(DSI_{non-prism\ pro})}{sign\,(DSI_{non-prism\ \mathrm{anti}})} \times \frac{\min\,(\left|DSI_{non-prism\ pro}\right|, \left|DSI_{non-prism\ anti}\right|)}{\max\,(\left|DSI_{non-prism\ pro}\right|, \left|DSI_{non-prism\ anti}\right|)}$$

$$DSI\ \mathrm{ratio}_{anti\ dissociation,\ prism} = \frac{sign\,(DSI_{prism\ pro})}{sign\,(DSI_{prism\ anti})} \times \frac{\min\,(\left|DSI_{prism\ pro}\right|, \left|DSI_{prism\ anti}\right|)}{\max\,(\left|DSI_{prism\ pro}\right|, \left|DSI_{prism\ anti}\right|)}$$

$$DSI\ \mathrm{ratio}_{\mathrm{prism}\ dissociation,\ pro} = \frac{sign\,(DSI_{non-prism\ pro})}{sign\,(DSI_{prism\ \mathrm{pro}})} \times \frac{\min\,(\left|DSI_{non-prism\ pro}\right|, \left|DSI_{prism\ \mathrm{pro}}\right|)}{\max\,(\left|DSI_{non-prism\ pro}\right|, \left|DSI_{prism\ \mathrm{pro}}\right|)}$$

$$DSI\ \mathrm{ratio}_{\mathrm{prism}\ dissociation,\ \mathrm{anti}} = \frac{sign\,(DSI_{non-prism\ \mathrm{anti}})}{sign\,(DSI_{prism\ \mathrm{anti}})} \times \frac{\min\,(\left|DSI_{non-prism\ \mathrm{anti}}\right|, \left|DSI_{prism\ \mathrm{anti}}\right|)}{\max\,(\left|DSI_{non-prism\ \mathrm{anti}}\right|, \left|DSI_{prism\ \mathrm{anti}}\right|)}$$

Where $|\ldots|$ denoting the absolute values. Here, we chose the "ratio" computations simply because we need to compare the DSI signs across task conditions to see which aspects of reach movements were correlated with neurons' spatial selectivity (to classified neurons). Whether the selectivity strength was strong or weak is not the deterministic factor when making the link between movement parameter and spatial selectivity of neurons, as long as those DSIs were statistically significant. For example, a DSI ratio of 1 or -1 would mean that the DSIs in the corresponding comparison had the same selectivity strength, with either the same or the opposite preferred directions.

We then calculated the mean DSI ratios for each dissociation dimension (averaged across non-prism and prism contexts for the anti dissociations, and across pro and anti rules for the prism dissociations) and plotted them against each other (**Fig. 5E**). Mean DSI ratios were computed as:

$$DSI\ \text{ratio}_{\text{anti}\ dissociation} = \frac{DSI\ \text{ratio}_{\text{anti}\ dissociation,\ \text{non-prism}} + DSI\ \text{ratio}_{\text{anti}\ dissociation,\ \text{prism}}}{2}$$

$$DSI\ \text{ratio}_{\text{prism}\ dissociation} = \frac{DSI\ \text{ratio}_{\text{prism}\ dissociation,\ \text{pro}} + DSI\ \text{ratio}_{\text{prism}\ dissociation,\ \text{anti}}}{2}$$

We also characterized the directional selectivity of each neuron in different task periods of the trial (**Fig. 7**). The same data analysis was conducted for neuronal activities during the cue period (200ms during the visual cue presentation), during the early delay period (from 100 to 900ms after visual cue offset), during the late delay period (last 800ms before the "go" cue) and during the reach movement period (200ms before reach target acquisition). Different window lengths were used because in the task design the visual cue and movement periods were relatively brief as comparing to the long sustained delay period.

### ***Randomization tests***

To test the statistical significances of the observed visual prediction neurons and physical intention neurons, we applied randomization test at two different levels. The first level of randomization served as an alternative to the *t-test* for directional selectivity in the main text. For this we shuffled trials across all task conditions (left/right x prism/no-prism x pro/anti) within each neuron. Direction selectivity was considered significant if the original DSI value fell outside the 95% confidence interval of the shuffled DSIs (comparable to $p<0.05$ criterion used in t-test).

At the second level of randomization tests, we asked the more specific question: Provided we preserve each neuron's general left/right selectivity, and its general motor intention encoding (according to the pro/anti comparison), and provided all neurons were selective for the physical movement intention, i.e., we preserve the putative physical intention encoding; how likely would neurons then be falsely classified as visual prediction neurons, due to the remaining uncertainty in estimating spike rates? To test this, we grouped the 2 x 4 task conditions across which a physical intention neuron is expected to be invariant; i.e., normal-pro-left, prism-pro-right, normal-anti-right, and prism-anti-left trials fell into one group, and normal-pro-right, prism-pro-left, normal-anti-left, and prism-anti-right fell in the other group (see example in **Fig. 3D**). For each neuron, we then shuffled trials within each of these two groups (N=1000 randomizations) and re-computed DSIs in each task condition. The dashed ellipses in **Fig. 5A-E** and **Fig. 6A-B** mark the 99% confidence intervals estimated from the resulting shuffle distribution of the DSIs combined from all neurons. Neurons which comply with the physical intention hypothesis should fall into this range. Neurons which fall outside this range and have a distance to the boundary of the ellipse which is large compared to the diameter of the ellipse into this direction, are extremely unlikely to be explained by random fluctuations under the assumption that the physical intention hypothesis is exclusively true.

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Figure 1

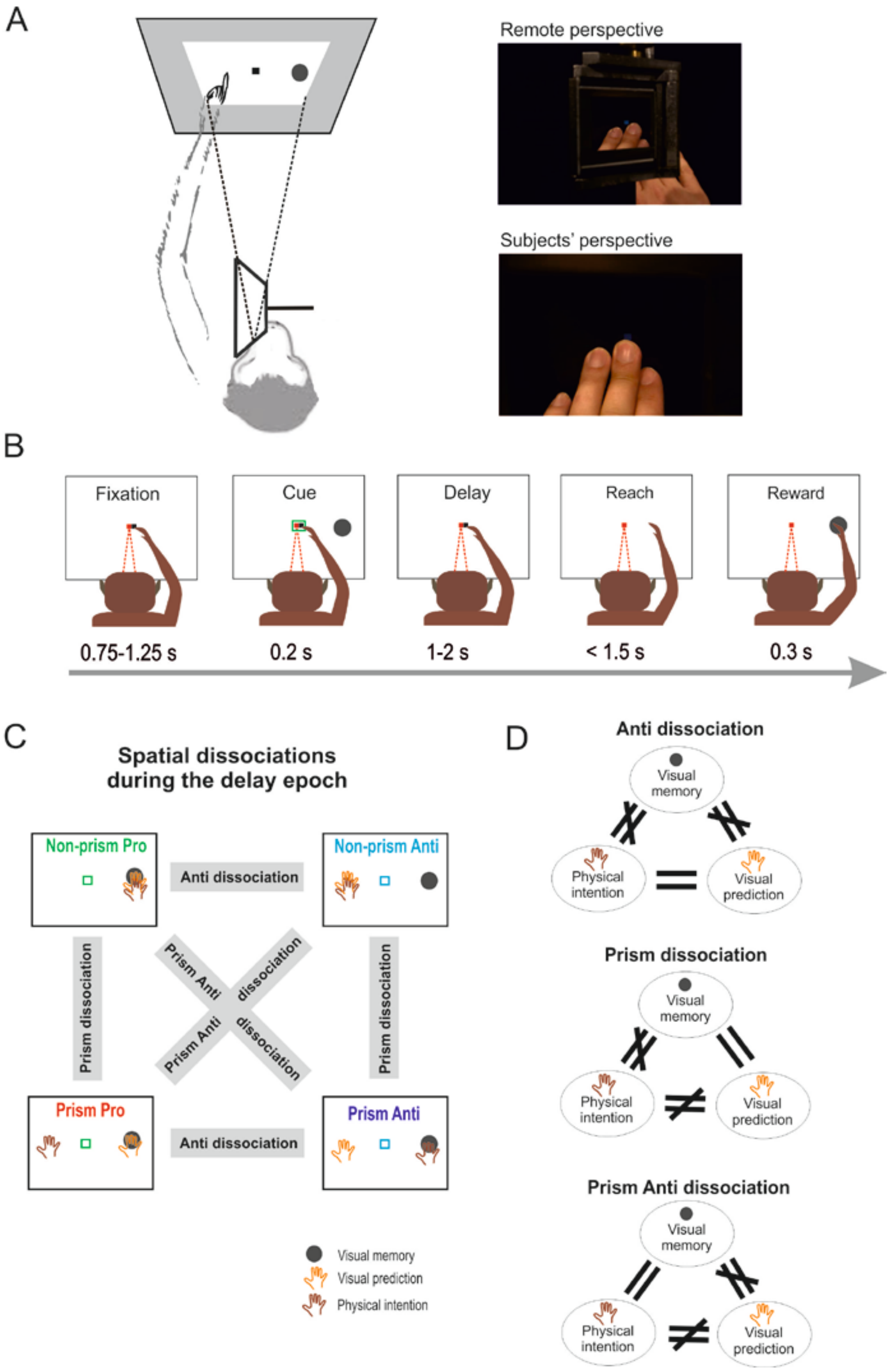

A
Remote perspective
Subjects' perspective
B
Fixation
Cue
Delay
Reach
Reward
0.75-1.25 s
0.2 s
1-2 s
< 1.5 s
0.3 s
C
Spatial dissociations during the delay epoch
Non-prism Pro
Anti dissociation
Non-prism Anti
Prism dissociation
Prism Anti dissociation
Prism Anti dissociation
Prism dissociation
Prism Pro
Anti dissociation
Prism Anti
Visual memory
Visual prediction
Physical intention
D
Anti dissociation
Visual memory
Physical intention
Visual prediction
Prism dissociation
Visual memory
Physical intention
Visual prediction
Prism Anti dissociation
Visual memory
Physical intention
Visual prediction

**Figure 1: Reversing-prism anti-reach task.** (**A**) Monkeys viewed the screen monocularly through an aperture filled with a dove prism or being empty (left and upper right). They saw a real reversed image of their fingertips and their eye was close enough to the aperture to not see the holding device (lower right, photo taken through prism). (**B**) Example timeline for a single trial of the reversing-prism center-out anti-reach task. A left or right peripheral visual cue required pro (towards the visual cue, green central cue) or anti (opposite to the visual cue, cyan cue) reaches in either the no-prism or prism viewing context. Reaches had to be withheld for a random delay until a go-cue instructed the reach. (**C**) During the delay period, the 2 (left/right cue) x 2 (pro/anti rules) x 2 (non-prism/prism viewing contexts) task design allowed spatial dissociation of the factors ‘visual memory’ (cue position), ‘physical intention’ (planned hand movement) and ‘visual prediction’ (to-be-anticipated visual hand feedback) (see Materials and Methods). (**D**) The combined reversing-prism anti-reach design dissociates the visual prediction signals from the visual memory and from the physical intention signals (bottom panel), which could not be achieved in either the anti dissociation alone (top panel) or the prism dissociation alone (middle panel).

Figure 2

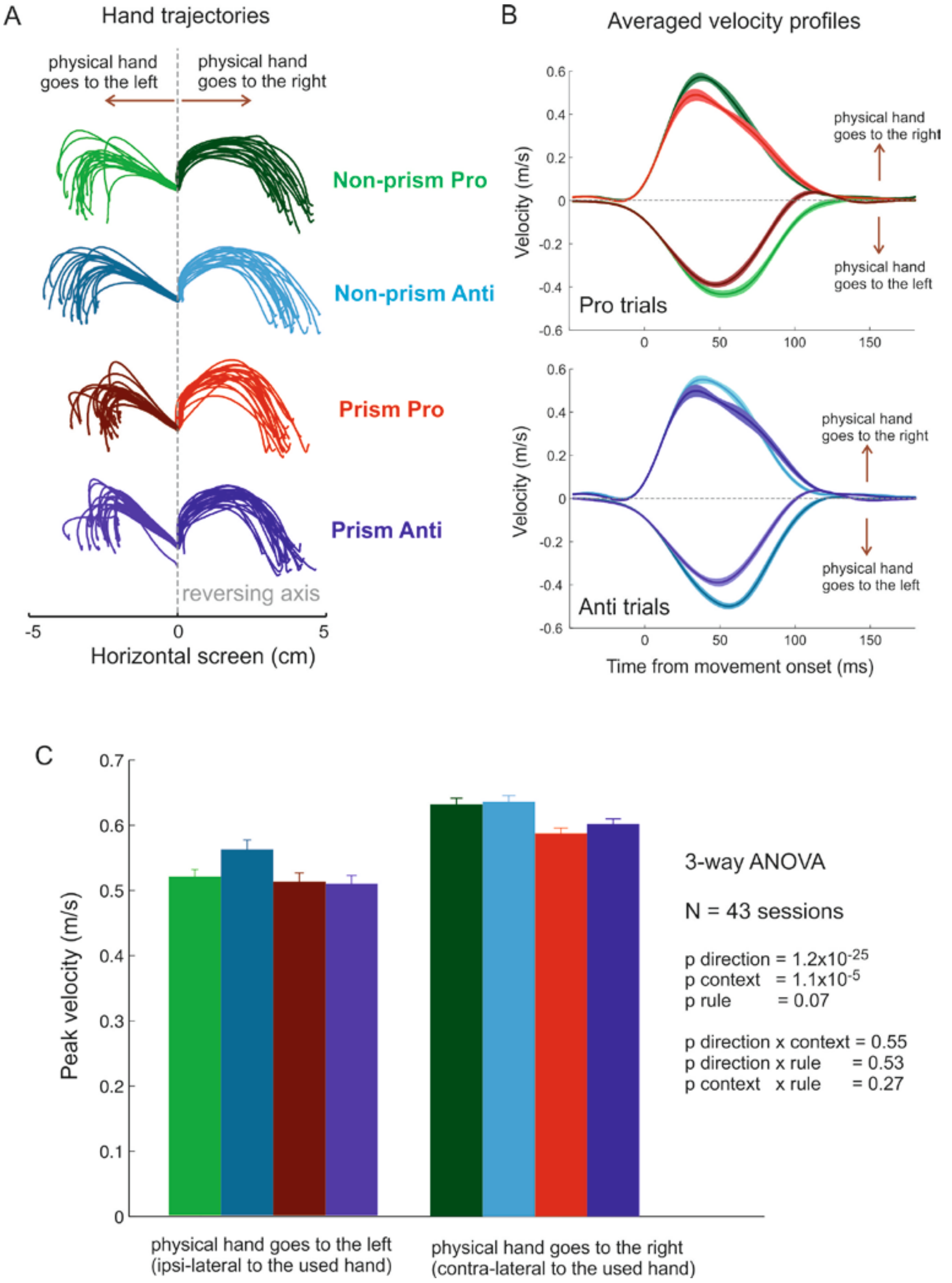

A
Hand trajectories
physical hand goes to the left
physical hand goes to the right
Non-prism Pro
Non-prism Anti
Prism Pro
Prism Anti
reversing axis
-5
0
5
Horizontal screen (cm)
B
Averaged velocity profiles
Velocity (m/s)
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
physical hand goes to the right
physical hand goes to the left
Pro trials
0
50
100
150
Anti trials
Time from movement onset (ms)
C
Peak velocity (m/s)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
physical hand goes to the left (ipsi-lateral to the used hand)
physical hand goes to the right (contra-lateral to the used hand)
3-way ANOVA
N = 43 sessions
p direction = 1.2x10-25
p context = 1.1x10-5
p rule = 0.07
p direction x context = 0.55
p direction x rule = 0.53
p context x rule = 0.27

**Figure 2: Reach trajectories and velocity profiles in the combined reversing-prism anti-reach task.** (**A**) The trial-by-trial hand physical paths from one example session in each task condition and in each direction (Raw data were filtered offline using 4th order Butterworth filter with a low-pass cut-off frequency of 20 Hz). (**B**) The averaged hand horizontal velocity profiles (aligned to movement onset) in each direction and for each task condition. The monkey was performing stereotyped hand movements with smooth speed profiles (**C**) The mean peak velocities were significantly different between ipsilateral- and contralateral- hand movement, and between prism and non-prism trials. The latter behavioral difference indicates that the monkey had prepared and executed the movement differently in the prism compared to non-prism viewing context. This implies that the monkey had been influenced by the to-be-anticipated reversed visual sensory consequences during the delay period.

**Figure 3: Spatial selectivity of two example neurons.** Spike rate differences between left- and right-side cue trials as a function of time in each task condition for two example neurons. The directional selectivity was analyzed during the sustained late delay period (800ms long period prior to ‘go’). This was true for most parts of the manuscript except in Fig. 7. (**A**) Visual prediction neuron, characterized by same-sign DSIs in the prism compared to the no-prism context during both pro and anti reaches. (**B**) Physical intention neuron, characterized by opposite-sign DSIs in the prism compared to the no-prism context during pro and anti reaches. (**C-D**) showed, for each example neuron, the corresponding raw trial-by-trial spike events and the averaged spike density curves (smoothed with 50ms Gaussian kernel) for each direction and each task condition separately for left and right, i.e., before computing the difference seen in A and B.

Figure 3

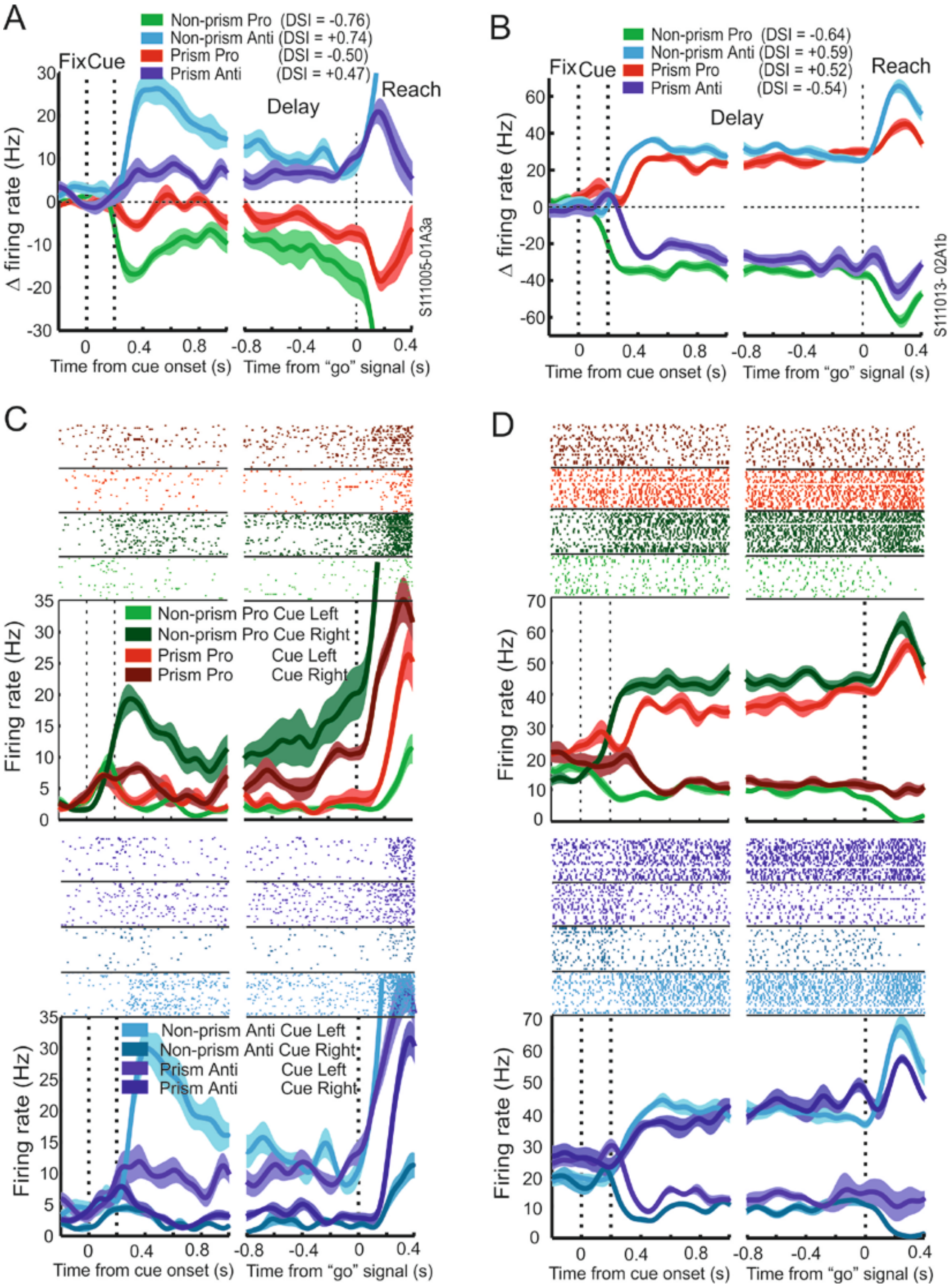

A
Non-prism Pro (DSI = -0.76)
Non-prism Anti (DSI = +0.74)
Prism Pro (DSI = -0.50)
Prism Anti (DSI = +0.47)
Fix
Cue
Delay
Reach
Δ firing rate (Hz)
S111005-01A3a
Time from cue onset (s)
Time from "go" signal (s)
B
Non-prism Pro (DSI = -0.64)
Non-prism Anti (DSI = +0.59)
Prism Pro (DSI = +0.52)
Prism Anti (DSI = -0.54)
Fix
Cue
Delay
Reach
Δ firing rate (Hz)
S111013- 02A1b
Time from cue onset (s)
Time from "go" signal (s)
C
Non-prism Pro Cue Left
Non-prism Pro Cue Right
Prism Pro Cue Left
Prism Pro Cue Right
Firing rate (Hz)
Non-prism Anti Cue Left
Non-prism Anti Cue Right
Prism Anti Cue Left
Prism Anti Cue Right
Firing rate (Hz)
Time from cue onset (s)
Time from "go" signal (s)
D
Firing rate (Hz)
Firing rate (Hz)
Time from cue onset (s)
Time from "go" signal (s)

Figure 4

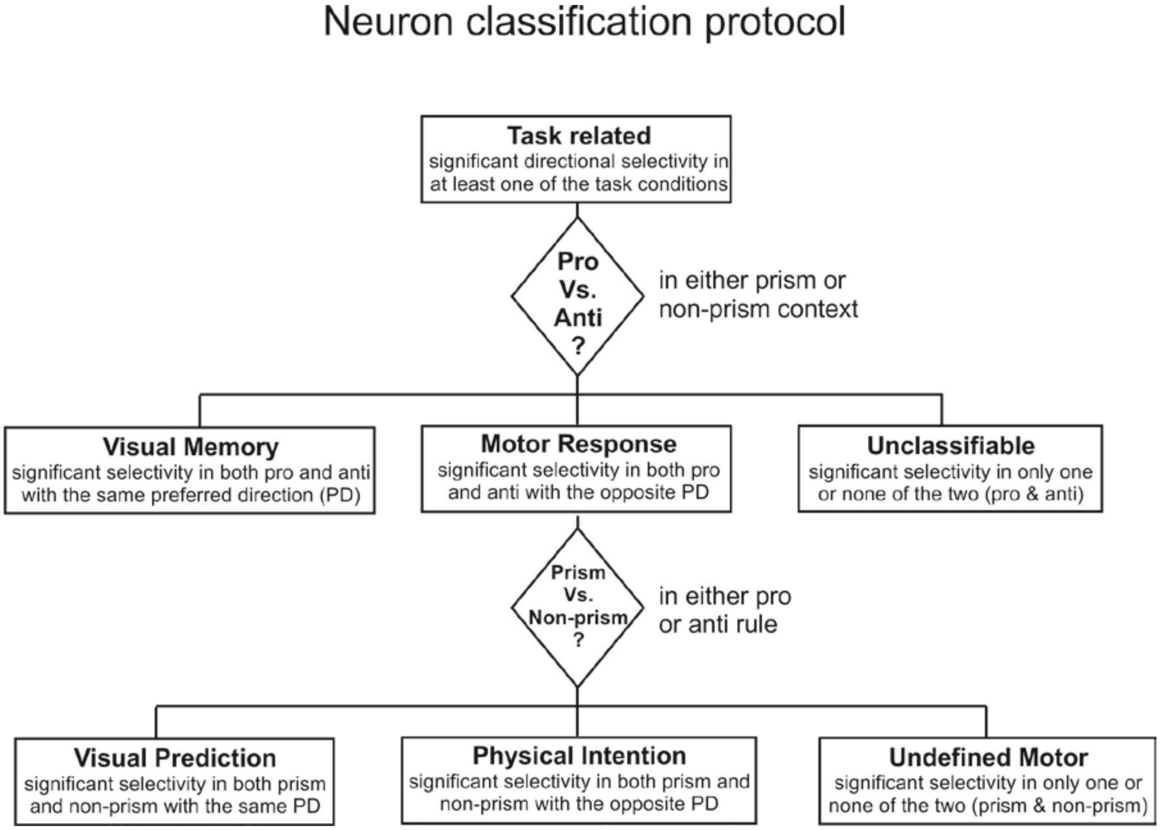


**Figure 4: Schematized illustrations of the procedures for classifying neurons.** A two-step categorization led to the distinction of visual prediction and physical intention neurons. For the dataset with the combined reversing-prism anti-reach task, the anti dissociation (upper classification) and the prism dissociations (lower classification) were applied sequentially; for the reduced prism task without anti trials, the anti dissociation could be by-passed due to the abundant motor-related selectivity (lack of sustained visual memory encoding) and the classification was done based on the prism dissociation alone (see Materials and Methods).

