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**Distributed sensitivity for movement amplitude
in directionally-tuned neuronal populations**

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Running head: Sensitivity for movement amplitude

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25 **Abstract**

26 Neurons in macaque primary motor cortex (M1) and dorsal premotor cortex (PMd) are
27 tuned to movement direction. In humans, neuronal populations tuned to movement
28 direction have recently been described using multi-voxel pattern analysis and functional
29 magnetic resonance imaging (fMRI) adaptation. It is unclear, however, to what extent
30 directionally-tuned neuronal populations are sensitive to movement amplitude. Here we
31 used fMRI adaptation to determine whether directionally-tuned neuronal populations are
32 modulated by movement amplitude. In different blocks, participants were adapted to
33 small or large amplitude hand reaching movements. On occasional test trials, we
34 parametrically varied the angular difference between adaptation and test direction and the
35 congruency between adapted and tested amplitude (same or different). We predicted that
36 the blood oxygen level dependent (BOLD) signal in directionally-tuned regions should be
37 adapted in proportion to the angular difference between adaptation and test direction.
38 Directionally-tuned regions insensitive to movement amplitude should show a transfer of
39 adaptation from the adapted to the non-adapted amplitude. In contrast, regions sensitive
40 to the specific combination of movement direction and amplitude should show directional
41 tuning only for the adapted amplitude. We identified a network of parietal and frontal
42 regions tuned to movement direction. We found that parietal areas contain neuronal
43 populations sensitive to specific combinations of movement direction and amplitude,
44 while frontal areas show transfer from the adapted to the non-adapted amplitude during
45 small amplitude movements after adaptation to large amplitude, but not vice versa. Our

46 results thus imply different processing of movement amplitude in directionally tuned
47 frontal and parietal areas.

48 **Keywords:** directional tuning, fMRI adaptation, movement direction, movement extent

49 **Introduction**

50 To be able to reach objects, both movement direction and amplitude need to be specified.
51 An extensive literature from monkey physiology reported directional tuning in many
52 regions of the monkey brain (Caminiti et al. 1991; Fortier et al. 1989; Georgopoulos et al.
53 1982; Kakei et al. 2001; Kalaska et al. 1983).

54 Less is known about the representation of movement amplitude. Neurophysiological
55 studies suggest that many neurons in M1 and PMd are sensitive to both movement
56 direction and amplitude, but only small proportions of cells seem to be sensitive to
57 movement amplitude alone (Fu et al. 1995; Fu et al. 1993; Kurata 1993; Messier and
58 Kalaska 2000; Riehle and Requin 1989). Moreover, it has been suggested that the
59 importance of direction and amplitude varies with time, with sensitivity to movement
60 amplitude increasing the closer it gets to the execution of the movement (Messier and
61 Kalaska 2000). It is unknown, however, whether directionally-tuned areas beyond M1
62 and PMd are sensitive to movement amplitude, and if so, whether there are qualitative
63 differences between these regions.

64 In humans, many neuroimaging studies investigated the neuronal basis of reaching
65 movements (Cavina-Pratesi et al. 2010; Connolly et al. 2007; Culham et al. 2003;
66 Desmurget et al. 2001; Filimon et al. 2007; Frey et al. 2005). Both parietal (Fernandez-
67 Ruiz et al. 2007; Van Der Werf et al. 2010) and frontal areas (Beurze et al. 2009) have

68 been shown to be sensitive to the difference between movements directed in ipsi- versus
69 contralateral space. It is unclear, however, if these results reflect a more general
70 preference for movements directed towards the space contralateral to the hand, or if these
71 areas contain neuronal populations that are tuned to movement direction

72 In humans, the representation of movement direction and amplitude are difficult to
73 examine due to the limited spatial resolution of non-invasive techniques such as
74 functional magnetic resonance imaging (fMRI). With the emergence of more
75 sophisticated methods such as fMRI-Adaptation (Grill-Spector and Malach 2001) and
76 multi-voxel pattern analysis (Haxby et al. 2001), sensitivity to movement direction in the
77 human motor system has recently been demonstrated in M1 (Eisenberg et al. 2010) as
78 well as in several additional premotor and parietal areas (Fabbri et al. 2010). It is
79 unknown, however, whether neuronal populations in these areas are sensitive to
80 movement direction only, irrespective of movement amplitude, or whether they are tuned
81 to specific combinations of movement direction and amplitude.

82 Here we address this question using an fMRI adaptation paradigm similar to our previous
83 study (Fabbri et al. 2010). We instructed participants to execute reaching movements
84 with a constant direction (90°) and amplitude (6 or 12 cm; see **Figure 1a, b**). After an
85 adaptation sequence of 3 to 8 trials, participants were instructed to execute a test reaching
86 movement that varied with respect to the adapted direction by 0° , $\pm 45^\circ$ or $\pm 90^\circ$

(Figure 1b, c). In half of these test trials, movement amplitude was kept constant (adapt small, test small/ adapt large, test large), while in the other half of the test trials movement amplitude varied (adapt small, test large/ adapt large, test small). We predicted that the BOLD signal within voxels containing directionally-tuned neurons would adapt maximally during movements with 0° angular difference between adaptation and test direction and show a recovery from adaptation in relation to the angular difference between adaptation and test direction, similar to our previous findings (Fabbri et al. 2010). Furthermore we reasoned that neuronal populations that represent movement direction irrespective of movement amplitude should adapt to movement direction both for adapted and non-adapted amplitudes (see Figure 1d). By contrast, within directionally-tuned neuronal populations that are sensitive both to movement direction and amplitude, we should find no transfer of adaptation to movement direction from the adapted to the non-adapted amplitude (see Figure 1e).

