University of Trento

Center for Mind/Brain Sciences

PhD Dissertation

SELECTIVITY FOR MOVEMENT DIRECTION IN THE HUMAN BRAIN

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Chapter 1

GENERAL INTRODUCTION

In daily life, we frequently execute reaching movements, for example to grasp our mobile phone, or to press the starting button of our computer. These actions are usually performed accurately and without effort. Nonetheless, reaching movements require that our brain perform complex computations, transforming the visual information into the corresponding motor program. To execute reaching movements, the information about the target location is used to compute the hand trajectory, that must be translated into the corresponding motor command that guides the muscles. In the present thesis, I aimed to study the representation of movement direction and amplitude in humans. In particular, I investigated whether there exist areas selective to movement direction in humans and to what extent directional selectivity is sensitive to changes in the type of grasp (experiment 1 & 2) and movement amplitude (experiment 3).

1.1. BACKGROUND

1.1.1. NEURONAL BASIS OF REACHING IN MONKEYS

A distributed network of fronto-parietal areas of the monkey brain is shown to be involved in the planning and execution of reaching movements (Kalaska et al., 1997): visual areas (V1, V2, V3, MT and MST) project to the to parieto-occipital area (PO). In turn, PO projects to medial intraparietal area (MIP) and to area 7m (Lacquaniti and Caminiti, 1998). Both these parietal areas are connected to frontal areas, dorsal premotor cortex (PMd) and to primary motor cortex (M1) (Lacquaniti and Caminiti, 1998) (see **Figure 1).**

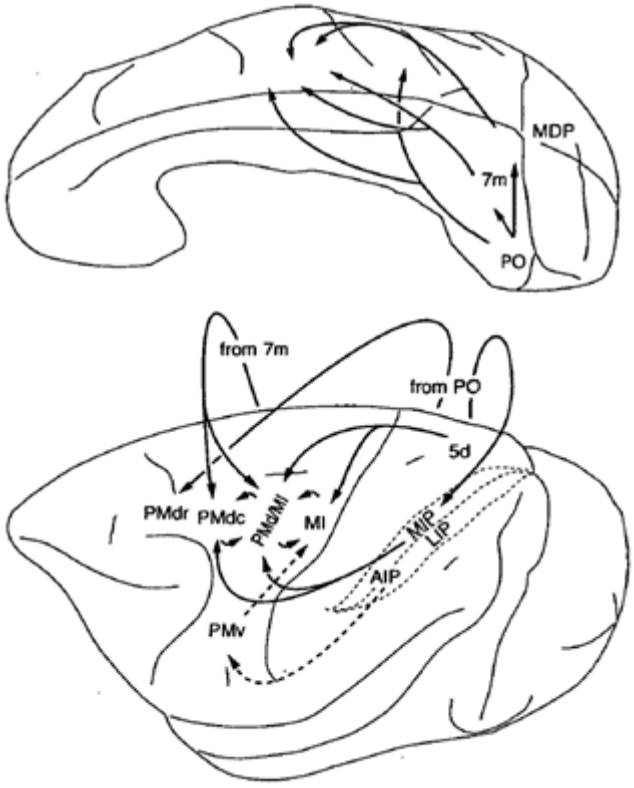

Figure 1. Parieto-frontal network during reaching. Mesial and lateral schematic views of the origin and terminations of main ipsilateral corticocortical pathways. MDP, medial dorsal

parietal areas;7m PO, parieto-occipital visual area; 5d, the dorsal surface of area 5; MIP, medial intraparietal area; LIP, lateral intraparietal area; AIP, anterior intraparietal area; PMv, ventral dorsal premotor cortex; PMd, dorsal premotor cortex; PMdr PMdc, rostral and caudal parts of dorsal premotor cortex, respectively; M1, primary motor cortex [Adapted from Caminiti et al. (1996)].

The role of parietal areas in reaching

Firing rates of neurons in area PO during reaching movements have been shown to be related to the processing of movement direction: Battaglia-Mayer et al. (2000) recorded from neurons in area V6, part of area PO, while monkeys were involved in different tasks where retinal, eye and arm related signals were separated. For neurons in this region, the orientation of the preferred direction computed across tasks clustered within a limited sector of space, the *field of global tuning*. These results suggest that PO might represent an early stage of reaching programming where information about both eyes and arm are combined.

Selectivity for movement direction was reported also in parietal area 5: activity of parietal cells was recorded while the monkey moved a manipulandum in different directions away from a common starting position. The discharge frequency of the cells was highest during movements in the preferred direction and decreased in an orderly fashion as the angular difference between the preferred and the other directions increased (Kalaska et al., 1983). In a similar setup, a weight was applied to the manipulandum, pulling it away from the center of the target board. In this condition, the monkey had to exert a continuous counterforce to the handle to restore the manipulandum over the board. Despite of changes in the pattern of

muscle activity, the frequency of discharge in neurons in area 5 did not change while the monkey had to compensate for loads applied to the manipulandum (Kalaska et al., 1990). These results indicate that neurons in this region are insensitive to loads, indicating the coding of movement kinematics, not dynamics.

In support of the processing of movement kinematics in parietal cortex, Lacquaniti and collaborators (1995) reported that neurons in area 5 code not only movement direction, but also distance. The monkey was trained to execute arm movements of similar direction within different parts of extrapersonal space, that is starting from 3 possible locations. Each starting position was located at the center of an imaginary cube where targets to be reached were located at each corner of the cube. This setting allowed to maintain similar movement directions across space, while varying the pattern of muscular activity and joints required for these movements. Results revealed that activity of most parietal neurons was related to hand position in space, within a shoulder-centered spherical coordinates system with neurons specific for the azimuth, other for the elevation, and others for movement distance. The activity of another population was not related to the final position, but rather to the vectorial difference between initial and final hand position. Neurons whose activity was related to both the initial position and to the difference between the initial and final position were also reported, probably encoding intermediate locations.

Neurons in parietal cortex are involved also in the processing of target distance: Genovesio and Ferraina (2004) reported that neurons in LIP combine the visual disparity signal with fixation distance information (the vergence angle) in a manner that can be used to determine 3-D egocentric distance to an object in space. Information from the eyes is transformed in a body-centered reference frame to compute the distance of the target to reach.

Parietal cortex plays a key role in the transformations of visual information into the corresponding motor command (Andersen et al., 1997; Andersen and Buneo, 2002). In particular, the aforementioned studies revealed that these areas are involved in processing of movement kinematics (e.g. direction and amplitude) during both hand and eye reaching movements.

The role of frontal areas in reaching

Since more studies investigated movement representation in M1 than in PMd, and since the type of involvement of these areas during reaching movements was very similar (Caminiti et al., 1991; Wu and Hatsopoulos, 2007), I will mainly focus here on data reported in M1.

Many studies investigated which movement parameters are coded in the primary motor cortex during reaching movements. Early studies suggested that activity of neurons in M1 co-varies with muscle activity in an intrinsic reference frame, dependent of the mechanical details of the movement (Evarts, 1968). Surprisingly, successive studies reported the involvement of these areas in coding a higher-level movement parameter: movement direction. Georgopoulos (1982) trained monkeys to execute a center-out task that consisted of moving a lever from the center of a circumference to one of eight surrounding target positions. The authors reported that populations of neurons in M1 are broadly tuned to movement direction: the activity of neuronal populations was highest for the preferred direction and decreased gradually as the angular difference between the preferred and the other direction increased. Moreover, the same population of neurons was similarly active for movement direction, irrespective of whether the movement was executed from the center to

the periphery or from the periphery to the center (Georgopoulos et al., 1985). For example, activity of a neuron was maximally active when the monkey was flexing the arm, regardless of whether the animal moved its arm from the center location to the 270° target or from the 90° target to the center location. In contrast to studies that reported the coding of intrinsic movement parameters, such as muscle force, the studies by Georgopoulos et al. suggested selectivity for movement direction in M1 in an extrinsic reference frame, that is invariant to the starting and end positions.

Since in the aforementioned studies by Georgopoulos and collaborators, movement direction co-varied with the muscular pattern (e.g. flexion of the arm), successive studies aimed to disentangle these two aspects of the movement. Caminiti and collaborators (1990) predicted that directional selectivity should not change during movements in the same direction but executed using different patterns of muscles if the movement direction is represented in extrinsic coordinates. Instead, an orderly shift of the orientation in the space of the cells' preferred direction would indicate that movement direction is represented in intrinsic reference frames, or a combination of the two coordinate systems. To test the two predictions, the authors used the experimental paradigm used by Lacquaniti et al. (1995) to measure neuronal activity during reaching movements in 3D space. Results showed that directional selectivity of neurons in M1 changed significantly when movements of similar direction were made within different parts of the space. To distinguish changes in the pattern of muscles from changes of the shoulder–centered coordinate system, Scott and Kalaska (1997) trained monkeys to execute reaching movements with two different arm orientations: the "natural" arm orientation consisted of locating the elbow below the line between the shoulder and the hand; the "non-natural" orientation consisted of rotating the arm with the

elbow abducted. If M1 cells represent the movement in extrinsic coordinates, their activity should be insensitive to changes in arm orientation. In contrast, if M1 activity reflects to some degree the limb geometry, the activity in the two arm orientations should be different. Results reported changes in directional tuning in relation to different arm orientations, suggesting that representation of movement direction in this region is influenced by intrinsic movement attributes. The authors concluded that cells in M1 do not exclusively encode movement direction per se, but rather a co-variation of intrinsic and extrinsic parameters. This interpretation was experimentally supported by the study of Kakei, Hoffman and Strick (1999) that reported the existence of both "intrinsic-like" and "extrinsic-like" neurons in M1. The former group consisted of cells (28/88) that orderly changed their preferred direction in relation to muscle changes following wrist rotation, while the latter group (44/88) showed no significant shift in their preferred direction with muscles changes. These results strongly support the idea that neurons in M1 represent both information about the specific muscle involved in the movement as well as movement trajectory, indicating that this region is involved in multiple stages of the transformation from extrinsic to intrinsic reference frame, and not just the final computation.

Compared to directional selectivity, fewer studies investigated how another important parameter to execute reaching movements, i.e. movement amplitude, is represented in the monkey brain. Riehle and Requin (1989) measured activity of cells in M1 and PMd in an instructed-delayed paradigm: prior instructions gave complete, partial or no information about direction and amplitude of the movement that the monkey had to execute after the "go" signal. Most of the neurons recorded in these regions showed directional tuning during both the preparatory and execution phase of the movement, whereas only 4 out of 207 neurons

showed sensitivity for movement amplitude. In contrast to these results, Kurata (1993) reported that most cells in PMd were sensitive to both direction and amplitude. Similarly, Fu and collaborators (1993) showed that, both in M1 and PMd, neurons are sensitive to direction and amplitude and to their interaction, that indicate the processing of the target location. Successive re-analysis of the aforementioned results revealed a temporal separation with movement direction encoded first, followed by target position, and finally by movement amplitude (Fu et al., 1995). In line with these studies, Messier and Kalaska (2000) reported that, during movement execution, the majority of cells in PMd codes for the interaction between direction and amplitude.

The aforementioned studies indicate that the execution of reaching movements requires the involvement of many areas that selectively process movement direction in the monkey brain. While parietal areas encode movement direction at an abstract level, similarly for different effectors (eye vs. hand) and irrespective of changes at the muscle level (e.g. with and without load), frontal areas encode movement direction in relation with other movement parameters (e.g. arm orientation, hand starting position). Moreover, information about movement direction is strictly related to information about movement amplitude, although their processing seems to be temporally separated.

1.1.2. NEURONAL BASIS OF REACHING IN HUMANS

Many neuroimaging studies on the human motor system investigated reach-to-grasp movements, where the important aspect that influences the motor plan is the shape of the

object to grasp (see Castiello, 2005; Castiello and Begliomini, 2008). Less is known about the neuronal basis of the transport phase of the hand trough the space (i.e., reaching).

Due to technical constrains in fMRI studies, such as the limited space in the scanner and the need to reduce head movement artifacts, reaching and grasping movements have been difficult to investigate in fMRI. Nonetheless, some fMRI studies investigate reach-to-point movements (Desmurget et al., 2001), reach-to-touch (Culham et al., 2003), and reach-to-grasp (Frey et al., 2005). Activations reported in these tasks revealed that both grasping and reaching activate the hemisphere controlateral to the moving hand substantially more than the ipsilateral hemisphere. Despite the similarities, reaching and grasping networks show some differences: activation for reaching tends to be more dorsal and medial in the parietal lobe compared to grasping (Filimon et al., 2007); studies that involved a transport phase (Culham et al., 2003) prior to the grasp tended to find more superior parietal activation compared to studies where the transport phase was not present.

The involvement of posterior parietal cortex in the control of the trajectory of reaching movements is suggested by optic ataxia: after lesions of the superior parietal lobe and parieto-occipital junction (Perenin and Vighetto, 1988; Karnath and Perenin, 2005), patients with optic ataxia misreach the target by showing errors of hand movement end-point, occurring often in peripheral vision, but also in central vision when reaches are made in absence of visual feedback (see Battaglia-Mayer et al., 2006 for review). These results are in line with the involvement of medial IPS, PMd and medial occipito-parietal junction (mPOJ) during visually-guided movements (Prado et al., 2005). mPOJ has been shown to be active when the reach was made either to a peripheral target or to a target that disappeared before a saccade was made to its location, but not when the target remained visible and a saccade

brought it into central vision. In line with these findings, reversible inactivation of posterior parietal cortex (PPC) through transcranical magnetic stimulation affects the accuracy of hand movement trajectory (Desmurget et al., 1999; Johnson and Haggard, 2005).

These findings support similarities between the functional role of parietal cortex in humans and monkeys during reaching movements (Caminiti et al., 2010), but information about which areas in the human brain selectively process movement direction and to what extent directional selectivity is related to other parameters (e.g. the type of grasp, movement amplitude) is still lacking.

1.1.3. DIRECTIONAL TUNING IN HUMANS

The investigation of neuronal selectivity in humans is limited by the low spatial resolution of standard fMRI paradigms, where the blood-oxygen-level dependent (BOLD) signal reflects the summed activity of neuronal populations within a voxel. Therefore, standard fMRI designs do not allow to distinguish between different neuronal populations within a voxel.

Recently, neuroimaging paradigms have been developed in order to increase the sensitivity of conventional functional magnetic resonance imaging (fMRI) designs: multi-voxel pattern analysis (MVPA) (Haxby et al., 2001; Norman et al., 2006) and fMRI adaptation (Grill-Spector and Malach, 2001). The former method consists of using pattern-classification algorithms to extract the signal that is present in the pattern of responses across multiple voxels. This method has been used successfully to demonstrate patterns of neuronal selectivity in humans similar to monkeys (see Kamitani and Tong, 2005 for orientation selectivity in visual areas). The latter method measures neuronal selectivity at a subvoxel

level, based on the finding that the BOLD amplitude decreases as a consequence of the repeated presentation of a stimulus to which that neuronal population is selective (Grill-Spector and Malach, 2001; Krekelberg et al., 2006). This technique has been used to investigate neuronal selectivity in different domains, including action representation (Dinstein et al., 2007; Lingnau et al., 2009).

Eisenberg and collaborators (2010) investigated the existence of directionally tuned neurons in humans M1, using MVPA. Participants were required to execute a center-out task by moving a cursor from the center of the screen to one out of five green targets. Targets were positioned at directions between 0° and 180°, 45° apart. Participants executed the task moving a joystick with their right hand. Results showed that voxels in M1 contained populations of neurons that are clustered according to their preferred movement direction. In the three experiments reported in the present thesis I used fMRI adaptation to investigate which areas show directional selectivity in the human brain beyond M1, and to which degree populations of directionally tuned neurons are sensitive to changes in the type of motor act (Experiments 1 and 2 in Study I) and in movement amplitude (Study II).

Chapter 2

STUDY I: TUNING CURVES FOR MOVEMENT DIRECTION IN THE HUMAN VISUO-MOTOR SYSTEM

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2.1. ABSTRACT

Neurons in macaque primary motor cortex (M1) are broadly tuned to arm movement direction. Recent evidence suggests that human M1 contains directionally tuned neurons, but it is unclear which other areas are part of the network coding movement direction, and what characterizes the responses of neuronal populations in those areas. Such information would be highly relevant for the implementation of brain-computer-interfaces (BCI) in paralyzed patients.

We used functional magnetic resonance imaging (fMRI) adaptation to identify which areas of the human brain show directional selectivity and the degree to which these areas are affected by the type of motor act (to press versus to grasp). After adapting participants to one particular hand movement direction, we measured the release from adaptation during

occasional test trials, parametrically varying the angular difference between adaptation and test direction.

We identified multiple areas broadly tuned to movement direction, including M1, dorsal premotor cortex, intraparietal sulcus and the parietal reach region. Within these areas, we observed a gradient of directional selectivity, with highest directional selectivity in the right parietal reach region, both for right and left hand movements. Moreover, directional selectivity was modulated by the type of motor act to varying degrees, with the largest effect in M1 and the smallest modulation in the parietal reach region. These data provide an important extension of our knowledge about directional tuning in the human brain. Furthermore, our results suggest that the parietal reach region might be an ideal candidate for the implementation of BCI in paralyzed patients.

2.2. *INTRODUCTION*

Cells in monkey M1 are broadly tuned to movement direction (Georgopoulos et al., 1982). Arm posture (Scott and Kalaska, 1997), wrist rotation (Kakei et al., 1999) and changes in the starting location (Caminiti et al., 1990) modulate directional selectivity in M1, suggesting that this area contains neuronal populations that represent movement direction at the level of parameters such as muscle forces and joint angles (Todorov, 2003).

Due to the lack of invasive electrophysiological data, little is known about directional tuning in humans. Using electrodes implanted in human tetraplegic patients, it has been demonstrated that activity of cells in M1 permits classification of the direction of an intended center-out movement with high accuracy (Hochberg et al., 2006; Truccolo et al., 2008). These studies indicate that human M1 contains neurons that are sensitive to movement direction (see Eisenberg et al., 2010, for similar results using multi-variate pattern analysis), and thus suggest that M1 might be a good candidate region for brain-computer-interfaces (BCIs). Though the studies by Hochberg et al. (2006) and Truccolo et al. (2008) demonstrate that spiking activity in M1 can persist even several years after spinal cord injury, there is evidence that motor cortex and descending motor tracts in patients suffering from complete spinal cord injury undergo degradation (Hains et al., 2003; Wrigley et al., 2009). Therefore, characterizing directional tuning in additional areas that are more closely linked to the visual system might reveal information that is relevant for the development of BCIs (see also Andersen and Buneo, 2002).

Here we used fMRI adaptation (Grill-Spector and Malach, 2001; Krekelberg et al., 2006) to determine which areas of the human brain are broadly tuned to hand movement direction. Participants were adapted to a reaching movement in one specific direction. During occasional test trials, we measured the amplitude of the blood-oxygen level dependent (BOLD) effect as a function of the angular difference between adaptation and test direction (see Piazza et al., 2004, for a similar approach in the number domain). We hypothesized that areas containing directionally tuned neuronal populations (see **Fig. 1a**) show a recovery from adaptation that is proportional to the angular difference between adaptation and test direction (see **Fig. 1b**).

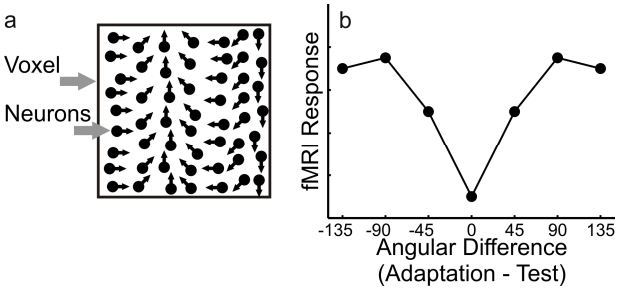

Figure 1. Prediction. **(a)** A voxel containing directionally tuned neurons. **(b)** Neuronal populations that contain directionally tuned neurons are assumed to show a recovery from adaptation that is proportional to the angular difference between adaptation and test direction.