Figure 5

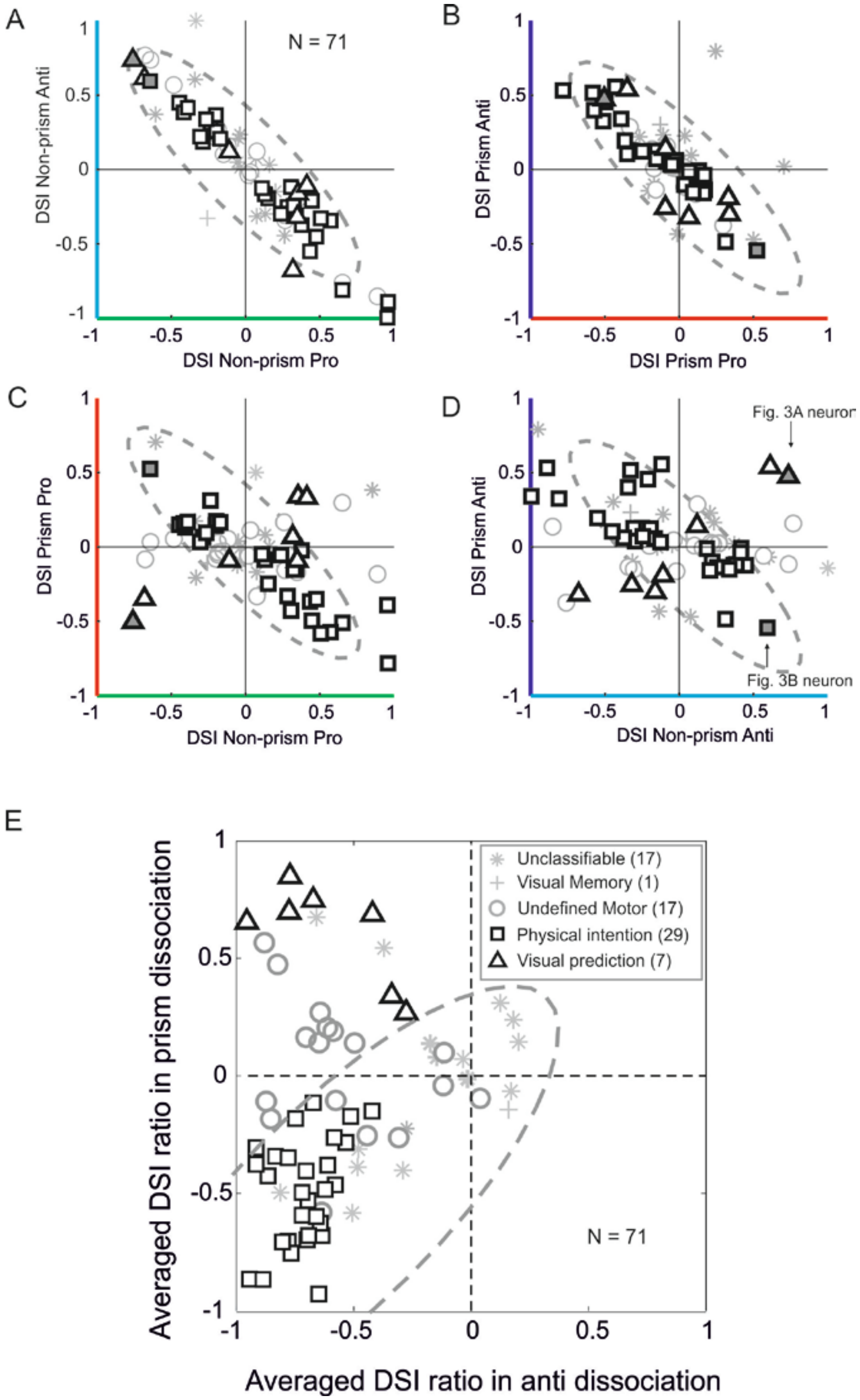

A
N = 71
DSI Non-prism Anti
DSI Non-prism Pro
B
DSI Prism Anti
DSI Prism Pro
C
DSI Prism Pro
DSI Non-prism Pro
D
DSI Prism Anti
DSI Non-prism Anti
Fig. 3A neuron
Fig. 3B neuron
E
Unclassifiable (17)
Visual Memory (1)
Undefined Motor (17)
Physical intention (29)
Visual prediction (7)
N = 71
Averaged DSI ratio in prism dissociation
Averaged DSI ratio in anti dissociation
1
0.5
0
-0.5
-1

**Figure 5: Classification of visual prediction and physical intention neurons across the population of neurons recorded with the combined reversing prism-anti task in Monkey S.** (**A–B**) DSI values between pro and anti reaches were strongly anti-correlated in the no-prism (A) and prism context (B), indicating almost exclusive motor-related encoding of movement intentions during the late delay. (**C–D**) Of the intention-related neurons (non-* symbols), many were classified as visual prediction neurons (triangles), the others as physical intention neurons (squares). Note, (C) and (D) contain the same data as (A) and (B), but contrasted differently. (A–D) Filled symbols indicate the examples from Fig. 2. Dashed ellipses denote the confidence limit within which 99% of the surrogate data falls when assuming exclusively physical intention encoding as null-hypothesis. (**E**) Distribution of DSI ratios in the prism dissociations and anti dissociations for each neuron.

**Figure 6: Relative percentages of visual prediction neurons vs. physical intention neurons across three independent datasets from two monkeys.** (**A-B**) Classification of visual prediction and physical intention neurons across the population of neurons recorded in the reversing prism task with the pro rule only, for monkeys S (A) and F (B). Conventions for dashed ellipses are identical to Fig. 5. Dataset from both monkeys revealed a significant co-existence of visual prediction neurons (triangles) and physical intention neurons (squares). Stars indicate neurons with significant left-right selectivity in only one of the viewing conditions, i.e. which were not eligible for testing the visual prediction hypothesis. (**C**) Relative percentages of neuron types across monkeys and tasks were highly comparable during the late delay period. (**D**) The relative percentages of visual prediction neurons are higher during the early delay period compared to the late delay period in each monkeys and tasks.

Figure 6

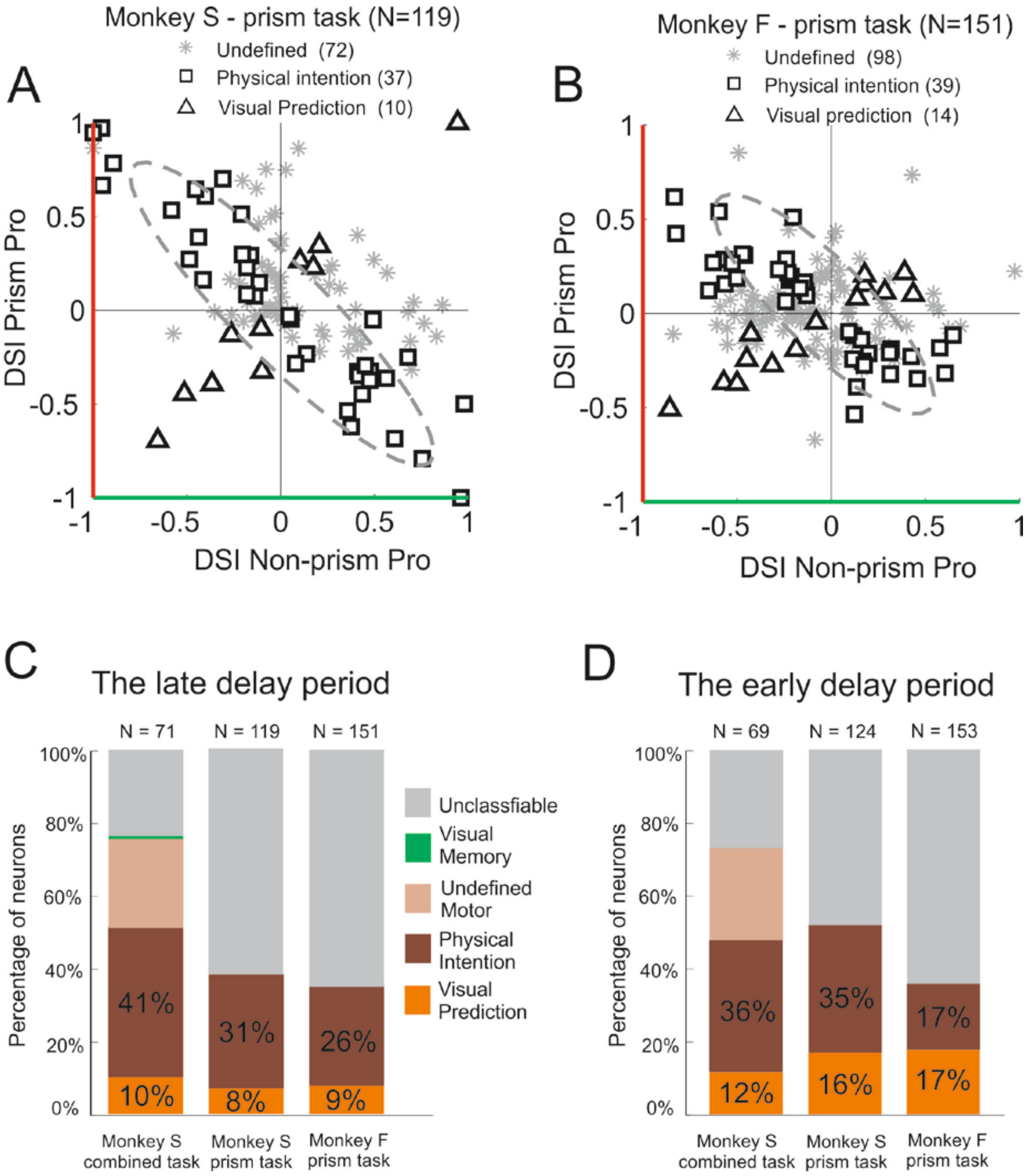

A
Monkey S - prism task (N=119)
Undefined (72)
Physical intention (37)
Visual Prediction (10)
DSI Prism Pro
DSI Non-prism Pro
1
0.5
0
-0.5
-1
-1
-0.5
0
0.5
1
B
Monkey F - prism task (N=151)
Undefined (98)
Physical intention (39)
Visual prediction (14)
DSI Prism Pro
DSI Non-prism Pro
1
0.5
0
-0.5
-1
-1
-0.5
0
0.5
1
C
The late delay period
N = 71
N = 119
N = 151
100%
80%
60%
40%
20%
0%
Percentage of neurons
41%
31%
26%
10%
8%
9%
Monkey S combined task
Monkey S prism task
Monkey F prism task
Unclassfiable
Visual Memory
Undefined Motor
Physical Intention
Visual Prediction
D
The early delay period
N = 69
N = 124
N = 153
100%
80%
60%
40%
20%
0%
Percentage of neurons
36%
35%
17%
12%
16%
17%
Monkey S combined task
Monkey S prism task
Monkey F prism task

Figure 7

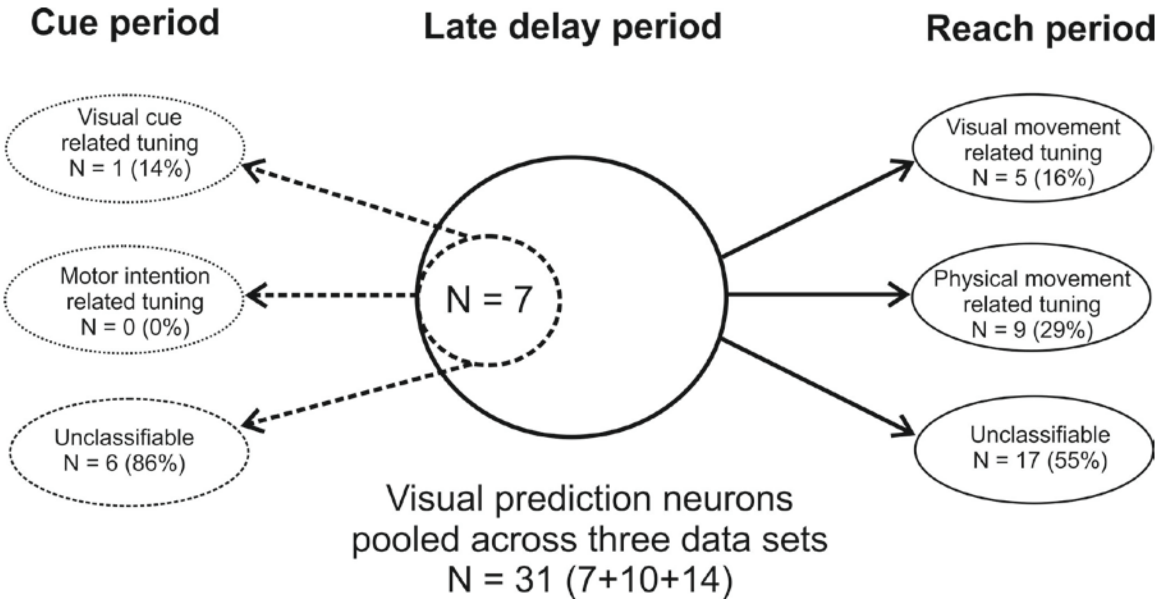


**Figure 7:** The visual prediction neurons are not sensitive to the visual input during both the cue period and the reach period when the visual spatial input about either the stimulus or the hand is available. Note, for testing the spatial selectivity during the cue period, we had to restrict the analysis to the data set from the combined reversing-prism anti-reach task, since we need the anti dissociation to identify a visual cue related tuning.

## Supporting Information

### Texts S1 – Trial-resolved success rates

Even though the monkeys could switch back and forth between the prism and non-prism viewing contexts quickly, they need at least a few trials to repeatedly ‘adapt’ to the switching viewing contexts. For both monkeys, the overall task performance in the first 5-8 trials after switching the viewing context was greatly reduced compared to later trials in the same viewing context. This was true for the switching both from the no-prism to prism context and from the prism to non-prism context (**Fig. S1**). Note that the relative low success rate in the first few trials after context switches was mainly due to the trials with ocular/hand fixation breaks before the “go” signal, rather than the confusion of reach directions. These adaptive behavioral performance indicates that the monkeys was not solving the task conditionally, but rather needed at least in some way to repeatedly ‘adapt’ to the switching viewing contexts. In other words, the monkeys might be in a different cognitive status between the prism and non-prism trials where movement preparations were affected by the to-be-expected visual sensory consequences of upcoming movements.

### Texts S2 – Example visual prediction neuron with weak but significant directional selectivity

In the main analysis, neurons with weak left-right selectivity (small absolute DSI) tend to fall within the range of possible random variations according to the shuffle test (confidence ellipse in Fig. 5C-D). Yet, the question of whether a neuron is consistently selective for the to-be-anticipated visual feedback or the intended physical movement should not depend on how strong the selectivity for leftward versus rightward movements is. For example, a weak selectivity could be the consequence of the preferred direction of the neuron not coinciding with the left-right axis of our experiment. Here we demonstrate that neurons, which fall into the non-significant data range of the shuffle testing, can still be significantly selective for visual predictions when tested on an individual neuron basis. We examined the raw PSTHs for a neuron with very weak directional selectivity (triangle that located closest to the origin in Fig. 5C panel). As shown in Fig. S2, this neuron showed directional selectivity with weak modulations between left and right trials in three out of the four task conditions ($p<0.01$ in non-prism pro, non-prism anti and prism anti conditions, unpaired t-test). While these directional modulations were small in amplitude, they were reliable and hence statistically significant. According to the neuron classification procedure (Fig. 4), this neuron had significant DSIs in both pro and anti trials in the non-prism context, therefore was motor intention related. From the prism dissociation, this neuron's responses were correlated with the to-be-anticipated visual hand movement direction rather than the physical movement direction, since the DSIs had the same sign between prism and non-prism trials in the anti rule. Hence, this neuron had been classified as a visual prediction neuron.

### Text S3 – Spatial representations by local field potentials (LFP)

At the level of individual neurons, the sustained activity during motor planning was related to the intended movement for basically all neurons which were selective in the reversing-prism task. This made the pro-anti comparison redundant in retrospect. Yet, providing evidence for sensory prediction encoding with the reversing-prism task alone is not a valid approach for other signal types or brain areas, unless one explicitly has demonstrated that the very same signal is motor-goal related (e.g. by combining the feedback manipulation with a pro/anti dissociation).

We characterized the spatial encoding properties in simultaneously recorded LFP signals which are thought to capture sub-threshold synaptic population activity, and are correlated more strongly to fMRI signals than to spiking data (Logothetis and Wandell, 2004;Logothetis, 2008). **Fig. S3** shows the population-average of the spatial selectivity of 62 LFP channels in our reversing-prism anti-reach task from monkey S. Each panel shows the time-frequency diagram (spectrogram) of the difference in LFP amplitude density (color-coded) between left-cued and right-cued trials. We used the left-right difference equivalently to what is typically used in EEG- or fMRI-based imaging data, for easier comparison. Sorting the LFP channels according to the preferred vs. non-preferred direction (as in the single neuron data) would not change our conclusions, since preferred directions across the LFP channels from the same area and hemisphere were very similar in our data, as was the case in previous studies (Scherberger et al., 2005;Hwang and Andersen, 2012). The LFP spectrograms in the no-prism viewing context (upper two panels) showed similar time-frequency regions of interest (ROI) in pro and in anti trials, in which the LFP amplitude density was significantly direction selective. This ROI ranged approx. from 15 to 20 Hz, started approx. from 600 ms latency after spatial cue onset, and continued to the onset of movement. These overlapping ROIs had significant directional selectivity with opposite sign in pro and anti reaches, which means LFPs in this time-frequency domain were motor-goal related. Similarly, the LFP spectrograms in the prism viewing context (lower two panels) showed overlapping ROIs which were direction selective and motor related. These overlapping ROIs ranged approx. from 15 to 25 Hz, started approx. from 250ms latency, and terminated after 900 ms. Yet, prism and non-prism pro-reach trials (left two panels), only partly share a common ROI with significant directional selectivity. In prism-pro trials significant directional selectivity started at approx. 250 ms and ended at approx. 900 ms latency, whereas in non-prism pro condition selectivity emerged not before 600ms latency. These barely overlapping ROIs mean that different predominating time-frequency ranges of LFP were motor-related in prism and no-prism trials, and, hence, neither of these ranges could be classified as either visual prediction or physical intention signals. Only a small time-frequency range around 600-900 ms qualifies for such classification and indicates visual prediction tuning. Additional direction selective ROIs at frequencies below 15 Hz appear during cue presentation in prism trials only, which do also not qualify for a classification according to our schema. This means, LFP signals did not show a result equivalent to our single unit spiking data. Importantly, LFPs could not grasp the dichotomy seen in the different characteristics of individual neurons which is important to our interpretation (see Discussion). Similar limitations affect human brain imaging data, e.g. fMRI (Fernandez-Ruiz et al., 2007).

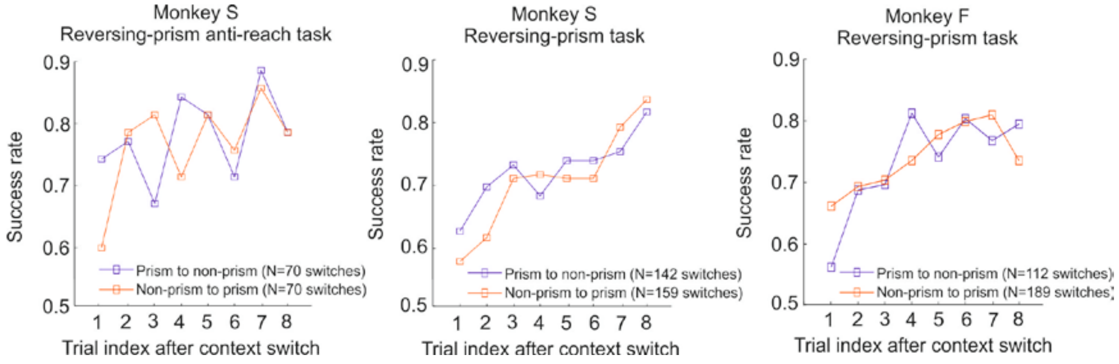
## Text S4 – Discussion: Motor intention or spatial attention?

Could the delay period activity we observed in the current study be explained by spatial attention, given the controversial interpretations of sustained PPC activity representing either the movement preparation (Gnadt and Andersen, 1988;Snyder et al., 1997) or visuospatial attention (Gottlieb and Goldberg, 1999;Bisley and Goldberg, 2003)? We argue that attention interpretation to our data is not plausible for the following reasons. Firstly, in terms of performing the task, during the delay period, especially the later part of the delay right before the occurrence of "go" cue, monkeys need to pay attention to the central fixation spot to detect the change in order to initiate the movement. Therefore, the observed spatial selectivity in the late delay period can unlikely be attributed to spatial attention to peripheral targets/movements. Secondly, the attention-intention contradictions involved mainly the saccade-related parietal areas located in the lateral intra-parietal sulcus (LIP) (Gnadt and Andersen, 1988;Snyder et al., 1997;Gottlieb and Goldberg, 1999;Bisley and Goldberg, 2003), but not in the reach-related parietal area PRR, since visuospatial attention is behaviourally strongly tied to eye-movements {REFs}. Previous studies have demonstrated that reach intention-related activity in PRR did not comply with visospatial attention (Cui and Andersen, 2007;Scherberger and Andersen, 2007;Snyder et al., 1998). Thirdly, the fact that we observed both visual and physical hand related neurons suggests that visual spatial attention as an explanation cannot fully account for our findings. Especially, in non-prism pro and prism anti trials, the monkey had identical sensory instructions and identical reach directions, one would expect the stimulus-driven bottom-up and motor intention related top-down attention are the same across these two task conditions, yet, visual prediction neuron responses correlated with neither of these spatial parameters.