<< Add Figure 1 here >>

We identified several areas within the human visuomotor system that showed directional tuning, similar to our previous results. Parietal areas showed no transfer from the adapted to the non-adapted amplitude, suggesting that these neuronal populations are tuned to specific combinations of movement direction and amplitude. Frontal areas, by contrast, showed a partial transfer from the adapted to the non-adapted amplitude when

106 participants were adapted to the large amplitude and tested with the small amplitude, but
107 not vice versa. We discuss several alternative neural mechanisms that might underlie this
108 asymmetry.
109

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 1c**). Participants had to execute a center-out reaching task on a device attached to their chest, using their right hand (see **Figure 1a**). 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 (see **Figure 1a**). 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: a red arrow instructed participants to reach towards a target on the near semicircle (small

amplitude); a blue arrow instructed participants to reach towards targets on the far semicircle (large amplitude).

Since we observed no qualitative differences between two different adaptation directions in our previous study (Fabbri et al. 2010), we used one adaptation direction, central ahead (see **Figure 1b**), in the current experiment. In half of the scanning runs, participants were adapted to small amplitude reaching movements; in the other half, they were adapted to large amplitude reaching movements. The sequence of scanning runs was alternated between small and large adaptation amplitudes within participants (e.g. ABAB), and the order was counterbalanced between participants (e.g. participant 1, ABAB vs. participant 2, BABA).

During the adaptation sequence, the same direction was repeated from 3 to 8 trials in order to reduce predictability of test trial occurrence. After each sequence of adaptation trials, a test trial was presented (**Figure 1c**). During test trials, we parametrically varied the angular difference between adaptation and test directions (0° , $\pm 45^\circ$, $\pm 90^\circ$) as well as movement amplitude (small, large) (see **Figure 1b**).

To ensure that any signs of directional sensitivity are due to adaptation 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 0.51° to 1.51° in steps of 0.25° . The x- and y- center coordinates of the arrow were jittered in a range of $\pm 0.07^\circ$ in steps of 0.035° .

152 Stimuli were back-projected onto a screen by a liquid-crystal projector at a frame rate of
153 60 Hz and a screen resolution of 1,280 x 1,024 pixels (mean luminance: 109 cd/m²).
154 Participants viewed the stimuli binocularly through a mirror above the head coil. The
155 screen was visible as a rectangular aperture of 17.5 x 14.3 degrees.

156 Visual stimulation was controlled by ASF (Schwarzbach 2011) based on the MATLAB
157 Psychtoolbox-3 for Windows (Brainard 1997; Pelli 1997).

158 **Instructions and Training**

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

168 **fMRI Adaptation Design**

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

In each run, test trials with angular difference $\pm 45^\circ$ and $\pm 90^\circ$ were repeated once for each test amplitude (small, large). Since we initially intended to collapse across test directions to the left (-) and right (+) of the adaptation direction in the analysis, we had two repetitions for each absolute angular difference: 45° and 90° for both test amplitudes. In order to have the same number of repetitions for each test direction, test trials with 0° angular difference were repeated twice for each test amplitude. Thus, there were 6 test trials for each test amplitude, for a total of 12 test trials per run.

There were 3 to 8 adaptation trials between two successive test trials, resulting in 6 different adaptation intervals, amounting to 33 ($3+4+5+6+7+8$) adaptation trials. Each adaptation interval was repeated twice resulting in 12 adaptation intervals and 66 adaptation trials per run. The number of adaptation trials between two successive test trials was randomly assigned to each condition.

To minimize muscle fatigue 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 run. In one half of the run, each test direction was repeated once, with the exception of 0° angular difference, which was repeated twice, for a total of 6 test trials. Each test direction was paired with one test amplitude in one half of the run and with the other test amplitude in the other half of the run. Since both test amplitudes appeared in each half run, half of the test directions were paired with one test amplitude and the other directions were paired

with the other test amplitude. The assignment was reversed in the other half run. The only exception was 0° angular difference, which was paired with both test amplitudes in each half run.

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 co-register 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 one participant 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 as well as linear trend removal. The time course of each voxel was normalized to reflect percent signal change using the following formula:

$$Y_{\text{normalized}} = 100 + ((Y - \mu) / \mu) \times 100,$$

where Y equals the observed time course of a single voxel, and μ equals the mean of the observed time course of that voxel.

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). To identify our regions of interest, we ran a massive univariate random effects (RFX) general linear model (GLM) analysis. In brief, for each voxel the GLM analysis of fMRI data is carried out to fit a model for that voxel's predicted time course. The predicted time course is based on the timing of the experimental conditions and the expected shape of the hemodynamic response function. The basic formula for this regression analysis is given by

$$\mathbf{y} = \boldsymbol{\beta}\mathbf{X} + \boldsymbol{\varepsilon},$$

where $\mathbf{y}$ is the observed time course of a single voxel, $\mathbf{X}$ is the design matrix with the different predictors, and $\boldsymbol{\beta}$ is a vector of the to be estimated weights for each of the predictors, and $\boldsymbol{\varepsilon}$ is the residual noise in the data. The GLM finds those weights that minimize the residual error.

