Preferential Encoding of Movement Amplitude and Speed in the Primary Motor Cortex and Cerebellum

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Abstract: Voluntary movements require control of multiple kinematic parameters, a task carried out by a distributed brain architecture. However, it remains unclear whether regions along the motor system encode single, or rather a mixture of, kinematic parameters during action execution. Here, rapid event-related functional magnetic resonance imaging was used to differentiate brain activity along the motor system during the encoding of movement amplitude, duration, and speed. We present cumulative evidence supporting preferential encoding of kinematic parameters along the motor system, based on blood-oxygenation-level dependent signal recorded in a well-controlled single-joint wrist-flexion task. Whereas activity in the left primary motor cortex (M1) showed preferential encoding of movement amplitude, the anterior lobe of the right cerebellum (primarily lobule V) showed preferential encoding of movement speed. Conversely, activity in the left supplementary motor area (SMA), basal ganglia (putamen), and anterior intraparietal sulcus was not preferentially modulated by any specific parameter. We found no preference in peak activation for duration encoding in any of the tested regions. Electromyographic data was mainly modulated by movement amplitude, restricting the distinction between amplitude and muscle force encoding. Together, these results suggest that during single-joint movements, distinct kinematic parameters are controlled by largely distinct brain-regions that work together to produce and control precise movements. *Hum Brain Mapp* 38:5970–5986, 2017. © 2017 Wiley Periodicals, Inc.

Key words: kinematics; rapid event-related fMRI; wrist; preferential encoding

INTRODUCTION

The execution of voluntary movements requires control over a large set of movement-related parameters. Yet it remains unclear how this complicated task is achieved, as most regions in the motor system have been implicated in

the encoding of a range of movement parameters. Of particular interest, attempts to link the primary motor cortex (M1) or cerebellum with one specific movement parameter have generally failed. Rather, studies have linked M1 to the encoding of various movement-related parameters, including movement dynamics, muscle activity and force [Cherian et al., 2013; Kakei et al., 1999]. Moreover, studies in both animal models and humans have documented modulation of activity in M1 by both directional [Eisenberg et al., 2010; Georgopoulos et al., 1982] and nondirectional movement kinematics, namely movement amplitude [Fu et al., 1995; Kurata, 1993; Riehle and Requin, 1989; Tunik et al., 2007; Turner et al., 2003] and/or speed [Aflalo and Graziano, 2007; Churchland et al., 2006; Johnson et al., 1999; Moran and Schwartz, 1999]. Sensitivity to movement dynamics and force, to movement direction, or nondirectional kinematic

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parameters, such as movement amplitude and/or speed were also reported in the cerebellum [Fortier et al., 1989; Lewis et al., 2003; Spraker et al., 2012], in addition to its reported roles in predictive state estimation, error correction, and coordination [Diedrichsen et al., 2005; Miall and King, 2008; Schlerf et al., 2012]. Sensitivity to nondirectional kinematic parameters of hand-trajectory, including movement amplitude and/or speed, was also observed in additional regions in the motor system in nonhuman primates and in human studies, including the supplementary motor area (SMA) [Tankus et al., 2009; Waldvogel et al., 1999], basal ganglia (BG) [Desmurget et al., 2004; Turner et al., 2003]), and parietal cortex [Kalaska et al., 1990].

The complexity of movement, and the corresponding richness and heterogeneity of the neuronal responses observed during movement execution suggest that, similar to M1, individual brain regions encode multiple parameters. Several studies support the contention of encoding of multiple parameters even by individual neurons within a specific brain region [Ashe and Georgopoulos, 1994; Fu et al., 1995; Paninski et al., 2004; Scott, 2003]. Yet, a number of questions regarding the encoding of multiple parameters remain. First, it is unknown if individual brain regions encode multiple parameters during a given movement. That is, it remains unclear if brain regions preferentially encode one parameter over others within a specific context and task, or rather encode multiple parameters to a similar extent and/or at the same time. Second, from a systems point of view, it remains to be tested if the same control architecture is maintained in various regions along the motor system. In other words, if multiple regions preferentially encode the same parameter (or nonpreferentially encode a few parameters), or rather different regions encode distinct kinematic parameters in a largely nonoverlapping manner within a specific context and task.