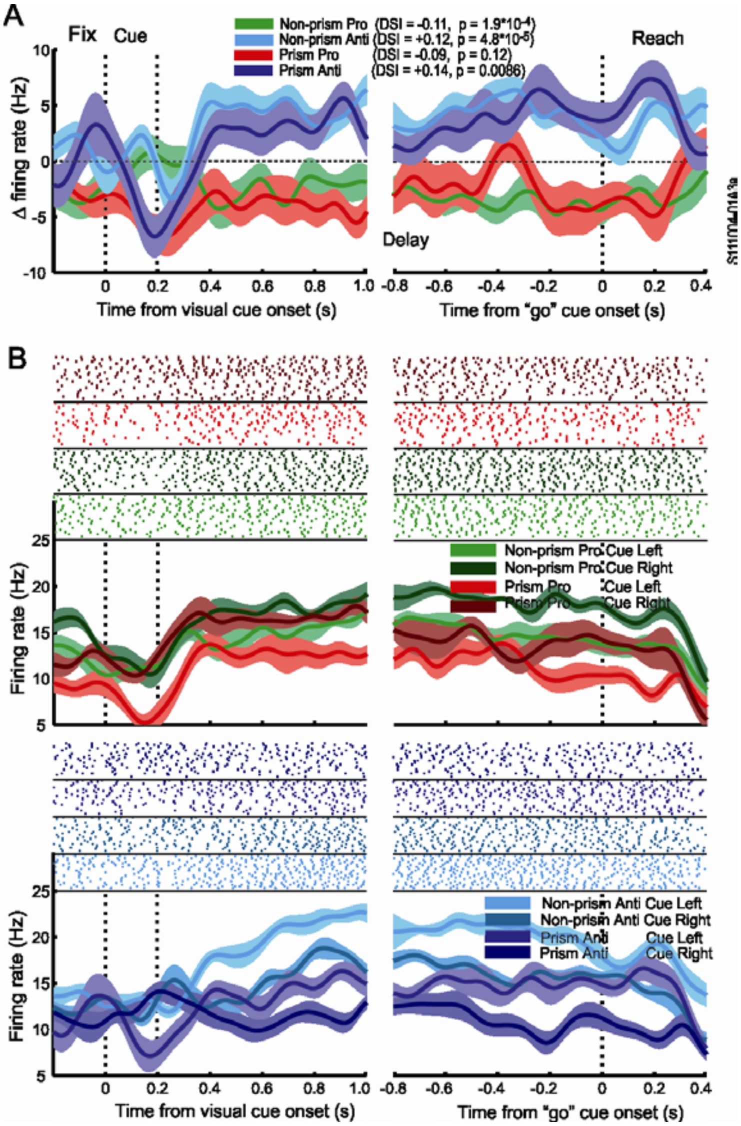
## Text S5 – Discussion: Old or new reference frames?

The dissociation between visual prediction and physical intention encoding cannot be derived from previous knowledge about spatial reference frames of motor intention signals in PPC. Reference-frame studies describe how spatial sensory inputs from different modalities are integrated in a feed-forward manner to form a motor goal in preparation of a motor command. Previous studies have shown that PRR encodes the target location or movement endpoint in a gaze-centered reference frame(Batista et al., 1999b;Buneo et al., 2002), or the movement vector in hand-centered reference frame(Chang and Snyder, 2010b;McGuire and Sabes, 2011b), and intermediate representations complying with a compound frame of reference(Chang and Snyder, 2010b),independent of the modality of sensory instruction(McGuire and Sabes, 2011b) or the spatial visual instruction (Gail and Andersen, 2006;Hwang and Andersen, 2012). The co-existence of sensory prediction neurons and physical intention neurons support a different view by showing that the observed spatial selectivity in PRR can neither be tied exclusively to the physical movement, nor exclusively to the spatial target in visual space. Instead, many neurons in PRR in our experiment distinguished between the different sensory consequences of the pending movement, while the spatial sensory input and the physical movement were the same. Since reference frame tasks and our reversing prism task varied independent task dimensions in a mutually exclusive way (our task did not vary relative initial eye and hand positions; reference frame tasks did not vary feedback), it is not possible to draw a simple one-to-one correspondence between sensory prediction neurons and encoding in a specific established spatial reference frame. For example, a neuron which encodes a movement target in a gaze-centered reference frame, and hence is not selective for the hand movement vector, does not have to be selective for the visual prediction in our task (even if this might be an intuitive association at first glance). The reason is that visual prediction encoding could still relate to either the anticipated visual endpoint of the movement relative to gaze, or to the anticipated visual motion input. In fact, neurons in ventral premotor cortex were shown to be spatially selective for visual (rather than physical) motion at movement onset while at the same time encoding the movement in a hand-centered frame of reference (Ochiai et al., 2005). Correspondingly, encoding in a hand-centered reference frame does not imply physical intention encoding, since physical intention encoding can also relate to either the endpoint of the movement or the vector of the movement.

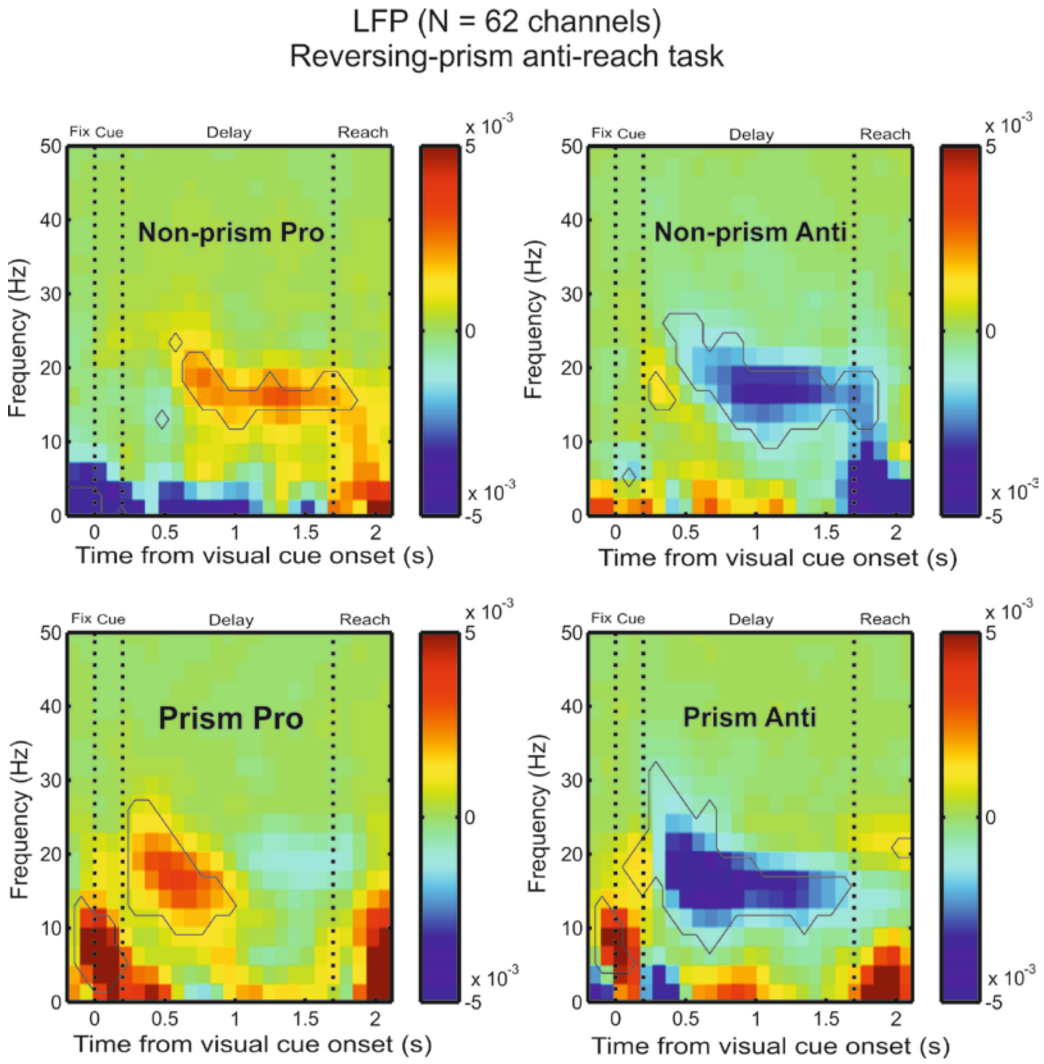
Hence, our findings are not at odds with previous neurophysiological reference frame studies. Instead, our results add a new sensory perspective to a signal which is otherwise related to motor planning. Our data suggest that representations of a “spatial motor goal” in sensorimotor cortex - at least in PRR - are partly determined by spatial sensory anticipation signals.



**Supplementary Figure 1**. The trial-resolved success rates after the viewing contexts switch in each monkey and each datasets. For the combined reversing-prism anti-reach task, pro and anti trials were pooled. Note that the success rate was computed relative to the total trials (including all fixation break trials, belated or erroneous responses). For both monkeys, there was a drop of overall performance in the first few trials after the contexts switches (held true for both the switching from the prism to the non-prism context and the reversed switching.



**Supplementary Figure 2**. One example of visual prediction neuron with weak but significant spatial selectivity. (A) Spike rate difference between left and right cue trials for each task condition. DSI were computed from the delay epoch. (B) The raw trial by trial raster plot of spike events and the averaged spike density curves.



**Supplementary Figure 3:** Spatial selectivity of local field potentials (LFP) in the reversing-prism anti-reach task. Each panel shows the time-frequency diagram (spectrogram) of the difference in LFP amplitude density (color-coded) between left-cued and right-cued trials. Black outlines mark the boundary of time-frequency bins where directional selectivity was statistically significant at the level of $p < 0.05$ (Bonferroni corrected t-test). LFP spectrograms were estimated via a discrete Fourier transformation of the LFPs using a sliding window of 384 ms length (tapered with a hamming window) and a step size of one quarter of the window length (96 ms).

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## 2.2 Differential encoding of anticipated visual sensory consequences during reach planning in the premotor cortex compared to the posterior parietal cortex

In this chapter, we are going to ask two further questions. First, do neurons in the dorsal premotor cortex also encode the visual sensory predictions of planned movement in a similar fashion to the parietal neurons? This is an nontrivial question, given that on the one hand, premotor and parietal areas are highly interconnected networks that both areas are involved in goal-directed behaviours and have been shown to exhibit similar spatial encoding properties. On the other hand, a couple of studies indicate that premotor areas are different from parietal areas in a number of ways, for example, reference frame studies show that the premotor neurons are more hand- centred representations whereas parietal neurons primarily eye-centred representations. Given these similarities and differences, premotor neurons could either encode purely physical movement intentions or be partially selective for the anticipated visual consequences as parietal neurons do. The second question is, if premotor neurons also encode the visual prediction of hand movement, what are the differences among parietal and premotor areas? The answers to these questions will help us to narrow down the possible functional roles played by each brain region in the context of goal-directed movement planning.

We found that, similar to PRR, PMd also contained a mixture of neurons whose spatial selectivity correlated with either the to-be-anticipated visual consequence or the planned physical action. However, the spatial representations were different among the premotor and parietal areas. Our data suggested that the anticipatory encoding of perceptual consequences of intended movements was not limited to one brain structure, but are rather widespread in the frontal and parietal sensorimotor circuits where each area might play distinct functional roles.

# Differential encoding of anticipated visual sensory consequence during reach planning in the premotor cortex compared to the posterior parietal cortex

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## Abstracts

The central nervous system maintains internal representations to predict the consequences of upcoming behavioral relevant events. In a recent study, we employed the optical reversing-prism anti-reach task design to dissociate the planned physical movement from the to-be-expected visual consequence, and found that a fraction of neurons in the parietal reach region (PRR) of parietal cortex encoded the to-be-expected visual consequence of intended movement while others encoded the physical movement intention. However, it remains unknown whether such visual sensory anticipatory representations would also exist in the dorsal premotor cortex (PMd), which is reciprocally connected with PRR and is critically involved in movement planning. And if so, how would these anticipatory representations differ among the parietal and premotor areas. To address these questions, we analyzed the single-unit activity in PMd that was recorded under the same behavioral tasks as in the previous study. Our results showed that, similar to PRR, PMd also contained a mixture of neurons whose spatial selectivity correlated with either the to-be-anticipated visual consequence or the planned physical movement. However, the spatial representations were different among the premotor and parietal areas. Specifically, we found that parietal but not premotor neurons showed reduced spatial selectivity strength under the reversed viewing context compared to the normal context. Our data suggests that the anticipatory encodings of perceptual consequences of intended movements are not limited to one brain structure, but are rather widespread in the frontal-parietal reach network in which each might play distinct functional roles during action planning.

## Introduction

Internal predictive representations about the future status of our body and the environment give us enormous advantages when we interact with the environment. Predicting the sensory consequences of a movement is essential during goal-directed behaviour, both, for controlling movements (Shadmehr et al., 2010b;Franklin and Wolpert, 2011) and for selecting among potential action alternatives (James, 1890b;Prinz, 1987;Waszak et al., 2012). Psychophysics studies have shown that the presence of task irrelevant but contingently experienced sensory stimuli during action planning could lead to faster reaction times or biased choices (Elsner and Hommel, 2001;Ziessler et al., 2004;Waszak et al., 2012). The idea of sensory predictions about an impending movement, prior to movement execution but as part of the prospective motor planning process, is fundamentally different and complementary to the canonical feed-forward perspective of sensory-to-motor integration. Action planning, and probably also action selection, could be based on the anticipated sensory action effects, i.e., based on a prediction about the to-be-expected sensory outcome of the pending movement, is conceivable but yet remain to be proved. At the level of single unit neurophysiology, a recent study from our laboratory (Kuang and Gail, 2013) has reported that a fraction of parietal reach region (PRR) neurons in the posterior parietal cortex encoded the to-be-anticipated visual consequences of upcoming actions while other neurons encoded the physical motor intentions. However, it is unclear whether the visual sensory predictive representations would also exist in the dorsal premotor cortex (PMd) which has direct anatomical connections with PRR and is considered to be important for movement planning.

Numerous studies have shown that PMd is involved in the planning and control of visually guided reaches. Inactivation of PMd causes deficits in reaching, in particular for complex stimulus-response associations (Kurata and Hoffman, 1994b). Individual PMd neurons are active during the delay period preceding an instructed movement, and are tuned for the direction (Scott et al., 1997b;Caminiti et al., 1991b), the distance (Messier and Kalaska, 2000b) and the speed (Churchland et al., 2006b) of reaches. Previous studies have shown that PMd and PRR share similar neuronal properties on the sustained motor goal representations during movement planning (Gail et al., 2009;Westendorff et al., 2010b;Klaes et al., 2011). On the other hand, studies on spatial reference frame in the sensorimotor system have identified a general hierarchical trend, with the PMd being more hand-centered representations (Buneo et al., 2002;Pesaran et al., 2006b) while PRR dominated by eye-centered representations (Batista et al., 1999b;Buneo et al., 2002;Chang and Snyder, 2010b;McGuire and Sabes, 2011b). Additionally, human electrical stimulation study shows that parietal stimulation induces an intention to move, without actual movements being elicited, while premotor stimulation induces explicit muscle twitches and body movements (Desmurget et al., 2009). These observations on the inter-area differences suggest differential encodings by the frontal and parietal sensorimotor areas, with PMd being more tied to the actual physical parameters of a movement, and PRR being tied to the more abstract motor goal representations in a visual reference frame.

The current study aims to explore whether the visual sensory predictive representations of intended movement are also encoded in the premotor area PMd, beyond its presence in the parietal area PRR (Kuang and Gail, 2013). Given the similarities and differences among the parietal and premotor areas mentioned above, there are two hypothetical outcomes. Either PMd neurons are invariant with respect to the visual sensory predictions and, in contrast to PRR, encode solely the kinematic variables of the actual physically intended movement. This finding would support the notion of differential functional roles of both areas in the movement planning. Or alternatively, the anticipatory encodings of visual consequences of intended movements are not limited to the parietal area, but rather are widespread properties in the frontal and parietal sensorimotor circuits. Then we should expect that PMd show the similar patterns of neural responses, partly selective for the visual sensory predictions as PRR neurons do. This finding would support the notion that sensory predictive encodings of intended movement are emerging properties of the frontal-parietal reach networks. Testing these two alternative hypotheses will be important for us to narrow down the possible functional roles of either component of the sensorimotor network in primates.

We examined the spatial encoding characteristics of PMd single neurons that were recorded with the same behavioral tasks and from the same monkeys as the PRR datasets reported in the previous study (Kuang and Gail, 2013). This allows a direct comparison between the brain areas. We obtained two main findings. Firstly, a significant proportion of PMd neurons encoded for the to-be-anticipated visual consequence of intended movement whereas others encoded for the planned physical action. This indicates that motor planning evokes sustained neuronal representations in PMd linked not only to a planned physical action per se but also to its anticipated perceivable visual sensory consequences, in a similar fashion to PRR. Secondly, we found that the spatial representations were nonetheless different among premotor and parietal neurons. The parietal but not premotor area showed reduced spatial selectivity strength in the reversing viewing context compared to the normal context. Our findings suggest that the anticipatory encodings of perceptual consequences of intended movements are not unique features in the parietal cortex but are generalizable to premotor cortex, while each area might be involved in different aspects of sensorimotor functions during movement planning.

## Materials and Methods

Technical details of the apparatus and the experimental procedures have been described previously (Kuang and Gail, 2013). All experimental procedures were conducted in accordance with German laws governing animal welfare. The experimental paradigm, data acquisition and data analysis were identical to the previous study (Kuang and Gail, 2013). In this study we examined neural responses of single cells in area PMd, and compared them with those obtained previously in PRR (Kuang and Gail, 2013). Below we will give a short summary of the methods.

### *Behavioral tasks*

We trained two male rhesus monkeys (Macaca mulatta; S and F) to perform a visually instructed, delayed centre-out reach task on a fronto-parallel screen. The monkeys sat comfortably in a primate chair facing a liquid crystal display screen (19 inch ViewSonic LCD VX922; 5ms off–on–off response time, refresh rate: 60Hz) covered with a transparent touch sensitive panel (IntelliTouch, ELO Systems, Menlo Park, CA). The touch sensitive panel registered the position of the monkey's hand on the screen. The fingertip movements were recorded by an optical motion tracking system (Visualeyez VZ 4000, PTI, Canada). The monkeys' visual field on the screen was approximately 10 x 10 cm square, restricted by the monocular viewing of the screen through a tube (the other eye was covered with a cardboard to block the vision of the screen). The tube was with either embedded with a Dove prism (12.5 x 3 x 3 cm) to achieve a left-right reversed view of the work space (prism viewing context), or kept empty to allow the normal viewing context. The distance between the display screen and monkeys' viewing eye was around40 cm. We kept this distance as long as possible to achieve the maximal visual field on the screen when viewing through the tube. A high speed infrared camera (224 Hz CCD camera, ET-49B, Thomas Recording, Giessen, Germany) was used to monitor the pupil position of the none-viewing eye for the gaze control.

The timeline of the memory-guided reach task (Fig.1A) was as follows: Each trial started after the monkeys held hand fixation around the central white spot (fixation period) for a random time of 0.75-1.25s, a peripheral visual cue (5cm eccentricity) was briefly flashed (cue period, 0.2s), indicating where they will have to reach later. Reach movements were not allowed to be executed until the "go" signal (the disappearance of central hand fixation spot) was given. During this delay period the monkeys had to keep the hand fixation and remember the location of the visual cue (memory period, 1.0-2.0s). After the "go" signal, the monkeys had to make a reach towards the previously cued location within a maximum of 1.5s (movement period). The visual cue reappeared at the same location to provide visual feedbacks to the monkeys after they acquire the target, or after the maximum allowed movement period had expired. Eye fixation had to be kept throughout the course of the trial (tolerance window, 2cm radius around fixation spot); otherwise the trial was aborted immediately without reward. Liquid reward and acoustic feedback indicated correct (high pitch tone, reward) or incorrect (low pitch tone, no reward) behaviour.

In the main experiment with the combined reversing-prism anti-reach task, there were two task rules (pro and anti) and two viewing contexts (non-prism and prism). The pro/anti task rules were instructed to the monkey by the colours of the central frames (green: pro rule; blue: anti rule) during the cue period. The pro rule required the monkey to reach towards the visual cue position whereas the anti rule meant reaching to the opposite of the visual cue location. Pro and anti trials were conducted either under the normal (non-prism) or the prismatic (prism) viewing contexts. Monkeys could distinguish prism and non-prism contexts either by visually noticing the reversed feedback about his hand movements during acquisition of the fixation spot at the beginning of the trial, or when we manually switch between prism box and empty box (see below). Note that the reach task was defined in the visual coordinate in all task conditions. This meant that, in the prism context, for instance, with a perceived right side visual cue, monkeys would need to physically reach to the left in order to bring the visual hand toward the visual cue location. In the prism anti trials, a perceived right side visual cue would be associated with a physical rightward movement in order to bring the visual hand to the left (away from the perceived visual cue). Left and right cues and pro and anti trials were randomly interleaved from trial to trial. Prism and no-prism trials were alternated by manually switching between the prism and the empty boxes in the aperture in blocks of 40 trials (most recording sessions had four blocks, with two in each context). The precise visual field alignment with and without prism was confirmed by constant central gaze direction across conditions.

The combined reversing-prism anti-reach task (2 contexts (prism/non-prism) x 2 rules (pro/anti)) was performed by one monkey (S). In a simplified version of the task (prism/non-prism contexts in pro rule only), two monkeys (S and F) participated in the experiments. We recorded three independent data sets from two monkeys in this study.

With the combined reversing-prism anti-reach task, we could unambiguously dissociate the sensory, motor and predictive aspects of the arm-reaching movement as described previously (Kuang and Gail, 2013). In brief, the pro vs. anti comparisons (anti-dissociation) dissociated the memory of visual stimulus (visual memory) from the motor response. The anti-dissociation can be achieved in both the non-prism and prism context, and allows identification of motor goal representations during reach planning (horizontal comparisons, Fig. 1B). To further determine whether the motor goal representations reflect the physical motor intentions (physical intention) or the anticipated visual consequences of an upcoming movement (visual prediction), we need to contrast the prism with the non-prism trials (prism-dissociation), since the same physical movement is associated with opposite to-be-expected visual feedbacks in the two viewing contexts. The prism-dissociation can be achieved in both pro and anti task rules (vertical comparisons, Fig. 1B). Notably, the combined prism and anti task created two pairs of conditions where the sensory cue and the physical movement directions were identical, but the anticipated visual consequences were opposite (diagonal comparisons, Fig. 1B). We tested whether or not PMd neural responses depended on the anticipated visual consequences.

### *Data collection*

Extracellular recordings from the dorsal premotor cortex of two rhesus monkeys were conducted using up to five microelectrodes in a five-channel Microdrive arranged in a concentric fashion (“mini-matrix”; Thomas Recording, Giessen, Germany). Pre-surgical structural MRI was used for the guidance of chamber placement (Horsley Clarke coordinates, monkey S: 13 mm lateral, 17 mm anterior; F: 20 mm lateral, 20 mm anterior). Post-surgical MRIs verified the correct chamber positions and guided the recording penetrations. Sustained directional selective neural response during the memory period was used as a physiological signature to confirm the imaging based electrode positioning.

### *Data analysis*

We mainly examined the neuronal activity during the late delay period as in the previous study (Kuang and Gail, 2013). Spatial selectivity was quantified by the average spike rate across trials in the last 800ms before the “go” signal (the delay period) to capture the sustained planning activity. The direction selectivity index (DSI) was defined as contrast in spike rate (r) between left (L)- and right (R)-side cued trials:

$$DSI = \frac{r_L - r_R}{r_L + r_R}$$

The cue position was defined in the subject’s visual field (i.e., viewed through the prism if present). The left-right direction selectivity was considered significant at $p<0.05$ (t-test).

To examine the spatial selectivity of each neuron across anti dissociations and prism dissociations, we computed the DSI ratios in the anti dissociations and in the prism dissociations separately for each neuron  (see details in the previous study (Kuang and Gail, 2013)).

We also characterized the directional selectivity of each neuron in different task periods of the trial. The same data analysis was conducted for neuronal activities during the cue period (200ms during the visual cue presentation), during the early delay period (from 100 to 900ms after visual cue offset), during the late delay period (last 800ms before the “go” cue) and during the reach movement period (200ms before reach target acquisition). Different window lengths were used because in the task design the visual cue and movement periods were relatively brief as comparing to the long sustained delay period.