To model our experimental conditions, we included the factors adaptation amplitude (small, large), angular difference between adaptation and test direction (0°, +/- 45°, +/- 90°), and test amplitude (small, large). Altogether, this resulted in the following 22 predictors:

adapt small;

adapt large;

249 test small preceded by adapt small, angular difference $-90^{\circ}/-45^{\circ}/0^{\circ}/+45^{\circ}/+90^{\circ}$;
250 test large preceded by adapt small, angular difference $-90^{\circ}/-45^{\circ}/0^{\circ}/+45^{\circ}/+90^{\circ}$;
251 test small preceded by adapt large, angular difference $-90^{\circ}/-45^{\circ}/0^{\circ}/+45^{\circ}/+90^{\circ}$; and
252 test large preceded by adapt large, angular difference $-90^{\circ}/-45^{\circ}/0^{\circ}/+45^{\circ}/+90^{\circ}$.

253 In addition to the predictors for our experimental conditions, we included the first and
254 second derivatives of each predictor time course in order to be able to model shift and
255 dispersion of the hemodynamic impulse response function, respectively. Moreover, six
256 additional parameters resulting from 3D motion correction (x, y, z rotation and
257 translation) were included in the model. The first and second derivatives and the 3D
258 motion correction parameters were included as predictors of no interest.

259 Each predictor time course was convolved with a dual-gamma hemodynamic impulse
260 response function (Friston et al. 1998), and the resulting reference time courses were used
261 to fit the signal time course of each voxel. For each predictor and each voxel, this
262 analysis resulted in one GLM parameter estimate (beta weight) for the amplitude of the
263 BOLD signal. Since the time course of each voxel was normalized to reflect percent
264 signal change, the beta estimates provide an estimate of percent signal change. We
265 submitted the individually estimated beta weights to a second level analysis with
266 participants as a random factor, which yields a random-effects (RFX) analysis.

267 In order to identify areas sensitive to a change in movement direction or test amplitude,
268 and to avoid selection of ROIs biased in favor of our hypothesis on movement selectivity

15

(Kriegeskorte et al. 2009), we functionally selected ROIs by computing the RFX GLM contrast test trials “adapted direction, adapted amplitude” versus all remaining test trials. Statistical maps were corrected for multiple comparisons using a False Discovery Rate (FDR) <.005 with a cluster threshold of 4 voxels.

In order to compare results between different regions, we selected spherical ROIs with a diameter of 5 mm (515 voxels) around the center of gravity of each region using the plugin “Talairach coordinates to VOI” available from BrainInnovation, The Netherlands. The resulting activations were plotted on the anatomy of the MNI Template Brain “Colin 27” (Van Essen 2002).

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 non-standardized beta estimates of the amplitude of the BOLD response resulting from the RFX GLM analysis described above in each ROI for each of the 5 angular differences between adaptation and test direction (-90°, -45°, 0°, +45°, +90°), separately for the two adaptation and test amplitudes. Next, we submitted these beta estimates to a 2 (Adaptation Amplitude) x 2 (Test Amplitude) x 5 (Angular Difference Between Adaptation and Test Direction) repeated-measures ANOVA, separately for each ROI. To examine directional tuning separately for the two adaptation amplitudes, we conducted two additional ANOVAs with factors Test Amplitude and Angular Difference, separately for small and large adaptation amplitudes. Finally, to quantify directional tuning, we

carried out complex contrasts for the factor Angular Difference [2 1 -6 1 2], separately for each combination of adaptation and test amplitude in each ROI.

Kinematics

To measure spatial and temporal accuracy of the reaching movements, we carried out an additional control experiment with 5 participants outside of the scanner using the same setup and design as during the fMRI session.

Participants were seated 70 cm in front of a screen, with the device placed 30 cm in front of them on a table. They were instructed to position their head in a chin rest. A black plastic surface positioned below the participants' chins prevented vision of the hand and the device.

To examine reaching kinematics, we attached a reflective marker to the tip of the right index finger of the participants and recorded the position of the marker with a movement analysis system (Qualisys) at 250 Hz. The onset of each trial was indicated by a voltage change sent from the stimulation PC via the parallel port to an analog board that was connected to the movement analysis system. In a separate block, we attached markers to the position of each of the 10 target positions and the central start position. These points served as reference for data analysis. After one run of training during which the participants became familiar with the device and the task, we collected data from 12 runs, using the same stimuli and number of repetitions as in the fMRI experiment.

309 To quantify **temporal accuracy**, we computed the time between the onset of the trial and
310 the end of the movement from the target back to the central target position. The latter
311 time point was determined by first computing the time of the peak of the movement
312 velocity towards the target as well as the peak from the target back towards the central
313 target position and then identifying the time point after the second peak at which
314 movement velocity dropped below 10 cm/ s.

315 To quantify **spatial accuracy**, we first computed the peak of the movement towards the
316 target as well as the peak from the target back towards the central target position. We
317 then determined the time of the trough between the two peaks and computed the standard
318 deviation of the horizontal and vertical distance between the index finger and the center
319 coordinate of the target location at the time of the trough (see Brouwer et al. 2000, for a
320 similar approach).

321 To test whether **movement velocity** co-varied with movement amplitude in our
322 experiment, we computed the peak velocity for the movement from the central start
323 position towards the target.

324

Results

Areas involved during hand reaching movements

Our first aim was to identify regions of interest (ROIs) that were sensitive to a change in movement direction or amplitude, as revealed by the contrast between test trials that differed from adaptation trials and test trials that were identical to adaptation trials. Areas that were revealed by this contrast are shown in **Figure 2** and consisted of bilateral insula, ventral premotor cortex (PMv), supplementary motor area (SMA), dorsal premotor cortex (PMd), left M1, bilateral inferior parietal lobule (IPL), anterior and posterior intraparietal sulcus (aIPS and pIPS, respectively), right anterior precuneus (aPCu) and bilateral superior parieto-occipital cortex (SPOC). An overview of the Talairach coordinates of these areas can be found in **Table 1**.