Identifying correlations between brain activity and a given movement-related parameter does not necessarily mean that the true nature of the parameter space is uncovered [Kalaska, 2009]. The interpretation of heterogenic encoding of movement parameters in the motor system should thus be done with caution due to correlations that exist between parameters, such as those between limb position and its time-derivatives, limb velocity and acceleration, and time itself (among other correlations). To address these considerations, one can decouple a limited number of motor parameters and observe whether brain activity follows more closely any of the decoupled parameters. However, movement parameters were often insufficiently decoupled in preceding studies, which may explain the diversity of findings reported thus far [Kalaska, 2009] (although see [Ashe and Georgopoulos, 1994; Stark et al., 2007]).

Here, taking advantage of the ability to track whole brain activity simultaneously using functional magnetic resonance imaging (fMRI), our objective was to determine whether blood-level-oxygen dependent (BOLD) activity in distinct regions along the motor system is modulated by

single, or rather a mixture of kinematic parameters, using a well-controlled wrist movement task that simplifies both kinematic and dynamic demands by requiring single-joint movements. Specifically, we sought to find whether there is an interaction between brain activity in motor regions and the encoding of non-directional kinematic parameters, including movement amplitude, duration, and speed. Four conditions of wrist flexion were controlled in a factorial design, disentangling the particular contribution of movement amplitude, duration, and speed to brain activity.

METHODS

Subjects

Twelve subjects (8 female), aged 26 (3.5) years [mean (SD); range 21–31] with no neurological or psychiatric history, participated in the study. All Subjects were right-handed (Edinburgh Handedness Inventory; [mean (SD) = 0.94 (0.09)], range 0.71–1, on a –1 to 1 scale). The Hadassah Medical Center Ethics Committee approved the experimental procedure, and a written informed consent was obtained from each subject. All methods and experiments were performed in accordance with the relevant guidelines and regulations.

Experimental Paradigm

During the experiment, subjects lay on the scanner bed with their eyes closed and covered, and wore earphones. They were required to hold a rod in a custom-made apparatus and to perform right wrist flexion and extension back-to-neutral movements (Fig. 1). To assure friction, rods were connected via a pulley, to a 500 g weight. Rod position was measured analogically by an optical encoder, transforming position (measured by slots on the encoder) to electrical pulses. Pulses were transformed to a recording box positioned in the control room using an optical fiber, and saved for offline analysis. Subjects' arms were supported by cushions to allow comfortable and isolated wrist movements.

Each trial in the rapid event-related fMRI single scan design (Fig. 2a) lasted 4 s and included a short verbal instruction delivered via the headphones, indicating the condition (1 s; e.g., “fast near,” and “fast far”), followed by a short silence (0.5 s), a decreasing sweep sound (“chirp”—a series of sequential pure tones from 1 KHz to 0; 0.45 or 0.9 s), a short silence (0.2 s), an increasing opposite chirp sound (0.45 or 0.9 s), and silence until the end of the trial (1.4 or 0.5 s). Subjects were required to flex their right wrist during the decreasing chirp sound, wait briefly, and then extend back to the neutral position along with the increasing chirp. The experimenter placed a rafter before each trial to limit wrist flexion to the instructed movement amplitude (45° or 90°). Subjects were easily trained to perform the movements in synchrony with the auditory signals during a short

Figure 1.