To test the statistical significances of the observed visual prediction neurons we used un-parametric randomization procedures as described in the previous study (Kuang and Gail, 2013). We tested against the null hypothesis that all task related neurons are physical intention neurons, i.e., we asked if it was possible that all task-related neurons actually were encoding the physical motor goal, but due to random fluctuations could have been miss-classified as visual prediction neurons. For this, we shuffled task conditions such that directional selectivity and general motor intention encoding were preserved. Otherwise trials were randomized such that the resulting surrogate data complies with the null-hypothesis of pure physical intention encoding, but not with visual prediction encoding. The dashed ellipses in Fig. 3 and Fig. 4 show the 99% confidence limits of the shuffle prediction**.**

To assess the population neural responses across task conditions in brain area, we computed the mean time-resolved firing rates, separately for the preferred (PD) and non-preferred (ND) directions. The PD was defined as the direction that had higher mean firing rates across the late delay period (800ms prior to the “go” signal). This was done for each task condition separately, to account for the fact that neurons often had reversed PDs across task conditions. To quantify whether the strengths of spatial selectivity or firing rates differ across task conditions, we took the absolute value of DSIs for each neuron and then averaged across the neuron populations. For the overall firing rates, we pooled left and right-cued trials for each task condition before averaging across neurons.

## Results:

The PMd datasets were obtained under the same behavioral paradigms and from the same monkeys as in the previous study (Kuang and Gail, 2013) (see Material and Methods). In short, there were two versions of the task design: one was the main experiment with the combined reversing-prism anti-reach task (thereafter referred to as the combined task), and the other was a simplified version with the reversing-prism in the pro task rule only (referred to as the prism task). Monkey S participated in both versions of the task design whereas monkey F participated in the prism task only. Thus, the results included three independent datasets from two monkeys. Majority of PMd neurons presented in this study were recorded simultaneously with PRR neurons in the previous study (Kuang and Gail, 2013). The detailed descriptions on the spatial dissociations with either task design to disentangle the sensory, motor, and predictive aspects of arm reaching movement can be found in the Material and Methods.

### *Spatial representations in PMd in the combined reversing-prism anti-reach task*

We correlated the spatial selectivity of delay period single unit activities with three spatial parameters of the task: the location of visual instruction (visual memory), the intended physical movement direction (physical intention) and the to-be-anticipated visual hand feedback (visual prediction). To determine the spatial representations by each neuron, we compared their preferred directions (PD) by extracting the signs of the directional selectivity index (DSI) during the instructed late delay period in each task condition (see Material and Methods). The example neuron in Fig. 2A showed a response pattern indicating selectivity for the visual prediction. First, the directional selectivity reversed in the pro vs. anti comparisons (anti dissociation) in both the no-prism and the prism context. This indicated that the neuron was selective for the motor intention rather than visual memory, since a right-side cue in a pro reach elicited a similarly strong response as a left side cue in an anti-reach, and vice versa. Second, the DSI had the same signs in the no-prism vs. prism comparisons (prism dissociation), in each, the pro and the anti trials, respectively. This meant that this neuron encoded the motor-related visual prediction of the planned movement rather than the physical intention. Other neurons showed response patterns that were selective for the physical intention (Fig. 2B). The physical intention neurons were characterized by the reversed PDs in the anti dissociations in both normal and prism contexts, and meanwhile the reversed PDs in the prism dissociations in both pro and anti rules.

At the population level, of 107 task-related neurons (significantly left-right selective in at least one of the four task conditions during the delay period), 43 neurons (40%, 43/107) were significantly motor intention related according to the anti dissociation (Fig. 3A, B, significant DSIs in both pro and anti trials with opposite signs, in at least one of the viewing contexts). Many neurons (58% = 62/107) dropped out because their directional selectivity did not reach the significance levels ($p<0.05$) concurrently for pro and anti trials. As in the previous studies (Kalaska, 1996;Gail et al., 2009), significant sustained encoding of the visual memory was very rare in PMd (2%, 2/107). Of the 43 neurons which were classified as motor intention neurons, 8 neurons (19%; 8/107=7% of all neurons) were further classified as visual prediction neurons, and 13 (30%; 13/107=12% of all neurons) as physical intention neurons (Fig. 3C, D). The remaining 22 neurons (51%; 22/107=21% of all neurons) were undefined motor intention neurons since their DSIs did not reach significance concurrently in both the prism and no-prism conditions in either pro or anti trials. Note that a considerable fraction of neurons were non-classifiable in the anti dissociation (62/107=58%), or were undefined motor intention neurons according to the prism dissociation (22/107=21%) because they might have close-to-vertical preferred directions which did not match well with our left-right task design (we only sampled left and right reach directions for all recorded neurons).

Visual prediction or physical intention neurons do not just reflect the margins of a random distribution of selectivity. First, if we randomly shuffle the neural responses across all task conditions and directions for each neuron, no individual neuron would be directional selective any more. This means that at the single neuron level spatial selectivity was not just a result of noisy responses. Second, we shuffled task conditions such that directional selectivity and general motor intention encoding were preserved. Otherwise trials were randomized such that the resulting surrogate data complies with the null-hypothesis of pure physical intention encoding, but not with visual prediction encoding (see Material and Methods). As a result, the intention encoding observed in the pro/anti comparison of the real data fitted very well with this null hypothesis. Almost all neurons which were classified as generally intention related fell into the 99% confidence limit of the shuffle prediction (Fig. 3A, B). Yet, more importantly, the observed DSI values of several visual prediction neurons in the prism/no-prism comparisons fell far outside the 99% confidence limits of the surrogate distribution (dashed ellipses in Fig. 3A-E), and thereby did not comply with the null hypothesis. The fact that this was especially true for neurons classified as visual prediction neurons strongly indicates that the existence of these visual prediction neurons cannot be explained by inherent random variability of left-right directional selectivity under assumption of pure physical intention encoding. Equivalently, the existence of physical intention neurons cannot be explained by random variability under the assumption of pure visual prediction encoding (data not shown). It should be noted, that although visual prediction neurons constituted only a minority of neuronal subpopulation, the reliance of their representations were highly statistically significant on a neuron by neuron basis and on the population level using the randomization techniques.

To illustrate the spatial encoding of each neuron across all conditions, i.e. in the anti dissociation and in the prism dissociation in combination, we plotted their DSI ratio from the anti dissociations (average across prism and no-prism contexts) against the DSI ratio from the prism dissociations (average across pro and anti rules) (Fig. 3E). It can be see that the motor intention related neurons (negative ratio due to opposite signed DSIs in pro and anti) were tuned either for visual prediction (positive ratio in prism/non-prism dissociation, top left quadrant) or physical intentions (negative ratio in prism/non-prism dissociation, bottom left quadrant). This means that the visual prediction neurons were not simply encoding for the visual memory of spatial cue. Instead, they were motor intention related neurons encoding for the visual consequences of the planned movement.

### *Spatial representations in PMd in the reversing-prism task*

In retrospect, our classification of visual prediction and physical intention neurons could be achieved purely based on the prism dissociation, without making the anti dissociation beforehand. The anti dissociation in our main experiment was essential to rule out that neurons encode a spatial cue memory, which could have been confounded with the visual prediction encoding when testing prism reversal with only pro reaches. But the anti dissociation exclusively revealed motor related neural selectivity during movement planning (no neurons had sustained visual memory representations during the delay period). This means, visual memory encoding is not a confounding factor in our PMd data, and, hence, we could by-pass the anti dissociation due to the strong dominance of motor intention encoding during the instructed delay period (Fig. 3A, B E).

Given that the anti dissociation in PMd is not mandatory for our type of classification of single neurons, we expanded our analysis to two additional datasets from two monkeys (including an independent second set from the same monkey S shown in Fig. 3) with a reversing-prism task only in the pro rule. The additional data sets comprised 198 task-related PMd neurons (monkey F: 100; S: 98). 46% (46/100, F) and 29% (28/98, S) of the task-related neurons were significantly directional selective in both the prism and no-prism task conditions, i.e., eligible for further neuron classifications. Of these eligible neurons, 61% (28/46, 28/100=28% of all neurons, F) and 75% (21/28, 21/98 = 21% of all neurons, S) were classified as physical intention neurons, and 39% (18/46, 18/100=18% of all neurons, F) and 25% (7/28, 7/98=7% of all neurons, S) as visual prediction neurons

(Fig. 4A, B). This means, in each of the three data sets, we observed an intermingled neural representation of visual prediction and physical intention neurons. Actually, the fraction of visual prediction neurons depends on the choice of the time window within the delay period (Fig. 4C, D). We focused on the late delay period as conservative approach, since the neural encoding typically becomes more “motor-like” towards the time of the movement. In fact, the fraction of visual prediction neurons during the early delay period is higher than during the late delay period (early delay: 7%, 7%, 18% in each data set as compared to late delay: 8%, 18%, 23%, relative to the total neurons).

### *The reduced selectivity strength in PRR but not in PMd under the reversed vision*

So far, we observed that PMd neurons reflected a combination of visual prediction and physical intention representations, similar to previous findings in the parietal area PRR (Kuang and Gail, 2013). In both sensorimotor areas, motor planning evokes sustained neuronal representations linked not only to a planned action per se, but also to its anticipated perceivable visual sensory consequences. However, the division of labor among them remains largely unknown. The next question we asked was, was there any differences in these spatial representations among the parietal and premotor cortices? More specifically, we examined the directional selectivity strength and the overall firing rates in each brain area, to see whether these neural representations were different.

The reversed viewing context reduced the spatial selectivity strength in the parietal but not premotor cortex. To assess the population neural responses in each area, we computed the mean firing rates separately for PRR and PMd neurons for the preferred direction (PD) and non-preferred direction (ND) in each task condition (Fig. 5A-B). In PRR, the averaged firing rates in the preferred directions were very close between pro and anti trials, and this held true in both the non-prism and the prism viewing context (Fig. 5A). There were clear separations between the non-prism and prism trials (in both the pro and anti trials). For the preferred directions, non-prism trials had higher firing rates than prism trials. For the non-preferred direction, the opposite trends were true, i.e., prism trials had higher firing rates than non-prism trials. As a result, the spatial selectivity strengths were weaker in the prism viewing context relative to the non-prism viewing context, whereas the overall firing rates were similar across contexts. This can see in Fig. 5C, D (left panels) when we quantified the mean selectivity strength and firing rates for the parietal neurons. Interestingly, these reversed viewing-induced reductions in the spatial selectivity did not generalize to PMd neuron populations. In PMd, firing rates were close across task conditions for both the preferred and non-preferred directions (Fig. 5B). Correspondingly, the mean selectivity strengths and firing rates in PMd did not show significant difference between the prism and non-prism trials in both pro and anti task rules (Fig. 5C, D).

We confirmed these observations of reduced spatial selectivity strength in PRR in the other two data sets from two monkeys in the reversing-prism with the pro rule only. For monkey F, prism trials had significantly reduced spatial selectivity strengths in PRR but not in PMd compared to the non-prism trials (Fig. 6A, B, E) whereas the overall firing rates were almost equal across viewing contexts in each brain area (Fig. 6F). For monkey S, the reduced selectivity was present in PMd neurons but only a non-significant trend in PRR neurons. This was to some extent contradicting the previous observations in the same monkey S with the combined task design (Fig. 5). One possible explanation for this seemingly contradiction could be the differences in the task design. The combined task had four task conditions which was a two-by-two factorial design where the prism task involved only a pair-wised comparison between prism and non-prism trials. In fact, if one do the prism vs. non-prism comparison only in the pro task rule in the data set with the combined task (Fig. 5C) (rather than the two-way ANOVA), the selectivity strength differences would become significant for PMd neurons, although the modulations were smaller in PMd than those in PRR.

The parietal-specific reductions in the spatial selectivity were similar across neuronal subpopulations. We assessed whether the modulations of the selectivity strength or firing rates by viewing contexts differ across neuron subpopulations. For this, we evaluated the spatial selectivity strength separately for physical intention neurons and visual prediction neurons in each area (Fig. 7). In general, similar patterns were observed for both neuron types. For physical intention neurons, there was a reduction of the selectivity strength in the prism trials compared to non-prism trials in the parietal area PRR but not premotor area PMd (Fig. 7A). For the visual prediction neurons, the reduction in PRR was only a non-significant trend (Fig. 7B).

### ***More temporal heterogeneity in PMd than PRR***

We tested to what extent the spatial selectivity stay constant between the motor planning and motor execution phases, and asked whether and how this would differ across premotor and parietal areas. Previous studies (Churchland and Shenoy, 2007;Churchland et al., 2010) have reported that the preferred direction of PMd neurons was typically dissimilar between the preparatory and peri-movement activity. We wonder if this would hold true for the parietal neurons. For this, we examined the PDs of each neuron during the late delay and the reach movement period for both PRR and PMd neurons in each task condition (Table 1). For this analysis we restricted to neurons that were significantly directional tuned during both task epochs so that we could compute the PDs. Similar to previous studies (Churchland and Shenoy, 2007;Churchland et al., 2010), PMd neurons often showed reversed directional tuning between the delay and the movement period, this reversal was much more frequent in PMd than PRR. In PMd, about 47%, 39%, 27%, 22% of neurons in each task condition had reversed PDs across task epochs, and in PRR the reversal frequencies were 10%, 10%, 15%, 9% respectively ($p = 0.0077$, t-test, treating each task condition as one independent observation).

The neural encoding in both brain areas showed a tendency of becoming more “motor-like” towards the time of the movement. As indicated by the example neuron (Fig. 2A) whose responses during the late delay period was selective for the visual prediction encoding, the PDs reversed during the reach period in both the prism pro and prism anti trials, and this reversal made it transit from an visual prediction related encoding (based on the delay period) to a physical movement related encoding (based on reach period). This trend of becoming physical intention tuned during the movement is not uncommon in both PRR and PMd, for both neuron types (Table 2).

## Discussions:

The main finding of the current study was that PMd neurons encoded a hybrid of visual prediction and physical intentions, in a similar fashion to the previous parietal encodings (Kuang and Gail, 2013). However, these spatial representations appeared to be different in the premotor cortex PMd as compared to the parietal area PRR. Our results revealed that the reversed viewing context reduced the spatial selectivity in PRR but not PMd. Our results suggest that the anticipatory encoding of visual perceptual consequences of intended movements is a common neural representation in the frontal and parietal sensorimotor circuits. We argue that the observed differential spatial representations in the parietal and premotor areas might indicate a division of labor these two sensorimotor areas in the planning of goal-directed behaviors.

### ***Representations in premotor cortex: physical action or perceivable sensory consequences?***

The main question we asked in this study was, to what extent did the neural activity in PMd co-vary with the upcoming motor command or its associated sensory consequences? With a combined task design we revealed two classes of motor-intention related neurons in PMd: some were encoding for the future physical movement direction per se, while others representing the visual prediction of those movements. One possible explanation for more physical motor neurons than visual prediction neurons in our study could be that, some (if not all) of the motor neurons are the proprioceptive prediction of upcoming reach movements, and they overlapped with the true physical motor intention neurons. The direction of “physical intention” in our experiment could not be dissociated from the anticipated proprioceptive feedback about the upcoming reach. We could not tell them apart with the current design, but it is highly unlikely that sensory predictions operate exclusively in the visual domain. Hence, the most parsimonious, yet at this point speculative interpretation of our data would be that all intention related neurons encoded anticipated sensory feedback, some in the visual domain, the other in the proprioceptive domain, with variable degree of overlap.

Consistent with our findings, previous study has observed some “visual” movement related representations in monkey premotor cortex in a motor illusion task which separates the perception of the arm movement from the actual arm movement (Schwartz et al., 2004). Monkeys controlled their hand circular movements via a visual cursor feedback, and the actual hand movement unnoticeably deviated more and more from the cursor movement. The authors reported that neural population responses in premotor cortex represented the visualized cursor trajectory while M1 reflected the physical hand movement. It should be noted, though, previous study focused on neural representations during movement execution whereas in the current study we observed “visual” movement encoding mainly during the movement planning phase.

Several studies have attempted to dissociate the physical hand movement from the visualized hand-image (or cursor representation) movements in PMd during movement planning (Shen and Alexander, 1997;Ochiai et al., 2002). It has been found that PMd neurons have directional responses that reflect both the arm-image/cursor movement and the actual physical movement, with the former representation being the majority. However, precautions should be exercised to interpret those image/cursor related encodings as visual predictive signals in the previous studies (Shen and Alexander, 1997;Ochiai et al., 2002), since their designs could not tell if inferred curse direction related neurons are the visual predictions or simply visual memories of spatial instructions. In the current study with the combined reversing-prism anti-reach paradigm we have ruled out this confound. In contrast to the previous studies (Shen and Alexander, 1997;Ochiai et al., 2002), we found that visual prediction neurons are comparably fewer than physical intention neurons. This quantitative difference in term of neural representations might be attributed to the methodological differences between them. For example, one critical difference was the behavioural task. In both previous studies (Shen and Alexander, 1997;Ochiai et al., 2002), the visual feedback to the monkeys about their hand positions were artificial, either a cursor or recorded image shown on a projected screen (dissociated visual and physical workspace). In contrast, in the current study monkeys could view a veridical representation of reversed hand in the same workspace as the physical movement. These differences in the feedbacks (artificial vs. veridical) and workspaces (dissociated vs. aligned) might render monkeys with different levels of sense of agency and therefore elicit different neural representations. Supporting this argument, recent study found a significant modulation of parietal activity by the dissociated workspace between perception and action during visually-guided hand reaches (Hawkins et al., 2012).

In short, with the visual prediction neurons we demonstrated the existence of motor intention-related neurons in the premotor cortex encoding the future sensory consequences of planned, but not yet executed movements, at least in the visual domain. Other neuron encodes the physical hand movement which potentially could reflect the sensory predictions in the proprioceptive domain.

### ***Sensory predictive representations across parietal and premotor cortex***

Our results showed that premotor and parietal areas exhibited similar spatial representations that linked to the anticipated visual sensory consequences of future hand movement. Similar spatial representations indicate that movement planning was an emerging property of the tight mutual interactions/coordination in the fronto-parietal networks (Haggard, 2005;Andersen et al., 2010b). Our data indicated that the frontal and parietal areas jointly elaborates and monitors motor plans in advance of action execution. This view is consistent with the notion that distributed processing recruiting multiple areas is essential especially for the execution of cognitive functions.

Previous studies have reported that PMd and PRR share a number of functional properties and are co-activated with very similar activity patterns during the planning of goal-directed hand movements (Gail et al., 2009;Westendorff et al., 2010b;Klaes et al., 2011). However, progress has also been made in identifying unique functions of each area. For instance, reference frame studies showed that motor goals representations in PRR were predominately eye-centered (Batista et al., 1999b;Buneo et al., 2002;Chang and Snyder, 2010b;McGuire and Sabes, 2011b) whereas in PMd more hand-centered (Buneo et al., 2002;Pesaran et al., 2006b). Electrical micro-stimulations in human PPC induced strong urges to move various body parts without overt movement execution. In contrast, stimulations in premotor areas introduced overt unconscious movement execution (Desmurget et al., 2009). Given the similarities and differences among these two areas, the concurrent parietal and frontal activation during movement planning should not be viewed as a sign of redundancy but could be more appropriately interpreted as a vital element of distributed processing, although the division of labor among them remained largely speculative (see below). Fronto-parietal neural latency differences have been shown to be present not only for peri-movement activity around movement initiation (Kalaska et al., 1983;Seal et al., 1982;Kalaska and Crammond, 1992), but also for the sustained planning phase (Pesaran et al., 2008;Westendorff et al., 2010b). This led to conceptual ideas of corollary discharge in the frontal-parietal circuits (Mountcastle et al., 1975;Kalaska et al., 1983;Wise et al., 1997b) during motor control (depending on explicit motor commands (Mulliken et al., 2008;Shadmehr et al., 2010b)) and during motor planning (efference copy of motor intentions prior to motor commands (Westendorff et al., 2010b)).

### *Spatial selectivity suppression was specific to parietal areas*

The second important finding in the current study was that the reversed viewing context reduced the strength of spatial selectivity in PRR but not PMd neurons. Notably, the reductions in the spatial selectivity strength were not due to a (visual) stimulus-(physical) response (S-R) incongruence effect that was associated with the presence of the reversing-prism. Both the normal anti trials and prism pro trials had the incompatible S-R relationships, but the reversed viewing was present in prism pro trials but not in normal anti trials. Our reasoning was, if the observed selectivity suppression reflected the S-R incompatibility, then we should observe selectivity reductions in the normal anti trials as well. It turned out that the strengths of spatial selectivity in the normal anti trials was as strong as the normal pro trials (Fig. 5C). This lack of spatial selectivity reductions in the normal anti trials ruled out the possibility that selectivity reduction was attributable to incongruent S-R effects. However, our findings of no significant modulations on the selectivity strength between pro and anti trials in PRR contradicted the previous result (Gail et al., 2009) where the anti task rule significantly reduced the selectivity strength. We speculate that this discrepancy might be due to the fact that animals were in a different behavioral status across these two studies. Specifically, we found that there was no reaction time (RT) differences between the pro and anti trials in the no-prism trials ($p>0.05$, t-test) (data not shown) in the current study, which is not surprising in an instructed delay task. In contrast, RTs were significantly different between pro and anti trials in the previous study (Gail et al., 2009;Westendorff et al., 2010b). Therefore, it is likely that the modulations of selectivity strength by the task rule are correlated with whether or not there is a RT differences between the task rules. Additionally, the reductions in the spatial selectivity were unrelated to differences in the overall response levels. We found that, for both areas, the firing rates (on average across PD and ND for each task condition) was equal across task conditions and did not reveal significant differences (Fig. 5D).

This parietal specific suppression was surprising to us, given that these two areas are tightly interconnected and has been shown to have highly similar spatial motor goal representations (Gail et al., 2009;Klaes et al., 2011) . The differences we saw in the current study among parietal and premotor areas might due to the unique task manipulations on sensory congruence. We speculate that these differences in neuronal properties may represent a divide of labor between parietal and frontal lobe and their differential functional involvement in the planning and control of visually-guided reaching movements (see below). Consistent with our results, previous single unit neurophysiology study (Bosco et al., 2010) have showed that reach-related activity and its spatial tuning in PPC subarea V6A were stronger in light (with visual feedback) than in dark (without visual feedback). Similarly, human fMRI study (Filimon et al., 2009) reported that the medial posterior parietal region responded more during visual than non-visual reaches. In the present study we compared the spatial selectivity strengths of single neurons in the parietal and premotor cortices and found that, parietal neurons exhibited suppressed spatial selectivity strength in the prism trial, but not in anti trials. Our data suggested that anti-reaching and reversing-prism reaching are fundamentally different tasks, though seemingly similar in a sense that both of them require nonstandard visuomotor mappings with opposite S-R relations. The reversing prism resulted in a physical motor command that produces an inappropriate visual output (incongruent between physical action and visual perceptual effects).

### *Functional implications*

We showed that both parietal and premotor cortices contained neurons that represented the physical motor intentions, and also neurons that reflected the visual consequences of intended movements. These results provide direct evidence for the notion that motor planning evokes sustained neuronal representations linked not only to a planned action per se, but also to its anticipated perceivable sensory consequences. Providing such evidence for anticipatory encoding of sensory effects during motor planning would not only serve to confirm a core principle of the ideomotor concept (James, 1890b;Prinz, 1987), but also are conceptually related, yet different, to a number of other motor cognition concepts including motor imagery (Decety et al., 1994;Sirigu et al., 1996), motor awareness (Desmurget et al., 2009;Desmurget and Sirigu, 2009) and forward model predictions during control of motor execution. There is emerging consensus in the field that the feed-forward integration of sensory cues, as addressed in the various frame-of-reference approaches, needs to be accompanied by feedback mechanisms (Kalaska et al., 1997;Andersen et al., 2010b;Buneo and Andersen, 2006). Feedback mechanisms allow updating of motor goals and movement corrections on the basis of real-time state estimations and motor error signals. Such predictions require internal models, which produce proper sensory "forward" predictions for the currently planned and controlled movement (Franklin and Wolpert, 2011;Shadmehr et al., 2010b;Lalazar and Vaadia, 2008). It has been suggested that PPC, probably through interaction with the cerebellum (Blakemore et al., 1998;Izawa et al., 2012;Miall et al., 2007), produces or at least uses internal sensory predictions to compute a motor error (Shadmehr et al., 2010b;Mulliken et al., 2008;Blakemore and Sirigu, 2003). During motor planning, motor intention related signals occurred earlier in PMd than PPC during non-standard mapping (Brozovic et al., 2007b;Westendorff et al., 2010b) or decision making (Pesaran et al., 2008), and these top-down projection signals has been suggested to be important for spatial updating to monitor and update motor goal representations in the parietal cortex. This hypothesis has partially been supported by the findings of predictive sensory representations in both PRR (Kuang and Gail, 2013) and PMd (with current study).