<< Add Figure 2 here>>

<< Add Table 1 here>>

Sensitivity for movement direction and amplitude

In our previous study, we identified directionally-tuned neuronal populations in several regions of the human visuomotor system: the BOLD signal adapted maximally for movements in the same direction as the adaptation direction and showed a recovery from adaptation in relation to the angular difference between adaptation and test direction (Fabbri et al. 2010). Here we investigated whether directionally-tuned neuronal populations are sensitive to movement amplitude. In particular, we were interested in

measuring the sensitivity for movement amplitude and direction in M1 and PMd, as reported in monkeys, and in other directionally-tuned regions, especially in parietal areas.

Results from frontal regions in the left hemisphere are shown in **Figure 3a**, separately for test trials following adaptation to small (upper row) and large (lower row) amplitude movements as a function of test amplitude (red: small, blue: large) and angular difference between adaptation and test direction. When movement amplitude was kept constant between adaptation and test trials (adapt small, test small; adapt large, test large), we observed the strongest adaptation for the adapted movement direction (angular difference: 0°), with a rebound of the BOLD signal for angular difference of $\pm 45^\circ$, and, to some extent, for angular differences of $\pm 90^\circ$, in line with our previous findings (Fabbri et al. 2010). When participants were adapted to the small amplitude and tested with the large amplitude (upper row, blue curve), tuning curves were essentially flat, indicating no transfer from the adapted to the non-adapted amplitude. When participants were adapted to large amplitude movements and tested with small amplitude movements (lower row, red curve), there were clear signs of directional tuning, indicating a transfer of adaptation from the adapted to the non-adapted amplitude.

Results from parietal regions in the left hemisphere are shown in **Figure 3b**. Similar to the results in frontal regions, parietal areas showed clear signs of directional tuning when adaptation and test amplitudes were kept constant (upper row: adapt small, test small, red curve; lower row: adapt large, test large, blue curve): the BOLD signal was maximally adapted for movements in the same direction as the adaptation direction (0° angular

difference) and showed a recovery from adaptation in relation to the angular difference between adaptation and test direction. By contrast, there is almost no transfer from the adapted to the non-adapted amplitude when adaptation and test amplitudes differed, as indicated by essentially flat tuning curves (upper row: adapt small, test large, blue curve; lower row: adapt large, test small, red curve).

<< Add Figure 3 here >>

The results of the corresponding ROIs in the right hemisphere are shown in **Figure 4**. Results in the right hemisphere essentially reproduce the same pattern observed in the left hemisphere.

<<Add Figure 4 here >>

To quantify our observations we carried out a repeated-measures ANOVA on the beta estimates with the factors Adaptation Amplitude (small, large), Test Amplitude (small, large) and Angular Difference between Adaptation and Test Direction (abbreviated as “Direction” in the following section), separately for each ROI. This analysis revealed a significant interaction between Adaptation Amplitude, Test Amplitude and Direction in each single ROI of the left hemisphere (see results in the section Full Model in **Table 2**). Based on **Figure 3a**, we reasoned that the nature of this 3-way interaction in frontal areas was due to a significant 2-way interaction for the factors Test Amplitude and Direction for small adaptation amplitudes (**Figure 3a**, upper row), and a non-significant 2-way interaction for the factor Test Amplitude and Direction for large adaptation amplitudes

(**Figure 3a**, lower row). The results of the corresponding statistics supported our observations in each of the areas shown in Figure 3a (see results of frontal regions in sections Adapt Small and Adapt Large in **Table 2**). Next, we reasoned that parietal areas (**Figure 3b**) should show a significant 2-way interaction for the factors Test Amplitude and Direction both for small (**Figure 3b**, upper row) and for large (**Figure 3b**, lower row) adaptation amplitudes. The corresponding statistics confirmed these predictions in all areas shown in **Figure 3b** (see results of parietal regions in sections Adapt Small and Adapt Large in **Table 2**), with the exception of pIPS LH, where the 2-way interaction was significant for large, but not for small adaptation amplitudes. Statistical analysis confirmed a similar pattern in the right hemisphere (**Table 3**).

<< Add Table 2 here>>

<< Add Table 3 here>>

Finally, to quantify which areas showed directional tuning, we carried out a complex contrast for the factor direction [2 1 -6 1 2], separately for each combination of adaptation amplitude and test amplitude. We reasoned that areas that show directional tuning should show a significant effect for this contrast when adaptation and test amplitude are identical (adapt small, test small; adapt large, test large). Furthermore we reasoned that those areas showing a transfer of adaptation from large amplitude to small amplitude test movements should also show a significant effect for this contrast. The results of these complex contrasts are visualized in **Figures 3** and **4** (significance level indicated by small asterisks next to the corresponding curve). Both frontal and parietal areas showed significant

directional tuning as revealed by the complex contrast when adaptation and test amplitudes were identical. In frontal areas, directional tuning was also present when participants were adapted to the large amplitude and tested with the small amplitude, but not vice versa. None of the parietal areas showed significant directional tuning when adaptation and test amplitudes differed, except for left SPOC and right aPCu. Note, however, that in contrast to frontal areas, these two regions showed a significant interaction for the factors Test Amplitude and Direction, indicating that the transfer from the adapted to the non-adapted amplitude was weak and qualitatively different from the transfer observed in frontal areas.