Since reaching is typically performed in combination with a grasping movement, we furthermore aimed to explore how directional tuning is modulated by the type of grasp. To this aim, we manipulated the type of motor act (to press versus to grasp) orthogonally to movement direction.

We observed a gradient of directional selectivity, with highest directional selectivity in the right dorsal premotor cortex and the right parietal reach region (PRR), both for movements of the right and the left hand. Activity in these areas was clearly modulated by the type of motor act, with the strongest modulation in M1, and the weakest effect in the PRR. These results provide an important extension of our knowledge on how the brain represents movement direction and furthermore suggest that the PRR might be well suited for BCIs application.

2.3. MATERIALS AND METHODS

Participants

Fourteen volunteers (8 males) took part in Experiment 1 (mean age 28.07; range, 22-34 years). Eight of these participants also took part in Experiment 2. All participants, except one, were right-handed. Thirteen right-handed volunteers (6 male) took part in Experiment 2 (mean age 29.23; range, 22-35 years). Vision was normal or corrected-to-normal using MR-compatible glasses. All participants except two (including one of the authors, A.L.) were naïve to the purpose of the study.

All of the participants were neurologically intact and gave written informed consent for their participation. The experimental procedures were approved by the ethical committee for research involving human subjects at the University of Trento.

Experiment 1: Right-hand movements

The aim of Experiment 1 was to determine which areas of the human brain are tuned to right-hand movement direction, and to which degree directional selectivity in these areas is affected by the type of motor act (to press versus to grasp).

Experiment 2: Left-hand movements

In Experiment 1, using right-hand movements, we observed the strongest directional selectivity in the right hemisphere. This led to the question of whether the highest directional selectivity is right-lateralized or whether it is specific to the hemisphere ipsilateral to the hand used in the movement. We therefore carried out Experiment 2, using the same procedure as in Experiment 1, but instructing participants to use the left instead of the right hand.

Procedure and Visual Stimulation

During each trial, we showed participants an arrow at the center of the screen for 2 seconds (s), followed by an inter-trial-interval (ITI) of 1 s (see **Fig. 2a**). Arrows instructed the participant about the direction of two center-out hand motor acts (to press vs to grasp). The orientation of the arrow indicated the direction of the movement participants had to execute using their right (Experiment 1) or left (Experiment 2) hand on the device attached to their chest (**Fig. 2b**), whereas the color indicated the type of motor act (red: to press, blue: to grasp).

Within the same scanning run, the same movement direction was repeated in sequences of 1 to 8 adaptation trials. After each sequence of adaptation trials, a test trial was presented. During test trials, we parametrically varied the angular difference between adaptation and test directions, as indicated by the direction of the arrow: 0° (“same”), +/-45° (“small”), +/-

90° (“medium”), +/-135° (“large”) (see **Fig. 2c**). In separate scanning runs, we used two different adaptation directions (45° or 225°, illustrated by the straight and broken arrow in **Fig. 2c**).

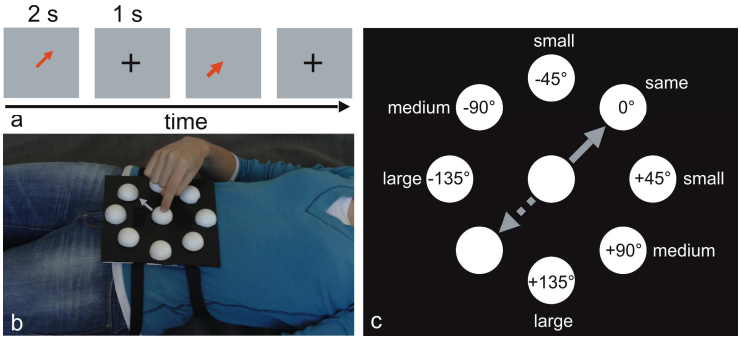

Figure 2. Setup. **(a)** Example sequence of two trials (direction of the arrow: 45°). **(b)** Participants laid in the scanner with the index finger on the center of a device attached to their chest and executed a reaching movement on the device in the direction indicated by the arrow on the screen. The straight arrow illustrates the direction of the movement to be performed on the device (in this example: 45°; arrow on the device not shown during the experiment). In Experiment 1, participants used their right hand, and in Experiment 2, participants used their left hand. **(c)** On the schematic device, the full set of test directions is shown for adaptation direction 45°, indicated by the straight arrow. On each target half-sphere, the angular difference between adaptation and test direction and the corresponding label is indicated. The broken arrow indicates adaptation direction 225°, used in separate blocks.

The device consisted of half-spheres of polystyrene on a black plastic surface (20 x 20 cm). They were placed at eight equidistant positions on an invisible circle (8 cm radius) as well as at the center of the circle.

During adaptation trials, participants were adapted to the motor act “to press”. On half of all test trials, participants were asked to perform the motor act “to press” (adapted motor act test trials) (see **Fig.3a**), whereas on the other half of all test trials, they were asked to execute the motor act “to grasp” (non-adapted motor act test trials) (see **Fig.3b**). The two motor acts only differed in the final part of the movement. In both cases, participants reached from the starting position at the center of the device to the target position as indicated by the arrow on the screen. For the motor act “to press”, they were asked to touch the center of the target with their index finger as if they were pressing a button. For the motor act “to grasp”, they were asked to grasp the target with a whole-hand grasp. At the end of each trial, they released the target and returned to the central starting position.

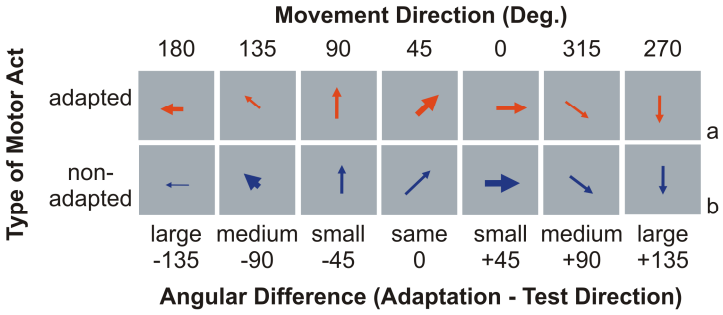

Figure 3. Design. **(a)** Adapted motor act test trials differed from adaptation trials with respect to movement direction only. (**b**) Non-adapted motor act test trials differed from adaptation trials with respect to movement direction and the type of motor act.

To ensure that the pattern of adaptation was specific to the movement direction and not due the repetition of low-level perceptual features, we varied the visual appearance of the arrow that indicated the movement direction and the type of motor act on each trial. Arrow width and length was varied randomly from 0.41° to 1.22° in steps of 0.41°. The x- and y- center coordinates of the arrow were jittered in a range of +/- 0.07° in steps of 0.035°.

Stimuli were back-projected onto a screen by a liquid-crystal projector at a frame rate of 60 Hz and a screen resolution of 1,280 x 1,024 pixels (mean luminance: 109 cd/m^2). Participants viewed the stimuli binocularly through a mirror above the head coil. The screen was visible as a rectangular aperture of 17.5 x 14.3 degree.

Visual stimulation was programmed with in-house software ("ASF", available from jens.schwarzbach@unitn.it), based on the MATLAB Psychtoolbox-3 for Windows (Brainard, 1997).

Instructions and Training

Training was performed outside the scanner. Participants sat in front of the computer that showed the visual instruction, with the device positioned on their chest similar to the setup inside the scanner. The experimenter explicitly asked participants to execute every motor act within a constant time window of 2 s corresponding to the presentation time of the arrow, rather than trying to move as fast as possible and thus risking head movements. Participants were asked to move their hand back to the center position before the arrow disappeared, and to start each trial from the center position.

Training consisted of several stages. At the beginning, the experimenter informed the participants that neither hand nor the device was visible to them inside the scanner. Therefore, they were allowed to get familiar with the spatial dimensions of the device and to practice the movements while looking directly at their hand and their device. Once they felt comfortable performing the task, they were asked to perform the movements without looking at the hands or the device. Training was finished once participants were able to perform the task correctly without visual feedback.

fMRI Adaptation design

Both Experiment 1 and 2 consisted of 12 event-related fMRI adaptation runs. Each run consisted of 88 trials (72 adaptation trials plus 16 test trials) and lasted 5.4 minutes.

In each run, each combination of angular difference between adaptation and test trial (+/- 45°, +/-90°, +/- 135°) and type of motor act test trial (adapted, non-adapted) was repeated once. Since we intended to collapse across test directions to the left (-) and right (+) of the adaptation direction in the analysis, we had two repetitions for angular differences 45°, 90°, and 135°. In order to have the same number of repetition for each test direction, test trials that contained no change in movement direction (angular difference 0°, “same”) were repeated twice per run for both types of motor act. Thus, there were 16 test trials in total per run.

There were 1 to 8 adaptation trials between two successive test trials, resulting in 8 different adaptation intervals. Each interval was repeated twice resulting in 72 adaptation trials per run. The number of adaptation trials between two successive test trials was randomly assigned to each condition.

To minimize fatigue of muscles related to the task, breaks of 20 s were inserted after half a block (i.e., after 2.2 min). Trials in both the first and the second half of each run consisted of 8 test trials each following one of the randomly distributed 8 adaptation intervals giving a total of 44 trials (36 adaptation trials + 8 test trials).

Data Acquisition

We acquired fMRI data using a 4T Bruker MedSpec Biospin MR scanner and an 8-channel birdcage head coil. Functional images were acquired with a T2*-weighted gradient-recalled echo-planar imaging (EPI) sequence. Before each functional scan, we performed an additional scan to measure the point-spread function (PSF) of the acquired sequence, which serves for correction of the distortion expected with high-field imaging (Zaitsev et al., 2004). We used 34 slices, acquired in ascending interleaved order, slightly tilted to run parallel to the calcarine sulcus (TR (time to repeat): 2000 ms; voxel resolution: 3x3x3 mm; TE (echo time): 33ms; flip angle (FA): 73°; field of view (FOV): 192 x 192 mm; gap size: 0.45 mm). Each participant completed 12 scans of 162 volumes each.

To be able to coregister the low-resolution functional images to a high-resolution anatomical scan, we acquired a T1 weighted anatomical scan (MP-RAGE; voxel resolution: 1x 1 x 1 mm; FOV: 256 x 224 mm; GRAPPA acquisition with an acceleration factor of 2; TR: 2700 ms, inversion time (TI), 1020 ms; FA: 7°).

Data Analysis

Data analysis was performed using BrainVoyager QX 2.1 (Brain Innovation, Maastricht, The Netherlands) and custom software written in MATLAB (Mathworks, Natick, MA, USA). In

Experiment 1, participant 13 was excluded from the analysis because of several abrupt head movements, as was evident from the first derivative of the 3D motion correction parameters.

Preprocessing, segmentation, and flattening. To correct for distortions in geometry and intensity in the EPI images, we applied distortion correction on the basis of the PSF data acquired before each EPI scan (Zeng and Constable, 2002). Before further analysis, we removed the first 4 volumes to avoid T1-saturation. Next, we performed 3D motion correction with trilinear interpolation using the first volume as reference followed by slice timing correction with ascending interleaved order. Functional data were temporally high-pass filtered using a cut-off frequency of 3 cycles per run. We applied spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum. Next, we aligned the first volume of each run to the high resolution anatomy. Both functional and anatomical data were transformed into Talairach space using trilinear interpolation.

Definition of Regions of Interest (ROIs). We ran a random effects (RFX) general linear model (GLM) analysis, including the factors adaptation direction (45°, 225°), angular difference between adaptation and test direction (0°, +/- 45°, +/- 90°, +/- 135°), and type of motor act (adapted, non-adapted). Each predictor time course was convolved with a dual-gamma hemodynamic impulse response function (Friston et al., 1998). The resulting reference time courses were used to fit the signal time course of each voxel. We also included the first and second derivatives of each predictor time course to be able to model shift and dispersion of the hemodynamic impulse response function, respectively. Furthermore, parameters from 3D motion correction were included in the model as predictors of no interest. To avoid selection of regions of interest (ROIs) biased in favor of our hypothesis on movement selectivity (Kriegeskorte et al., 2009), we functionally selected our

ROIs by computing the following contrasts: 1) adaptation trials vs baseline, in order to identify motor areas active during the adaptation trials, 2) test trials “same direction, adapted” versus all remaining test trials, in order to identify areas sensitive to a change in movement direction or the type of motor act. Statistical maps were Bonferroni-corrected ($p < .05$) for multiple comparisons.

Statistical analysis. To quantify the effect of the angular difference between adaptation and test directions as well as the effect of type of motor act, we extracted z-transformed beta estimates of the BOLD response for each of the 7 angular differences between adaptation and test direction, separately for the two adaptation directions and the type of motor act. Next, we computed a 2 (adaptation directions 45° and 225°) x 7 (angular difference between adaptation and test direction: 0°,+/-45°,+/-90°,+/-135°) x 2 (type of motor act: adapted, non-adapted) repeated-measures ANOVA on the extracted beta values. Degrees of freedom were adjusted by the Greenhouse-Geisser procedure when Mauchly’s tests indicated violation of sphericity, with corrected p-values denoted as pGG. We corrected the critical p value for the number of ROIs ($p < 0.005$ in Experiment 1, $p<0.007$ in Experiment 2).

2.4. RESULTS

2.4.1. EXPERIMENT 1 (RIGHT-HAND MOVEMENTS)

Areas involved during hand reaching movements

Our first aim was to identify regions of interest that were (a) active during adaptation trials ("motor areas"), resulting from the RFX GLM contrast between adaptation versus baseline, and (b) areas that were sensitive to a change in movement direction or the type of motor act ("change areas"), as revealed by the contrast between test trials that differed from adaptation trials and test trials that were identical to adaptation trials.

Fig. 4 shows that "Motor" areas (yellow) consist of the left primary motor area and the right cerebellum (not shown in **Fig. 4**). Note that there appear to be two additional yellow areas in the vicinity of dorsal premotor cortex (PMd) and medial intraparietal sulcus (mIPS), but these are actually part of one larger region, including M1. "Change" areas (green) include the medial aspect of the left and right posterior parietal cortex (parietal reach region, Connolly et al., 2003), medial and anterior intraparietal sulcus, and dorsal premotor cortex.

An overview of the Talairach coordinates of these areas can be found in **Table 1**.

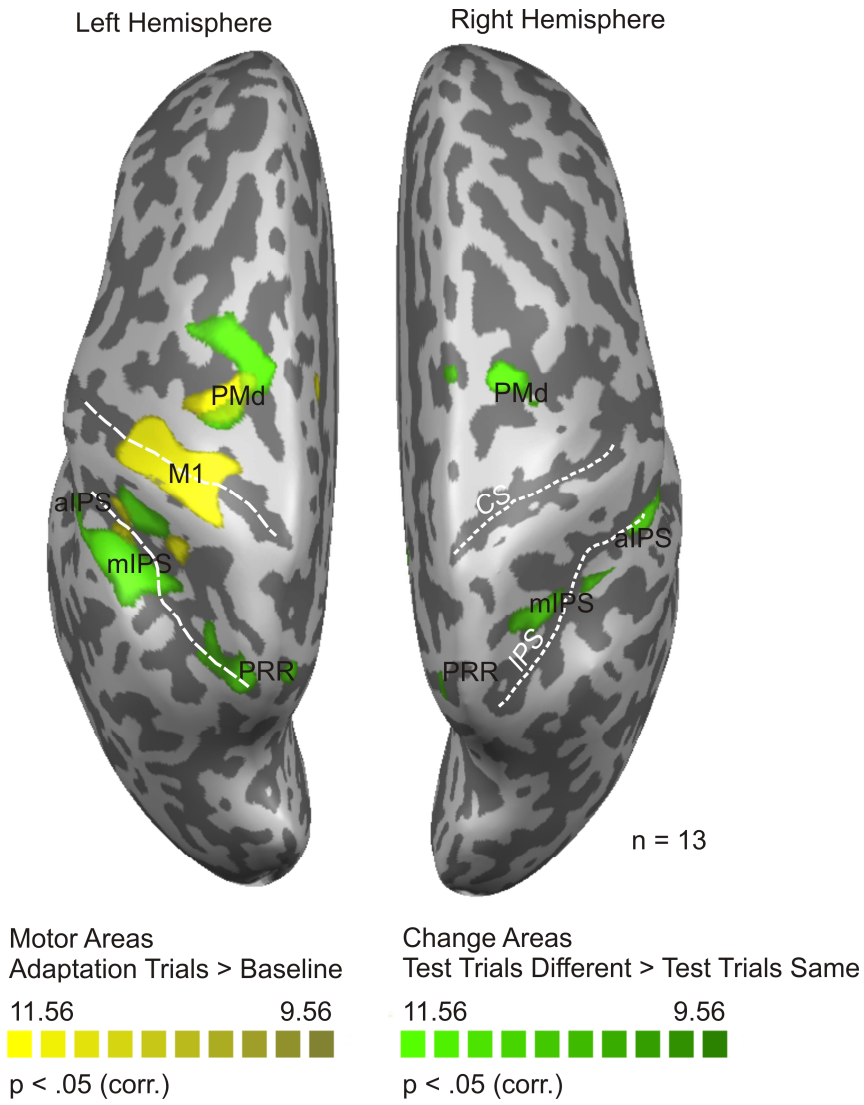

Figure 4. Statistical map of Experiment 1. “Motor areas” and “Change areas” are shown in yellow and green, respectively (see Results for details). Functional data (Bonferroni corrected, p<.05) are superimposed on the segmented and inflated left and right hemispheres of one of the participants. “Motor areas” are: left primary motor cortex (**M1** LH), and right cerebellum (**cer** RH) (not shown in the figure). “Change areas” are: left and right parietal reach region (**PRR** LH, RH), left and right anterior intraparietal sulcus (**aIPS** LH, RH), left and right medial intraparietal sulcus (**mIPS** LH, RH), left and right dorsal premotor cortex

(**PMd** LH, RH). White dotted lines mark the central sulcus (**CS**) and the intraparietal sulcus (**IPS**).

Table 1. Talairach coordinates (mean x, y, and z center of mass; standard deviation in brackets).

	Experiment 1			Experiment 2		
ROIs	x	Y	z	x	y	z
M1 LH	-30 (+/- 6.2)	-23 (+/- 6.2)	52 (+/- 7.8)			
M1 RH				31 (+/- 4.0)	-24 (+/- 3.3)	53 (+/- 6.3)
cer LH				-5 (+/- 3.1)	-52 (+/- 4.0)	-19 (+/- 1.9)
cer RH	13 (+/- 8.2)	-47 (+/- 5.9)	-22 (+/- 3.6)			
aIPS LH	-54 (+/- 4.4)	-24 (+/- 3.3)	22 (+/- 4.9)	-54 (+/- 5.6)	-28 (+/- 4.4)	36 (+/- 5.8)
aIPS RH	47 (+/- 4.5)	-27 (+/- 3.1)	36 (+/- 3.8)	44 (+/-5.8)	-31 (+/- 3.0)	40 (+/- 4.4)
mIPS LH	-39 (+/- 7.3)	-35 (+/- 6.6)	43 (+/- 7.6)			
mIPS RH	27 (+/- 3.8)	-45 (+/- 2.8)	46 (+/- 4.9)			
PMd LH	-21 (+/- 4.2)	-9 (+/- 3.6)	56 (+/- 5.0)	-23 (+/- 4.8)	-13 (+/- 2.5)	58 (+/- 4.0)
PMd RH	20 (+/- 3.6)	-11 (+/- 2.7)	54 (+/- 3.5)	23 (+/- 3.0)	-14 (+/- 1.6)	57 (+/- 3.9)
PRR LH	-19 (+/- 3.8)	-61 (+/- 3.5)	51 (+/- 3.7)			
PRR RH	11 (+/- 2.1)	-64 (+/- 2.1)	47 (+/- 3.0)	13 (+/- 2.1)	-67 (+/- 3.4)	47 (+/- 2.6)

Table 1: M1*: primary motor cortex,* ***cer****: cerebellum,* ***aIPS****: anterior intraparietal sulcus,* ***mIPS:*** *medial intraparietal sulcus,* ***PMd:*** *dorsal premotor cortex,* ***PRR:*** *parietal reach region;* ***LH:*** *left hemisphere,* ***RH:*** *right hemisphere.*

The modulation of the BOLD response by the angular difference between adaptation and test direction

Next we investigated how the BOLD signal is modulated by the angular difference between adaptation and test direction. Specifically, we asked if the BOLD response follows the pattern depicted in **Fig. 1b**: if the examined region contains populations of neurons that are tuned to hand movement direction, we expected to see the lowest BOLD signal for test directions that are identical with the adaptation direction, and an increasing BOLD signal with increasing angles between adaptation and test direction. To this end, we extracted beta estimates for z-transformed voxel time-courses from the regions of interest shown in **Fig. 4**.