Our results of reduced spatial selectivity strength might serve as a neural basis for the suppression of fast online correction observed recently in human psychophysics (Gritsenko and Kalaska, 2010b). It was reported that, after a few trials of practice in mirrored visuomotor transformation where visual feedback of their hand position were inverted, subjects showed suppressed rapid online corrections and the suppression was strongest for the movements in which the vision-proprioception dissociation were largest. In our study, vision-proprioception conflict was associated with reduced spatial selectivity strengths in PPC. It is conceivable and tempting to speculate that PPC may, on the one hand, play a role in predicting the consequences of planned action in different sensory domains (Wolpert and Kawato, 1998b;Shadmehr et al., 2010a), and on the other hand, in part function as “integrator”/comparator to integrate these signals from different sources. From this perspective, the reversed viewing context in our study created mismatch signals between vision and proprioception, which should be expected to modulate the reach-related activity in PPC as we observed.

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Figure 1

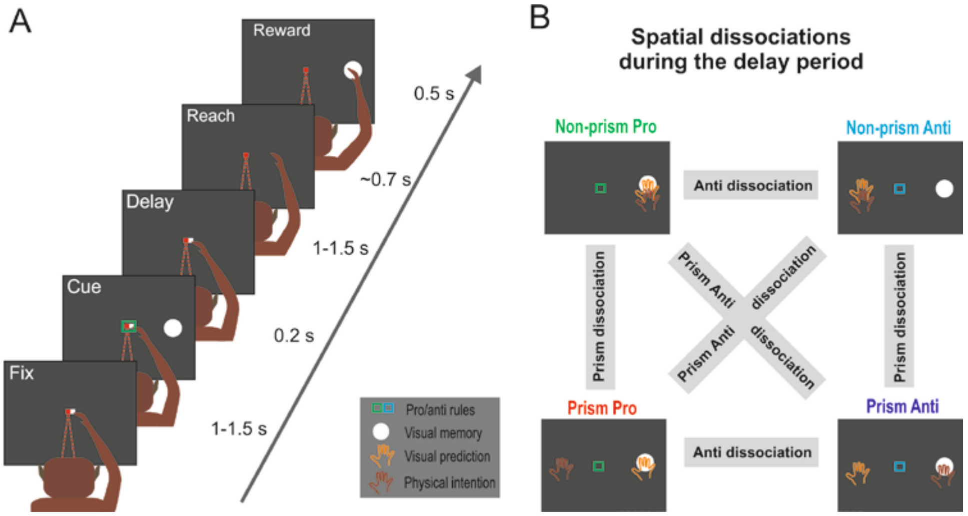


**Figure 1:** Reversing-prism anti-reach task designs (A) Delayed center-out reach task. Monkeys conducted hand reach movement after instructed delay. (B) 2x2 task conditions. The reach movement should go either towards the visual stimulus (pro reach, green central cue) or to the opposite location of visual stimulus (cyan central cue, anti reach). Pro and anti reaches could be performed under either the normal (Non-prism) or the reversing-prism (Prism) viewing contexts. During the delay epoch, the 2 (pro/anti rules) x 2 (non-prism/prism contexts) task design allowed spatial dissociation of the factors ‘visual memory’ (cue position), ‘physical intention’ (planned hand movement) and ‘visual prediction’ (anticipated visual hand feedback), where the first parameter is instruction-related, while the latter two are motor-related.

Figure 2

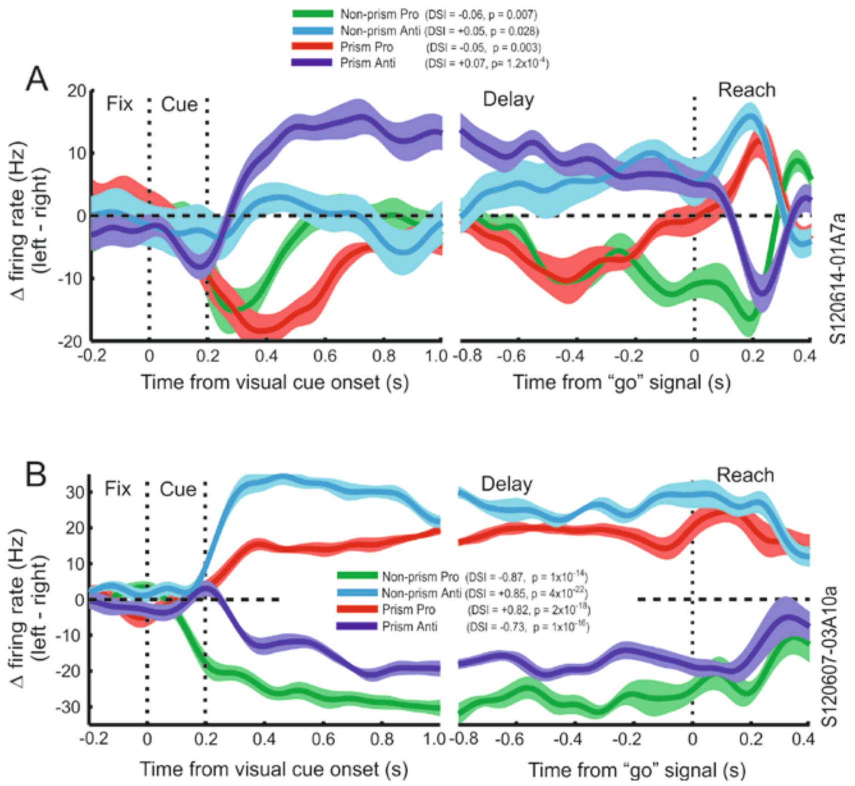


**Figure 2:** The spike rate differences between with left- and right- cued trials in each task condition for two single neuron examples. Directional selectivity was analyzed during the delay period (800ms prior to the ‘go’ signal). (A) Visual prediction neuron, characterized by opposite-signed DSIs between pro and anti trials (motor response related) and same-signed DSIs between prism and non-prism trials (visual prediction related).(B) Physical intention neuron, characterized by opposite-signed DSIs between pro and anti trials (motor response related), and at the same time opposite-signed DSIs between prism and non-prism trials (physical intention related).

Figure 3

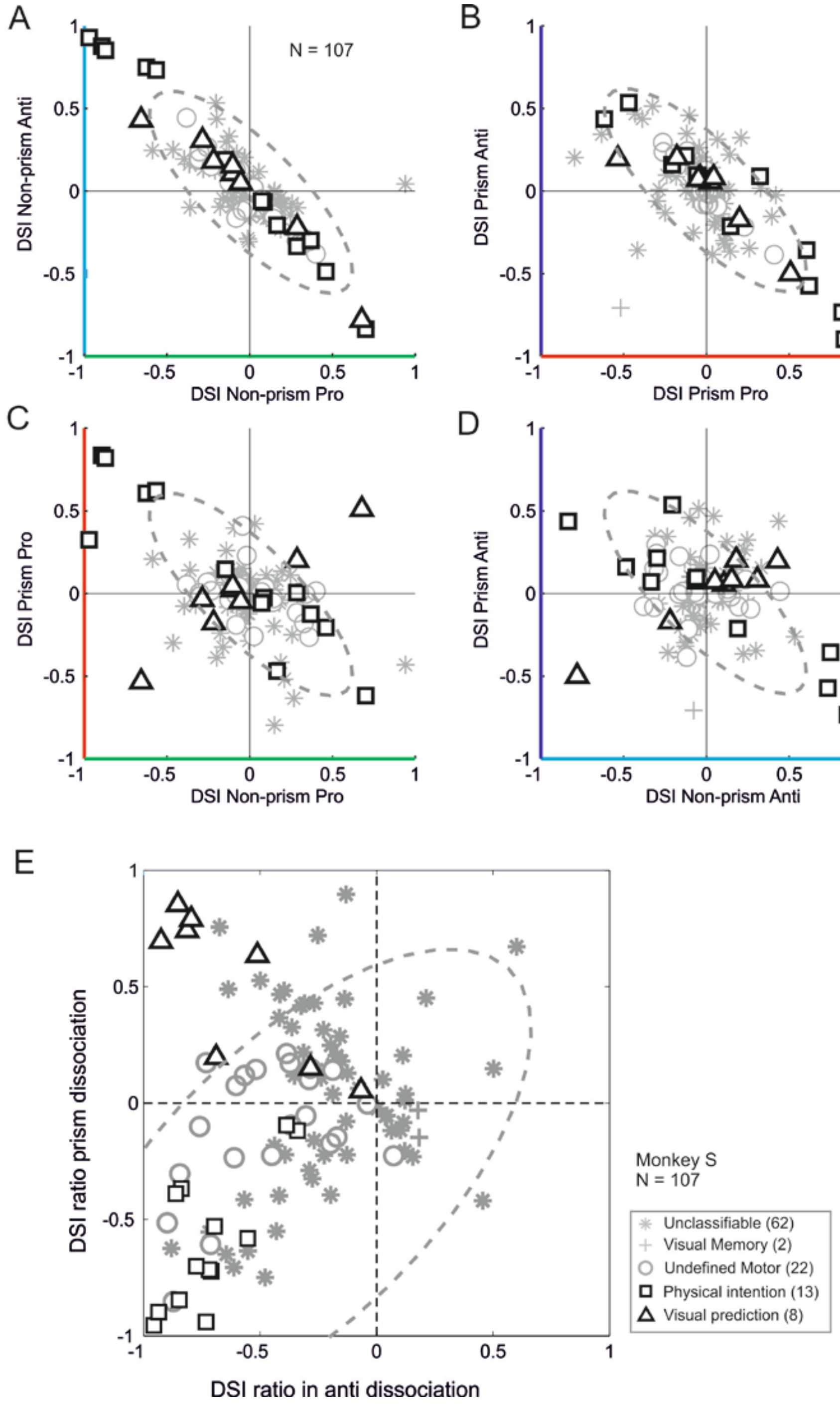

A
N = 107
DSI Non-prism Anti
DSI Non-prism Pro
B
DSI Prism Anti
DSI Prism Pro
C
DSI Prism Pro
DSI Non-prism Pro
D
DSI Prism Anti
DSI Non-prism Anti
E
DSI ratio prism dissociation
DSI ratio in anti dissociation
Monkey S
N = 107
Unclassifiable (62)
Visual Memory (2)
Undefined Motor (22)
Physical intention (13)
Visual prediction (8)
-1
-0.5
0
0.5
1

**Figure 3:** Classification of visual prediction and physical intention neurons in the combined reversing-prism anti-reach task from monkey S. (A–B) DSI values between pro and anti reaches were strongly anti-correlated, indicating almost exclusive encoding of movement intentions during the delay period in the no-prism (A) and prism context (B). (C–D) Of all intention-related neurons (non-* symbols), several were classified as visual prediction neurons (triangles), others as physical intention neurons (squares). Note, (C) and (D) contain the same data as (A) and (B), but contrasted differently. (A–E) Dashed ellipses denote the confidence limit within which 99% of the surrogate data falls when assuming exclusively physical intention encoding as null-hypothesis (see Methods). (E) Distribution of DSI ratios for in the prism dissociation and anti dissociation for each neuron.

**Figure 4**: Classification of visual prediction and physical intention neurons in the reversing-prism task (with pro rule only) from two monkeys (including the same monkey S). (A) The dataset from monkey S was independent from the previous dataset with the combined task design (shown in Fig. 2). (B) The dataset from monkey F. Conventions for dashed ellipses are identical to Fig. 2. Datasets from both monkeys revealed a significant co-existence of visual prediction neurons (triangles) and physical intention neurons (squares). Stars indicate neurons with significant left-right selectivity in only one of the viewing conditions, i.e. which were not eligible for testing the visual prediction hypothesis. (C) Relative percentages of neuron types across monkeys and tasks based on the neural activity during the late delay period. (D) Relative percentages of neuron types across monkeys and tasks based on the neural activity during the early delay period.

Figure 4

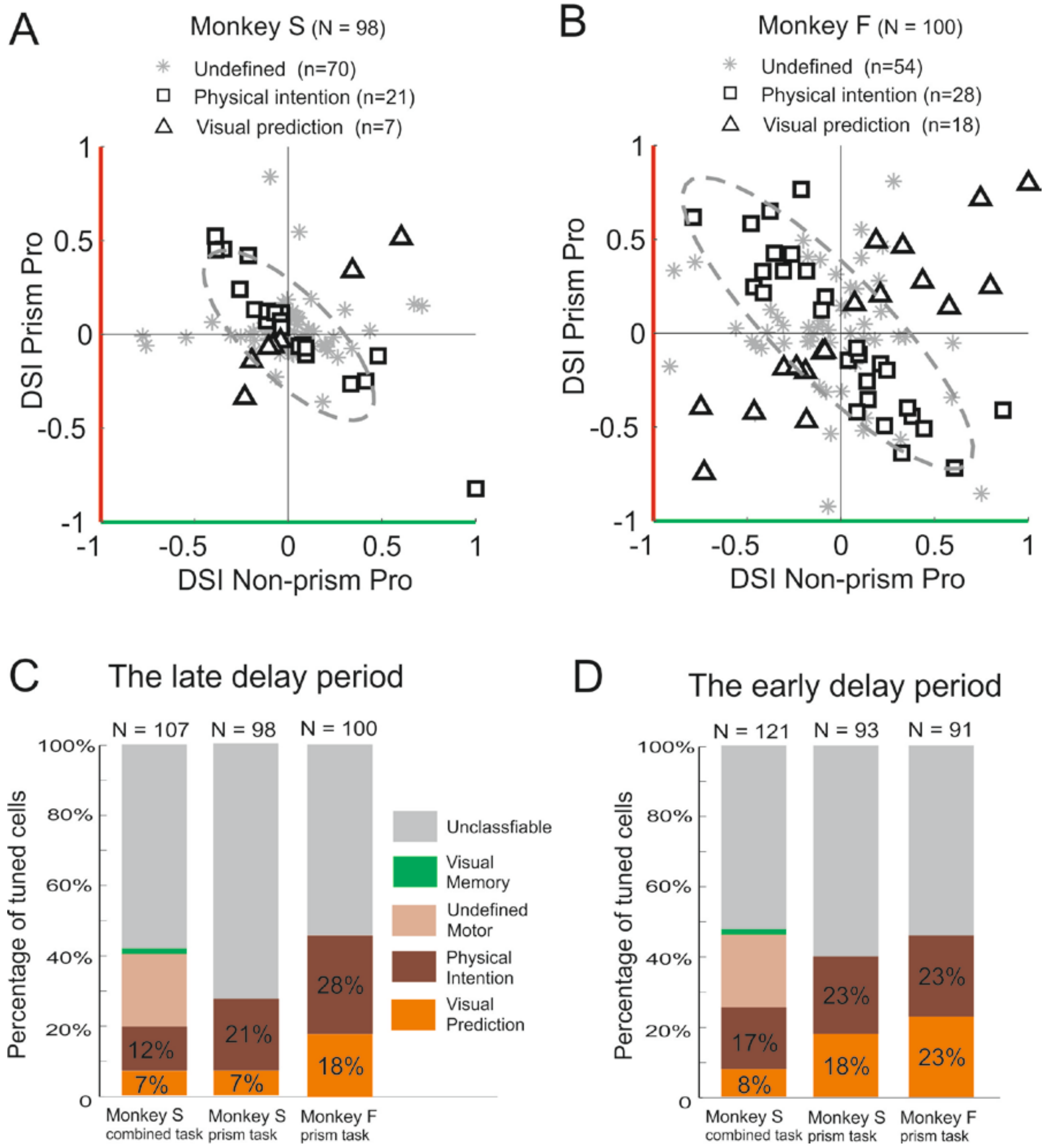

A
Monkey S (N = 98)
Undefined (n=70)
Physical intention (n=21)
Visual prediction (n=7)
1
0.5
0
-0.5
-1
-1
-0.5
0
0.5
1
DSI Prism Pro
DSI Non-prism Pro
B
Monkey F (N = 100)
Undefined (n=54)
Physical intention (n=28)
Visual prediction (n=18)
1
0.5
0
-0.5
-1
-1
-0.5
0
0.5
1
DSI Prism Pro
DSI Non-prism Pro
C
The late delay period
N = 107
N = 98
N = 100
100%
80%
60%
40%
20%
0
Percentage of tuned cells
12%
7%
21%
7%
28%
18%
Monkey S combined task
Monkey S prism task
Monkey F prism task
Unclassfiable
Visual Memory
Undefined Motor
Physical Intention
Visual Prediction
D
The early delay period
N = 121
N = 93
N = 91
100%
80%
60%
40%
20%
0
Percentage of tuned cells
17%
8%
23%
18%
23%
23%
Monkey S combined task
Monkey S prism task
Monkey F prism task

Figure 5

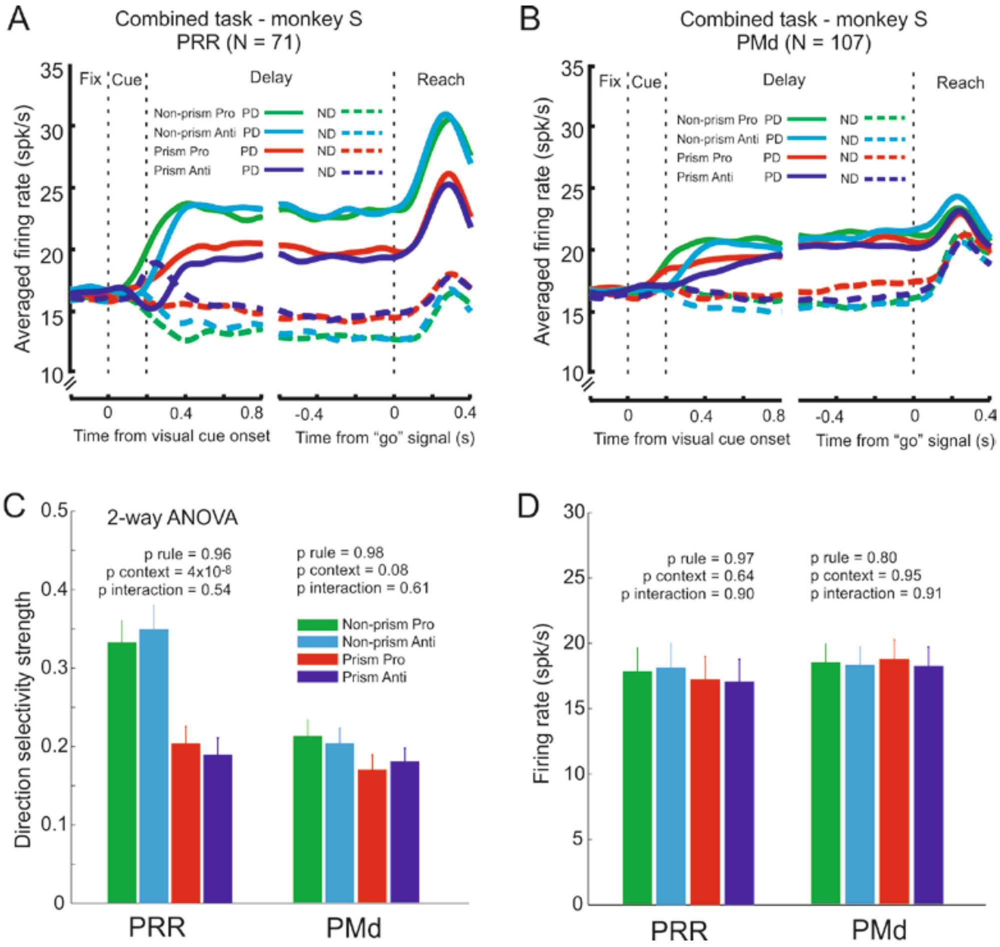


**Figure 5:** The reversed viewing context reduced the strength of spatial selectivity in PRR but not PMd in the combined reversing-prism anti-reach task in monkey S. (A-B) Neural population averaged responses in each task condition shown separately for the preferred direction (PD) and the non-preferred direction (ND), for both the PRR (A) and PMd (B). (C-D) The quantification of delay period selectivity strength (C) and firing rates (D) in each brain area for each task condition. Note that the reversing-prism viewing contexts (in both the pro and anti task rules) were associated with reduced selectivity strength in PRR but not in PMd. For either brain area there was no significant modulations on the firing rates.

Figure 6

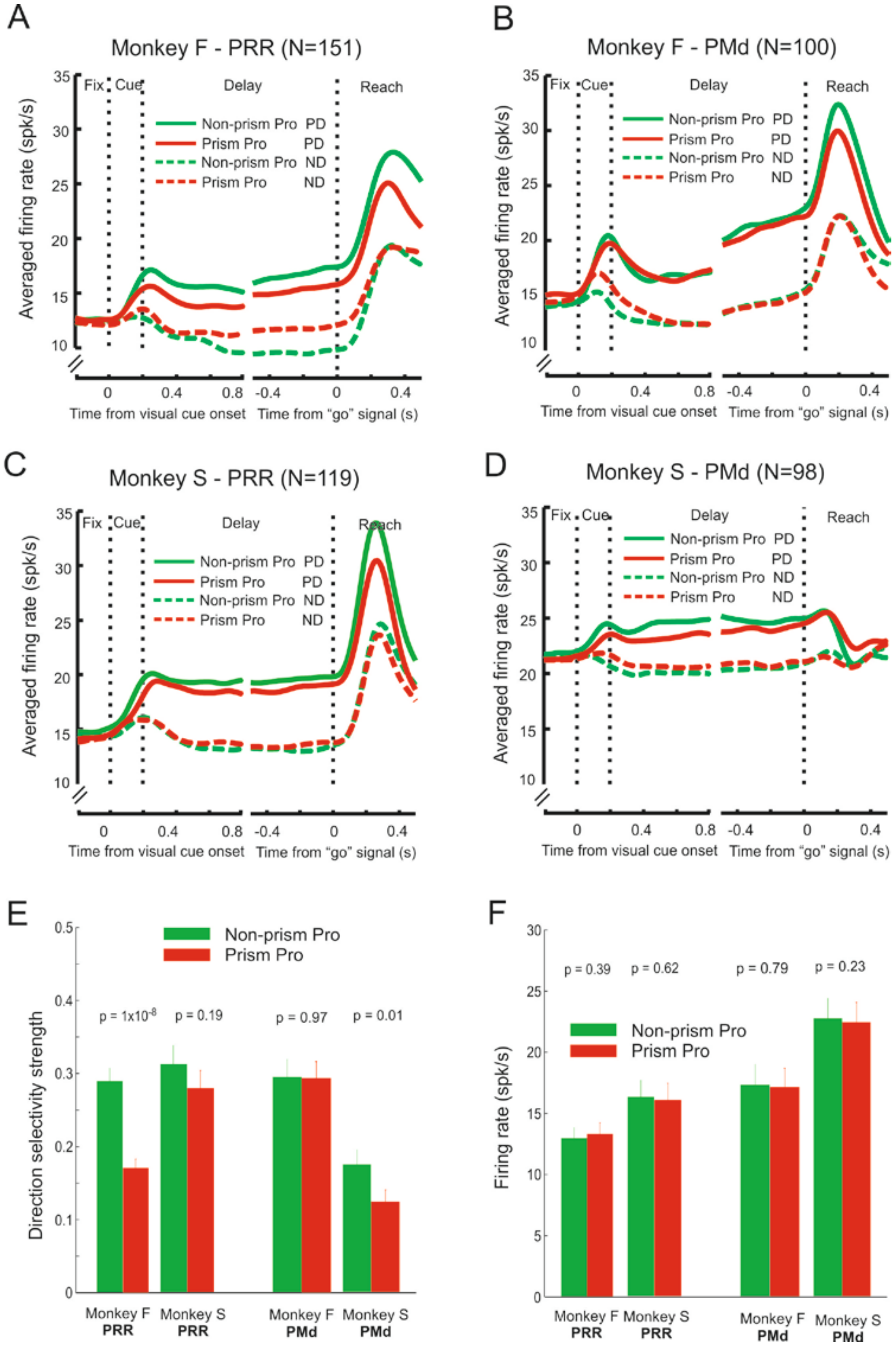

A
Monkey F - PRR (N=151)
B
Monkey F - PMd (N=100)
C
Monkey S - PRR (N=119)
D
Monkey S - PMd (N=98)
Fix
Cue
Delay
Reach
Non-prism Pro PD
Prism Pro PD
Non-prism Pro ND
Prism Pro ND
Averaged firing rate (spk/s)
35
30
25
20
15
10
0
0.4
0.8
-0.4
0
0.4
Time from visual cue onset
Time from "go" signal (s)
E
Non-prism Pro
Prism Pro
Direction selectivity strength
0.5
0.4
0.3
0.2
0.1
0
p = 1x10^-8
p = 0.19
p = 0.97
p = 0.01
Monkey F PRR
Monkey S PRR
Monkey F PMd
Monkey S PMd
F
Firing rate (spk/s)
30
25
20
15
10
5
0
p = 0.39
p = 0.62
p = 0.79
p = 0.23
Non-prism Pro
Prism Pro
Monkey F PRR
Monkey S PRR
Monkey F PMd
Monkey S PMd

**Figure 6:** The reversed viewing context reduced the strength of spatial selectivity in PRR but not PMd in the reversing-prism task (with pro rule only) in two monkeys. (A-B) Neural population averaged responses in the normal and reversed viewing context shown separately for the preferred direction (PD) and the non-preferred direction (ND), for both the PRR (A) and PMd (B). (C-D) The quantification of delay period selectivity strength (C) and firing rates (D) in each brain area for each task condition. Confirming the preceding observations in two monkeys, the reversed viewing contexts were associated with reduced selectivity strength in PRR but not in PM, and no significant modulations on the firing rates in either brain area.