Kinematics

Participants performed the task accurately, as indicated by **Figure 5**, which shows the 2D-trajectories of the hand reaching movements of one representative participant during small (**Figure 5a**) and large (**Figure 5b**) amplitude movements. The target movement direction is color-coded. A certain amount of variation around the target location is expected due to the fact that there was no visual feedback. However, as can be seen, both direction and amplitude were chosen correctly in almost every trial.

<< add figure 5 here >>

Figure 6 shows that spatial accuracy differed between conditions, both along the horizontal (**Figure 6a**) and vertical (**Figure 6b**) dimension. In particular, horizontal errors were smaller during small than large amplitude movements and during 0°

compared to other angular differences. Vertical errors were bigger during movements executed after small than large adaptation amplitudes.

<< add figure 6 here >>

For statistical analysis, we submitted the standard deviation of the horizontal and vertical variable error to a 2 (Adaptation Amplitude) x 2 (Test Amplitude) x 5 (Direction) repeated-measures ANOVA. Mean horizontal variable error was 1.38 cm. The horizontal variable error was larger for large in comparison to small amplitude test movements [$F(1, 4) = 12.428$, $p = .024$; small amplitude: 1.1 cm, large amplitude: 1.7 cm]. There was a marginally significant main effect of adaptation amplitude [$F(1,4) = 6.328$, $p = .066$; small amplitude: 1.96 cm; large amplitude: 0.81 cm]. The horizontal variable error varied with movement direction [$F(4, 16) = 5.254$, $p = .007$; $-90^\circ/-45^\circ/0^\circ/+45^\circ/+90^\circ$: 1.9/ 1.2/ 0.5/ 1.5/ 1.8 cm], and was modulated by the interaction between adaptation amplitude and movement direction [$F(4, 16) = 4.829$, $p = .01$]. All remaining interactions and main effects were non-significant (all $p > .1$). Mean vertical variable error was 1.05 cm. Vertical variable error was larger when participants were adapted to small (1.4 cm) in comparison to large (0.6 cm) amplitude movements [$F(1,4) = 31.426$, $p = .005$]. Vertical variable error was modulated by the interaction between adaptation amplitude and direction [$F(4, 16) = 5.358$, $p = .006$]. No other interaction was significant (all $p > .2$).

Finally, we tested whether movement velocity covaried with movement amplitude and direction. **Figure 7** shows that velocity varied with movement amplitude but not with

movement direction: small movements were faster than large movements, similarly for all directions.

<< add figure 7 here >>

We submitted the peak velocity to a 2 (Adaptation Amplitude) x 2 (Test Amplitude) x 5 (Movement Direction) repeated-measures ANOVA. Across conditions, mean peak velocity was 38.96 cm/ s. Large amplitude test trials were faster (45.96 cm/s) than small amplitude test trials (31.95 cm/s) [$F(1, 4) = 45.51, p = .003$]. Likewise, movements were faster when participants were adapted to large (40.05 cm/ s) in comparison to small (37.86 cm/ s) amplitude movements [$F(1, 4) = 8.029, p = .049$]. Peak velocity did not vary with direction [$F(4, 16) = 1.591, p = .225$], and none of the interactions were significant (all $p > .16$).

Discussion

Sensitivity for movement amplitude in directionally-tuned neuronal populations

Using fMRI adaptation, we recently reported evidence for directionally-tuned neurons in several areas of the human visuomotor system (Fabbri et al. 2010). Here we investigated the extent to which directionally-tuned neuronal populations are sensitive to movement amplitude. To this aim, we adapted participants to the execution of reaching movements in one specific direction and amplitude, and measured the recovery from adaptation of the BOLD signal during the execution of movements at varying directions with either the adapted or non-adapted amplitude.

When movement amplitude was kept constant between adaptation and test trials, the BOLD signal in bilateral Insula, PMv, SMA, PMd, left M1, bilateral IPL, aIPS, pIPS, SPOC and right aPCu showed clear signs of directional selectivity: adaptation was strongest during test trials with 0° angular difference from the adaptation direction and decreased as the angular difference increased, in line with our previous results (Fabbri et al. 2010). This pattern of directional selectivity was similar for small (6 cm) and large (12 cm) amplitude movements.

When movement amplitude was varied between adaptation and test trials, parietal areas showed no transfer from the adapted to the non-adapted amplitude. This observation was the same for adaptation to small and adaptation to large amplitude movements. By contrast, we observed a partial transfer from the adapted to the non-adapted amplitude when participants were adapted to the large and tested with the small amplitude in frontal

480 areas. We observed no such transfer when participants were adapted to the small
481 amplitude and tested with large amplitude movements.

482 Messier and Kalaska (2000) reported that a sizeable number of PMd cells showed a main
483 effect of direction alone in different behavioral epochs of a trial, in an instructed-delay
484 task in which prior information about direction and amplitude had to be memorized
485 before movement initiation. In particular, the percentage of cells sensitive to direction
486 only decreased from 59% in the epoch when the information was given, to 35% in the
487 epoch of movement execution. In contrast, very few cells (2-4%) showed a main effect of
488 only movement amplitude in a given epoch. Our paradigm does not allow distinguishing
489 between different epochs of a trial, so we cannot rule out that there exist neuronal
490 populations that code only movement direction during the movement planning phase, and
491 not during the movement execution phase. However, if the importance of movement
492 amplitude were to increase over the course of planning and executing a movement, one
493 might assume that the representation of movement amplitude would differ between
494 parietal areas, which are mainly involved with the planning of the movement (Andersen
495 and Buneo 2002; Andersen et al. 1997; Kalaska et al. 1997), and frontal areas, which are
496 closer to the execution of the movement. In line with this view, our results suggest
497 different organizing principles between frontal and parietal regions, as will be discussed
498 in the following sections.