Fig. 5 shows the beta estimates as a function of the angular difference between adaptation and test direction, separately for the two adaptation directions (45° and 225°, indicated by downward and upward triangles, respectively) and for adapted (red) and non-adapted (blue) motor act test trials. As can be seen, the BOLD response in the left primary motor cortex for adapted motor act test trials (red) follows the pattern expected for areas that contain directionally tuned neuronal populations: the red curve is lowest for the test direction that is identical with the adaptation direction and increases with the angular difference between adaptation and test direction, both to the left and to the right of the adaptation direction.

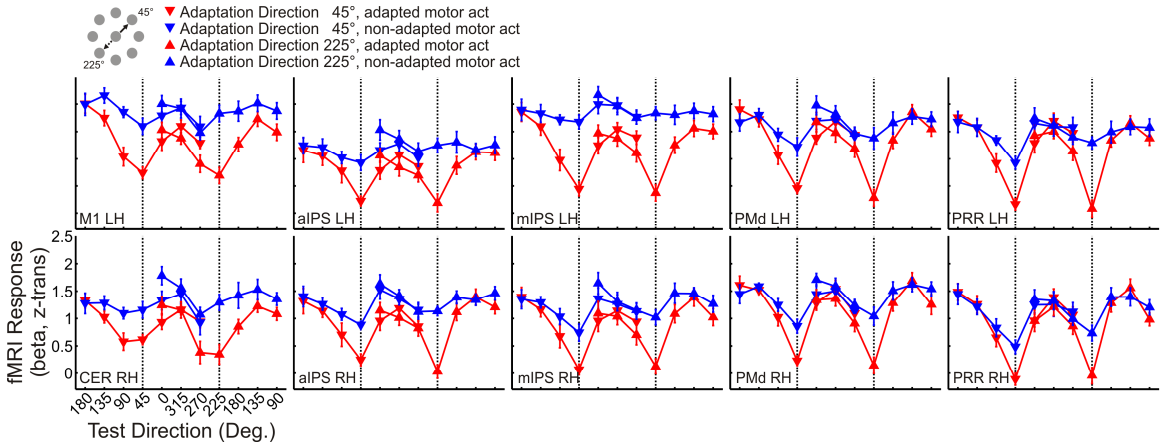

Figure 5. BOLD response (reported as z-transformed beta weights) in each ROI in Experiment 1. The pattern of the BOLD response in adapted (red curve) and non-adapted (blue curve) motor act test trials is plotted as a function of the test direction, separately for adaptation direction 45° (downward triangles) and 225° (upward triangles). Adaptation directions 45° and 225° are indicated by vertical dotted lines. Data are averaged across individually extracted z-transformed beta values from N = 13 participants. Error bars, +-s.e.m.

Visual inspection of the data in the remaining areas suggests that the BOLD response is modulated by the angular difference between adaptation and test direction also in the remaining regions of interest, indicating directional tuning beyond primary motor cortex.

Our observations are supported by the corresponding statistics. Across regions, the BOLD response was affected by the angular difference between adaptation and test direction [$F(6, 72) = 27.086$, $p < 0.0001$]. However, the strength of directional selectivity differed between regions, as indicated by the interaction between test direction and ROI [$F(54, 648) = 5.299$, $p < 0.0001$]. This observation is further explored in the section “Variation of the strength of directional tuning across areas”.

The BOLD amplitude did not differ between the two adaptation directions, as indicated by the absence of a main effect of adaptation direction [$F(1, 12) = 0.606$, $p = 0.452$]. We therefore collapsed data across the two adaptation directions in the following analyses. It should be noted, however, that there was an interaction between the type of motor act and adaptation direction [$F(1, 12) = 4.790$, $p = 0.049$], indicating that the BOLD signal for the two types of motor acts was different for the two adaptation directions. The three-way interaction between adaptation direction, test direction and ROI [$F(54, 648) = 2.056$, $p < 0.0001$] suggests that the two adaptation directions were differently modulated by test direction across regions.

Separate ANOVAs computed for each ROI revealed that the effect of test direction as well as the quadratic trend was significant in each single ROI (see **Table 2** for details).

Table 2: Results of ANOVAs on z-transformed BETA values

	Adaptation direction				Type of motor act				Test direction				Quadratic Trend			
ROIs	Experiment 1		Experiment 2		Experiment 1		Experiment 2		Experiment 1		Experiment 2		Experiment 1		Experiment 2	
	F(1,12)	p	F	p	F(1,12)	P	F	p	F(6,72)	p	F	p	F(1,12)	p	F	p
M1 LH	0,712	0,415			33,687	<0,0001			15,431	<0,0001			56,360	<0,0001		
M1 RH			10,327	0,007			126,069	<0,0001			6,819	<0,0001			13,786	0,003
cer LH			15,216	0,002			108,976	<0,0001			8,079	<0,0001			28,885	<0,0001
cer RH	1,373	0,264			50,921	<0,0001			12,540	<0,0001			25,997	<0,0001		
aIPS LH	0,868	0,370	0,653	0,435	53,213	<0,0001	126,884	<0,0001	8,896	<0,0001	9,698	<0,0001	17,915	0,001	15,136	0,002
aIPS RH	1,956	0,187	2,611	0,132	29,005	<0,0001	61,611	<0,0001	20,474	<0,0001	19,511	<0,0001	46,118	<0,0001	35,859	<0,0001
mIPS LH	0,004	0,950			45,887	<0,0001			16,596	<0,0001			51,293	<0,0001		
mIPS RH	2,546	0,137			35,419	<0,0001			19,451	<0,0001			29,118	<0,0001		
PMd LH	0,372	0,553	2,126	0,170	10,535	0,007	47,372	<0,0001	22,907	<0,0001	21,069	<0,0001	46,757	<0,0001	69,324	<0,0001
PMd RH	0,652	0,435	5,914	0,032	15,178	0,002	30,761	<0,0001	26,986	<0,0001	21,664	<0,0001	26,570	<0,0001	47,209	<0,0001
PRR LH	0,001	0,977			14,128	0,003			28,701	<0,0001			57,590	<0,0001		
PRR RH	0,802	0,388	1,001	0,337	7,697	0,017	9,085	0,011	28,299	<0,0001	20,942	<0,0001	34,849	<0,0001	99,048	<0,0001

Table 2: *Critical p-values were corrected with respect to the number of ROIs ($p_{corrected}$ Experiment 1: 0.05/10 = 0.005; $p_{corrected}$ Experiment 2: 0.05/ 7 = .007). Same labels as in Table 1.*

Variation of the strength of directional tuning across areas

Fig. 5 suggests that the increase of the BOLD signal as a function of the angular difference between adaptation and test direction becomes steeper from left M1, and right cerebellum, through bilateral aIPS and mIPS, to bilateral PMd, and bilateral PRR. In line with this view, our previous analyses revealed a significant interaction between the effect of test direction and ROI.

To further explore this effect, we transformed the beta weights extracted from each ROI by subtracting each beta weight from 1. The purpose of this transformation was to use a visualization that is similar to the tuning functions known in monkey physiology. Furthermore, we shifted the baseline of the resulting curves to zero, separately for the two adaptation directions and the type of motor acts. Next, we fitted a Gaussian function of the form

$$f(x) = Ae^{-\frac{(x-\mu)^2}{2\sigma^2}} \qquad (1)$$

to the resulting values (see **Fig. 6**), where x is the angular difference between adaptation and test direction, A is the amplitude, μ is the mean, and σ is the half width of the estimated tuning curve. Since individual data in some of the regions were too noisy for Gaussian fitting, we collapsed data across participants for this analysis, so this analysis serves mainly a visualization function.

Fig. 6 clearly shows that tuning curves for adapted motor act test trials (red) become sharper from left M1 and right cerebellum, over bilateral aIPS and mIPS, to bilateral PMd and PRR, suggesting that the strength of directional tuning increases from M1 to PRR. Tuning curves for non-adapted motor act test trials (blue) are flatter in all regions, but still show some directional tuning in most of the regions in the right hemisphere (aIPS, mIPS,

PMd, and PRR) and left PMd, and PRR. By contrast, tuning curves for non-adapted motor act test trials are essentially flat in the remaining regions of the left hemisphere (M1, aIPS, and mIPS), indicating that in these regions directional tuning is weak for the non-adapted motor act.

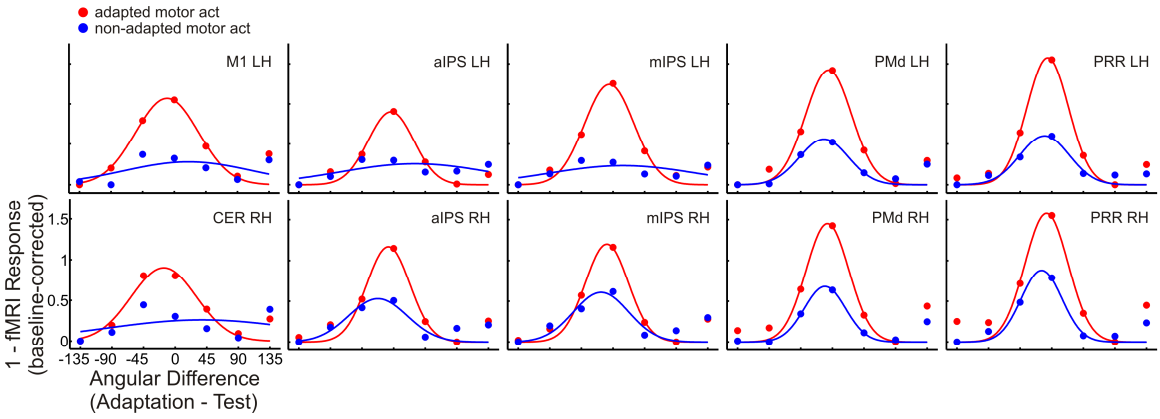

Figure 6. Gaussian function fitted to beta weights extracted from ROIs in Experiment 1. A Gaussian function has been fitted to the data shown in Figure 5 after collapsing over the two adaptation directions, transforming the resulting values (1-x) and shifting the baseline to zero.

To quantify the variation of directional selectivity across areas, we collapsed over both adaptation directions (45°, 225°) as well as over left (-45°, -90°, -135°) and right (+45°, +90°, +135°) test directions, separately for each area and each participant. Next, we estimated the slope of the BOLD amplitude, as quantified by the z-transformed beta weights extracted from each single ROI, as a function of the angular difference between adaptation and test direction. We reasoned that, just as the width of the tuning function in electrophysiology relates to the strength of selectivity, the slope of the BOLD amplitude should relate to the strength of directional selectivity in our adaptation design. We restricted the slope estimation to angular differences of 0°, 45° and 90° since the 135°

condition led to a lower BOLD amplitude than the 90° condition in most areas (see **Fig. 5**). **Fig. 7** shows that directional selectivity for the adapted motor act (white bars) clearly differs between ROIs: the slope increases from left M1, and right cerebellum, to bilateral aIPS, and mIPS, and reaches the highest values in bilateral PMd and PRR.

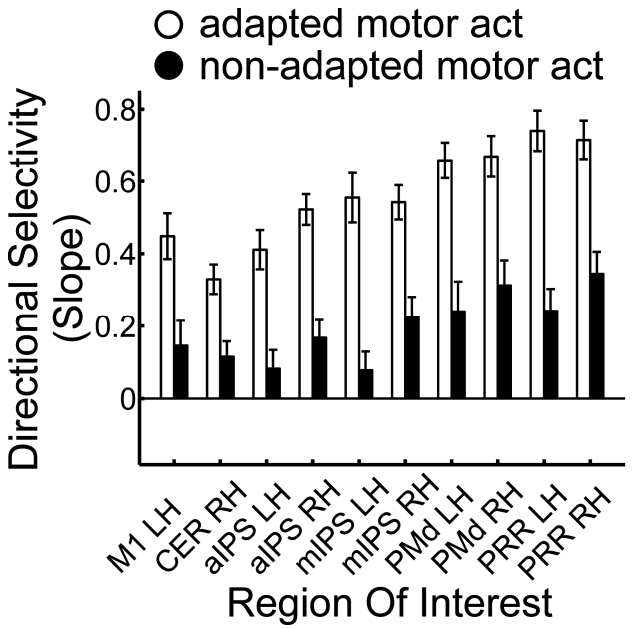

Figure 7. Strength of directional selectivity in ROIs in Experiment 1. The slope of the beta estimates is measured for test directions 0°, 45° and 90°, collapsed over both adaptation directions and left (-45°, -90°) and right (+45°, +90°) test directions. White and black bars indicate adapted and non-adapted motor act test trials, respectively. Error bars, +-s.e.m.

These observations were confirmed by a 2-factorial repeated measures ANOVA on the slope of the BOLD response, with ROI (10 levels) and type of motor act (2 levels) as factors. The strength of directional selectivity differed significantly between regions, as indicated by the main effect of ROI [$F(9,108) = 18.517$, $pGG < 0.0001$]. A significant linear trend [$F(1,12) = 34.461$, $p < .0001$] supported the observation of a gradient of

directional selectivity from left M1 and right cerebellum throughout anterior and medial intraparietal cortex to PMd and PRR. The strength of directional selectivity differed between adapted and non-adapted motor act test trials, as indicated by the main effect of motor act [$F(1, 12) = 22.949$, $p < 0.0001$]. Moreover, the modulation of directional selectivity by the type of motor act differed between ROIs [interaction “type of motor act” x ROI: $F(9, 108) = 5.750$, $pGG = 0.001$].

Modulation of the BOLD response by the type of motor act

Next we asked how directional selectivity is modulated by a change in the type of motor act. To this aim, we compared the extracted beta values for adapted and non-adapted motor act test trials. **Figures 5, 6 and 7** show that all areas are sensitive to the type of motor act. This effect, however, is not simply additive: whereas the red curves (**Figures 5 and 6**) and the white bars (**Fig. 7**), depicting adapted motor act test trials, reveals clear directional selectivity in all areas, the blue curves (**Figures 5 and 6**) and the black bars (**Fig. 7**), showing non-adapted motor act test trials, shows a much weaker (if any) modulation by test direction. This interaction between the effect of test direction and the type of motor act differs between areas: in left M1 and the right cerebellum, the blue curve is essentially flat, indicating that there is no sensitivity to test direction for the non-adapted type of motor act. In contrast, right PMd and PRR show a substantial modulation by movement direction also for the non-adapted type of motor act, suggesting that these areas contain neurons that are sensitive to both types of motor acts.

Statistical analyses supported these observations: directional selectivity differed between the adapted and the non-adapted motor act, as revealed by the interaction between test direction and type of motor act [$F(6,72) = 6.177$, $p < 0.0001$]. This modulation differed between ROIs, as suggested by the interaction of test direction x type of motor act x ROI [$F(54, 648) = 1.647$, $p = 0.003$]. Moreover, across regions, there was a significant main effect of the type of motor act [$F(1, 12) = 32.549$, $p < 0.0001$], and this sensitivity differed between ROIs [Type of motor act x ROI: $F(9, 108) = 14.693$, $p < 0.0001$]. To further explore these interactions, we examined the effect of the type of motor act and the interaction between angular difference between adaptation and test direction and type of motor act separately in each ROI (see **Table 2** for details). This analysis supported the observation that directional selectivity in all areas differs between adapted and non-

adapted motor acts, as indicated by the interaction between test test direction and type of motor act.

The effect of hemisphere on directional tuning

Figures 6 and 7 suggest that directional tuning measured for the non-adapted motor act test trials (blue curves in **Fig. 6**, black bars in **Fig. 7**) is stronger in the right in comparison to the left hemisphere. To further examine this effect, we computed an additional ANOVA on the slope of the BOLD response with the factors hemisphere (2 levels), ROI (4 levels), and type of motor act (2 levels) in those ROIs defined in both hemispheres (i.e., aIPS, mIPS, PMd, and PRR; see **Supplementary Table 1** for an overview of the results). In support of our observations, directional selectivity as measured by the slope of the BOLD response differed between the two hemispheres [main effect hemisphere: $F(1,12)=9.458$, $p=0.01$] and between ROIs [main effect ROI: $F(3,36)=19.307$, $pGG < .0001$]. The effect of hemisphere on the slope of the BOLD response was modulated by the type of motor act [interaction hemisphere x type of motor act: $F(1,12) =9.173$, $p = .01$]. Furthermore, the interaction between type of motor act and hemisphere differed between areas [interaction type of motor act x hemisphere x ROI: $F(3, 36=5.240$, $p=0.004)$]. Paired t-tests revealed that the strength of directional tuning for non-adapted motor act test trials was higher in the right than in the left hemisphere in aIPS [$t(11)=-2.597$, $p=0.023$], mIPS [$t(11)=-4.142$, $p=0.001$], PMd [$t(11)=-2.483$, $p=0.029$], and PRR [$t(11)=-3.204$, $p=0.008$].

2.4.2. EXPERIMENT 2 (LEFT-HAND MOVEMENTS)

Areas involved during hand reaching movements

First we identified regions of interest that were (a) active during adaptation trials ("motor areas"), and (b) areas that were sensitive to a change in movement direction or the type of motor act ("change areas"). **Fig. 8** shows the results of the RFX GLM contrasts computed to identify these two types of areas.

Similar to the results obtained in Experiment 1, we identified multiple regions sensitive to hand movement direction. "Motor" areas (yellow) were right M1 and left cerebellum (not shown in **Fig. 8**). "Change" areas (green) were bilateral PMd and aIPS, and right PRR. An overview of the Talairach coordinates of these areas can be found in **Table 1**. In contrast to Experiment 1, we did not identify bilateral mIPS and left PRR in Experiment 2, probably due to an overall weaker activation during the execution of movements with the non-dominant hand (**Fig. 8**) in comparison to movements performed with the dominant hand (**Fig. 4**) (Dassonville et al., 1997).