Figure 7

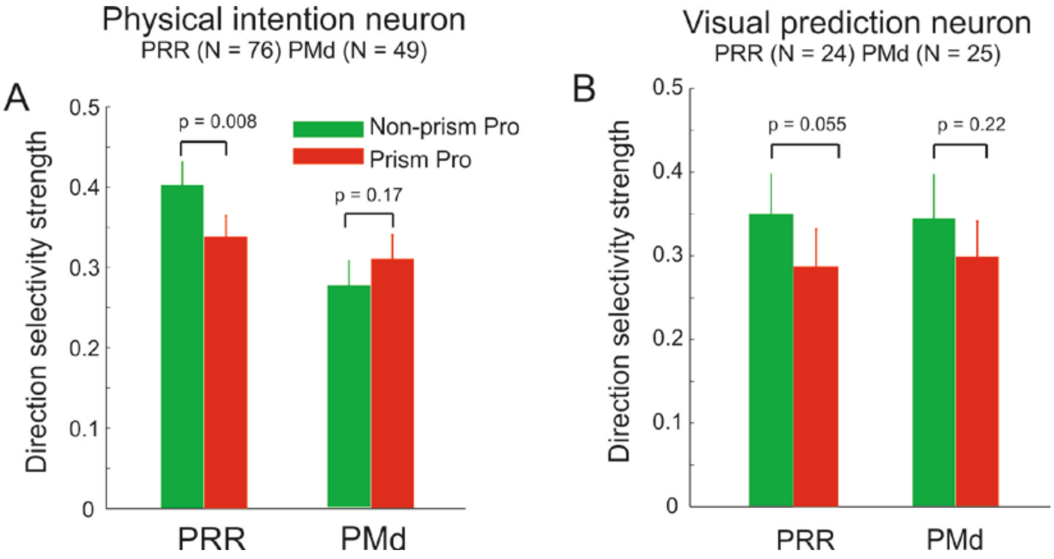
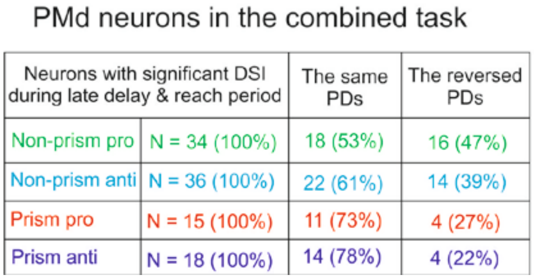
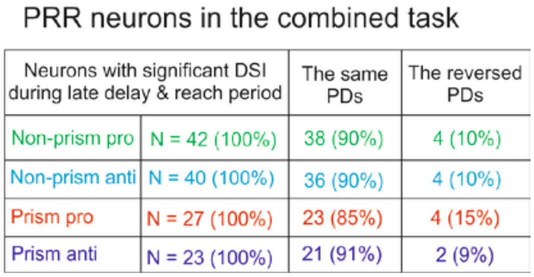


**Figure 7:** The reversed viewing context reduced the strength of spatial selectivity in PRR but not PMd for both visual prediction and physical intention neurons. Analysis was based on the datasets from two monkeys in the reversing-prism task (with pro rule only). (A) Physical intention neurons in PRR but not PMd reduced spatial selectivity strength in the reversed viewing relative to the normal viewing. (B) The same analysis as in (A) but for the visual prediction neurons.



PMd neurons in the combined task

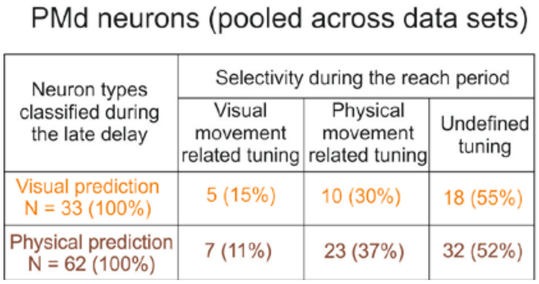
| Neurons with significant DSI during late delay & reach period | | The same PDs | The reversed PDs |
|---|---|---|---|
| Non-prism pro | N = 34 (100%) | 18 (53%) | 16 (47%) |
| Non-prism anti | N = 36 (100%) | 22 (61%) | 14 (39%) |
| Prism pro | N = 15 (100%) | 11 (73%) | 4 (27%) |
| Prism anti | N = 18 (100%) | 14 (78%) | 4 (22%) |



PRR neurons in the combined task

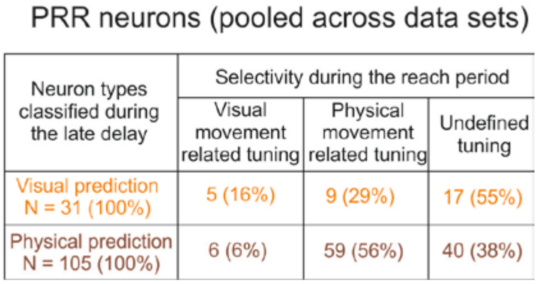
| Neurons with significant DSI during late delay & reach period | | The same PDs | The reversed PDs |
|---|---|---|---|
| Non-prism pro | N = 42 (100%) | 38 (90%) | 4 (10%) |
| Non-prism anti | N = 40 (100%) | 36 (90%) | 4 (10%) |
| Prism pro | N = 27 (100%) | 23 (85%) | 4 (15%) |
| Prism anti | N = 23 (100%) | 21 (91%) | 2 (9%) |

**Table 1:** The frequencies of preferred direction reversal between the late delay and the reach period in each task condition in each brain area. Analysis was restricted to neurons that were directional tuned during both epochs. PMd shows higher percentages of neurons that have opposite directional tunings across task epochs in each task condition.



PMd neurons (pooled across data sets)

| Neuron types classified during the late delay | Selectivity during the reach period | | |
|---|---|---|---|
| | Visual movement related tuning | Physical movement related tuning | Undefined tuning |
| Visual prediction<br>N = 33 (100%) | 5 (15%) | 10 (30%) | 18 (55%) |
| Physical prediction<br>N = 62 (100%) | 7 (11%) | 23 (37%) | 32 (52%) |



PRR neurons (pooled across data sets)

| Neuron types classified during the late delay | Selectivity during the reach period | | |
|---|---|---|---|
| | Visual movement related tuning | Physical movement related tuning | Undefined tuning |
| Visual prediction<br>N = 31 (100%) | 5 (16%) | 9 (29%) | 17 (55%) |
| Physical prediction<br>N = 105 (100%) | 6 (6%) | 59 (56%) | 40 (38%) |

**Table 2:** The frequencies of spatial representation reversal between the late delay and the reach period for each neuron type in each brain area.

## 2.3 When adaptive control fails: Slow recovery of reduced rapid online control during reaching under reversed vision

Goal-directed reach movements are subject to multiple forms of motor controls including fast online corrections prior to the availability of sensory feedback, slow online corrections with the availability of sensory feedback and trial-by-trial offline adaptations especially when errors cannot be fully corrected online within a trial. Previous studies have shown that short-term exposure to mirror-reversed visual feedback was sufficient for subjects to make movements to the correct spatial location but with reduced fast online corrections, in response to a sudden target displacement.

Here we tested if the reduced online corrections under reversed vision can be observed under situations without target displacement, i.e. without corrective movements that are driven by visual input perturbation. We were interested in whether subjects can regain such fast online movement control during extended exposure, or if instead they would try to minimize movement planning errors to compensate for the impaired online control of movements. We asked human subjects to perform hand-reaching movements to a fixed visual target (along the reversing axis) under reversed vision for a few hundred consecutive trials. We interpreted our results in relation to the general notion of flexible strategies underlying movement control in situations with positive versus negative sensory feedback.

*Journal: Experimental Brain Research*

# When adaptive control fails: Slow recovery of reduced rapid online control during reaching under reversed vision

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**Keywords:**

Rapid online control; visually-guided reaching; reversed visual feedback; offline adaptation; internal model

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Abstracts

## Abstract

Previous studies have shown that short-term exposure to mirror-reversed visual feedback suppresses rapid online control (ROC) of arm movements in response to a sudden target displacement. This has been taken as an indication that movement corrections are independent of visual feedback and likely based on an internal model contributing less to motor control during reversed vision. Here we tested if the reduced ROC under reversed vision can be observed under situations without target displacement, i.e. without corrective movements that are driven by visual input perturbation, and if it generalizes to movement phases without visibility of the hand. Additionally, we asked if subjects would be able to re-gain ROC with prolonged exposure to the reversed visual input, or if instead they would try to minimize movement planning errors to compensate for the impaired online control of movements. As previous studies, we found that ROC was reduced immediately after exposure to reversed visual feedback, in our case in the absence of visual target displacements. Trial-by-trial movement planning did not improve. The reduced ROC was restricted to late movement phases in which the hand was visible and did not generalize to movement phases without the hand being visible. ROC gradually recovered over the course of several hundred trials, affecting both early and late movement phases independent of visual feedback, but failed to re-gain the baseline level. Our results show that under reversed vision ROC is reduced even for goal-directed reaches aiming at fixed targets. The observed immediately reduced ROC is partly feedback-dependent, hence probably independent of internal model adaptation, while an additional slow adaptation of ROC is independent of visual feedback and could indicate slow adaptation of an internal model to the reversed feedback.

## Introduction

Interacting with constantly changing environments requires flexible motor control and adaptation. In goal-directed reaching, at least two major processes have been suggested to contribute to the reduction of motor errors (Magescas et al., 2009). During movement execution, rapid online control (ROC) can be performed to minimize the discrepancy between goal and hand position (Goodale et al., 1986;Prablanc and Martin, 1992;Elliot et al., 1999). When motor errors cannot be fully corrected online, trial-by-trial adaptive adjustment of the motor planning occurs for subsequent iterations (offline adaptation) to counteract target errors (Desmurget and Grafton, 2000a;Shadmehr et al., 2010b;Franklin and Wolpert, 2011). When adapting to changing sensorimotor environments, often both mechanism will be engaged with varying degree of importance, depending how beneficial either of them will be for improving performance (Magescas et al., 2009). Most psychophysical and theoretical studies have investigated motor control and adaptation under conditions in which the movement kinematics or dynamics were perturbed in such a way that gradual re-adjustment of online movement parameters or offline motor planning would allow gradually compensating the consequences of the perturbation. This was achieved, for example, by off-setting the feedback about the hand from the actual hand position via a translational shift of the visual input with shifting prisms, or with a rotation of the cursor movement relative to the hand movement direction (Harris, 1965;Wolpert and Kawato, 1998b;Shadmehr and Mussa-Ivaldi, 1994;Desmurget et al., 1999b;Todorov, 2004;Redding et al., 2005;Cheng and Sabes, 2007;Shadmehr et al., 2010b;Cressman and Henriques, 2010). In a control-theoretical sense, subjects in these types of experiments experienced regular negative feedback signals about the own body movements. “Negative” here means that the sensory error signal induced by the perturbation is suited to counteract the consequences of the perturbation in a sensorimotor control loop with negative feedback gain, i.e., a motor correction which is negatively proportional to the measured error will improve the performance. “Regular” means that this is true for sensorimotor control in natural environments, i.e. it is the type of feedback that subjects experience in everyday life. Little is known about whether and how the sensorimotor system adapts to perturbations which do not just off-set the relation between the sensed error and the required motor correction, but actually revert this relationship.

From a control-theoretical perspective, reversed feedback turns a negative feedback loop into a positive feedback loop, creating a challenge for accuracy and system stability (Burdet et al., 2001;Abdelghani and Tweed, 2010). This is the case, for example, when the visual feedback about the hand movement is mirror-reversed (Gritsenko and Kalaska, 2010b;Werner and Bock, 2010;Lillicrap et al., 2013). Previous studies showed that it takes weeks and months of continuous exposure to reversed vision for subjects to reacquire skilled visuomotor performance (Harris, 1965;Sugita, 1996;Sekiyama et al., 2000). Short-term exposure of a few trials to mirrored visual input was sufficient to allow subjects to reach towards the correct spatial direction (Marotta et al., 2005;Dionne and

Henriques, 2008), but with non-optimal motor responses characterized by larger movement variability (Werner and Bock, 2010). Even longer exposure to reversing prisms over more than 500 trials in many subjects led to continued impaired reach endpoint accuracy, while other subjects were able to re-gain high endpoint accuracy (Lillicrap et al., 2013). It is not clear from pure endpoint data, though, if and what aspect of online motor control or offline motor planning is adapted under reversed vision.

When subjects have to online-adjust their movement trajectories to a sudden unpredictable target displacement under reversed vision, their maladaptive (since going in the wrong direction) rapid online movement corrections get partly suppressed (Gritsenko and Kalaska, 2010b). The rapid online corrections in response to the visual target displacement are characterized by short latencies (typically 100-200ms) after movement onset (Higgins and Angel, 1970;Jaeger et al., 1979;Cooke and Diggles, 1984;Desmurget et al., 1999b;Sarlegna et al., 2003;Sarlegna et al., 2004;Pisella et al., 2000b;Liu and Todorov, 2007;Gritsenko et al., 2009) and can occur without the hand being visible (Goodale et al., 1986;Gosselin-Kessiby et al., 2009). Hence, the rapid online corrections are considered to be a form of ROC, which is independent of sensory feedback, but which instead relies on error signals between the estimated arm state (internal model) and the goal state (Desmurget and Grafton, 2000a;Sarlegna et al., 2003;Sarlegna et al., 2004). In this sense, the reduced ROC in the previous reversed-feedback study (Gritsenko and Kalaska, 2010b) suggested that the sensorimotor system might reduce the (mal-) adaptive motor control based on the erroneous internal model output during reversed visual feedback.

One open question is if only rapid corrective movements in response to visual target displacements get reduced during reversed vision, or if rapid online control (ROC) in general gets reduced, i.e., even independently of any sudden motor goal updating induced by a target displacement. The question is relevant since movement corrections triggered by visual perturbations can only occur at latencies at which visual information about the perturbation itself and, hence – if visible – also about the position of the hand is already accessible to subjects. Therefore, such rapid online corrections in response to target displacements could also be dependent on sensory feedback about the hand. If the hand is invisible then corrective hand movements still occur in response to sudden target displacements (Goodale et al., 1986;Prablanc et al., 1986;Prablanc and Martin, 1992;Gritsenko and Kalaska, 2010b), but they could be coupled to corresponding corrective eye movements since subject had free gaze (Neggers and Bekkering, 2000;Neggers and Bekkering, 2001;Neggers and Bekkering, 2002). In neither case (hand visible or not) it would be mandatory for the system to rely on an internal forward estimate of the visual hand position to trigger the movement correction. If we can show that ROC of hand position is reduced in conditions of reversed visual feedback independent of visual target displacements and that this reduced ROC generalizes to movement phases without vision of the hand then this would argue in favor of a reduced motor control independent of gaze adjustments and independent of visual feedback.

A second question is if and how the system over the course of longer exposure might compensates for the reduced ROC during which performance is impaired. The sensorimotor system could either manage to re-gain ROC, or it could compensate by relying more strongly on other adaptive mechanisms such as trial-by-trial offline adaptation. For example, – knowing that online control is maladaptive and impaired – subjects could try to minimize their initial movement errors by planning the next movement more precisely based on the previous trial error.

Here we test if ROC is reduced independent of visual input, and if the initially reduced ROC during reversed vision can be compensated by re-gaining baseline levels of ROC, or by re-adjusting trial-by-trial adaptation. For this, firstly, we asked if reversed vision would reduce ROC even under situations without target displacement and without hand visibility. Secondly, we asked how ROC and offline adaptation of endpoint errors and planning errors would evolve over prolonged exposure of several hundred trials to the reversed visual input.

## Methods

### *Subjects*

In total, 23 right-handed subjects with normal or corrected-to-normal vision (11 male and 12 females) volunteered to participate in the experiments described in the following. All subjects were naïve with respect to the scientific purpose of this study. They were given detailed written instructions about how to perform the task correctly. In addition, before data collection they had the opportunity to familiarize and practice the tasks. We randomly divided these subjects into two groups. The first group with 17 subjects participated in the main experiment (with the reversing prism task) and the second group with 6 subjects participated in the control experiment (with the shifting prism task).

All subjects gave informed consent, and the experiments were conducted in accordance with institutional ethical guidelines.

### *Apparatus and data collection*

In the main experiment, we asked subjects to perform visually-guided 3D reaching movements from a close-to-body starting position (‘home’ push button) to a visual target on a fronto-parallel touch screen while looking through a small aperture embedded with the prism assembly (Fig. 1a). Subjects were invited to sit comfortably on the chair, resting their chins on a chinrest for stabilization of the head. We placed the prism assembly, which consisted of a high quality optical reversing prism (“Dove” prism, size

W:3×H:3×L:12.5 cm, ThorLabs, New Jersey, USA), immediately in front of one of the subjects' eyes while blocking the other eye's view with a cardboard (monocular viewing). The distance between the eye and the monitor was about 40cm. The field of view for prism and no-prism trials was identical (10 x 10cm square) due to the aperture, only the visual feedback of the hand was mirrored to the physical movement of the hand along the horizontal reversing axis once it entered the field of view (Fig. 1a, the zone defined by dashed lines). The visual target was presented in every trial at the same position in the center of the visual field. This means that the reach target was invariant to the mirror transformation and constant throughout the experiment. Importantly, any trajectory from the home button to the target position which stayed within the XOZ plane was invariant to the mirror reversal, while any deviation in the x-dimension from zero was subject to the mirror transformation. The distance from the hand starting position to the reach target in the projected fronto-parallel plane (XOY plane, Fig. 1b-c) was 32 cm and 17cm in depth (Z dimension). Typical movement durations were close to 500ms. The visual feedback about hand position was available to subjects during the last 25-35% (approx. 125-175ms) of each movement, when the hand crossed the visibility boundary at 5cm vertical eccentricity from the target. The visual target was presented on a liquid crystal display monitor (19 inch ViewSonic VX924; <5ms off-on-off response time) mounted behind the touch-sensitive screen (IntelliTouch; ELO System, Menlo Park, CA) which allowed recording of the reach endpoint on the screen. The index finger tip trajectories during reaching movements were recorded at 200Hz with an optical motion tracking system (Visualeyez VZ 4300, PTI, Canada), leading to close to 100 samples per trajectory for the typical movement durations.

In the control experiment, we asked subjects to perform similar 3D hand reaching movements, except that we used an optical shifting prism (9 degrees, POG GmbH, Gera, Germany) instead of the reversing prism. For the shifting prism dataset, only endpoint data via the touch sensitive panel is available, no 3D trajectory data.

### *Task procedures*

Each trial started after subjects pressed the home button and held hand fixation at this starting position. After a random delay (500-1000ms), a white circular patch (diameter: 0.5cm) flashed on the screen (50ms) signaling the location of the visual target. Subjects needed to reach towards the remembered location of this cue stimulus within 1500ms. Once the finger touched the touch screen, a high tone indicated a successful trial, or a low tone indicated a failed trial. While subjects were instructed to respond as fast and precise as possible, any reach to the screen within the required time was considered a successful trial, independent of the achieved spatial precision.

Each subject in the main experiment performed three blocks of trials (Fig. 1d): (1) 20 pre-exposure trials without the prism to measure the baseline performance of the subjects; (2) 400 exposure trials with the perturbation (reversing prism) to characterize the trial-by-trial reaching behavior; and (3) 40 post-exposure trials with the perturbations being removed to measure any behavioral after-effects (Fig. 1d). Subjects in the control experiment (with the shifting prism) performed 15 trials in each, the pre-, during- and post-exposure periods. They repeated the experimental session four times, which means in total each control subject performed 180 (=15x3x4) trials. Fewer trials were recorded during shifting prism exposure compared to the reversing prism experiment, because subjects typically adapt their movements within a few trials of exposure to the shifting prism (Kitazawa et al., 1995;Redding et al., 2005) and our main purpose of this control experiment was to characterize the trial-to-trial endpoint corrections during these phases.

### *Analysis of movement trajectories*

The recorded hand trajectories were low-pass filtered at 20Hz (fourth-order Butterworth filter; varying the cut-off frequencies between 10Hz and 30Hz did not lead to different conclusions). Seventeen trials (0.2% of all trials) were excluded from the analysis, since the LED trace was interrupted during the movement. Fig. 1b shows the 3D movement trajectories of one example subject in the main experiment during baseline. The reaction time (RT) was defined as the time difference between the onset of the target presentation and hand movement onset (release of home button). The movement time (MT) was defined as the duration between movement onset and the end of the movement (touch of the screen).

For the purpose of this study, the hand positions along the mirror-reversing axis were analyzed (X-dimension in Fig. 1b-c). In every trial we analyzed deviations of the trajectories from the mean baseline trajectory. For this, the X-positions of the hand along the average baseline trajectory were subtracted from the trial-by-trial trajectories. To subtract trajectories we re-sampled the trajectories with 80 samples per movement. Samples were distributed equidistantly along the y-dimension. An analysis based on data with and without subtraction of the baseline mean produced qualitatively similar results. Also, an analysis with double or half of the re-sampling density did not change the results. Negative x-position values indicate a deviation to the left of the mean baseline trajectory, positive values indicate rightward deviations.