Topographic representations in parietal cortex

We observed that directionally-tuned parietal regions show no transfer from the adapted to the non-adapted amplitude, suggesting that these areas are sensitive to specific combinations of movement direction and amplitude. Several authors have argued for a posterior-to-anterior gradient in parietal cortex, with more posterior regions such as pIPS and SPOC more sensitive to visual aspects of reaching, grasping or the visual location of targets, and anterior regions such as mIPS and aPCu involved in the encoding of motor aspects of actions such as proprioception (e.g. Filimon et al. 2009; Stark and Zohary 2008). In line with this view, we recently demonstrated that the modulation of directional tuning by the type of motor act increases from posterior to anterior regions (Fabbri et al. 2010). A similar gradient is likely to underlie the representation of movement direction and amplitude, with posterior regions encoding the spatial location of the endpoint of the movement, and anterior regions involved in the encoding of the displacement of effectors from the start to the goal position in spatial coordinates.

The representation of movement direction and amplitude in frontal areas

In contrast to parietal regions, frontal regions showed a partial transfer of adaptation to movement direction from the large to the small amplitude, but not vice versa. Several mechanisms might underlie this finding:

- i. Let us assume that one of the organizing principles in frontal regions is an arrangement in motor maps coding both movement direction and amplitude, similar to the motor maps described in the superior colliculus (Lee et al. 1988)

(see **Figure 8a**). If participants are adapted to large amplitude movements, it is possible that the entire range of amplitudes from the start to the end position would be activated (**Figure 8a**, left column). As a result, when participants are tested with a small amplitude movement, we should expect to see transfer since this amplitude was adapted during large amplitude movements. By contrast, no such transfer should occur from the small to the large amplitude movement (**Figure 8a**, right column).

ii. Alternatively, we might assume that the size of motor fields representing the end points of movements on these motor maps increase with increasing movement amplitude (see **Figure 8b**), in line with the fact that the precision of reaching movements tend to decrease with movement amplitude. If that were the case, adaptation to small amplitudes would be expected to lead to relatively small transfer to large amplitudes (**Figure 8b**, left column). By contrast, adaptation to large amplitudes would be expected to lead to larger amounts of transfer when followed by small amplitude movements (**Figure 8b**, right column; black circles indicate hypothetical size of motor field for tested movement).

iii. Finally, movement amplitude in frontal, but not in parietal areas, might be coded by discharge rate, with increasing amplitudes leading to larger discharge rates (**Figure 8 c**, upper row). Such an explanation would be in line with neurophysiological studies that reported an increase in firing rates in frontal areas with increasing movement amplitude (Fu et al. 1995; Fu et al. 1993). We assume that adaptation is proportional to the initial strength of activation (**Figure 8 c**,

middle row). Consequently, when participants are adapted to large amplitude movements and tested with small amplitude movements, tuning curves would be expected to be more pronounced in comparison to adaptation to small amplitude movements followed by adaptation to large amplitude movements (**Figure 8 c**, lower row).

<< add figure 8 here>>

Serial correlations in fMRI data

fMRI time courses are correlated from one scan (or time point) to the next (see also Christova et al. 2011). It is therefore not correct to assume that the degrees of freedom (df) are simply the number of scans minus the dfs used in the model; there should be fewer. This inflates the p-values in fixed-effects models (i.e., when model parameters are estimated based on the concatenated data of all participants), and a correction for autocorrelation would be due for statistical inferences pertaining to the group.

However, in order to make population-inferences (as opposed to the group of participants) we performed a hierarchical random effects analysis in which a summary statistic for each subject and voxel was calculated (in our case a beta estimate) (see e.g. Holmes and Friston 1998; Penny et al. 2003). These summary statistics were then submitted to a random effects analysis, looking at the variance between effect sizes as a random effect ($df = \text{number of subjects} - 1$). Accordingly, the p-values of the fixed-effects analysis, which might be inflated because of serial correlations, did not enter this second-level analysis since the critical standard error was based on the difference of

parameter estimates between subjects. As a consequence, any wrong assumption of the p-values of the fixed effects analysis does not affect the results of our random-effects analysis.

Finally, we compared the statistical maps revealed by the contrast “test trials adapted direction, adapted amplitude versus all remaining test trials” with and without correction for serial correlation. Correction for serial correlations was performed within BrainVoyager by computing a RFX GLM without correcting for serial correlations, computing the one-lag autocorrelation [AR(1)] of the residuals, subtracting these from each time course, and recomputing the RFX GLM on the basis of these adjusted time courses. Both the corrected and the non-corrected RFX GLM revealed the same regions, with a slightly wider extent for the corrected in comparison for the non-corrected RFX GLM. In summary, this shows that our results were stable and unbiased.

Possible complicating factors

It is known that movement amplitude co-varies with velocity and that neurons in M1 are sensitive to movement velocity (Moran and Schwartz 1999). Indeed, we measured an increase in movement velocity with increasing movement amplitude in our kinematics experiment. Does this mean that our experiment measured sensitivity to movement speed rather than movement amplitude? If this were the case, we would have expected to have seen an interaction between adaptation and test amplitude, as well as an interaction between adaptation amplitude, test amplitude and movement direction in the kinematic

data. We observed none of these effects. Therefore, differences in movement speed between small and large amplitude movements alone cannot explain our results.