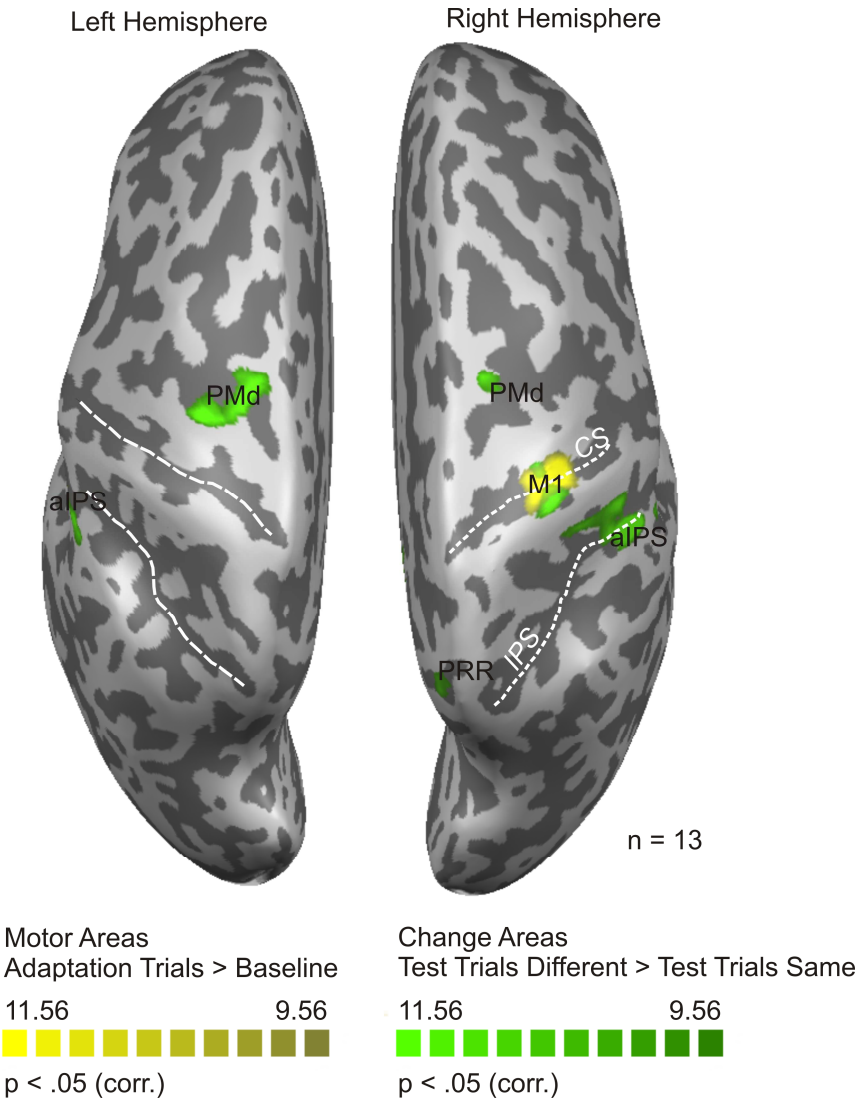

Figure 8. Statistical map of Experiment 2. Statistical maps (Bonferroni-corrected, p < .05) are superimposed on the segmented and inflated left and right hemispheres of one of the participants (same color code as in figure 4). “Motor areas” are: right primary motor cortex (**M1** RH), and left cerebellum (**cer** LH) (not shown in the figure). “Change areas” are: right parietal reach region (**PRR** RH), left and right anterior intraparietal sulcus (**aIPS** LH, RH), and left and right dorsal premotor cortex (**PMd** LH, RH).

The modulation of the BOLD response by the angular difference between adaptation and test direction

Next, we examined how the BOLD signal is modulated by the angular difference between adaptation and test direction. **Fig. 9** shows the beta estimates in each ROI, separately for the two types of motor act test trials and for the two adaptation directions. Visual inspection indicates that all areas show directional selectivity during adapted motor act test trials (red curves). Directional selectivity is modest only in left M1 and the right cerebellum, and becomes more pronounced in left and right aIPS, PMd, and right PRR.

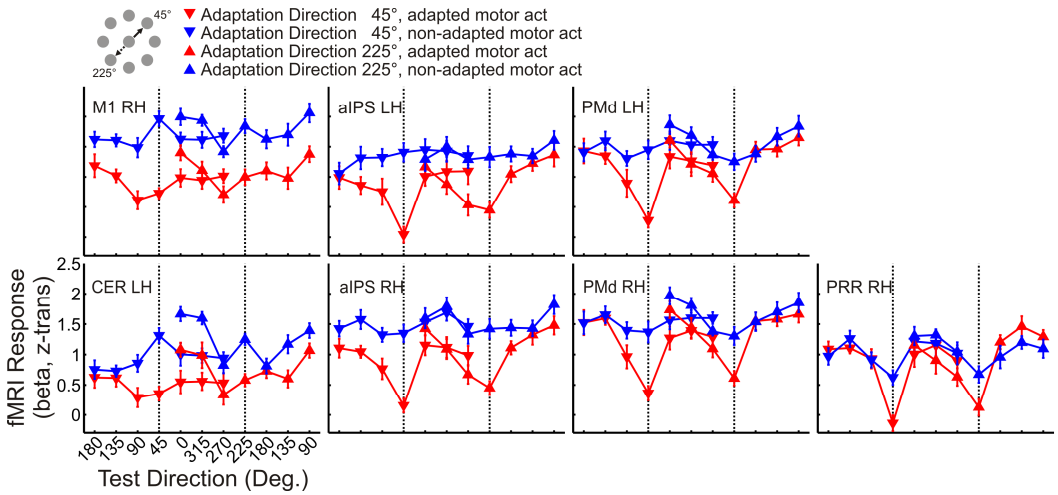

Figure 9. BOLD response (reported as z-transformed beta weights) in each ROI in Experiment 2. The pattern of the BOLD response in adapted (red) and non-adapted motor act (blue) test trials is plotted as a function of the test direction. Adaptation directions 45° and 225° are indicated by vertical dotted lines. Data are averaged across individually extracted z-transformed beta values from N = 13 participants. Error bars, +-s.e.m.

All regions showed directional selectivity [main effect test direction: $F(6, 72) = 16.068$, < 0.0001], and the strength of this effect differed between regions [test direction x ROI: $F(36, 432) = 10.565$, $p < 0.0001$].

As in Experiment 1, we computed separate repeated-measure ANOVAs for each ROI (see **Table 2)**. Similarly to the results in Experiment 1, both our "motor" and "change" areas showed directional selectivity, as indicated by a main effect of test direction in each single area.

The two adaptation directions showed the same general pattern, as indicated by the absence of a main effect of adaptation direction [$F(1, 12) = 4.415$, $p = 0.057$]. However, this pattern differed between regions, as revealed by the interaction between ROI and adaptation direction [$F(6,72) = 2.485$, $p = 0.031$]. Moreover, the effect of adaptation direction on directional selectivity differed between regions, as indicated by the three-way interaction between adaptation direction, test direction and ROI [$F(36, 432) = 1.893$, $p = 0.002$].

Variation of the strength of directional tuning across areas

To compare the strength of directional tuning between areas, we investigated the width of the tuning functions and the slope of the increase of the BOLD response with increasing angular difference between adaptation and test direction in each ROI, similar to the procedures described in the results section of Experiment 1.

Fig. 10 shows the inverted and baseline-corrected beta values from each ROI, fitted by a Gaussian function. Similarly to Experiment 1, we can notice that directional tuning curves measured during adapted motor act test trials (red) become sharper from right M1 and left cerebellum, over bilateral aIPS, to bilateral PMd and right PRR. Directional tuning curves measured during non-adapted motor act test trials are essentially flat in right M1 as well as the left cerebellum and aIPS, whereas they tend to become more narrow from right aIPS over left and right PMd to right PRR.

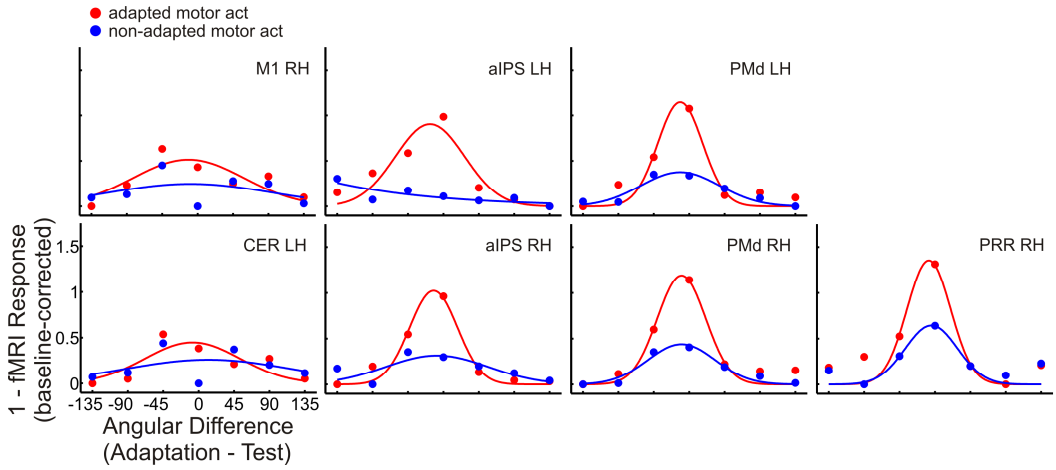

Figure 10. Gaussian function fitted to beta weights extracted from ROIs in Experiment 2. A Gaussian function has been fitted to the data shown in Figure 9 after collapsing over the two adaptation directions, inverting the resulting values and shifting the baseline to zero.

Next, we quantified the strength of directional tuning by examining the slope of the BOLD amplitude as a function of type of motor act and ROI. As can be seen in **Fig. 11**, directional selectivity measured during adapted motor act test trials (white bars) differed between ROIs, with low directional selectivity in left M1 and right cerebellum, intermediate directional selectivity in left and right aIPS and PMd, and highest directional selectivity in right PRR. During non-adapted motor act test trials (black bars), directional selectivity was substantially weaker, but shows a similar trend as during adapted motor act test trials.

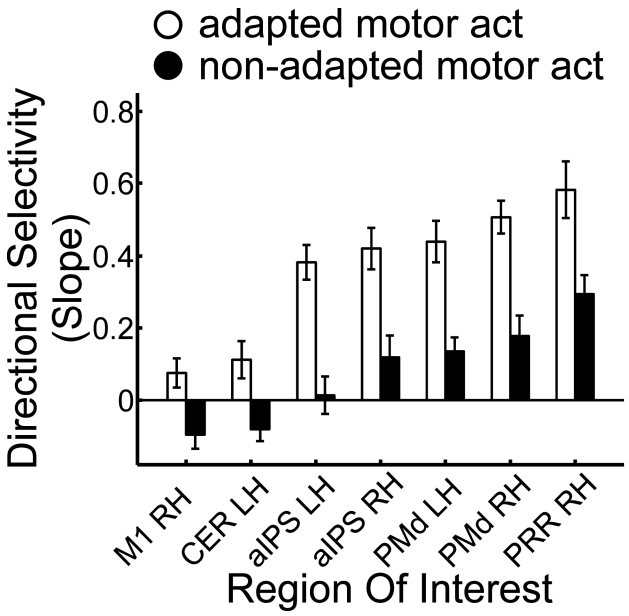

Figure 11. Strength of directional selectivity in ROIs in Experiment 2. The slope of the beta estimates is measured for test directions 0°, 45° and 90° (collapsed over both adaptation directions and left and right test directions).

These observations are supported by the corresponding 2-factorial (ROI x type of motor act) repeated-measures ANOVA on the slope of the BOLD response. Directional selectivity differed between ROIs [$F(6,72) = 43.507$, < 0.0001]. A significant linear trend [$F(1,12) = 167.667$, $p < .0001$] supported the observation of a gradient of directional selectivity from right M1 and left cerebellum throughout anterior intraparietal cortex to PMd and PRR. The slope of the BOLD response was significantly lower for non-adapted in comparison to adapted motor acts, as indicated by the main effect of the type of motor act [$F(1, 12) = 20.592$, $p = 0.001$]. Furthermore, the modulation of the slope of the BOLD effect by the type of motor act differed between ROIs [interaction ROI x type of motor act: $F(6, 72) = 2.958$, $p = 0.012$].

Modulation of the BOLD response by the type of motor act

Next, we explored how the BOLD response is affected by the type of motor act. As can be seen in **Figures 9, 10,** and **11**, directional selectivity in all examined regions was modulated by the type of motor act, as indicated by the difference between the red and the blue curves (**Figures 9 and 10**) and the white and black bars (**Fig. 11**). Across regions, directional selectivity was stronger for adapted in comparison to non-adapted motor act test trials. This interaction differed between areas. The blue curve in **Fig. 9**, depicting the BOLD response during non-adapted motor act test trials, shows almost no modulation by test direction in left aIPS. In right aIPS as well as left and right PMd, the modulation of the BOLD response by test direction during non-adapted motor act test trials is modest, whereas the modulation in right PRR is clearly pronounced. Interestingly, the blue curves in M1 and the cerebellum show an increased BOLD response during test trials that are identical to the adaptation direction, an observation for which we have no explanation.

In support of these observations, movement direction selectivity was affected by the type of motor act [test direction x type of motor act: $F(6, 72) = 5.507$, $p < 0.0001$], and this modulation differed between ROIs [test direction x type of motor act x ROI: $F(36, 432) = 1.476$, $p = 0.041$]. Moreover, all regions also showed a sensitivity for the type of motor act [$F(1, 12) = 130.811$, $p < 0.0001$], and this effect differed between ROIs [motor act x ROI: $F(6, 72) = 19.881$, $p < 0.0001$].

Separate ANOVAs in each single ROI (see **Table 2** for details) revealed that the interaction between test direction and type of motor act was significant in all regions, except in right M1 and left cerebellum.

The effect of hemisphere on directional tuning

To evaluate if the effect of the type of motor act on directional selectivity differs between the two hemispheres, we computed an additional repeated measures ANOVA on the slope of the BOLD response in those regions identified in both hemispheres using the factors hemisphere (left, right), ROI (aIPS, PMd) and type of motor act (adapted, non-adapted) (see **Supplementary Table 1** for a summary of the results).

The strength of directional selectivity as measured by the slope of the BOLD response differed between the two hemispheres [$F(1, 12) = 12.797$, $p = 0.004$], and between ROIs [$F(1, 12) = 5.810$, $p = 0.033$]. The interaction between type of motor act x ROI x hemisphere is marginally significant [$F(1, 12) = 4.177$, $p=0.064$], indicating that the right hemisphere tends to show stronger directional selectivity than the left hemisphere for non-adapted motor act test trials. Pairwise comparisons revealed that this is the case only for aIPS [$t(12)=-3.331$, $p=0.006$]. In contrast to Experiment 1, PMd did not show an hemispheric difference [$t(12)=-1.670$, $p=0.121$].

Given that the interaction between type of motor act x ROI x hemisphere is only marginally significant ($p = .064$), one should not draw too firm conclusions from Experiment 2 alone. However, Experiment 1 showed the same interaction ($p = .004$) with a different subset of participants, suggesting that there may be stronger directional selectivity measured during non-adapted motor act test trials in the right in comparison to the left hemisphere both for movements performed with the right and the left hand.

2.5. DISCUSSION

Tuning for hand movement direction in the human brain

Macaque primary motor cortex contains neurons that are tuned to movement direction. Similar properties have been reported to exist in the human primary motor cortex using invasive single-cell recordings in paralyzed patients (Hochberg et al., 2006; Truccolo et al., 2008) as well as multi-variate pattern analysis (Eisenberg et al., 2010). However, little is known about directional tuning in the human brain beyond these areas. Such information would be highly relevant for the development of brain-computer interfaces since it is unclear which area in the brain is best suited for these applications.

Here we asked which areas of the human brain are tuned to hand movement direction, and what characterizes their responses. In two experiments, we adapted participants to hand movement directions performed with the right (Experiment 1) or the left (Experiment 2) hand and measured the release from adaptation as a function of the angular difference between adaptation and test direction. We observed that neuronal populations in M1, the cerebellum, PMd, aIPS, mIPS and PRR are tuned to hand movement direction. These findings are in line with reports on directional tuning in monkey M1 (Georgopoulos et al., 1982), cerebellum (Fortier et al., 1989), dorsal (Caminiti et al., 1991) and ventral premotor (Kakei et al., 2001) cortex, and areas 2 and 5 of the parietal cortex (Kalaska et al., 1983).

Directional tuning in all identified areas was modulated by the type of motor act, with strongest sensitivity to the type of motor act in M1, and lowest sensitivity in the PRR. Furthermore, we observed a gradient of directional selectivity, with lowest directional selectivity in M1 and the cerebellum, and highest directional selectivity in the right PRR,

irrespective of whether the left or right hand was used. Finally, we observed that directional tuning for the non-adapted motor act tended to be stronger in the right in comparison to the left hemisphere, both for left- and right-hand movements. Taken together, these results suggest that the strongest directional selectivity and the highest level of abstractness can be found in the right parietal reach region (see also Gourtzelidis et al., 2005). In this context, an "abstract" level may be defined as a level of processing before information about the effector is specified, e.g. in the form of a motor program. We assume that the lowest level of abstractness can be found in areas such as M1, where actions are likely to be coded at the level of parameters such as muscle activation and joint angles.

Modulation of the BOLD response by the type of motor act

Directional selectivity was high for adapted motor act test trials and weak for the non-adapted motor act test trials in M1, the cerebellum and aIPS, suggesting that these regions contain separate populations of directionally selective neurons specific for the type of motor act (see **Fig. 12a**). In contrast, directional selectivity was high for both types of motor acts in PMd and in right PRR, suggesting that in these areas neurons are sensitive for both types of motor acts, and that adaptation for one motor act leads to adaptation for the other motor act (see **Fig. 12b**).

Which aspects of an action are coded in those areas that show a strong modulation by the type of motor act? The motor acts "press" and "grasp" share common reaching components but differ in the way in which the hand interacts with the object. For the motor act "press", participants have to stretch out the index finger towards the center of the target, leading to tactile stimulation of the index finger. This requires a precise

coordination of the index finger towards a specific spatial location. In contrast, for the motor act “grasp”, participants have to rotate and shape the entire hand according to the outer shape of the target, giving rise to tactile stimulation of all fingers.

Any of these behavioral aspects are likely to be involved in the modulation of directional tuning by the type of motor act. In line with this view, neurons in monkey aIPS are involved in tactile exploration of an object (Grefkes et al., 2002). Likewise, neurons in monkey aIPS and M1 are sensitive to the shape of the handgrip (Murata et al., 2000; Graziano, 2006), and neurons within the intermediate cerebellum have been reported to be more active during grasping in comparison to reaching (Gibson et al., 1994).

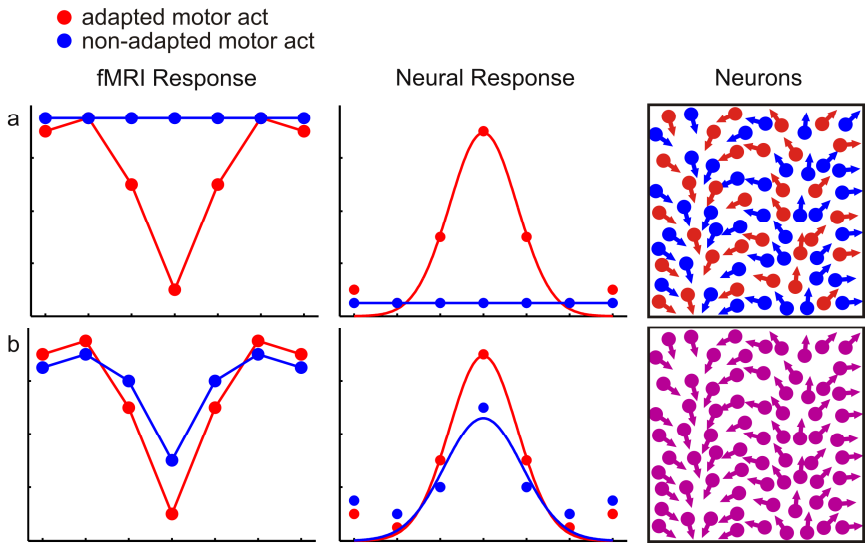

Figure 12. Different patterns of adaptation and the assumed underlying physiology. **(a)** Directional selectivity, as measured by a release from adaptation that is proportional to the angular difference between adaptation and test direction, for the adapted motor act (red curve), and no directional selectivity for the non-adapted motor act (blue curve) indicates that the neural response is selective for the direction of the adapted motor act, suggesting that this region contains populations of directionally selective neurons specific

for the type of motor act. **(b)** Directional selectivity both for adapted and non-adapted motor act test trials suggests that this region contains populations of directionally selective neurons sensitive to both types of motor act.