### ***ROC estimation***

We used a within-trial regression analysis to quantify the magnitude of ROC at different times during the movement (Elliot et al., 1999;Messier and Kalaska, 1999;Heath et al., 2004;Heath, 2005). The regression technique evaluates how much of later hand position variance can be explained by the hand position at earlier periods of the movement. Previous work has shown that the differences in the magnitude of the coefficient of determination ($R^2$ value) reflected differences in how a motor response is controlled online (Messier and Kalaska, 1999;Heath et al., 2004;Heath, 2005;West et al., 2009;Heath et al., 2010;Richardson et al., 2011). The reasoning is that if a movement is ballistic without online control, then early deviations in trajectory are predictive for later deviations. Vice versa, with online control early deviations are less predictive for later deviations. For uncontrolled movements (with no external movement perturbation and little inherent noise) one expects high levels of explained endpoint variance ($R^2$) between earlier and later hand positions. Conversely, more online corrections would result in lower $R^2$ values.

We performed the within-trajectory regression analysis sequentially for brief peri-movement time windows with duration of 20% MT and 50% overlap between consecutive windows ("sliding window" analysis). This way we obtained a time-resolved estimate of ROC along the movement trajectories, including early movement phases without the hand being visible and late movement phases with the hand being visible. For example, ROC at 20% MT was computed as the regression coefficient (across trials) of the hand positions between 10% and 30% MT after movement onset. Equivalently, the ROC at 90% MT was computed as the $R^2$ value of hand positions at 80% MT relative to 100% MT (reach endpoint).  Previous studies computed $R^2$ values either as a function of the eye/hand position at various kinematic markers, like peak acceleration, peak velocity or peak deceleration (Heath et al., 2004;West et al., 2009), or as a function of normalized MT (Heath et al., 2010;Richardson et al., 2011). We used the normalized MT since it allowed a time-continuous evaluation of the early and late part of reach trajectories which were divided by the feedback visibility boundary within the same trial. Previous work has demonstrated no interpretational difference in $R^2$ values computed as a function of kinematic marker or normalized MT (Krigolson et al., 2007;Heath et al., 2008;Neely et al., 2008).

The quantification of the ROC via the within-trial regression analysis was applied only to the data from the main experiment (reversing prisms) for which trajectory data was available, not for the shifting prism control experiment.

### *Estimation of offline adaptation*

We quantified trial-by-trial kinematic reach errors in two ways. We measured the initial reach directions and the reach endpoints. The endpoint error reflects the combined effects of offline adaptation and any form of online corrections. We defined endpoint error as the horizontal deviation between the movement endpoint and the target in the touch screen plane (Fig. 1c). The fluctuations in the initial reach directions indicate trial-by-trial changes in the initial motor commands (plus peripheral motor noise) and thereby can capture the trial-by-trial offline adaptation of the motor plan. We defined the planning error as the horizontal deviation between the extrapolated reaching endpoint in the touch screen plane (assuming no corrections to the initial angular deviation of the reach trajectory would occur) and the target in the touch screen plane (Fig. 1c). We measured the angular deviation of the initial reach direction as the angle between the positions of the hand at 10% MT after movement onset (corresponding to approx. 50ms) and the corresponding point in the mean baseline trajectory relative to the starting location. We chose such short latency for measuring the initial reach direction to quantify the direction prior to ROC, which typically occurs around 100-200ms after movement onset (Desmurget and Grafton, 2000a). The analysis of planning errors was applied only to the data from the main experiment where trajectory data was available, while the endpoint analysis was conducted in both the main and the control experiment.

We quantified offline adaptation in each subject by computing how much the initial reach direction or the endpoint on each trial was corrected as a function of the previous-trial endpoint error, i.e. we measured the relative correction to measure how much an endpoint error in trials influences the earliest part of the movement (i.e., planning error) or the whole movement (i.e., endpoint error) in the subsequent trial. According to a simple model of trial-by-trial error-driven adaptation (Kitazawa et al., 1995;Wolpert and Ghahramani, 2000;Thoroughman et al., 2007;Wolpert and Flanagan, 2010), we make the assumption that the correction in one trial is proportional to the error in the previous trial:

$$E(n) = E(n-1) - K * E(n-1)$$

Where *E(n)* denotes the error size in the *n*-th trial, and *K* denotes the learning parameter. When *K* is constant, then:

$$E(n) = E(1) - K * \sum_{i=1}^{n-1} E(i)$$

In this case, the error in the *n*-th trial is a linear function of the sum of errors experienced from the first to the (*n*-1)-th trial. To estimate *K*, we computed the slope of the linear regression of the error size in the current trial versus the cumulative errors from previous trials (Kitazawa et al., 1995). We computed the error size in the current trial either based on the planning errors or based on the endpoint errors. The cumulative errors from previous trials were always computed based on the endpoint errors, since the endpoint errors were the error signal which subjects received as visual feedback. The absolute values of the errors were used for this regression analysis to allow deviations of the motor plan or reach endpoint to either side of the target. The slope of the regression tells how large on average the corrections were relative to the error size in the preceding trials.

### Evolution of ROC and offline adaptation during exposure

To capture changes in ROC and offline adaptation over the course of the extended exposure period in the main experiment, we divided the 400 exposure trials into 10 blocks of 40 trials, from each of which we computed the magnitude of ROC and offline adaptation. We systematically varied the block sizes, and obtained qualitatively the same results. For non-exposure trials (baseline and post-exposure phases) the block size was always 20 due to limited number of trials. For the data from the shifting-prism control experiment, block sizes were kept at 15 trials, which was the duration of the pre-, during- and post-exposure experimental phases.

In Results, we will first quantify the trial-by-trial planning and endpoint errors to analyze offline adaptation, and compare it between the reversing prism task and the control data set recorded with the shifting prism task. We will then in the next step quantify the amount of ROC during different phases of the movement over the course of the reversing prism experiment.

## Results:

### *Trial-by-trial endpoint and planning errors*

Typical hand trajectories and reach endpoints of a single subject during baseline, exposure, and post-exposure are shown in Fig. 2a-b. Baseline trajectories were relatively straight with small trial-by-trial variability, and the reach endpoints generally were close to the target. When exposed to the reversing prism, movement trajectory exhibited larger variability and endpoints substantially deviated from the target, in a seemingly random fashion to either side. Even with prolonged practice, repeating 400 reaches to the same target from the same starting point, the subject did not become proficient at producing straighter trajectories or smaller endpoint errors (Fig. 2 a-b). These observations in the example subject held true across subjects (Fig. 2c). The absolute reach endpoint errors during the early exposure trials were significantly higher than those during the baseline ($p < 0.001$, *t*-test). Endpoint errors remained high during the whole extended exposure phase, without convergence to baseline level ($p < 0.001$, late exposure trials vs. baseline). However, interestingly, we observed significant after-effects with exponential decay of endpoint errors to baseline level in the first few post-exposure trials (Fig. 2c, dark blue curve, $p = 0.002$ for early post-exposure trials vs. baseline), which we will analyze in more detail below.

In contrast to endpoint errors, the trial-by-trial planning errors were comparably small throughout all phases of the experiment (Fig. 2d). Planning errors during the early exposure phase were at the same levels as the baseline (baseline: 0.40±0.13cm (mean ± standard deviation); early exposure: 0.41±0.08cm; *t*-test, $p = 0.74$), and were higher than baseline during the late exposure trials (late exposure: 0.81±0.15cm, $p < 0.001$, *t*-test) after 400 trials of exposure.

This means that over the course of 400 stereotyped reaches to the same target we did neither observe an improvement in endpoint accuracy nor in planning accuracy, but rather a worsening of the planning accuracy.

### *Non-random endpoint errors*

Even though the endpoint errors during exposure at first glance look like random fluctuations, similar to the baseline but with larger amplitude, they actually had different statistical properties. This suggests that subjects tried to compensate the poor performance, but without success. To test this, we defined three types of trials based on the endpoint location in the current trial in comparison to the endpoint location in the preceding trial (Fig. 3a). Assume that in the preceding trial the reach endpoint (grey circle) was located to the right of the target (intersection of dashed lines). If the endpoint in the current trial was again to the right of the target, we called this trial as a “worsening” trial in case the endpoint deviated more from the target than in the previous trial (Fig. 3a, top); in case the endpoint was closer to the target than in the previous trial, we called it an “improving” trial (Fig. 3a, bottom). If the endpoint in the current trial was on the opposite side of the target compared to the previous trial, we called it a “switching” trial (Fig. 3a, middle), independent of the amount of absolute deviation between endpoint and target.

We applied this trial classification to our reversing prism data to see if the subjects’ endpoint errors would comply with a random process during exposure, or if the statistics would suggest a trial-by-trial systematic dependency instead. When the data complies with a random process for which the endpoints are distributed symmetrically around the target (no bias) and successive trials are statistically independent, for example, then one would have to expect a switching probability of 50%. We compared the subjects’ data to the probabilities of each trial type obtained from a random dataset with Gaussian endpoint distribution, where mean and variance of the simulated data were matched with the experimental data. Further, we estimated the probability of trial types as a function of error size (Fig. 3b) to see if the behaviour depended on the previous-trial error size. For example, if the previous-trial error was as small as it would typically be during baseline (and hence maybe attributable to “motor noise”), the next-trial error could be expected to be random. If instead the previous trial error was larger than expected from baseline fluctuations, the next trial error could be the result of an attempt to correct for the error.

As a result, the reach endpoints during baseline showed Gaussian-like random variability (data not shown). But when exposed to the reversing prism, subjects showed only 20-30% of switching when the previous-trial endpoint error was larger than the mean error during baseline (≈0.5cm), while they showed close to 50% switching when the error was smaller (Fig. 3b middle). This means, subject had an above chance likelihood of sticking to the same side of the target from one trial to the next, but mostly only when the previous trial error was larger than the typical error during baseline. Both, the number of improving and the number of worsening trials systematically increased compared to the chance level for medium-size previous-trial errors. For large previous-trial errors the lower-than-chance switching probability is exclusively explained by an above-chance probability of worsening trials (Fig. 3b, top & bottom). There were no obvious differences for these results between early and late exposure.

### ***Comparison between shifting prism and reversing prism offline adaptation***

As seen from the previous paragraph, the trial-to-trial behavior during exposure to reversing prisms was not random. But improving and worsening trials were equally likely (Fig. 3b top and bottom) for the most typical size of the previous-trial endpoint error around 1.5 to 2.5cm and worsening trials even dominated for large previous-trial errors (Fig. 2c). This gave rise to the fact that the endpoint errors stayed high even after prolonged exposure to the reversing prism. Such lacking improvement is in sharp contrast to adaptive behaviour under exposure to shifting prisms (Kitazawa et al., 1995;Redding et al., 2005). We compared our reversing prism data to a set of control data with shifting prism perturbation to test for differences and commonalities in the trial-by-trial behaviour between the positive and negative feedback perturbation experiments.

All other parameters being equal, subjects could easily adapt their reach movements to the shifting prism perturbation within a few trials of practise (less than 10 trials, Fig. 4a), as was the case in previous studies (Kitazawa et al., 1995;Redding et al., 2005;Lillicrap et al., 2013). We quantified this fact by regressing the endpoint error size with the cumulative error size of the preceding trials (Fig. 4b). For the endpoint data during shifting prism exposure the average regression slope was significantly negative (Fig. 4c), indicating the typical systematic reduction of the error size due to adaptation. For the endpoint data during reversing prism exposure, in contrast, the average regression slope was zero (Fig. 4d), like it was the case for the endpoint fluctuations during baseline for both types of experiments (Fig. 4c, d).

However, common between the reversing prism and the shifting prism behavioural data was that both groups exhibited significant after-effects. In both cases, the absolute endpoint errors during post-exposure decayed in an exponential fashion with similar decaying parameters of -0.35cm/trial (reversing prism; Fig. 2c), and -0.31cm/trial (shifting prism; Fig. 4a), respectively. Correspondingly, the regression slopes were significantly negative for the endpoint data during the post-exposure phases (Fig. 4c, d).

We also analysed the dependency of the trial-by-trial planning errors on the cumulative endpoint errors to test the hypothesis that subjects would try to compensate the poor performance in reversing prism trials by minimizing their planning errors. If this was true, we would have to expect a reduction of the planning error with increasing cumulative endpoint errors. This was not the case, the average regression slope for the planning errors were zero during exposure to reversing prisms (Fig. 4d). If at all, the opposite was the case, since the average planning error across subjects increased during exposure (Fig. 2d). Also, in the reversing prism task the planning errors, unlike the endpoint errors, did not show significant after-effects during the post-exposure phase (Fig. 2d and Fig. 4d). The absence of movement after-effects for planning errors indicates that there was no offline adaptation of motor plans. This means, if at all, then the previous-trial endpoint errors had a lasting effect on the future trials' online control, but not on the motor planning.

### *Fast reduction and slow partial recovery of rapid online control*

Since we found no indication for offline adaptation of motor plans during exposure to the reversing prisms, but observed an after-effect in the post-exposure period, we tested for adaptation of the within-trial ROC of movements during exposure.

As a first step in quantifying the ROC, we measured the horizontal spatial variability of the hand position as a function of the time during the reach. We computed the within-subject standard deviation in hand position at all deciles of the MT. These standard deviations are then averaged across subjects for population analyses. As previous studies pointed out, without online control movement variability should increase linearly with the progression of the movement (Khan et al., 2002;West et al., 2009;Richardson et al., 2011). With ROC we should expect a decline in the variability profile at some point during the movement trajectory. Fig. 5a shows that for reach movements during baseline, hand variability has an initial tendency to increase, followed then by a tendency to decline. This decline in the spatial variability indicates the presence of ROC, as can be expected for regular reaching. In contrast, spatial variability increased monotonously for early exposure trials, and similarly for late exposure trials. The differences in the spatial variability profile between the exposure and baseline trials suggest a significant difference in the way how reach movements were online-controlled in the two viewing conditions. The continuously increasing variability in movement trajectories for exposure trials indicates reduced or erroneous ROC.

We used a kinematic regression analysis to further quantify the amount of ROC in different phases of the movement over the course of the experiment (see Methods). As an example, Fig. 5b shows the hand position at 80% MT relative to the reach endpoints (=100% MT) for baseline and early exposure trials in one subject. The 80% and 100% hand positions were correlated in both cases but differently strong (baseline $R^2$=0.52, early exposure $R^2$=0.84). We computed the time-resolved $R^2$ values for peri-movement time windows along the trajectories (see Methods). Note that regressions from early parts of movement (up to 50% MT) capture ROC without visual feedback whereas regressions from late parts of movement (70% MT onwards) capture the ROCs with visual feedback being available to subjects (see Material and Methods). The predictability of the trajectories was significantly weaker in exposure trials compared to the baseline levels, as indicated by higher $R^2$ values from 70% to 90% MT ($p<0.05$, paired *t*-test). $R^2$ values up to 60% MT did not differ between exposure and baseline trials (Fig. 5c). This shows that ROC was reduced as a consequence of the exposure to the reversing prisms, but only during the phase of the movement when the hand was visible. This means the quick reduction of ROC during reversing prism exposure was dependent on the visual feedback.

The reduction of the ROC was not constant over the course of the experiment. The $R^2$ values during the late movement phase were systematically smaller in the late exposure trials than in the early exposure trials (Fig. 5c). To quantify these learning effects on the ROC, we analyzed their evolution over the time course of exposure trials (Fig. 5d). $R^2$ increased immediately after exposure to the reversing prism. For the late movement phase (90% MT, Fig. 5d), the $R^2$ value in the first exposure block was significantly bigger than the baseline levels ($p<0.05$, paired *t*-test). Over the exposure phases, these ROCs gradually recovered towards the baseline level, as indicated by decreasing $R^2$ values ($p<0.05$, linear regression analysis). However, the $R^2$ in the last exposure block remains still significantly larger than the baseline level ($p<0.05$). This means that subjects increased their level of ROC during prolonged practice, but did not reacquire the same level as without reversing visual input even after 400 reaches to the same target. Notably, these practice-induced regaining of ROC affected not only the late movement phase but also the early movement phase without hand visibility ($p<0.01$; Fig. 5d). The slowly increasing ROC during prolonged exposure to reversing prisms which was similar between movement phases with and without visibility of the hand suggest that the learning effect on ROC early and late during movement likely share the same underlying mechanism, and that this mechanism is independent of visual feedback.

## Discussions:

In this study we examined how human subjects adapt their reaching movements under reversed visual feedback. We show that even after 400 repetitive exposure trials subjects did not improve their endpoint accuracy, nor did they improve their precision in motor planning. Instead, subjects showed reduced ROC immediately after exposure to reversed vision. This reduced ROC was independent of target displacement but occurred only late during the movement when in our experiment the hand became visible. We further show that ROC gradually recovered over the course of 400 exposure trials, but failed to re-acquire the baseline levels even after this prolonged exposure. This slow learning process affected the ROC for movement phases both during and before visibility of the hand, indicating a feedback-independent mechanism of slow ROC adaptation. The results suggest that in response to exposure to reversed visual input, subjects do not adapt their motor planning, but rather their motor control in a way that affects earlier and late phases of the movement selectively.

### *Immediate suppression of late-movement ROC under reversed vision*

Our finding that the ROC was substantially suppressed immediately after exposure to reversed visual feedback (Fig. 5a) is in line with a previous study using reversed visual cursor feedback (Gritsenko and Kalaska, 2010b). Complementary to the previous study, in our data we quantify ROC under reversed vision without using additional visual input perturbations, i.e., without sudden target displacements. We thereby could show that the reduced online control of hand movements during reversed vision affects not just corrective movements in response to an visually triggered update of the motor goal (target jump), but also affects ongoing movement control while approaching a fixed reach target.

Different to the previous study (Gritsenko and Kalaska, 2010b), we found that ROC was reduced only during late movement phases, starting around the time when the hand became visible. This suggests that the type of ROC which was immediately reduced during reversed vision in our experiment might have partly depended on visual feedback, or at least on the expectation that visual feedback becomes available at this time. Movement corrections without visibility of the hand or within up to 200ms latency after a displacement of the visual input are often thought to reflect motor control based on an estimation of hand position that results from an internal forward model computation (Liu and Todorov, 2007;Gritsenko et al., 2009;Gritsenko and Kalaska, 2010b;Oostwoud et al., 2011). According to this view, even the late movement phase (>=70% MT) in our data would have to be considered independent of visual feedback, since movements lasted typically less than 200ms after vision of the hand became available. To what exact extend the reduced ROC during visibility of the hand was dependent on visual feedback remains elusive, though. Since the point along the trajectory at which vision of the hand became available was predictable for subjects (and, unfortunately, for technical reasons could not be varied as part of the experimental protocol), we assume that motor control adapted to the reversed vision in such a way that ROC was specifically reduced for the time of the expected mirrored feedback. In agreement with this speculation, a recent finding (Burkitt et al., 2013) shows that the expectation of visual feedback (prior knowledge about the presence/absence of visual feedback) can have an impact on movement controls.

In contrast, the previously observed reduced corrective movements in response to target jumps during reversed vision (Gritsenko and Kalaska, 2010b) were also observed when subjects did not see their hand (or its cursor representation) showing that these corrective movements were independent of visual feedback. The fact that online corrections in visually guided reaching can be very fast (Liu and Todorov, 2007;Gritsenko et al., 2009;Gritsenko and Kalaska, 2010b;Oostwoud et al., 2011) and can occur independently of hand vision (Goodale et al., 1986;Gritsenko and Kalaska, 2010b) has been taken as evidence that these corrections are driven by an internal model-based estimate of hand position. This view does not well fit our data about the immediate ROC reduction since only late (and putatively feedback-dependent) ROC was reduced, while the earlier ROC during hand invisibility was unchanged. Two main critical differences might explain why our ROC reduction did not generalize to periods of hand invisibility, while previously observations showed reduction of feedback-independent motor corrections (Gritsenko and Kalaska, 2010b). First, we measured online control via a coefficient of determination of the movement trajectories. Compared to the corrective movements in response to target jumps our ROC measure is less specific, since it does not take into account whether corrective movements are mirror-inversed or not, but more generally quantifies the overall level of control as deviation from a fully deterministic (“ballistic”) movement (Goodale et al., 1986;Prablanc et al., 1986;Prablanc and Martin, 1992;Gritsenko and Kalaska, 2010b). Second, a sudden updating of a visual reach goal triggers a saccadic response when eye movements are not constraint (Goodale et al., 1986;Prablanc and Martin, 1992;Neggers and Bekkering, 2002). Such gaze updating could serve as triggers for corresponding hand path corrections, since gaze re-orienting and online hand motor goal updating are tightly coupled and gaze changes precede the manual path correction (Neggers and Bekkering, 2002). Online control of hand movements in our data was not accompanied by re-orientation of the gaze to an updated target position, hence such mechanism cannot account for our data.

In summary, if reduced online movement corrections during reversed vision were purely carried by reduced internal model-based control, we would have expected similar reduction during hand visibility and invisibility. Since we did not find this, we suspect that at least part of the reduction is explained by mechanisms which depend on visual feedback or its expectation. This view of feedback-dependent ROC during late movement is consistent with a two-component model concept for online control of movement (Elliott et al., 2001), which states that visual motor control involves both an early process comparing actual and expected sensory consequences and a late process reducing the errors between the visual feedback of hand and the target.

### *Slow recovery of feedback-independent ROC during prolonged exposure to reversed vision*

The fact that the partial recovery of ROC after prolonged exposure affected both earlier (40-60% MT) and late (>= 70% MT) movement phases with the same rate of change implies that the observed slow adaption of ROC was independent of hand visibility, hence independent of visual feedback. One reason for this could be that subject start relying more and more on proprioceptive control (Gosselin-Kessiby et al., 2008;Gosselin-Kessiby et al., 2009), or they slowly start trusting again the internal model based control which (putatively) was initially assigned very little credit after the revered feedback was introduced. Only once the system has learned to cope with inverted feedback it would make sense to re-establish its impact on motor control. The fact that the recovery rate for the ROC was slow might explain why it takes several weeks/months' continuous exposure to the reversing prism for subjects to completely adapt (Harris, 1965;Sugita, 1996;Sekiyama et al., 2000). Consistent with this slow adaptation effect, one recent study (Lillicrap et al., 2013) found that subjects' endpoints showed jagged and unstable performance after >500 trials of practice or even 8 days of continuous exposure to inverted vision. Similarly, in our data, we also observed large movement variability which failed to converge back to baseline levels even after prolonged practice in response to reversed visual feedback.

### *Differences between adaptation with positive and negative feedback*

In the current study we compared the movement adaptations in two distinct scenarios of either positive (reversing-prism experiment) or negative (shifting-prism experiment) feedback conditions. In the shifting prism condition (or equivalent rotated cursor task) subjects experienced systematic movement errors with an offset in the reach endpoints or reach direction which can quickly be compensated to a large extent with the trial-by-trial learning effects (Harris, 1965;Wolpert and Kawato, 1998b;Shadmehr and Mussa-Ivaldi, 1994;Desmurget et al., 1999b;Todorov, 2004;Redding et al., 2005;Cheng and Sabes, 2007;Shadmehr et al., 2010b;Cressman and Henriques, 2010), for example, via internal model adaptation as described in adaptive motor control theory (Desmurget and Grafton, 2000a;Shadmehr et al., 2010b;Franklin and Wolpert, 2011). In this negative feedback scenario, movement corrections which are negatively proportional to the sensed error are beneficial to the performance. In contrast, in the positive feedback scenario, reversing prisms in our data did not induce a systematic offset of reach endpoints since the target position was on the mirror axis. Rather, in this case, any unavoidable movement variability (e.g. due to planning errors or "motor noise") got emphasized since the mechanisms for online movement control and for offline adaptation apparently were maladaptive. Consequently, we found that when exposed to the reversing prism subjects showed significantly higher than chance level probability of worsening trials, especially when the errors in the preceding trials exceed baseline level (Fig. 3). This indicates that the normal motor control mechanism is counterproductive in the case of positive feedback. Under such circumstances, subjects both in our study and in the previous study

(Lillicrap et al., 2013) exhibited highly sustained unstable movement behaviors even after prolonged practice. Additionally, we found that subjects could not overcome this by minimizing the trial-by-trial planning errors. Instead, subjects under reversed vision reduce the level of online motor control, as evident by a suppressed level of rapid movement corrections in response to sudden target displacements (Gritsenko and Kalaska, 2010b) and by a higher degree of within-trajectory determinism (Fig. 5) compared to baseline levels. That subjects adapt trial-by-trial without benefiting with improvement in their performance is not specific to positive feedback tasks, though. It can also be observed in force-field adaptation and visuomotor rotation tasks when perturbations are randomized (Donchin et al., 2003;Diedrichsen et al., 2005).