Experimental setup and apparatus. (a) Diagram showing the experimental setup from a top view. Note that the computer recording hand position was located outside the scanner room. (b) Picture of the experimental setup in the scanner. (c) Top view of the experimental apparatus, as taken outside of the scanner.

training session preceding the scan. The same experimenter, who was well trained prior to the scans, was in the scanner room in all scans and followed a color-coded table indicating the trial type and rod position before each trial. The experimenter stood next to subject's left body side, away from the subject's moving hand, having easy access to the rod. The experimenter took measure not to touch the subject or enter into the magnet's bore throughout the whole experiment. We confirmed that the magnetic field was not influenced by the presence and movements of the experimenter by running a series of tests on a phantom, with and without the experimenter, and noticed no difference, as was also reported by others who had a moving experimenter in the room [Tal et al., 2017].

Four movement conditions were included in the study. They were created by different nominal values of the three manipulated kinematic parameters: movement amplitude, duration, and speed (Fig. 2b,c). An important feature of the experimental design was that it allowed the assessment of the effect of any of the three single kinematic parameters on the fMRI activity, addressing the issue of interparameter correlations. This assessment was made possible because each condition shared the same value in one of the three parameters with one other condition, while differing from that condition in the two other manipulated parameters.

Each condition was repeated 40 times within the session, in a randomly interspersed and counterbalanced manner (achieved using the Optseq program, Charlestown, MA). A short verbal instruction indicated the condition type and the chirp sound was the "Go" signal. Rest periods

(spanning between 0 and 3 TRs, in units of 1 TR) were evenly distributed among the movement conditions. The combined duration of all the rest periods was equal to the combined duration of each condition (160 s). During the rest periods, subjects were instructed not to move and to keep their wrist in the neutral position. The experiment began and ended with 20 and 16 s rest periods, respectively. A dummy trial administered at the beginning of the run was not included in the analysis to allow for stabilization of the signal. Stimulus delivery was controlled using Presentation software (Neurobehavioral Systems, Albany, CA). The first fMRI pulse triggered the start of the Presentation software (i.e., the experiment) to synchronize the scanner with the experiment. Overall, the functional experiment took 13 min and 56 s. The functional scan was preceded with an anatomical localizer and followed by an anatomical scan.

MRI Acquisition

The BOLD fMRI measurements were performed in a whole-body 3T TRIO SIEMENS scanner, using a 12-channel "birdcage" head coil. The functional MRI protocols were based on multislice gradient echo-planar imaging. The functional data were obtained with the following parameters: TR = 2 s, TE = 30 ms, flip angle = 90°, imaging matrix = 80 × 80, FOV = 24 cm. Thirty ascending slices with slice thickness of 3.5 mm (0.5 mm gap) were oriented in an oblique axis, covering the entire brain including the cerebellum, excluding the rostral edge of the temporal lobe in a few subjects. The functional voxels were thus 3 × 3 × 4 mm³. Structural

Figure 2.

Experimental Paradigm and movement kinematics. (a) Trial sequence showing auditory cues (top) and wrist movements (bottom) as a function of time (middle) within a trial. (b) Four experimental conditions were created by changing the values of three kinematic parameters: movement amplitude (low, high), movement duration (low, high), and movement speed (low, intermediate, high). Roman numerals indicate the conditions as used throughout the manuscript. (c) Schematic kinematic profiles (wrist position vs. time) of the four experimental conditions. I (gray-dashed): flexion-amplitude of 45°, in a low (short) duration and intermediate forward speed (expressed by the slope). II (black-solid): movement duration as in condition I, with twice as high amplitude of 90°, and high (fast) speed. III (gray-solid): flexion-amplitude of 45° as in condition I, with high duration and low

(slow) speed. IV (black-dashed): movement speed as in condition I, amplitude of 90° as in condition II, over a high time duration as in condition III. (d) Online kinematic recordings from a representative subject (subject #1; mean—darker lines, SEM (Standard Error of the Mean)—lighter backgrounds). Noteworthy is the similarity between the actual kinematic behavior and the schematic kinematic profile of the instructed conditions (panel c). (e) Three kinematic values were calculated out of the movement profiles for each of the 12 subjects (dotted gray lines; one line per subject) and averaged over subjects (thick black line): Maximal wrist flexion (left); Total movement duration (flexion and extension; center); Peak speed of the flexion movement (right). Similar peak speed profiles were seen for the extension movement back to neutral position.