Hemispheric asymmetries in directional tuning

Our results revealed strongest directional tuning in the right PRR, both for movements of the left and the right hand, suggesting that this region represents movement direction irrespective of the side of the effector. In support of this view, Chang et al. (2008) reported a continuum of limb-dependent and limb-independent neurons in monkey PRR.

In both experiments, directional selectivity tended to be stronger in the right in comparison to the left aIPS for the non-adapted motor act, both for movements of the left and the right hand. This observation is compatible with the view that the left and right aIPS might code different levels of a motor act: whereas the left aIPS might contain separate neuronal populations for different types of motor acts, the right aIPS might contain neuronal populations that are sensitive to several types of motor acts.

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Relation between BOLD adaptation and underlying neuronal selectivity

Our data show that it is possible to derive directional information in humans not only from invasive multi-unit recordings (Hochberg et al., 2006; Truccolo et al., 2008), but also noninvasively from hemodynamic measures, using fMRI adaptation (see also Eisenberg et al., 2010). Tuning functions in humans have been used to investigate neuronal selectivity in several different domains, e.g. motion direction (Busse et al., 2008), numerical knowledge (Piazza et al., 2004), and face perception (Martini et al.,

2006). However, care needs to be taken when directly comparing tuning functions as measured with fMRI adaptation with tuning functions from spiking activity, since fMRI adaptation can overestimate neuronal selectivity (Sawamura et al., 2006). Note, however, that we do not claim to be able to make such a direct comparison. Instead, we are comparing how directional tuning functions as measured with fMRI adaptation are affected by the type of motor act, and how this interaction differs between regions.

The role of attention in fMRI adaptation

It is sometimes argued that neuronal selectivity measured with fMRI adaptation in fact reflects attentional effects (Mur et al., 2010), e.g. due to a general change in movement direction. If so, we would expect a similar recovery of the BOLD signal for all test directions except same direction, adapted motor act test trials. Instead we measured a recovery proportional to the angular difference between adaptation and test direction. Such a parametric modulation of the BOLD signal is hard to reconcile with an unspecific attentional mechanism that is insensitive to movement direction.

The role of spatial orienting

It could be argued that our finding in parietal areas could as well be explained by sensitivity to attentional orienting toward the target location, instead of selectivity for the direction of the movement, given that parietal cortex is known to be involved in spatial orienting (Colby and Goldberg, 1999; Corbetta and Shulman, 2002; Yantis et al., 2002). Since attentional orienting was required to perform the task, we cannot exclude the possibility that our data were modulated by this process. However, one would expect that in areas that are dominated by attentional orienting (i.e., at a stage before spatial

information is transformed into the appropriate motor program), there should be an effect of movement direction, but no difference between the two motor acts. The fact that we found a strong modulation of directional tuning by the type of motor act in PRR, aIPS and mIPS indicates to us that these areas are involved in the preparation of the motor act and not just in attentional orienting, in line with previous studies (Kalaska et al., 1997; Murata et al., 2000; Andersen and Buneo, 2002; Connolly et al., 2003; Quian Quiroga et al., 2006).

2.6. CONCLUSIONS

We have reported evidence for directional selectivity in multiple areas of the human visuo-motor system. We show that the extent of directionally selective regions includes areas beyond M1, with a gradient of directional selectivity that increases from the primary motor cortex and the cerebellum through dorso-premotor and intraparietal areas, to the PRR. We obtained strongest directional tuning in the right PRR both for left and right hand reaching movements, suggesting a special role of the right hemisphere in directional tuning.

Our results provide important constrains for models on motor control. Furthermore, our data indicate that the right PRR might be well suited for brain-computer interfaces for the control of movement direction. An interesting challenge for future studies will be to determine how BCI devices can combine information from PRR and additional areas to provide control over additional components of an action such as the type of hand-object interaction.

Chapter 3

STUDY II: SENSITIVITY FOR MOVEMENT AMPLITUDE IN DIRECTIONALLY TUNED NEURONS

3.1. ABSTRACT

Neurons in macaque primary motor cortex (M1) and dorsal premotor cortex (PMd) have been shown to be tuned to movement direction. The degree to which directionally tuned neurons are modulated by movement amplitude in these areas and beyond is debated. We used functional magnetic resonance imaging adaptation to identify areas that contain directionally tuned neurons, and to measure sensitivity of these populations to changes in movement amplitude. We found that in several regions of the visuomotor system there was clear adaptation to movement direction, but almost no transfer of adaptation to movement direction from the adapted to the non-adapted amplitude. These data indicate that several areas in the human brain in M1, PMd and beyond contain populations of neurons tuned for movement direction in combination with movement amplitude. Our data thus support models on motor control that state that movement direction and amplitude interact.

3.2. *INTRODUCTION*

We frequently execute reaching movements, for example when we switch on the light or hit a button on the keyboard. To efficiently perform these actions, our brain needs to plan and execute a motor program where multiple parameters of the movement need to be specified, such as direction and amplitude.

Many studies report the existence of populations of neurons that selectively process the information about movement direction in many areas of the monkey motor system. Neurons in macaque primary motor cortex (Georgopoulos et al., 1982), dorsal (Caminiti et al., 1991) and ventral (Kakei et al., 2001) premotor cortex, cerebellum (Fortier et al., 1989) and parietal regions (Kalaska et al., 1983) have been shown to be broadly tuned to movement direction with the maximal activity for the preferred direction and decreasing activity as the angular difference between the preferred and the other directions increased. Since reaching movements are typically executed towards a particular target location, both movement direction and amplitude need to be specified in the motor program. According to the *Vectorial Parametric hypothesis* (Bock and Eckmiller, 1986; Vindras and Viviani, 1998), these two parameters are combined to create the reaching trajectory by computing the differential vector between the hand and the target locations. Once the motor program is created, direction and amplitude are specified in independent neuronal pathways. In support of this view, Rosenbaum (1980) reported that reaction times (RTs) to specify direction were not influenced by the specification of amplitude, and vice versa, suggesting that direction and amplitude were planned independently from each other. Gordon, Ghilardi and Ghez (1994) reached a similar conclusion evaluating the types of error made by participants during uncorrected movements towards different targets that

varied in direction, amplitude and size. End-points of the movement described an elliptical distribution along the line connecting the starting point to the target point, indicating that variability in movement amplitude was greater than variability in movement direction. Moreover, direction and amplitude errors were differentially influenced by target distance.

In contrast to these results, other behavioral studies reported that direction and amplitude interact (Favilla et al., 1989; Bhat and Sanes, 1998; Sarlegna and Blouin, 2010). As an example, the time required to specify movement direction slows down the processing of amplitude (Favilla et al., 1989). In summary, behavioral studies on the relation between the specification of movement direction and amplitude has not led to conclusive results.

Only a few neurophysiological studies investigated the neuronal basis of direction and amplitude. These studies reported controversial evidence: Riehle and Requin (1989) found directionally tuned neurons but very few neurons sensitive to movement amplitude in PMd, suggesting that the processing of amplitude and direction might involve separate areas. Instead, Kurata (1993) reported that most cells in PMd are sensitive to both direction and amplitude. The two parameters influenced cells activity irrespective of the order in which they were given during the experiment, suggesting that direction and amplitude are specified independently. In contrast of the independent specification of direction and amplitude, other studies reported that these two movement parameters interact in M1(Fu et al., 1993) and PMd neurons (Fu et al., 1993; Messier and Kalaska, 2000). Therefore, similar to behavioral studies, neurophysiological studies did not reach conclusive results about the relation between movement direction and amplitude.

Recent results on neuroimaging studies in humans focused on the representation of movement direction. Eisenberg et al. (2010) reported evidence for directionally tuned

neuronal populations in human M1 using multi-voxel pattern analysis. Our own group recently extended evidence for directional selectivity from M1 to many areas of the human visuomotor system using fMRI adaptation (Fabbri et al., 2010).

According to the *Vectorial parametric hypothesis*, both movement direction and amplitude need to be specified for the computation of movement trajectory. Here we aimed to determine the degree to which directionally tuned neurons are independent of movement amplitude in the human brain. To this aim, we used an fMRI adaptation paradigm, similar to our previous study (Fabbri et al., 2010). Participants were adapted to execute reaching movements with a constant direction (90°) and amplitude (6 cm or 12 cm). We predicted that, during the adaptation sequence, the BOLD signal would adapt in populations selective for the repeated combination of direction and amplitude. After the adaptation sequence, we presented different types of test trials. In half of the test trials, the direction of the movement could be the same as the adaptation sequence (0° angular difference), or different (45° or 90° angular difference), while movement amplitude was kept constant (e.g. small). We predicted that the BOLD signal within voxels containing directionally tuned neurons should adapt maximally during movements with 0° angular difference from the adaptation direction and show a recovery from adaptation proportional to the angular difference between the adapted and test direction, similar to our previous findings (Fabbri et al., 2010). Importantly, in the other half of the test trials, we varied both direction (0°, 45°, and 90° angular difference) and amplitude (e.g. large) of the movement compared to the adaptation sequence. If directionally tuned neurons are insensitive to changes in the amplitude of the movement, we would expected the same pattern of adaptation both for adapted and non-adapted amplitudes. On the contrary, if directionally tuned neurons are sensitive to changes in the amplitude of the movement, we would expected adaptation of the BOLD signal only for the adapted movement amplitude

and no adaptation for the non-adapted amplitude. To control for possible differences in sensitivity of directionally tuned neurons for small and large amplitudes, in half of the runs we adapted participants with small adaptation amplitude and tested with small and large amplitudes; in the other half of the runs we used the opposite order (e.g. adaptation amplitude large and test with small and large amplitudes).

We found that many areas of the human visuomotor system showed directional tuning for small and large adaptation amplitudes, in line with our previous findings. Importantly, the BOLD signal adapted only during test trials with the same amplitude as the adaptation amplitude, suggesting that populations of neurons within the identified regions are sensitive to a combination of movement direction and amplitude. Our findings are compatible with behavioral and neurophysiological studies that reported the importance of both movement amplitude and direction to compute the trajectory. Our results are in line with neurophysiological evidence of sensitivity of directionally tuned neurons to movement amplitude. Moreover, we reported similar patterns in directionally tuned regions beyond M1 and PMd. These findings challenge the hypothesis that movement direction and amplitude are specified independently in the human brain.

3.3. *MATERIALS AND METHODS*

Participants

Fourteen volunteers (6 males) took part in the Experiment (mean age 27; range, 23-35 years). All participants were right handed. Vision was normal or corrected-to-normal using MR-compatible glasses. All participants were naïve to the purpose of the study; they were neurologically intact and gave written informed consent for their participation. The experimental procedures were approved by the ethical committee for research involving human subjects at the University of Trento.

Procedure and Visual Stimulation

During each trial, participants were presented with an arrow at the center of the screen for 2 seconds (s), followed by an inter-trial-interval (ITI) of 1 s (see **Figure 1a**). Participants had to execute a center-out reaching task on a device attached to their chest, using their right hand (see **Figure 1b**). The device consisted of 11 half-spheres of polystyrene (3 cm diameter) glued on a black plastic surface (15 x 27,5 cm). The half-spheres were arranged on two concentric semicircles (6 and 12 cm radius) of 5 half-spheres each and 1 at the common center.

At the beginning of each trial, participants positioned their index finger on the central half-sphere. As soon as the arrow appeared on the screen, participants started the reaching movement on the device in the direction indicated by the orientation of the arrow. The color of the arrow specified the amplitude of the movement: red arrow instructed participants to execute a movement with small amplitude to reach targets on the near

semicircle; blue arrow instructed participants to execute movements with large amplitude to reach targets on the far semicircle.

In our previous experiments we found no difference between two adaptation directions (Fabbri et al., 2010); therefore we used only one adaptation direction in the current experiment.

After each sequence of 3 to 8 adaptation trials, a test trial was presented (see **Figure 1a** for an example of 3 adaptation trials, followed by a test trial different with respect to movement direction, but was of similar amplitude). During test trials, we parametrically varied the angular difference between adaptation and test directions (0° , +/-45° , +/-90°) as well as movement amplitude (small, large) (see **Figure 1b**). In relation to the adaptation amplitude (small or large), test trials were either Congruent, when they had the same amplitude as the adaptation, or Incongruent, when they has an amplitude different from adaptation.

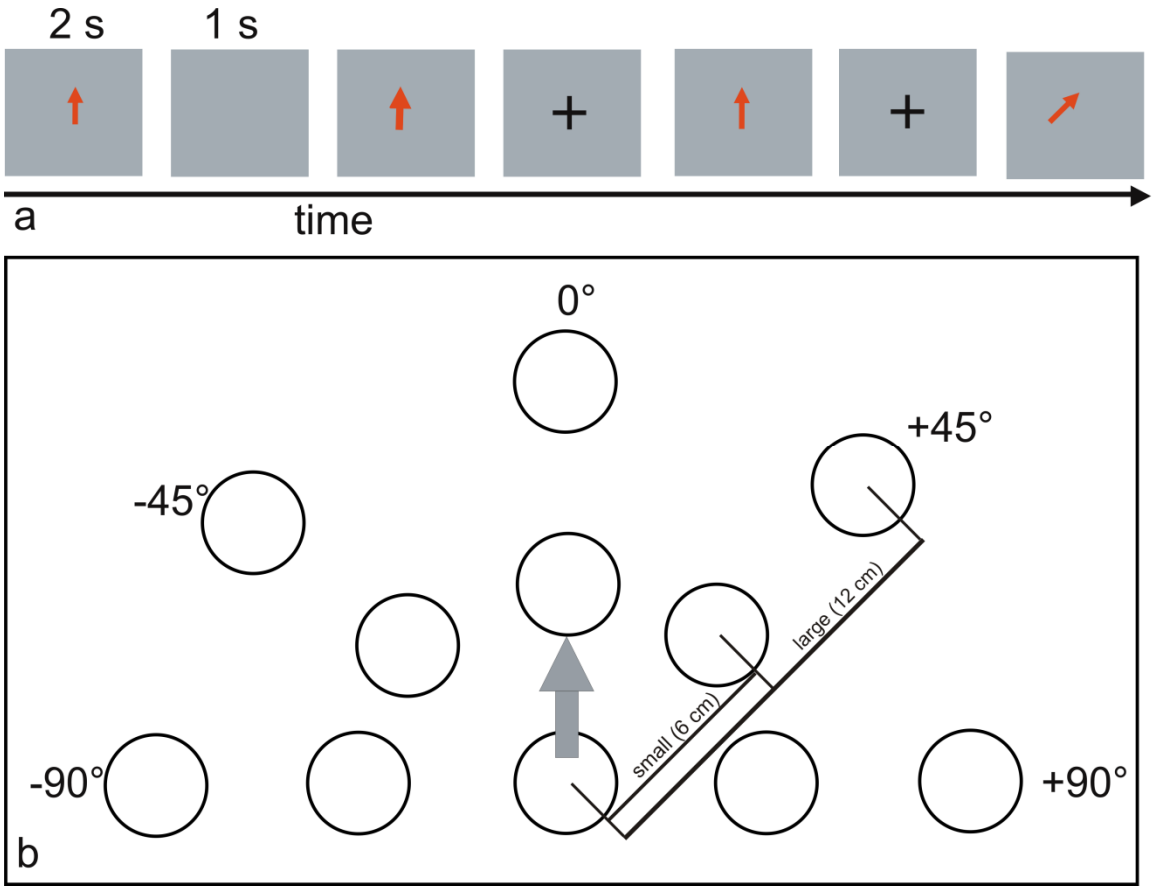


Figure 1. Setup. **(a)** Example sequence of three adaptation trials and one test trial. During adaptation trials, participants executed the movement in the adaptation direction 90°. In separate scanning runs, adaptation amplitude was either small (red arrow) or large (blue arrow). The example depicts a test trial that required a small amplitude reaching movement in 45° direction. **(b)** On the schematic device the full set of angular differences (0°, +/-45°, +/-90°) and movement amplitudes (small and large) are shown.

To ensure that the pattern of adaptation was specific to movement direction and not due to the repetition of low-level perceptual features of the arrows, we varied the visual appearance of the arrow that indicated the movement direction and movement amplitude on each trial (see Fabbri et al., 2010 for a similar approach). Arrow width and length was

varied randomly from 0.41° to 1.22° in steps of 0.41°. The x- and y- center coordinates of the arrow were jittered in a range of +/- 0.07° in steps of 0.035°.

Stimuli were back-projected onto a screen by a liquid-crystal projector at a frame rate of 60 Hz and a screen resolution of 1,280 x 1,024 pixels (mean luminance: 109 cd/m^2). Participants viewed the stimuli binocularly through a mirror above the head coil. The screen was visible as a rectangular aperture of 17.5 x 14.3 degree.

Visual stimulation was programmed with in-house software ("ASF", available from jens.schwarzbach@unitn.it), based on the MATLAB Psychtoolbox-3 for Windows (Brainard, 1997).

Instructions and Training

Before entering the scanner, participants learned to execute the motor act corresponding to the visual instruction, and they familiarized themselves with the location of the half spheres on the device such that they were able to perform accurate motor acts in the absence of visual feedback. The experimenter explicitly asked participants to execute every motor act within a constant time window of 2 s corresponding to the presentation time of the arrow, rather than trying to move as fast as possible and thus risking head movements. Participants were asked to move their hand back to the center position before the arrow disappeared, and to start each trial from the center position.

fMRI Adaptation design

The entire experiment consisted of 12 event-related fMRI adaptation runs. Each run consisted of 78 trials (66 adaptation trials plus 12 test trials) and lasted 4.9 minutes.

In each run, each combination of angular difference between adaptation and test direction (+/- 45°, +/-90°) and test amplitude (small, large) was repeated once. Since we intended

to collapse across test directions to the left (-) and right (+) of the adaptation direction in the analysis, we had two repetitions for angular differences 45°and 90°. In order to have the same number of repetition for each test direction, test trials that contained no change in movement direction (angular difference 0°) were repeated twice per run for both test amplitudes. Thus, there were 12 test trials in total per run.

There were 3 to 8 adaptation trials between two successive test trials, resulting in 6 different adaptation intervals. Each interval was repeated twice resulting in 66 adaptation trials per run. The number of adaptation trials between two successive test trials was randomly assigned to each condition.

To minimize fatigue of muscles related to the task, breaks of 20 s were inserted after half a run (i.e., after 2.45 min). Trials in both the first and the second half of each run consisted of 6 test trials each following one of the randomly distributed 6 adaptation intervals giving a total of 39 trials (33 adaptation trials + 6 test trials) per half block.

Data Acquisition

We acquired fMRI data using a 4T Bruker MedSpec Biospin MR scanner and an 8-channel birdcage head coil. Functional images were acquired with a T2*-weighted gradient-recalled echo-planar imaging (EPI) sequence. Before each functional scan, we performed an additional scan to measure the point-spread function (PSF) of the acquired sequence, which serves for correction of the distortion expected with high-field imaging (Zaitsev et al., 2004). We used 34 slices, acquired in ascending interleaved order, slightly tilted to run parallel to the calcarine sulcus (TR (time to repeat): 2000 ms; voxel resolution: 3x3x3 mm; TE (echo time): 33ms; flip angle (FA): 73°; field of view (FOV): 192 x 192 mm; gap size: 0.45 mm). Each participant completed 12 scans of 147 volumes each.