How would a covariation between movement amplitude and speed affect the interpretation of our results? We observed that parietal areas showed no transfer of adaptation to movement direction from the adapted to the non-adapted amplitude, whereas frontal areas showed a partial transfer from large to small amplitudes, but not vice versa. This finding holds irrespective of whether the difference between the adapted and the non-adapted amplitude was introduced by a change in movement amplitude alone, or whether it was introduced by a change in movement amplitude and speed. Further experiments will be required to quantify the sensitivity to amplitude and speed in directionally tuned neuronal populations.

Although we manipulated the visual appearance of the instruction arrows to reduce adaptation for low-level visual features, it could be argued that the direction of the visual instruction alone caused directional tuning. Moreover, direction of the arrow was spatially congruent with the direction of the reaching movement, while the color of the arrow was arbitrarily associated to the amplitude of the reaching movement. To test whether the modality of the instruction could account for our results, we conducted a control experiment (not reported here) where we instructed participants about the direction of the movement following the procedure used in our previous study (Fabbri et al. 2010) but using arbitrary auditory cues (e.g. “A” indicated the central left target). The control experiment identified directional tuning in similar regions as those reported in the

current study, indicating that the results are due to the direction of the reaching movement and not to the visual instructions.

Conclusions

Our results show that sensitivity for movement direction and amplitude is not restricted to PMd and M1, but extends to PMv, SMA, the insula as well as several anterior and posterior parietal regions. Our results suggest that parietal areas represent specific combinations of movement amplitude and direction, while frontal areas show some transfer from the adapted to the non-adapted amplitude. These results provide an important extension of our knowledge about the representation of reaching movements.

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623

624 **Disclosures**

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Figure legends

Figure 1. Paradigm and predictions. **(a)** Participants lay in the scanner with their index finger on the starting position of a device attached to their stomach, and executed small and large amplitude reaching movements on the device. **(b)** On the schematic device is shown the full set of angular differences between adaptation and test directions (0° , $\pm 45^\circ$, $\pm 90^\circ$) for small (red) and large (blue) amplitude movements. **(c)** Visual instructions presented on the screen informed participants about the direction (orientation of the arrow) and amplitude (color of the arrow; red: small amplitude, blue: large amplitude) of the reaching movement. The example shows a sequence consisting of three small amplitude adaptation trials (highlighted by dashed rectangle; adaptation direction: central ahead) followed by a large amplitude test trial (indicated by solid line rectangle) with an angular difference of 45° between adaptation and test direction. **(d)** Directionally-tuned regions insensitive to movement amplitude should show a transfer of adaptation from the adapted to the non-adapted amplitude, as measured by adaptation in relation to the angular difference between adaptation and test directions, for both adapted (red line) and non-adapted (blue line) amplitude test trials. **(e)** Regions sensitive to the specific combination of movement direction and amplitude should show directional tuning only for the adapted amplitude and no transfer to the non-adapted amplitude.

Figure 2. Regions more active during a change in either movement direction or amplitude compared to baseline consist of bilateral insula, ventral premotor (PMv), supplementary motor area (SMA), dorsal premotor (PMd), left M1, bilateral inferior

parietal lobule (IPL), anterior and posterior intraparietal sulcus (aIPS and pIPS, respectively), right anterior precuneus (aPCu) and superior parieto-occipital cortex (SPOC).

Figure 3. fMRI Response (reported as percent signal change) in frontal (a) and parietal (b) regions of the left hemisphere. Results are reported separately for test trials following adaptation to the small (upper row) and the large (lower row) amplitude. Separate lines show the fMRI Response during test trials with small (red) and large (blue) amplitude movements as a function of the angular difference between adaptation and test trial. Asterisks indicate statistical significance of complex contrasts (see Results section for details). *: $p < .05$; **: $p < .01$; ***: $p < .0001$.

Figure 4. fMRI Response (reported as percent signal change) in frontal (a) and parietal (b) regions of the right hemisphere (for labeling conventions see Figure 3).

Figure 5. Trajectories of hand reaching movements for small (a) and large (b) amplitude test trials, for one representative participant, collapsed across the entire length of the experiment. Colors indicate target directions (dark blue: -90° ; light blue: -45° ; green: 0° , yellow: $+45^\circ$, red: 90°). Gray circles mark the positions of the target locations.

Figure 6. Horizontal (a) and vertical (b) error of movements with small (black and dark gray) and large (light gray and white) amplitudes as a function of the angular difference between adaptation and test direction.

Figure 7. Peak velocity (cm/s) of movements with small and large adaptation and test amplitudes as a function of the angular difference between adaptation and test direction (for labeling conventions see Figure 6).

Figure 8. Graphical depiction of three alternative explanations that might underlie the results observed in frontal areas (see text for details). Panels **(a)** and **(b)** illustrate two explanations based on movement direction and amplitude organized as motor maps. Panel **(c)** shows an explanation based on directionally tuned neuronal populations that are up- and down-regulated by movement amplitude. **(a, b)** Movement direction and amplitude are coded as motor maps similar to those described in the superior colliculus (Lee et al. 1988): amplitude is coded along the horizontal and direction along the vertical dimension (upper row: before adaptation, middle row: during adaptation, lower row: during test trials). **(a)** We assume that small amplitude movements lead to adaptation for small amplitude movements that gradually decreases with angular difference between the adapted and neighboring directions (a, middle left panel). When adaptation to small amplitudes is followed by testing with large amplitudes, there is no transfer of adaptation since large amplitudes were not adapted (a, lower left panel; strength of adaptation is coded by gray level, darker gray indicates stronger adaptation; length of black arrow indicates amplitude). By contrast, when participants are adapted to large amplitudes, we assume that the entire range of amplitudes, including small ones, are adapted (a, middle right panel). As a result, testing with small amplitudes shows a transfer of adaptation (a, lower right panel). **(b)** Alternatively, it is possible that the size of motor fields