TABLE I. Regions of Interest (ROIs)

	#	Center of mass (TAL coordinates)	Cluster size, anatomical voxels ($1 \times 1 \times 1 \text{ mm}^3$)	Cluster size, functional voxels ($3 \times 3 \times 4 \text{ mm}^3$)
M1	12	33, -28, 52 (1, 1, 1)	1036 (38)	91 (3)
Cerebellum	9	-8, -56, -16 (2, 2, 2)	875 (44)	74 (4)
SMA	12	3, -12, 56 (1, 1, 2)	957 (46)	82 (4)
BG	12	24, -1, 7 (1, 1, 1)	1022 (13)	88 (1)
AIP	8	40, -38, 51 (1, 2, 2)	582 (84)	50 (6)

For each ROI: the number of subjects for whom the ROI was defined (significant in the GLM contrast all > rest, and well isolated), the center of mass of Talairach (TAL) coordinates (mm), and cluster size (mm^3) in anatomical voxels and in functional voxels; average (and SEM) over the subjects.

T1-weighted images were acquired with a magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR = 2.3 s; TE = 2.98 ms; flip angle = 9° ; voxel size = $1 \times 1 \times 1 \text{ mm}^3$). A total of 190 T1-weighted images were acquired immediately after the functional run.

fMRI Data Analysis

Preprocessing

Initial data analysis was performed using BrainVoyager QX 1.9 (Brain Innovation, Maastricht, The Netherlands). Prior to the statistical analysis, slice time correction, head motion correction, and high-pass temporal filtering in the frequency domain (3 cycles/total scan time) were applied to remove drifts and improve the signal-to-noise ratio. No spatial smoothing was performed, to allow for voxel-by-voxel analysis. We then applied rigid body motion correction in six directions (three translations and three rotations), using trilinear interpolation, and allowing for a maximum of 100 iterations. A threshold of 3 mm maximum, over all 6 directions, was used, and all subjects met this criterion. The functional images were incorporated into the 3D data sets through trilinear interpolation. The anatomical images were incorporated into the 3D data sets through cubic spline interpolation to create 3D data sets aligned to the anterior and posterior commissures, and then transformed into Talairach space using trilinear interpolation.

Regions of interest (ROI)

ROIs were individually defined for each participant, based on joint functional and anatomical criteria [Eisenberg et al., 2010; Pertzov et al., 2011; Stark and Zohary, 2008], and based on the conventional general linear model (GLM) implemented in the BrainVoyager software, where responses are estimated as boxcar functions convolved with a standard hemodynamic response function (HRF). Voxels were selected using a combination of three criteria: location, functional contrast, and a cluster extent threshold.

ROIs were defined independently of the kinematic parameter manipulation [Pertzov et al., 2011; Poldrack, 2007] by choosing the clusters of voxels that most consistently exhibited stronger activity during limb movement versus rest (i.e.,

treating all four conditions as one), and conducting a *t*-test independently per voxel. Thus, any difference between the conditions is indeed independent of the overall (average) selection criterion (GLM analysis, Bonferroni-corrected $P < 0.05$). Active voxels were subject to a cluster extent threshold, targeting the largest spatially isolated clusters within a well-defined anatomical region, a prerequisite for the functional voxel-by-voxel analysis [Pertzov et al., 2011] (Table I).