To be able to coregister the low-resolution functional images to a high-resolution anatomical scan, we acquired a T1 weighted anatomical scan (MP-RAGE; voxel resolution: 1x 1 x 1 mm; FOV: 256 x 224 mm; GRAPPA acquisition with an acceleration factor of 2; TR: 2700 ms, inversion time (TI), 1020 ms; FA: 7°).

Data Analysis

Data analysis was performed using BrainVoyager QX 2.1 (Brain Innovation) and custom software written in MATLAB (Mathworks). Data recorded from participant 12 were excluded from the analysis because of several abrupt head movements, as was evident from the first derivative of the 3D motion correction parameters.

Preprocessing, segmentation, and flattening. To correct for distortions in geometry and intensity in the EPI images, we applied distortion correction on the basis of the PSF data acquired before each EPI scan (Zeng and Constable, 2002). Before further analysis, we removed the first 4 volumes to avoid T1-saturation. Next, we performed 3D motion correction with trilinear interpolation using the first volume as reference followed by slice timing correction with ascending interleaved order. Functional data were temporally high-pass filtered using a cut-off frequency of 3 cycles per run. We applied spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum. Next, we aligned the first volume of each run to the high resolution anatomy. Both functional and anatomical data were transformed into Talairach space using trilinear interpolation.

Definition of Regions of Interest (ROIs). We ran a random effects (RFX) general linear model (GLM) analysis, including the factors adaptation amplitude (small, large),

angular difference between adaptation and test direction (0°, +/- 45°, +/- 90°), and test amplitude (small, large). Each predictor time course was convolved with a dual-gamma hemodynamic impulse response function (Friston et al., 1998). The resulting reference time courses were used to fit the signal time course of each voxel. We also included the first and second derivatives of each predictor time course to be able to model shift and dispersion of the hemodynamic impulse response function, respectively. Furthermore, parameters from 3D motion correction were included in the model as predictors of no interest. To avoid selection of regions of interest (ROIs) biased in favor of our hypothesis on movement selectivity (Kriegeskorte et al., 2009), we functionally selected our ROIs by computing the following contrasts: 1) adaptation trials vs baseline, in order to identify motor areas active during the adaptation trials, 2) test trials "same direction, congruent" versus all remaining test trials, in order to identify areas sensitive to a change in movement direction or test amplitude. Statistical maps were Bonferroni-corrected ($p < .05$) for multiple comparisons.

Statistical analysis. To quantify the effect of the angular difference between adaptation and test directions as well as the effect of test amplitude, we extracted z-transformed beta estimates of the BOLD response for each of the 5 angular differences between adaptation and test direction, separately for the two adaptation and test amplitudes. Next, we computed a 9 (number of ROIs) x 2 (adaptation amplitude small and large) x 2 (test amplitude small and large) x 5 (angular difference between adaptation and test direction: 0°,+/-45°,+/-90°) repeated-measures ANOVA on the extracted beta values. Degrees of freedom were adjusted by the Greenhouse-Geisser procedure when Mauchly's tests indicated violation of sphericity, with corrected p-values denoted as pGG. We corrected the critical p value for the number of ROIs ($p < 0.005$).

3.4. RESULTS

Areas involved during hand reaching movements

Our first aim was to identify regions of interest (ROIs) that were (a) active during adaptation trials ("motor areas"), resulting from the RFX GLM contrast between adaptation versus baseline, and (b) areas that were sensitive to a change in movement direction or amplitude ("change areas"), as revealed by the contrast between test trials that differed from adaptation trials and test trials that were identical to adaptation trials.

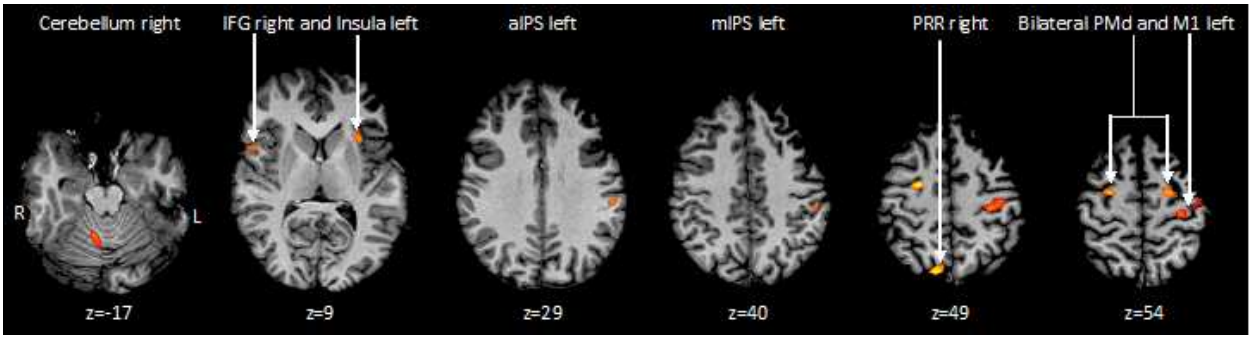


Figure 2 shows that Motor areas consist of the left primary motor area (M1 LH) and the right cerebellum (Cer RH). "Change" areas include the medial aspect of the right posterior parietal cortex (parietal reach region, Connolly et al., 2003), left medial and anterior intraparietal sulcus (mIPS LH and aIPS LH), bilateral dorsal premotor cortex (PMd), right inferior frontal gyrus (IFG RH) and left Insula.

An overview of the Talairach coordinates of these areas can be found in **Table 1**.

Table 1. **Talairach coordinates (mean x, y, and z center of mass; standard deviation in brackets).**

ROIs	x	y	z
cer RH	7.3 (+/- 2.9)	-51 (+/- 3.3)	-17 (+/- 1.9)
IFG RH	51 (+/- 2.5)	-7.6 (+/- 1.4)	6.5 (+/- 2)
insula LH	-29 (+/-1.5)	14 (+/-2.3)	9 (+/-1.3)
M1 LH	-33 (+/- 5.7)	-24 (+/- 3.1)	54 (+/- 5.1)
mIPS LH	-50 (+/-1.3)	-32 (+/- 1.9)	40 (+/- 2.3)
aIPS LH	-54 (+/- 1.9)	-29 (+/- 1.3)	29 (+/- 1.6)
PRR RH	11 (+/- 2.3)	-74 (+/- 1.7)	49 (+/- 2)
PMd RH	25 (+/- 2.8)	-10 (+/- 1.5)	51 (+/- 3)
PMd LH	-20 (+/- 3.2)	-11 (+/-2.4)	58 (+/-2.9)

Table 1: cer*: cerebellum,* ***IFG:*** *inferior frontal gyrus,* ***M1****: primary motor cortex,* ***mIPS:*** *medial intraparietal sulcus,* ***aIPS****: anterior intraparietal sulcus,* ***PRR:*** *parietal reach region,* ***PMd:*** *dorsal premotor cortex;* ***LH:*** *left hemisphere,* ***RH:*** *right hemisphere.*

Most of the regions resulting from the contrasts (M1 LH, CER RH, aIPS, mIPS, bilateral PMd, PRR RH) are identical with those identified in our previous study (Fabbri et al., 2010). In contrast to the regions reported in Study 1 using right hand movements, namely, bilateral aIPS, mIPS and PRR activations we only identified left aIPS, mIPS and right PRR in the current study. Moreover, left Insula and right IFG were active in Study II and not in Study I (see the Discussion section for the interpretation of this different activation maps in Study II compared to Study I).

Directional tuning during congruent movement amplitudes

In our previous study, we identified populations of directionally tuned neurons in several regions of the human visuomotor system: the BOLD signal adapted maximally for movements in the same direction as the adaptation and showed a recovery from adaptation proportional to the angular difference between adaptation and test directions. Here we investigated whether directionally tuned neuronal populations are selective for the direction of the movement only, irrespective of the amplitude necessary to reach the target, or whether these populations are selective to a combination of these parameters, coding reaching direction in relation to the target location. The former case would predict a transfer of adaptation of the BOLD signal from the adapted to the non-adapted movement amplitude. The latter case, instead, would predict no transfer of adaptation of the BOLD signal from the adapted to the non-adapted movement amplitude. To test these alternative hypotheses, we analyzed the BOLD signal extracted from "Motor" and "Change" ROIs and performed an analysis of variance (ANOVA) with the factors ROI (9 levels) x adaptation amplitude (2 levels) x test amplitude (2 levels) x movement direction (5 levels) (see also Materials and Methods). See **Supplementary Table 1** for a full report of the results.

CONGRUENT INCONGRUENT

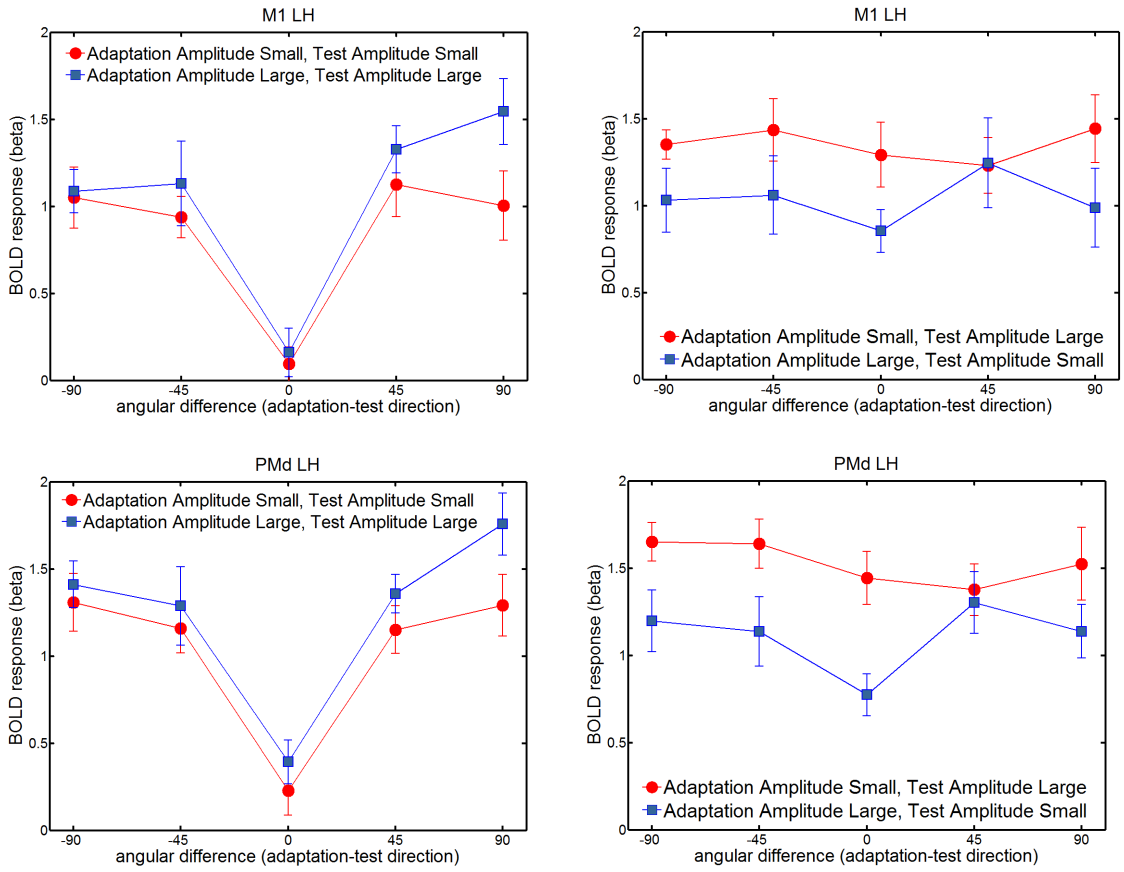


Figure 3 shows the beta estimates as a function of the angular difference between adaptation and test direction during test trials congruent (left column) and incongruent (right column), after adaptation to small (red curve) and large (blue curve) amplitudes in left M1 (upper panel) and left PMd (lower panel).

The left column of **Figure 3** shows the BOLD signal in left M1 and PMd during congruent test trials (red curve: small adaptation and test amplitudes; blue curve: large adaptation and test amplitudes). Both the red curve and the blue curve show directional tuning: the BOLD signal is maximally adapted for movements in the same direction as the adaptation direction (0° angular difference) and shows a recovery from adaptation proportional to the angular difference between adaptation and test direction. These results

extend our previous findings indicating that directionally tuned neurons adapt for amplitudes within a range of 6 and 12 cm.

The right column of **Figure 3** shows that adaptation of the BOLD signal in left M1 and PMd during congruent test trials does not transfer to incongruent test trials. The BOLD during incongruent test trials shows no directional tuning both after adaptation to small amplitude (red curve) and after adaptation to large amplitude (blue curve), as indicated by the two almost flat curves.As can be seen in **Figure 3**, test trials with small movement amplitude show an overall lower BOLD signal in comparison to test trials with large movement amplitude, irrespective of the adaptation amplitude. We will return to this observation in the Discussion.

Taken together, results shown in **Figure 3** indicate that populations of directionally tuned neurons both in left and M1 and PMd do not code for movement direction alone, but rather for a combination of direction and amplitude. The results are very similar for all examined regions (see **Supplementary Figure 1** for plots of each ROI), indicating that neuronal populations that are tuned to specific combinations of movement direction and amplitude can be found in areas beyond M1 and PMd.

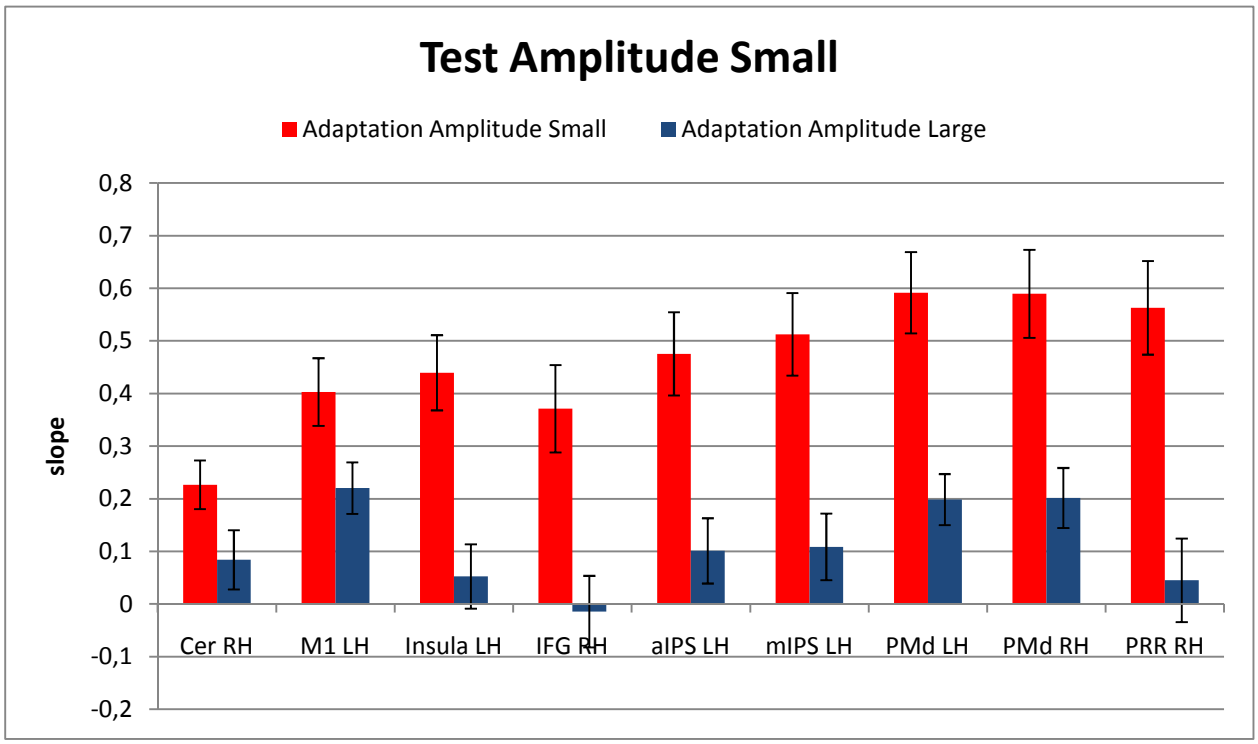
Our observations were supported by the corresponding statistics. The different effects of movement direction on the BOLD signal during congruent and incongruent test trials was supported by the significant three-way interaction between adaptation amplitude x test amplitude x movement direction [$F(4,48)=10.937$, $p<.001$]. Similar patterns were present in all ROIs, as indicated by the non-significant interaction between ROI, adaptation amplitude, test amplitude and movement direction [$F(32,384)=1.203$, $p=.212$]. ANOVAs on beta weights on individual regions, separately for congruent and incongruent test trials, confirmed that the BOLD signal in left M1 and PMd was significantly modulated by

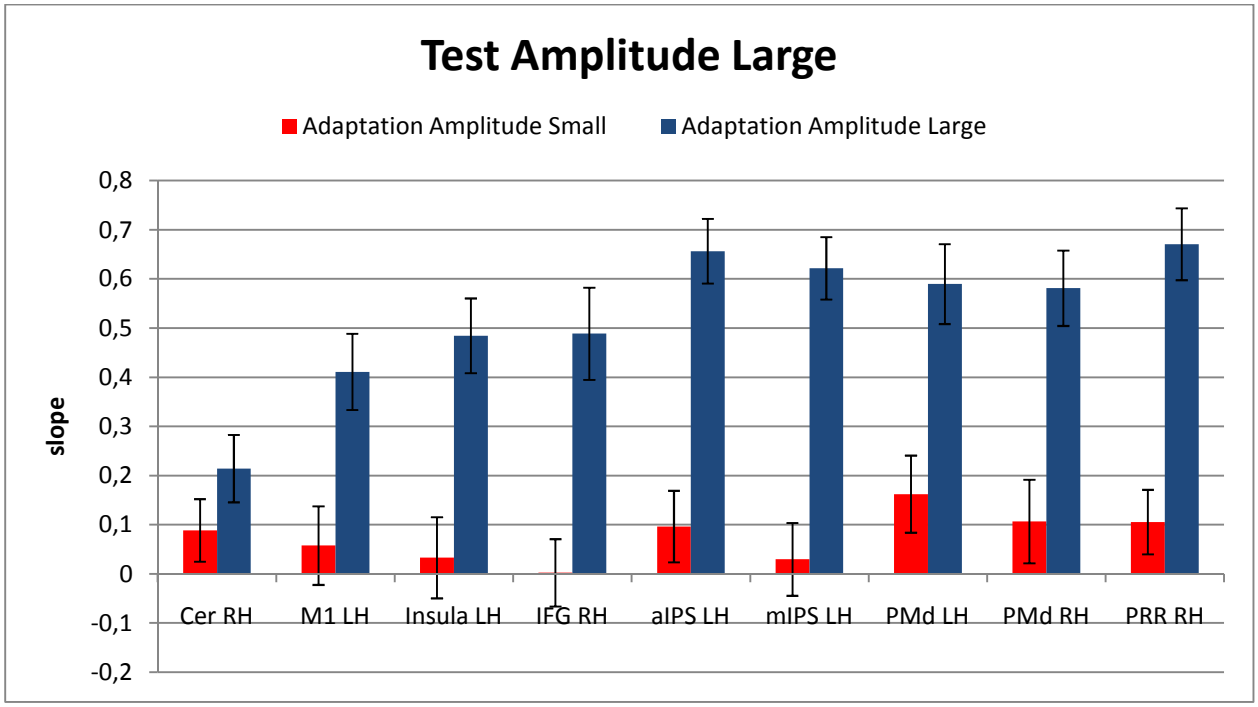
movement direction during congruent test trials [left M1: $F(4,48)= 22.188$, $p<.0001$; left PMd: $F(4,48)=19.944$, $p<.0001$] and not during incongruent test trials [left M1: $F(4,48)=.554$, $p=.697$; left PMd: $F(4,48)=1.533$, $p=.202$], indicating that directional tuning in left M1 and PMd for movements with the same amplitude as adaptation did not transfer to movements with different amplitude. This result was confirmed for all identified regions (see **Supplementary Table 2** for results of ANOVAs in each region).