representing the end points of movements on these motor maps, highlighted by gray discs, increases with movement amplitude. If that were the case, adaptation to small amplitudes (b, middle left panel) would be expected to lead to no or relatively little transfer to the large amplitudes (b, lower left panel; black circle indicates hypothetical size of motor field for tested movement). By contrast, adaptation to large amplitude (b, middle right panel) would be expected to lead to a larger transfer of adaptation when followed by small amplitude movements (b, lower right panel). (c) Explanation based on directionally tuned neuronal populations that are up- and down-regulated by movement amplitude. X-axis represents movement direction, y-axis represents strength of fMRI activation (in arbitrary units) within a hypothetical voxel containing neuronal populations tuned to various different directions. We assume that for small amplitude movements, overall strength of activation is weaker in comparison to large amplitude movements, irrespective of direction (c, upper row). During adaptation, we assume that the strength of activation adapts proportionally to the strength of the signal before adaptation (c, middle row). During large amplitude test trials, we assume that the overall signal increases by a constant factor due to the change from small to large amplitude movements (c, lower left panel). During small amplitude test trials, we assume that the signal decreases by a constant factor due to the change from large to small amplitude movements. The resulting tuning curves are clearly more pronounced for small amplitude test trials (c, lower right panel).

814 **Table legends**

815 **Table 1.** Talairach coordinates of regions of interest shown in Figure 2. PMv, ventral
816 premotor cortex; SMA, supplementary motor area; PMd, dorsal premotor cortex; M1,
817 primary motor cortex; IPL, inferior parietal lobule; aIPS, anterior intraparietal sulcus;
818 aPCu, anterior precuneus; pIPS, posterior intraparietal sulcus; SPOC, superior parieto-
819 occipital cortex. LH: left hemisphere, RH: right hemisphere.

820 **Table 2.** Summary of the statistical analysis of beta estimates as a function of adaptation
821 amplitude, test amplitude and angular difference between adaptation and test direction for
822 ROIs in the left hemisphere. Non-significant effects are highlighted in gray.

823 **Table 3.** Summary of the statistical analysis of beta estimates as a function of adaptation
824 amplitude, test amplitude and angular difference between adaptation and test direction for
825 ROIs in the right hemisphere. Non-significant effects are highlighted in gray.

— central sulcus
 intraparietal sulcus
 --- parieto-occipital sulcus

a

b

	Talairach coordinates		
	x	y	z
insula LH	-33.00	8.00	5.00
insula RH	31.00	6.00	6.00
PMv LH	-48.00	0.00	24.00
PMv RH	41.00	-3.00	36.00
SMA LH	-9.00	-7.00	46.00
SMA RH	8.00	-2.00	50.00
PMd LH	-27.00	-16.00	56.00
PMd RH	24.00	-11.00	53.00
M1 LH	-33.00	-32.00	53.00
IPL LH	-53.00	-33.00	31.00
IPL RH	52.00	-33.00	33.00
aIPS LH	-35.00	-44.00	40.00
aIPS RH	31.00	-49.00	43.00
aPCu RH	11.00	-63.00	53.00
pIPS LH	-18.00	-65.00	52.00
pIPS RH	10.00	-73.00	45.00
SPOC LH	-17.00	-72.00	37.00
SPOC RH	21.00	-73.00	31.00

Table 1

	Full Model		Adapt Small		Adapt Large	
	Interaction Adaptation Amplitude x Test Amplitude x Direction		Interaction Test Amplitude x Direction		Interaction Test Amplitude x Direction	
	F (4, 48)	p	F (4, 48)	p	F (4, 48)	p
M1 LH	2.786	.037	3.869	.008	2.131	.091
PMd LH	4.179	.006	4.355	.004	2.267	.076
insula LH	4.031	.007	2.533	.052	2.467	.057
SMA LH	2.709	.041	4.071	.006	1.147	.346
PMv LH	4.346	.004	3.563	.013	1.869	.131
IPL LH	6.953	<.0001	3.518	.013	5.246	.001
aIPS LH	6.450	<.0001	4.149	.006	3.203	.021
pIPS LH	7.853	<.0001	1.996	.110	5.960	.001
SPOC LH	9.524	<.0001	3.262	.019	4.359	.004

Table 2

	Full Model		Adapt Small		Adapt Large	
	Interaction Adaptation Amplitude x Test Amplitude x Direction		Interaction Test Amplitude x Direction		Interaction Test Amplitude x Direction	
	F (4, 48)	p	F (4, 48)	p	F (4, 48)	p
PMd RH	6.272	<.0001	4.669	.003	1.736	.158
insula RH	2.358	.067	1.797	.145	1.409	.245
SMA RH	3.656	.011	4.035	.007	1.042	.395
PMv RH	2.555	.051	5.461	.001	.189	.943
IPL RH	5.880	.001	3.553	.013	3.051	.026
aIPS RH	7.102	<.0001	5.156	.002	2.634	.045
aPCu RH	7.503	<.0001	5.023	.002	4.068	.006
pIPS RH	6.162	<.0001	2.352	.067	5.131	.002
SPOC RH	5.729	.001	2.856	.033	1.235	.309

Table 3