We defined five discrete clusters (ROIs) within clear anatomical landmarks, separately for each subject. Primary analysis focused on M1 and the cerebellum. Left M1, hypothesized to play a role in movement encoding, was defined as the “knob” hand area emerging from the central sulcus to the posterior part of the precentral gyrus. Cerebellar clusters, hypothesized to be implicated in movement encoding as well were identified along the right anterior cerebellum, were labeled using the Spatially Unbiased Infratentorial Template (SUIT) template of the cerebellum and brainstem [Diedrichsen, 2006; Diedrichsen et al., 2009] in SPM8. We first converted each subject’s anatomical image from BrainVoyager’s native format into Analyze format. Single subject clusters of activation were converted to NIfTI format using MRICron (<http://www.mccauslandcenter.sc.edu/mricro/mricron/>). The anatomical images were segmented and the cerebellum was isolated, cropped, and normalized to the SUIT atlas template. Single-subject cerebellar activation maps were masked with the cerebellar isolation map generated as described above and resliced into the SUIT atlas space. Lobule locations for each of the clusters were identified based the SUIT’s probabilistic atlas. Lobule borders, as depicted in the SUIT-based MRICron atlas, were additionally rendered for visualization purposes. We focused on the anterior intermediate cerebellar ROIs, and specifically on lobule V, as the motor cerebellar region showing arm somatotopy and expected to be most involved in encoding motor parameters [Schlerf et al., 2010; Stoodley et al., 2012]. Post-hoc, these were indeed the most consistent cerebellar ROIs across subjects (Table II).

Secondary analyses focused on other regions in the motor system. Left SMA was defined near the midline, adjacent to the cingulate sulcus, and posterior to the vertical commissure anterior line (perpendicular to the anterior commissure - posterior commissure line), based on previously published anatomical landmarks [Picard and Strick,

TABLE II. Cerebellar activation

	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
x	−5	−11	−10	−5	−5	−9	−8	−22	−4	1
y	−62	−48	−55	−60	−60	−45	−54	−50	−72	−63
z	−20	−22	−16	−23	−17	−16	−16	−23	−48	−23
Left I_IV										
Right I_IV		X	X	X	X	X	X	X		
Left V				X	X					X
Right V	X	X	X	X	X	X	X	X	X	X
Left VI										
Vermis VI	X			X	X					X
Right VI	X	X	X	X	X		X	X	X	X
Left Crus I										
Vermis Crus I										
Right Crus I										
Left Crus II										
Vermis Crus II										
Right Crus II									X	
Left VIIb										
Vermis VIIb										
Right VIIb									X	
Left VIIa										
Vermis VIIa				X					X	
Right VIIa									X	
Left VIIIb										
Vermis VIIIb				X						
Right VIIIb										
Left IX										
Vermis IX				X						
Right IX				X						
Left X										
Vermis X										
Right X										

Data for Cerebellar ROIs are shown for 10 subjects (S1–S10). Two additional subjects who participated in the experiment did not show clusters of activity in the cerebellum. The table includes the center of mass in Talairach space (mm) per cluster, although lobule locations were estimated in SUIT atlas space (see Methods) of the cerebellum. Lobule locations are reported for clusters that were labeled by SUIT with a probability > 25%.

2001]. In the basal ganglia, we focused on the left putamen, routinely linked with movement kinematics [Desmurget et al., 2004; Jung et al., 2014]. A well-isolated cluster in the left putamen, posterior to the internal capsule and caudate was used. Post-hoc, this was indeed the most consistent basal ganglia ROI across subjects. The left anterior intraparietal area (AIP) was defined as extending posterior to the junction between the postcentral sulcus and the anterior edge of the intraparietal sulcus [Stark and Zohary, 2008]. This was the most consistent parietal region among participants. Additional motor system regions were not analyzed in this article because we failed to observe spatially consistent BOLD activity in these regions in response to wrist movements, or we did not observe a spatially discrete cluster of activity (i.e., in the premotor cortex).