Different strength of directional tuning across regions

To provide a summary of directional tuning across regions, we measured the steepness of the recovery from adaptation by collapsing the BOLD signal over left (-90° and -45°) and right (+45° and +90°) test directions in each region. To compare the strength of directional selectivity during congruent and incongruent movement amplitudes, we measured the steepness of the recovery from adaptation separately for adaptation and test amplitudes. Next, we estimated the slope of the BOLD signal, as quantified by the z-transformed beta weights extracted from each single ROI, as a function of the angular difference between adaptation and test direction. We reasoned that, just as the width of the tuning function in monkey studies related to the strength of selectivity, the slope of the BOLD signal relates to the strength of directional tuning in our adaptation design (see Fabbri et al., 2010). On the values of the slopes, we computed the ANOVA with factors ROI and adaptation amplitude, separately for small and large test amplitudes.

a





b

Figure 4. Strength of directional tuning in each region during small (red) and large (blue) adaptation amplitudes, separately for small (**a**) and large (**b**) test trials.

Figure 4 shows that the strength of directional tuning clearly differed between congruent and incongruent test trials after both adaptation amplitudes. **Figure 4a** indicates higher directional tuning during small amplitude test trials when the adapted amplitude was small (red) compared to large (blue) in all regions. Similarly, **Figure 4b** indicates higher directional tuning during large amplitude test trials when the adapted amplitude was large (blue) compared to small (red).

These results indicate strong directional tuning during congruent test trials and weak, if any, transfer of directional selectivity from congruent to incongruent test trials. Moreover, directional selectivity observed in congruent test trials is broader in left M1 and steeper in premotor and parietal reach regions, in line with our previous findings (Fabbri et al., 2010).

These observations were supported by the corresponding statistics. The effect of adaptation amplitude was significant both during small [$F(1,12)=24.970$, $p<.0001$] and large amplitude test trials [$F(1,12)=37.223$, $p<.0001$]. Moreover, the strength of directional tuning for congruent test trials differed between regions, as indicated by the significant main effect of ROI [small amplitude test trials, $F(8,96)=4.415$, $pG<.05$; large amplitude test trials, $F(8,96)=5.089$, $p<.0001$] and the interaction between ROI and adaptation amplitude [small amplitude test trials, $F(8,96)=2.578$, $p<.014$; large amplitude test trials, $F(8,96)=4.921$, $pG<.01$]. In particular, during small amplitude test trials the BOLD signal in right cerebellum was significantly different from left PMd [$t(12)=4.637$, $p<.005$] and right PMd [$t(12)=4.199$, $p<.005$]. During large amplitude test trials, the BOLD signal in right cerebellum was significantly different from right PRR [$t(12)=4.744$, $p<.0001$], right PMd [$t(12)=6.724$, $p<.0001$], left PMd [$t(12)=5.546$, $p<.0001$], left mIPS [$t(12)=5.375$, $p<.0001$] and left aIPS [$t(12)=4.277$, $p<.005$] and the BOLD signal in left M1 was significantly different from left PMd [$t(12)=4.231$, $p<.005$]. The BOLD signal

during incongruent test trials did not differ significantly between regions, neither for small nor for large adaptation amplitudes [all $p > .0014$].

3.5. *DISCUSSION*

Directionally tuned neurons sensitive to movement amplitude

In humans, we recently reported evidence for directionally tuned neurons in several areas of the visuomotor system, using fMRI adaptation (Fabbri et al., 2010). Here we investigated the relation between movement direction and amplitude, by measuring the sensitivity of populations of directionally tuned neurons to changes in movement amplitude. We adapted participants to execute reaching movements in one specific direction and amplitude, and tested the recovery from adaptation of the BOLD signal during the execution of movements of varying directions with the same or a different amplitude.

When movement amplitude was kept constant between adaptation and test trials, the BOLD signal both in left M1 and PMd showed clear signs of directional selectivity: adaptation was stronger during test trials with the same direction as the adaptation direction and showed a recovery from adaptation in proportion to the angular difference between adaptation and test direction. This pattern of directional selectivity was measured after adaptation to both small and large amplitudes, indicating that directionally tuned neurons in left M1 and PMd adapt for a range of amplitudes between 6 and 12 cm, in line with our previous studies were adaptation amplitude was 8 cm. The same pattern of results was present in several other regions of the human visuomotor system, in particular right PMd, right cerebellum, left mIPS, left aIPS, right IFG, left Insula, and right PRR.

In our previous study, we used two different adaptation directions (45° and 225°) and observed very similar results regarding directional tuning in bilateral PMd, right cerebellum, bilateral mIPS, aIPS and PRR. We are therefore confident that the results of

the current study, where we used one single adaptation direction (90°), can be extended to other adaptation directions as well, in areas common to the two experiments (left M1, right cerebellum, bilateral PMd, left aIPS and mIPS and right PRR).

It is worth noting that in Study I "change areas" indicated sensitivity to changes in the type of motor act (to press vs. to grasp) or in movement direction, whereas in Study II "change areas" indicated sensitivity to changes either in movement amplitude or in movement direction. Since changes in movement direction were present in both studies, differences in the activation map in Study I and II are related to different sensitivities to the type of motor act in Study I and to movement amplitude in Study II. Activity in right aIPS, mIPS and left PRR in Study I might be related to the involvement of these areas during the execution of the motor act "to grasp" (Study I), in line with evidence of stronger activation in bilateral IPS during grasping compared to reaching (Culham et al., 2003). Instead, activity of the same areas in the hemisphere controlateral to the hand might be related to the execution of the motor act "to press" (both in Study I and Study II). Change areas included right IFG and left Insula only in Study II, indicating that these areas are sensitive to changes in movement amplitude. These areas are reported to be part of a network of regions involved in response inhibition (Hwang et al., 2010), suggesting that their involvement in Study II might be related to the necessity to inhibit the motor act with the adapted movement amplitude.

Selectivity for specific combinations of direction and amplitude

Importantly, the BOLD signal in left M1 and PMd showed directional tuning during movements with the same amplitude as during adaptation (congruent test trials) and no sensitivity to movement direction during movements with an amplitude different from adaptation (incongruent test trials). Similar findings were reported also in all the other

ROIs, including parietal regions. These results suggest that many regions of the human visuomotor system contain populations of neurons where a specific combination of movement direction and amplitude is coded. These findings are in line with results from monkey physiology that reported that the majority of cells in PMd and M1 code for the interaction between direction and amplitude of the movement (Fu et al., 1995; Messier and Kalaska, 2000). Our study reported similar results also for regions beyond M1 and PMd, indicating that the specific combination of movement direction and amplitude is represented in many more regions of the human visuomotor system than previously reported in monkeys. These findings are also in line with behavioral studies that reported that amplitude and direction are not independent, given that they interfere with each other during control of reaching movements (Favilla et al., 1989; Bhat and Sanes, 1998; Sarlegna and Blouin, 2010). In contrast, our data are not compatible with the *Vectorial parametric hypothesis*, which would predict no interaction between direction and amplitude in the human brain, as these two movement parameters should be specified independently (Rosenbaum, 1980; Bock and Eckmiller, 1986; Gordon et al., 1994; Vindras and Viviani, 1998).

Our data suggest that movement direction and amplitude are specified within the same populations of neurons in many regions of the human brain. It should be mentioned that no physiological study reported convincing evidence of the separate channels hypothesis: there is a large number of studies showing selectivity for movement direction, but only a few studies investigated sensitivity for movement amplitude, reporting that only a relatively small number of neurons are sensitive for movement amplitude alone (Riehle and Requin, 1989; Messier and Kalaska, 2000). In the absence of evidence showing the existence of areas selective for movement amplitude alone, it is difficult to explain how

the brain can control reaching movements without using shared neuronal resources for processing of movement amplitude and direction.

Selectivity for a specific combination of direction and amplitude might indicate selectivity for the spatial location of the target. However, if the brain was coding the representation of a point in space, directional selectivity in the identified regions should be invariant to changes in other parameters of the movement, like trajectory or type of reaching. In our previous experiment we reported that directionally tuned neurons in these regions were sensitive to the type of motor act, indicating the representation of movement programming and not simply of the spatial location of the target (Fabbri et al., 2010). For this reason, our results more likely indicate that we are measuring a motor act toward that spatial location.

Lower BOLD signal during small movement amplitude

The BOLD signal during small amplitude test trials was significantly lower than during large amplitude test trials both in congruent and incongruent conditions. One possible reason for this finding is that small amplitude movements require less activation because they were executed with lower speed. It is reported that directionally tuned neurons in M1 and PMd are sensitive to movement speed. In particular, speed acts as a gain factor of the directional tuning function, increasing discharge activity with increasing speed (Moran and Schwartz, 1999). It is worth to mention that in our paradigm we had a fixed and limited amount of time for movement execution (2 secs) so that large amplitude movements might have been executed faster than small amplitude movements, leading to a co-variation of amplitude and speed. Although we did not measure movement speed during execution of the task and, therefore, we cannot be sure that all movements with

large amplitudes were executed faster than all movements with small amplitude, it is possible that our results are due to a combination of movement amplitude and speed. This sensitivity might be the reason for the lower BOLD signal during small test trials after both small and large adaptation amplitudes.

Underlying neurophysiology of the adapted BOLD signal

The absence of a transfer of adaptation from the adapted to the non-adapted amplitude indicates that directionally tuned neurons are sensitive to the amplitude of the movement. This pattern of results is in line with monkey findings that report a sizable number of cells in PMd and M1 that code for the interaction between direction and amplitude during movement execution (Fu et al., 1995; Messier and Kalaska, 2000). Messier and Kalaska (Messier and Kalaska, 2000) reported that a sizeble number of cells showed a main effect of direction alone in different behavioral epochs of a trial. In particular, the percentage of cells decreased from 59% in the epoch when the cue appeared to 35% in the epoch of movement execution. In contrast, very few cells (2-4%) showed a main effect of movement direction only in a given epoch. With our paradigm, it is not possible to distinguish between the BOLD signal during different movement epochs, so we cannot test the existence of neuronal populations that code movement direction only and amplitude only during the movement planning phase, and not during the movement execution phase.

Since our technique measures the average activity of neuronal populations within a voxel, we cannot exclude the existence of small populations of neurons within voxels that code for movement direction only without changing its average activity in relation to movement amplitude.

To summarize, we do not exclude the existence of neurons that code for movement direction or movement amplitude only, but our data suggest that the majority of neuronal populations within our ROIs are sensitive to a combination of movement direction and amplitude. Our study thus extends data from monkey studies to the human brain by showing that the execution of reaching movements requires the involvement of neuronal populations sensitive for a combination of direction and amplitude.

3.6. CONCLUSIONS

Our results indicate that information about direction and amplitude interact both in parietal and frontal areas of the human visuomotor system, suggesting that these regions are involved in the execution of motor commands containing a specific combination of movement direction and amplitude. These findings are in line with behavioral results that report an interaction between direction and amplitude as well as with neurophysiological studies that indicate that these movement parameters share common neuronal substrates. Our data might provide important information for models of the motor control that hypothesize that direction and amplitude are planned by distinct neuronal populations.

Chapter 4

GENERAL DISCUSSION

To execute reaching movements, our brain needs to compute the information about movement direction and amplitude. In the three experiments presented in this thesis we investigated where and how these movement parameters are represented in the human brain. In particular, we investigated which areas in the human brain contain populations of neurons sensitive to movement direction, and to which degree directional selectivity is sensitive to movement amplitude.

4.1. SUMMARY OF PRINCIPAL EXPERIMENTAL FINDINGS

The aim of **Study I** was twofold. First, we wanted to identify areas in the human visuomotor system that contain directionally tuned neuronal populations. Second, we wanted to measure to what extent directionally tuned neuronal populations are sensitive to different types of motor acts (to press vs. to grasp). Our results indicated that several areas in frontal and parietal regions contain populations of neurons selective for movement direction.

We identified a gradient of directional selectivity that was broader in M1, controlateral to the hand, and in cerebellum, ipsilateral to the hand, and steeper in bilateral PMd and right PRR. Furthermore, activity in these regions was modulated by the type of motor act with

the strongest modulation in M1 and the weakest effect in right PRR. This finding was similar for left and right hand movements.

The aim of **Study II (Experiment 3)** was to investigate the degree to which directionally tuned neurons are sensitive to movement amplitude. We found that in many areas of the human visuomotor system, similar to those reported in Study I, populations of neurons were sensitive to movement direction, both with small and large adaptation amplitude. Importantly, adaptation measured during test trials was restricted to movements with the adapted amplitude, indicating that directionally tuned regions are selective for a specific combination of direction and amplitude.

4.2. SUMMARY OF THEORETICAL IMPLICATIONS ACROSS THE TWO STUDIES

Tuning curves for hand movement direction in the human brain

All three experiments revealed directional tuning in many areas of the fronto-parietal network responsible for the control of reaching. Despite of differences in the side of the effector (right vs. left hand) and the task (change in the motor act vs. change in movement amplitude) in all three experiments we reported directional tuning in left M1, right cerebellum, left aIPS and mIPS and right PRR. The recruitment of an extensive network of areas in the processing of movement direction indicates that the control of this parameter is important to execute reaching movements in humans. This finding extends previous knowledge of directional selectivity in human M1 (Eisenberg et al., 2010) to several regions of the visuomotor system.

Our findings are in line with neurophysiological studies that showed directional tuning in similar regions of the monkey brain: M1 (Georgopoulos et al., 1982), PMd (Caminiti et al., 1991), cerebellum (Fortier et al., 1989), and area 5 (Kalaska et al., 1983). Our results support similarities between humans and monkeys in the representation of reaching movements, in particular for the direction component (Caminiti et al., 2010).

The strength of directional selectivity changed between regions, with broader directional selectivity in M1 and cerebellum and higher in PMd and PRR. This finding was not expected on the basis of previous studies in monkeys. However, in monkey studies the recorded activity of neurons is usually restricted to limited areas and the comparison between neuronal selectivity of different areas is often based on results obtained with different experimental paradigms. fMRI adaptation, instead, allows to measure the activity of different areas at the same time under the same experimental conditions. This advantage allowed us to indentify a gradient of directional selectivity between areas not reported in monkey studies. Although results from monkey studies already suggested different levels of representation of movement direction from M1 and PMd to area 5, our results extend these findings to other regions indicating a wider network of areas involved in movement direction hierarchy. For the same reason, we were able to extend previous evidence of the interaction between movement direction and amplitude to areas beyond M1 and PMd. Our finding of a gradient of directional selectivity thus demonstrates how fMRI adaptation can be used to not only replicate, but also extend findings from the monkey to the human brain.

In light of the results of Study II, where we reported that directionally tuned neurons are sensitive for the specific movement amplitude (see paragraph “Sensitivity of directional tuning for movement amplitude” for a discussion of these findings), the network of areas reported for directional selectivity in Study I might be better defined as a network that

codes for a specific combination of movement direction and amplitude (e.g. movement trajectory or a displacement of an effector from one specific starting position to the target location).

For the sake of simplicity, from now on I will use the term “directional selectivity” referring to the combination of direction and amplitude information.

Modulation of directional tuning by the type of grasp

As directional selectivity increases, the sensitivity of these neuronal populations for the type of motor act decreases. M1 showed directional selectivity mainly for the adapted motor act (to press), whereas directional selectivity was very weak for the non-adapted motor act (to grasp). These results indicate that M1 contains separate populations of directional selective neurons, each sensitive to a specific type of motor act. These two actions shared common reaching components, but differed in the final part, when the hand interacts with the object. During the movement to press, participants had to stretch their index finger and touch the object, whereas during the movement to grasp, participants had to shape all their fingers around the target object with a whole hand grip. Therefore, the sensitivity for the type of motor act reported in M1 indicates that populations of neurons in this region are sensitive to any of these behavioral aspects that distinguish the two motor acts.

Modulation by the side of the effector

Right PRR showed similar pattern of directional tuning for both types of motor act, both during right (**Experiment 1**) and left (**Experiment 2**) hand movements. This result indicates that directionally tuned populations of neurons in right PRR are similarly sensitive to the type of motor act and insensitive to the side of the effector.

The different levels of sensitivity for changes at the muscle level from parietal to frontal regions are compatible with monkey findings. In particular, the high sensitivity of directionally tuned neurons for the type of motor act is in line with the sensitivity of directional selective neurons in monkey M1 to changes in the arm posture (Scott and Kalaska, 1997), wrist rotation (Kakei et al., 1999), and hand starting location (Caminiti et al., 1990).

The lower level of sensitivity for the type of motor act in right PRR is in line with the low sensitivity for load changes in directionally tuned neurons of monkey area 5 (Kalaska et al., 1983). The abstract representation of movement direction, irrespective of changes of the side of the effector, is compatible with a continuum of limb-dependent an limb-independent neurons in monkey PRR during reaching (Chang et al., 2008).

Sensitivity of directional tuning for movement amplitude

In Study II we found that directionally tuned neurons adapted to a particular movement amplitude (e.g., small) and showed a recovery from adaptation during test trials with a different amplitude (e.g., large). This pattern of results was reported in all directionally tuned regions, indicating that the majority of neuronal populations in these regions code for a specific combination of direction and amplitude, rather than direction only.

The sensitivity reported in all directionally tuned areas for a specific combination of direction and amplitude is in line with results from monkey physiology that reported the existence of cells sensitive to the interaction between direction and amplitude in M1 and PMd (Fu et al., 1995; Messier and Kalaska, 2000), indicating that these two movement parameters share common neuronal substrates. Our results extend monkey findings indicating that these two movement parameters are strictly linked in regions of the reaching network beyond M1 and PMd.

In contrast to the aforementioned studies that reported the existence of neurons selective for movement amplitude only, we did not find evidence for the existence of neuronal populations that are tuned to movement direction only. Since our technique measures the average activity of neuronal populations within a voxel, we cannot exclude the existence of small populations of neurons within voxels that code for movement direction only without changing its average activity in relation to movement amplitude. However, our data suggest that the majority of neuronal populations within the network of frontal and parietal areas we identified code movement direction in combination with movement amplitude.

The role of spatial orienting towards the target location

It could be argued that the selectivity we measured in PRR is due to spatial orienting towards the target location, instead of selectivity for movement direction, also in light of the fact that parietal cortex is involved in spatial orienting (Colby and Goldberg, 1999; Corbetta and Shulman, 2002; Yantis et al., 2002). Though we cannot exclude an involvement of spatial orienting in our tasks, we do not believe spatial orienting alone can fully explain our result since in this case we should have found no modulation by the type of motor act in parietal regions in experiment 1 and 2. Instead, our results are compatible with the role of parietal cortex in translating visual information into the motor plan (Andersen and Buneo, 2002).

Because the combination of direction and amplitude information represents the target location, one might argue that what we measured in Study II was selectivity for the exact spatial location of the target. Similar to our argument above, we do not think that our data can be explained on the basis of sensitivity to the target location alone, since in this case we should have observed similar results irrespective of the type of motor act in

experiment 1 and 2. However, we assume that the coding of movement direction in the areas we examined is dominated by a displacement vector of the effector from the start to the target location. The critical difference is that instead of coding target location, we assume that our data indicate sensitivity for a motor act towards a target location.

A gradient of directional selectivity

The three studies presented in this thesis revealed that, during the execution of reaching movements, the movement direction, referring to a specific combination of direction and amplitude, is widely represented in the distributed parieto-frontal network responsible for reaching in humans. The identification of areas that selectively represent movement direction increases previous knowledge about how the motor program for reaching movements is created in the human brain. Moreover, the gradient of directional selectivity from a more abstract representation in posterior parietal cortex, to a less abstract representation in M1, indicates that movement direction in humans is represented hierarchically, as will be described in the following section.