### ***Conclusions***

The immediate suppression and slow recovery of ROC under reversed vision revealed a unique form of motor plasticity, which is associated the reversed feedback gain and which is distinct from negative feedback scenarios. Our results might indicate that in situations where gradually and adaptively compensating the feedback perturbation is impossible due to a sign-inversion of the sensorimotor loop, the system employs the strategy of instantaneously reducing the levels of ROC which is then capable of slowly recovering with repeated practice.

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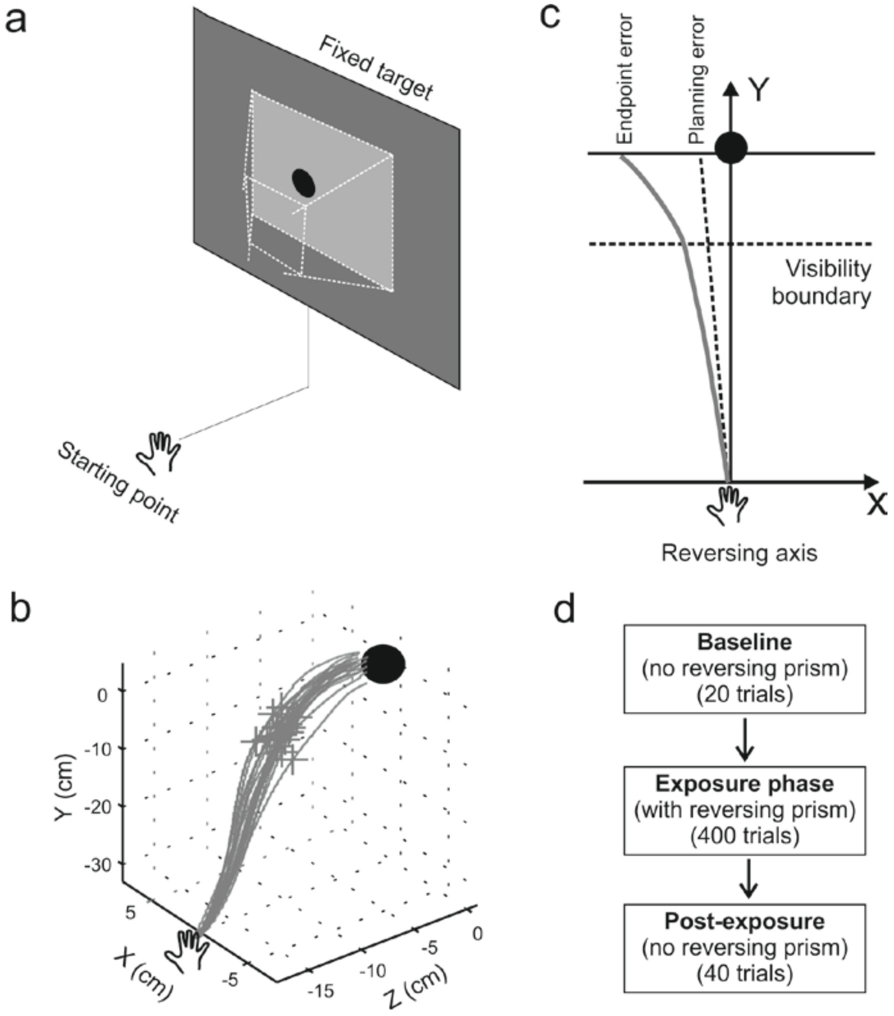

**Figure 1:** Experimental set-up and reaching behavior. **a**: Schematic of the 3D hand reaching movements under reversed-viewing condition. We used an optical Dove prism, which ensured a highest-quality monocular view of the own hand once it enters the visual field that is defined by dashed lines. **b**: Example 3D reaching trajectories of one subject. Crosses mark the hand position at 50% movement time after reach onset. **c**: Schematic trajectory projection onto the fronto-parallel plane. Note that the visual feedback (normal or reversed) about the hand position is available to the subjects only during the late part of the reach movements. **d**: Task sequence.

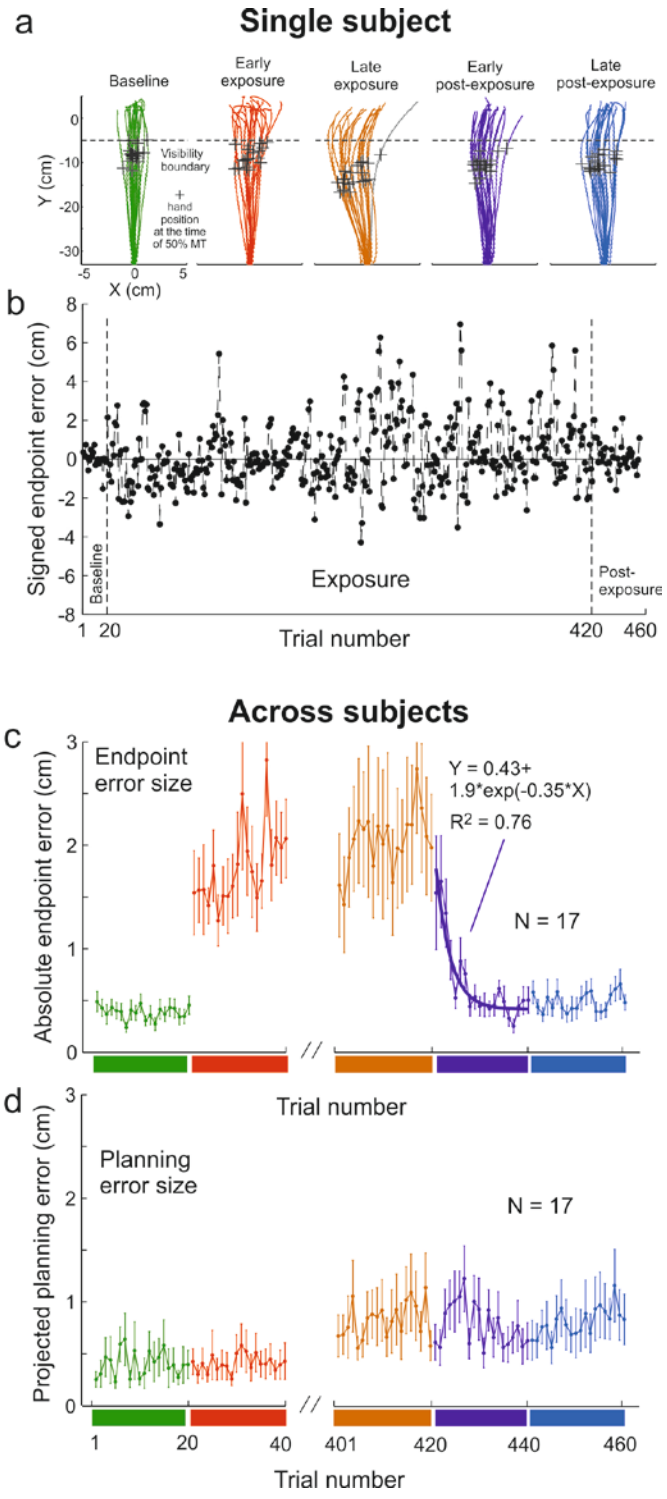
a
Single subject
Baseline
Early exposure
Late exposure
Early post-exposure
Late post-exposure
Y (cm)
0
-10
-20
-30
-5
0
5
X (cm)
Visibility boundary
+ hand position at the time of 50% MT
b
Signed endpoint error (cm)
8
6
4
2
0
-2
-4
-6
-8
Baseline
Exposure
Post-exposure
1
20
420
460
Trial number
Across subjects
c
Absolute endpoint error (cm)
Endpoint error size
Y = 0.43+ 1.9*exp(-0.35*X)
R2 = 0.76
N = 17
3
2
1
0
Trial number
d
Projected planning error (cm)
Planning error size
N = 17
3
2
1
0
1
20
40
401
420
440
460
Trial number

**Figure 2:** Trial-by-trial reach performance. **a**: 20 consecutive trajectories of one representative subject during baseline (green), early exposure (red) and late exposure (orange) to the reversing prism, as well as early (blue) and late (cyan) post-exposure trials. Note, the 50% hand position along the trajectory (“+”) only seems to occur late during the movement since the late part of the movement progresses mostly along the z-direction, and hence is compressed in the x-y plane. **b**: The trial-by-trial signed endpoint errors from the same subject as in **a**. **c**: The average absolute endpoint errors across subjects, shown for baseline, early and late exposure, as well as early and late post-exposure trials. The color conventions are identical to those in **a**. The solid line marks the exponential fitting for the early post-exposure trials and the text provides the fit parameters. **d**: The average absolute planning errors across subjects in the different experimental phases.

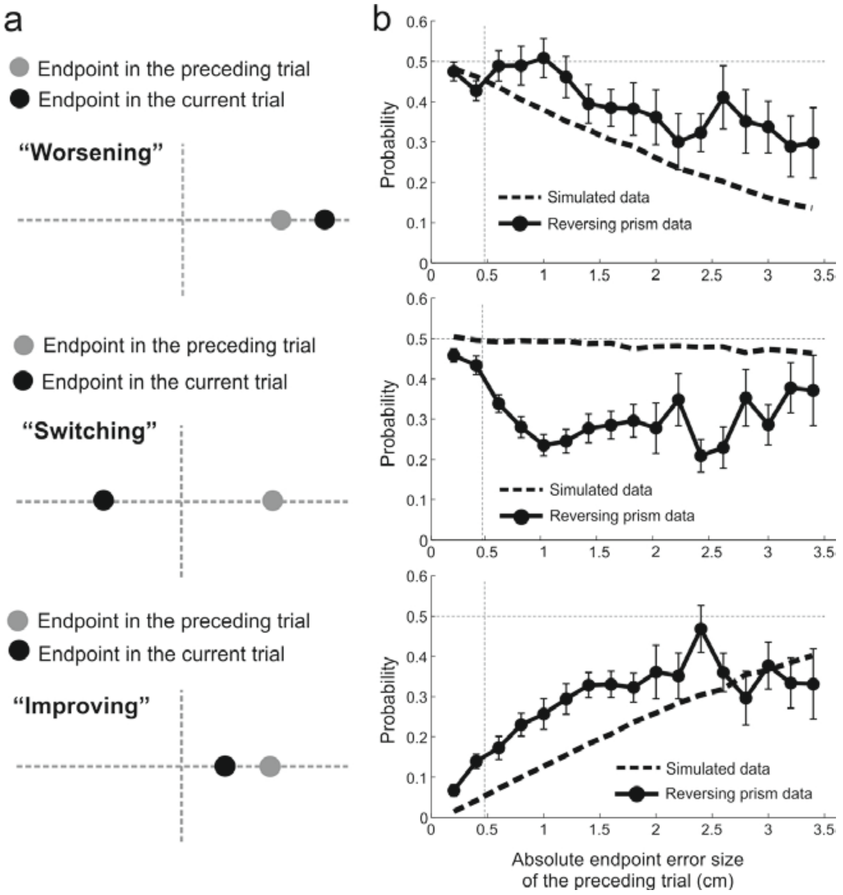

**Figure 3**: Trial type statistics based on trial-by-trial endpoint errors when exposed to reversed vision. a: Schematic of trial type classification. Top panel: a "worsening" trial has a same-side increased endpoint error compared to the preceding trial endpoint error; middle panel: a "switching" trial has an opposite-side endpoint error; bottom panel: an "improving" trial has a same-side reduced endpoint error. b: Frequency of each trial type (all exposure trials were pooled across subjects). Dashed lines mark the corresponding trial statistics estimated from a random dataset with Gaussian distribution for which the mean and variance were matched with the experimental data.

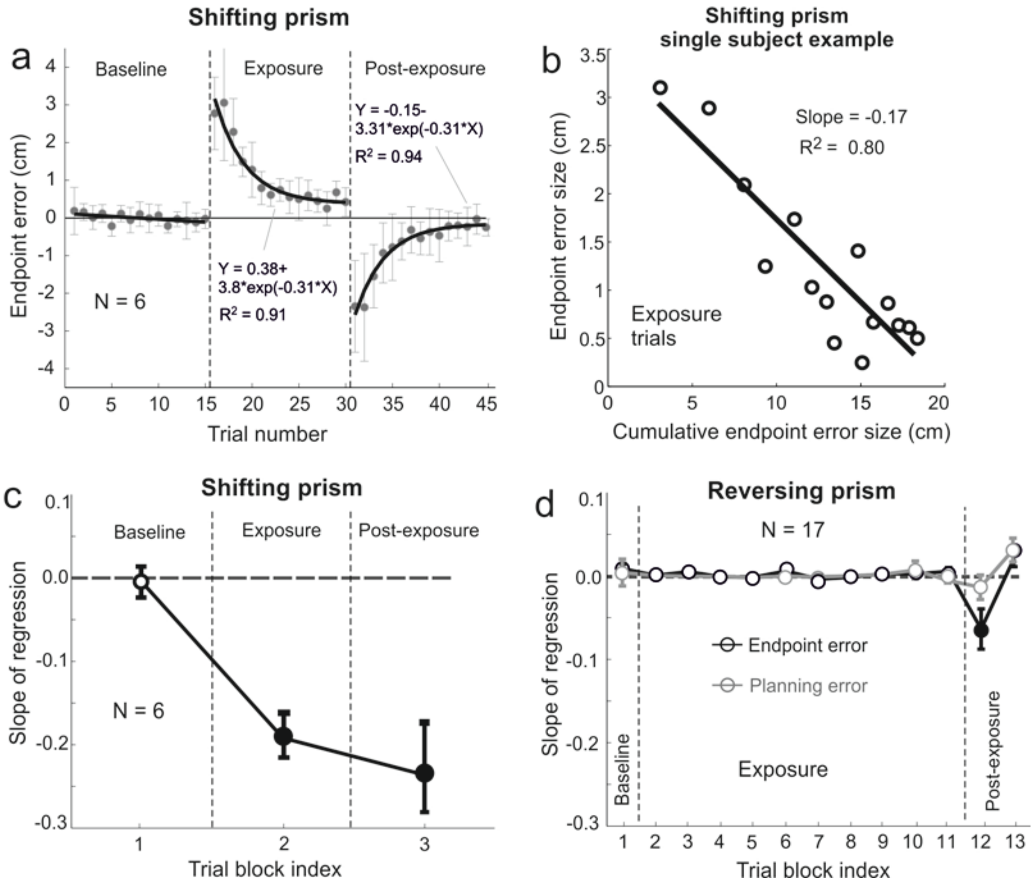

**Figure 4**: Comparison of trial-by-trial endpoint and planning errors for reversing prism and shifting prism. a: Average trial-by-trial endpoint errors across subjects in the shifting prism experiment. b: Quantification of the learning rate by regressing the trial-by-trial endpoint error sizes with the cumulative error sizes for a single example subject during exposure to the shifting prism. Solid line marks the linear regression. c: The average slopes of regression in each experimental block of the shifting prism experiment. d: The same analysis as in c but for the endpoint error sizes (black symbol) and the planning error sizes (grey symbol) from the reversing prism experiment. Note that 400 exposure trials were divided into 10 blocks of 40 trials to capture the temporal evolution of the learning rate (see Methods).

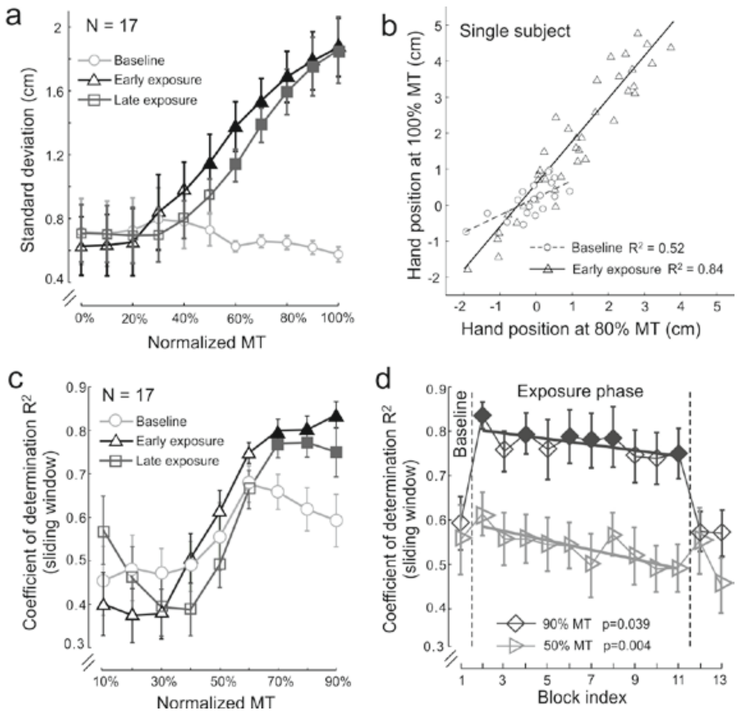

**Figure 5**: Online movement corrections over the course of the movement. a: The average horizontal variability in the movement trajectories of all subjects in the baseline, early and late exposure trials as a functions of normalized movement time (MT). Filled symbols mark points which are significantly different from the baseline level ($p<0.05$), and this rule also applies to panels c and d. b: The scatter plot of hand positions at 100% MT (endpoint) relative to hand positions at 80% MT for baseline and early exposure trials of the same subject. The solid lines denote the linear regressions. The coefficient of determination, the R2 value, is taken as the magnitude of ROC (see Methods) c: Mean coefficients of determination (R2) as a function of normalized deciles of movement time in a sliding window fashion (e.g., a ROC at 90% means the regression coefficient between hand positions at 80% and 100% MT), for baseline, early and late exposure trials respectively. d: Evolution of ROC over the course of extended exposure for the late movement phase (90% MT when the hand is visible) and the early movement phase (50% MT, hand invisible). Solid lines mark the linear regression of the ROC during the exposure phase.

# 3 Summary

In summary, the work presented in this thesis employed both neurophysiologic and psychophysical approaches and yielded three important findings to the current understandings about the functional and neural basis underlying the planning and control of goal-directed arm reaching movements.

First of all, the monkey neurophysiologic results add a significant new perspective to the current understanding of spatial representations in the PPC of primates. Sustained encoding of anticipated visual sensory consequences of an intended movement is a property that has not been observed before and thereby shed a new light on the concept of ‘motor goal’. They suggest that the formation of a motor goal implies a prediction of the visuo-spatial consequences of the intended action. It is tempting to speculate that, in contrast to the traditional view of parietal encoding, this anticipatory component marks the very nature of spatial motor-goal representations in PPC during the motor planning process.

Secondly, we found that these visual sensory predictive representations are not limited to parietal neurons, but are rather wide spread into the dorsal premotor cortex that reciprocally connected with the parietal cortex. Interestingly, these spatial representations are different across the parietal and premotor areas in terms of selectivity strength. More specifically, we found that the reversed view reduced the strength of spatial selectivity in the parietal but not premotor cortex. Our data suggests that the anticipatory encoding of perceptual consequences of intended movements are not limited to one brain structure, but are rather widespread in the frontal and parietal sensorimotor circuits where each area might play distinct functional roles.

Thirdly, in the psychophysical study we examined how human subjects could flexibly control their reaching movements under the conditions with the reversed visual feedback. We confirmed the previous finding of immediately reduced fast online corrections under the reversed visual feedback, but in our case we showed it even when there was no external target displacement. The reduced online control gradually recovered over the course of several hundred trials but failed to re-gain the baseline level. We showed that the observed immediately reduced online control is partly feedback-dependent, hence probably independent of internal model adaptation, while the additional slow adaptation of online control over repeated practice is independent of visual feedback and could indicate slow adaptation of an internal model to the reversed feedback.

As an outlook for future researches, there are two main aspects that need extra work to further substantiate our observations. (1) To what extent do the physical intention representations reflect the proprioceptive prediction of planned action? Future experiments need to further dissociate the planned physical action from the proprioceptive sensory predictions. For example, using vibration techniques to manipulate proprioceptive feedbacks and produce mismatches between perceived and actual movements. The combined visual and proprioceptive manipulations would allow us to fully disentangle the action planning from the sensory predictions in both the visual and proprioceptive domains. (2) What are the divisions of labor among premotor and parietal areas in the context of sensory prediction and action planning? We speculated that the premotor area may be more tied to forming the action plans whereas the parietal area predicting the sensory consequences of motor plans and integrate them with the actual sensations to estimate the body status. Though it sounds attractive and plausible, it remains largely speculative at this point. Further experiments are needed to either reject or corroborate this hypothesis. For instances, transient and reversible inactivation in one brain region in combination with simultaneous neurophysiologic recordings in the other might be helpful to causally determine the roles of each areas.

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# Curriculum Vitae

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## Personal details

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| Date of birth | 12th of August, 1983 |
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## Scientific education

| | |
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| since 2008 | PhD student<br>Sensorimotor Group<br>Cognitive Neuroscience Laboratory<br>German Primate Centre, Göttingen, Germany<br>Advisor: Prof. Dr. Alexander Gail |
| 2005 – 2008 | Master student, Department of Physics/biophysics<br>Wuhan Univ. Technol., Wuhan, China<br>Advisor: Prof. Dr. Jiafu Wang |
| 2001 – 2005 | Bachelor student, Department of Physics<br>Wuhan Univ. Technol., Wuhan, China |

## Courses & workshops

| | |
|---|---|
| July 2011 | GGNB course on “Multi-electrode array recording”, Max Planck Institute for Dynamics and Self-organization, Goettingen |
| March 2009 | NWG workshop on “Transcranial magnetic and electrical stimulation”, Klinikum, Goettingen |
| August 2008 | BCCN/NWG workshop on “Analysis and models in neurophysiology”, Univ. Freiburg, Freiburg |

# Publications & manuscripts

**Kuang, S**, Gail, A. Predicting sensory consequences of intended movement in monkey posterior parietal cortex. submitted

**Kuang, S**, Gail, A. Differential encoding of anticipated visual sensory consequences during reach planning in the premotor cortex compared to the posterior parietal cortex. Prepared for submission

**Kuang, S,** Gail, A. When adaptive control fails: Slow recovery of reduced rapid online control during reaching under reversed vision. Submitted

Westendorff, S; **Kuang, S**; Taghizadeh, B; Schwarz, I; Donchin, O; Gail, A (2012) Asymmetric generalization in adaptation to target displacement errors. Submitted

# Abstracts

**Kuang S** and Gail A (2012). Predicting sensory consequences of intended movements in monkey posterior parietal cortex. Society for Neuroscience, New Orleans, Oct. 13-17.

**Kuang S** and Gail A (2012). Learning not to control: complementary effects of fast and slow online corrections during reaching under reversed vision. Society for Neuroscience, New Orleans, Oct. 13-17.

**Kuang S** and Gail A (2012). Predicting sensory consequences of intended movements in monkey posterior parietal cortex. Primate Neurobiology Meeting, Tuebingen, Mar.12-14.

**Kuang S** and Gail A (2011). Sensorimotor integration by spikes and local field potentials in macaque parietal cortex. Society for Neuroscience, Washington D.C., USA, November. 12-16.

**Kuang S** and Gail A (2011). Sensorimotor encoding by spiking and local field potentials in monkey posterior parietal cortex under reversed vision. NEURIZON, Goettingen, Germany, May. 25-28.

**Kuang S** and Gail A (2011). Local field potentials and spike rates in monkey posterior parietal cortex conveys independent information about movement plans in a reversing prism task. NWG, Goettingen, Germany, January. 23-27.

**Kuang S** and Gail A (2011). Dynamical encoding of motor plans by spike rates and local field potentials in monkey posterior parietal cortex. Primate Neurobiology Meeting, Goettingen, Germany, January 21-23.

**Kuang S** and Gail A (2010). Neurons in monkey posterior parietal cortex encode proprioceptive rather than visual motor goals in a reversing prism task. BCCN, Berlin, Germany, September 27-31.