High-level

At the higher level of this hierarchy, movement direction is represented in parietal areas, where the motor plan is programmed, indicating that information about movement direction is relevant for the computation of the motor plan. By contrast, the specification of the motor plan at the level of parietal areas contains fewer details about the type of motor act, and this representation is invariant to the side of the effector. These results suggest that movement direction at the highest level of the hierarchy is represented at an abstract level, irrespective of lower-level details of the movement.

Low-level

At the other extreme of the hierarchy, M1 represents movement direction in relation with the specific muscles involved in the reaching movement. The representation of movement direction in M1 indicates that this information is represented also in areas responsible for the execution of the motor plan and that, at this level of the hierarchy, the representation of movement direction is combined with the muscular details of the movement.

4.3. PRACTICAL IMPLICATIONS

The identification of the area responsible for the representation of the direction of the intended movement might be useful for BCI studies that aim to guide neuronal prosthesis to execute reaching movements with high accuracy relative to movement direction and limited constrains related to the side of the effector and to the type of motor act (Andersen and Buneo, 2002). Hochberg and collaborators (2006) showed that the neuronal activity in area M1 of a paraplegic patient can be successfully decoded and translated into useful motor commands. Since M1 is reported to undergo degradation in paralyzed patients (Hains et al., 2003; Wrigley et al., 2009), the pattern reported in right PRR might be useful for BCI studies that aim to record information about movement direction in areas more closely linked to the visual system (Andersen and Buneo, 2002).

4.4. FUTURE DEVELOPMENTS

One of the most exciting findings of the studies reported in this thesis is that movement direction is processed at different level of abstractness across regions. Right PRR revealed to contain neuronal populations that process the information about movement direction similarly during reach-to-press and reach-to-grasp movements. Moreover, this

region showed similar patterns for both right and left hand movements. Finally, right PRR codes for a specific combination of direction and amplitude, indicating the specification of a effector displacement from the start to the target location. Parietal cortex is hypothesized to contain an abstract representation of action, independent of the type of the effector (eyes vs. arm) (Andersen and Buneo, 2002; Cohen and Andersen, 2002). Since movement direction and amplitude are essential parameters not only during reaching but also for saccades, future developments of these studies could investigate how movement direction, indicating a specific combination of direction and amplitude, is represented in PRR for different types of effector (eyes vs. hand). Such information would be relevant for models of motor control that aim to identify how visuomotor transformations are implemented in the human brain.

Because coordinate transformations are assumed to take place during the planning phase, another important aspect to investigate is how movement direction is processed at different phases of directional movements (Andersen and Buneo, 2002; Beurze et al., 2007, 2009). A recent neurophysiological study reported that the activity of cells in PRR allows to predict the direction of the planned reaching, whereas activity of cells in LIP allows to predict the direction of the planned saccade movement (Quian Quiroga et al., 2006). It would be interesting to test selectivity for movement direction during planned reaching and saccades also in humans. It is reasonable to hypothesize that movement direction is processed at an abstract level during movement planning when details of the movement (e.g. side of effector or type of effector) are known but not executed. This issue can be investigated by separating the movement planning and execution phases in an fMRI experiment.

Finally, to better characterize the role of different areas of the hierarchy during the execution of reaching movements, transcranial magnetic stimulation (TMS) could be

applied to different areas (e.g. PRR and M1). The TMS pulse would be delivered at different time intervals between the instruction and the execution phase while the kinematics of the reaching movements (e.g., latency of the response, curvature, total movement time, precision of the final reaching position with respect to target location) is recorded. The different effects of the TMS pulse on movement kinematics would allow to identify the role of different areas on different aspects of the planning and/ or execution of directional movements.

4.5. *CONCLUSIONS*

Research that investigated how humans execute reaching movements mainly focused on reach-to-grasp actions and, consequently, on the role of visual target in activating areas selective to the specific type of grasp (Castiello, 2005; Castiello and Begliomini, 2008). In this thesis, I focused on the neural basis of reaching. In particular, I investigated the processing of the movement parameter studied most frequently in the monkey brain, i.e. movement direction. The results suggest that movement direction is represented hierarchically in the human brain from a more abstract level in posterior parietal cortex to a less abstract level in M1. Moreover, our results indicate that the majority of neuronal populations in frontal and parietal regions represent movement direction strictly related to the representation of movement amplitude. Our studies thus provide important information about the representation of reaching movements in humans, by showing that a distributed network of areas is involved in the transformation of information about movement direction and amplitude from an abstract representation to the specific pattern of muscle activity.

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SUPPLEMENTAL MATERIALS

6.1. SUPPLEMENTAL MATERIALS STUDY I

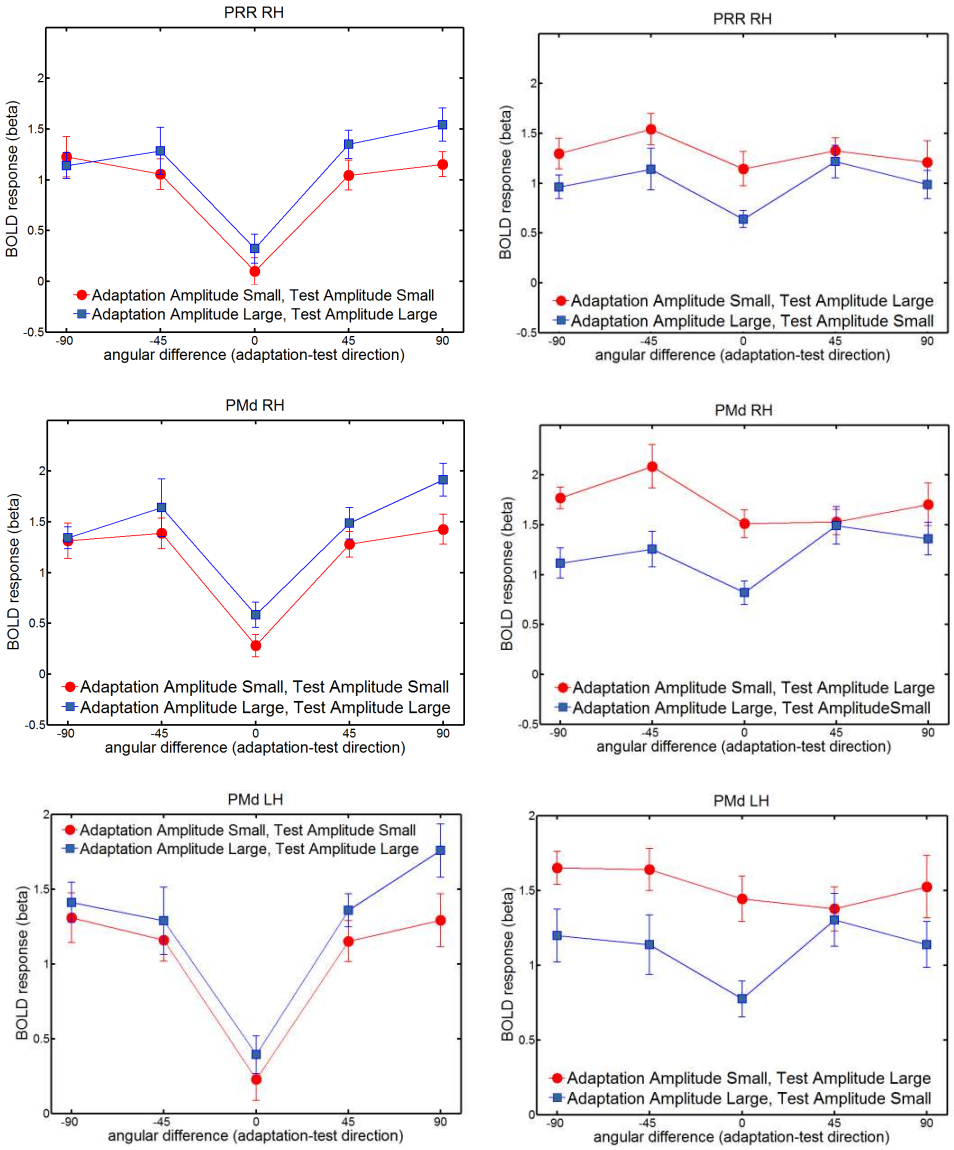
SUPPLEMENTARY TABLE 1
ANOVA on the effect of hemisphere on directional tuning

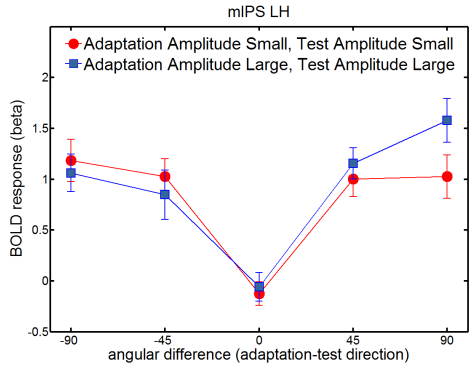
	Experiment 1		Experiment 2	
Type of motor act	F(1,12)	p	F(1,12)	p
	25,742	<0,0001	24,420	<0,0001
ROI	F(3,36)	p	F(1,12)	p
	19,307	<0,0001	5,810	0,033
Hemisphere	F(1,12)	p	F(1,12)	p
	9,458	0,010	12,797	0,004
Type of motor act x ROI	F(3,36)	p	F(1,12)	p
	2,085	0,119	0,129	0,725
Type of motor act x Hemisphere	F(1,12)	p	F(1,12)	p
	9,173	0,010	0,499	0,494
ROI x Hemisphere	F(3,26)	p	F(1,12)	p
	1,698	0,185	0,364	0,558
Type of motor act x ROI x Hemisphere	F(3,36)	p	F(1,12)	p
	5,240	0,004	4,177	0,064

6.2. SUPPLEMENTAL MATERIALS STUDY II

SUPPLEMENTARY FIGURE 1shows the beta estimates as a function of the angular difference between adaptation and test direction during test trials congruent (left column) and incongruent (right column), after small (red curve) and large (blue curve) adaptation amplitudes in each ROI.

CONGRUENT INCONGRUENT

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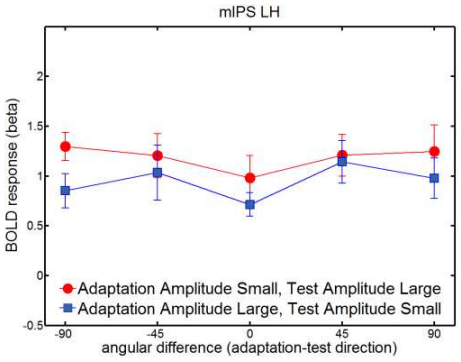
Adaptation Amplitude Large, Test Amplitude Large
BOLD response (beta)
angular difference (adaptation-test direction)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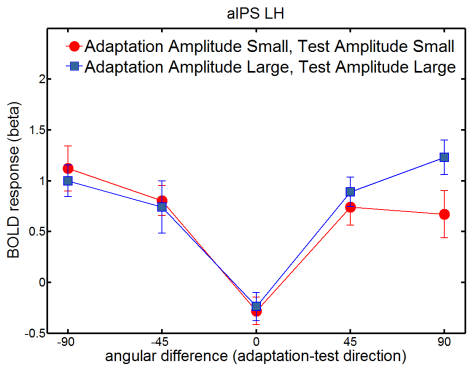
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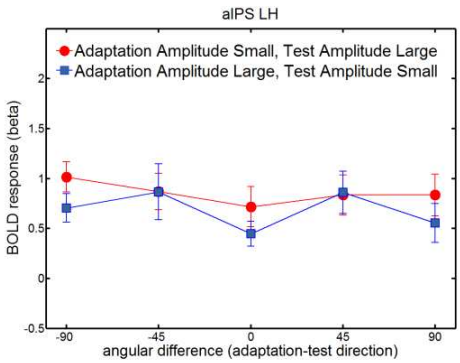
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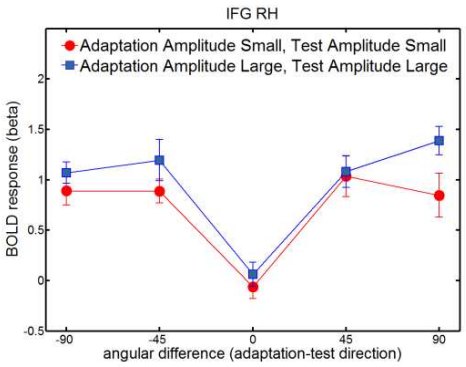
angular difference (adaptation-test direction)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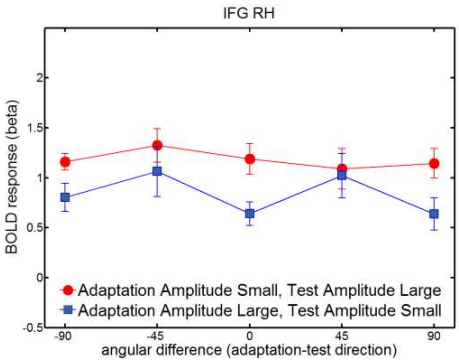
angular difference (adaptation-test direction)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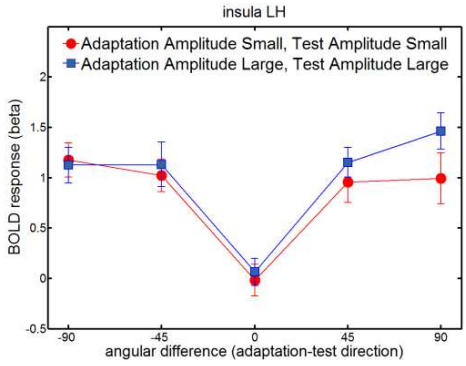
angular difference (adaptation-test direction)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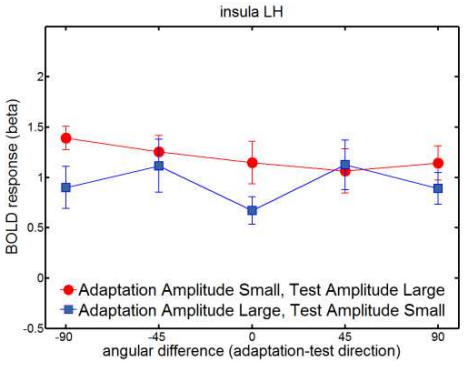
BOLD response (beta)
angular difference (adaptation-test direction)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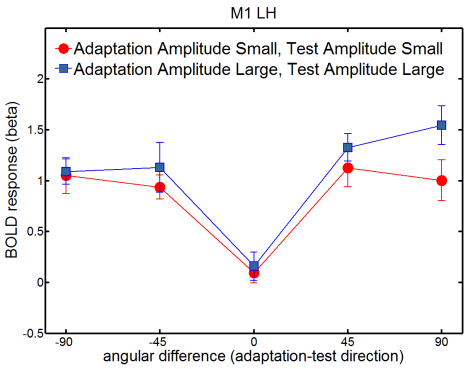
BOLD response (beta)
angular difference (adaptation-test direction)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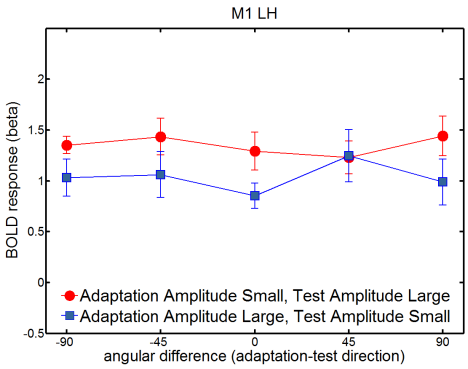
Adaptation Amplitude Large, Test Amplitude Large
BOLD response (beta)
angular difference (adaptation-test direction)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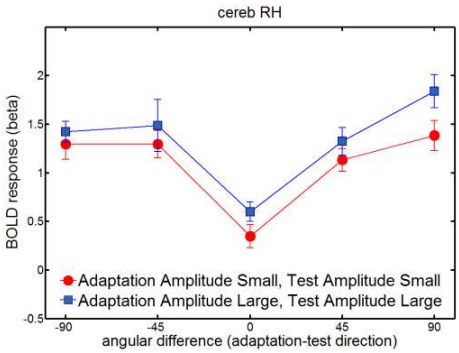
angular difference (adaptation-test direction)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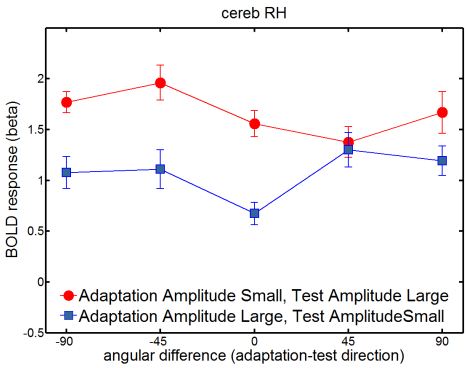
Adaptation Amplitude Large, Test Amplitude Large
BOLD response (beta)
angular difference (adaptation-test direction)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BOLD response (beta)
angular difference (adaptation-test direction)

SUPPLEMENTARY TABLE 1
Results of the ANOVA on beta weights from each region

	F	p
ROI	F(8,96) = 9.617	<.001
adaptation amplitude	F(1,12) = 2.519	.138
test amplitude	F(1,12)=32.563	<.001
movement direction	F(4,48)=18.707	<.001
ROI x adaptation amplitude	F(8,96)=1.484	.225
ROI x test amplitude	F(8,96)=5.557	<.005
adaptation amplitude x test amplitude	F(1,12)=14.566	<.005
ROI x adaptation amplitude x test amplitude	F(8,96)=1.540	.223
ROI x movement direction	F(32,384)=2.267	<.001
adaptation amplitude x movement direction	F(4,48)=1.229	.311
ROI x adaptation amplitude x movement direction	F(32,384)=1.219	.196
test amplitude x movement direction	F(4,48)=1.005	.414
ROI x test amplitude x movement direction	F(32,384)=2.059	<.005
adaptation amplitude x test amplitude x movement direction	F(4,48)=10.937	<.001
ROI x adaptation amplitude x test amplitude x movement direction	F(4,48)=1.203	.212

SUPPLEMENTARY TABLE 2

Results of the ANOVA on beta weights in each region, separately for congruent (left part) and incongruent (right part) test trials.

	Movement Amplitude		Movement Direction		Movement Amplitude x Movement Direction		Movement Amplitude		Movement Direction		Movement Amplitude x Movement Direction	
	F(1,12)	p	F(4,48)	p	F(4,48)	p	F(1,12)	p	F(4,48)	p	F(4,48)	p
cer RH	11.119	.006	14.910	<.0001	.528	.716	32.121	<.0001	2.409	.062	3.293	.018
M1 LH	12.726	.004	22.188	<.0001	1.083	.376	14.935	.002	.554	.697	.936	.451
IFG RH	11.548	.005	18.763	<.0001	.940	.449	12.542	.004	1.574	.222	.978	.428
PMd RH	12.226	.004	18.366	<.0001	.776	.546	35.245	<.0001	3.282	.019	3.287	.018
PRR RH	5.133	.043	21.989	<.0001	.802	.530	11.340	.006	3.072	.025	.633	.641
PMd LH	8.732	.012	19.944	<.0001	.703	.593	17.295	.001	1.533	.202	1.202	.322
Insula LH	4.200	.063	21.141	<.0001	1.094	.370	9.637	.009	1.100	.367	1.334	.271
mIPS LH	1.782	.207	29.951	<.0001	2.547	.051	5.179	.042	1.536	.207	.449	.773
aIPS LH	3.220	.098	25.995	<.0001	1.642	.179	1.924	.191	1.742	.156	.601	.664