Linear regression

More advanced analysis was performed using Matlab R2009a (MathWorks, Natick, MA). Linear regression

(deconvolution) was used to estimate the average activity amplitude (regression coefficients) of each voxel in each condition. This method makes no a priori assumptions about the shape of the HRF, which can vary across subjects and brain regions [Handwerker et al., 2004]. This minimized the dependence between the selection criteria for each ROI and the specific pattern of activity in each voxel within the ROI [Eisenberg et al., 2010 2011; Poldrack, 2007]. This approach is particularly suited for rapid event-related designs where the normal convolution GLM is still valid but less effective due to the severe response overlap between two or more consecutive trials of the experiment. To that end, an equation of the form $y = Xb$ was solved based on the $y = Xb + e$ linear model, where the vector y is the measured time course of activity in a voxel, X is the regression (convolution) matrix determined by the sequence of events (see below), the vector b contains a series of estimated activity amplitudes for each of the four experimental conditions, and e is an error term assumed to be Gaussian noise. The vector of response amplitudes, b , was estimated using the equation $b = (X'X)^{-1}X'y$.

Due to the hemodynamic delay and temporal low pass filtering of the BOLD signal, the activity amplitude in each trial was estimated over 10 time points, starting from the beginning of the trial (that is, given $TR = 2$ s, between 0 and 18 s after the beginning of a trial), thus b is respectively comprised of 10 values (estimated β values) for each condition. The average activity amplitude for each condition at each time-point (averaged over multiple trials of each condition) was therefore estimated independently.

Average activity

The following statistical analyses and calculations were based on the estimated activity amplitude β values. Because there was considerable variation in the absolute level of ROI activity across subjects, we first normalized activity by dividing the regression value at each time-point by the maximal value for that voxel (over time-points and conditions, per subject). Hence, the maximal value in all voxels and subjects was 1. We then averaged the normalized activations across subjects. To further assess the effect of each parameter, we subtracted the mean activity (over all conditions) from the un-normalized β values for each voxel. Analysis was performed on the activity level 6 s after the beginning of the trial, which was the observed peak value in 11/12 of the subjects (in subject 12, the peak activity occurred 8 s after the beginning of trials in all ROIs and, therefore, the value at that time point was used). Next, a 1-way ANOVA was performed on the peak activity values, over subjects, to test if conditions differed significantly. If this test revealed a significant difference between conditions, post-hoc t -tests were performed between each pair of conditions, corrected for multiple comparisons.

Rank-Order Analysis of Conditions for Each Voxel

The spatial resolution of BOLD fMRI limits the level of information to voxels, yet each voxel might contain multiple local pools of neurons that encode different parameters. Stronger encoding of one parameter over others within a limited region may result from a relative homogenous neuronal pool, or from one local pool having a stronger effect than another local pool within a voxel, causing the overall activity of the voxel to prefer one parameter over the others. To provide additional insight into within-ROI spatial response patterns and examine the possibility that the group results were influenced by outlying subjects or voxels, a non-parametric analysis was performed at the voxel level, focusing on each and all voxels within an ROI. For each ROI of each subject, conditions were rank-ordered by the β values that they elicited 6 s after the beginning of the trial, per voxel (8 s in subject 12). That is, in each voxel, the condition that led to the strongest activity was labeled as first; the condition that led to the second strongest activity was labeled second; and so on. The frequency of the rank-orders over

voxels was then checked by calculating the percent of voxels within the ROI for which each condition was in each rank. The results were then averaged over subjects. Complementarily, a Kruskal-Wallis nonparametric test was performed on the rank of the peak activity values, over subjects, corrected for multiple comparisons.

Parameter Analysis

The four experimental conditions were characterized by three parameters: amplitude, duration, and speed. Although the immediate result was the dependence of fMRI activity on the experimental conditions, our main goal was to assess the effect that each kinematic parameter has on brain activity. Because the three parameters were dependent (precluding the use of the standard 3-way ANOVA), three independent 1-way ANOVA analyses were first performed, each time partitioning the data according to a single parameter (namely amplitude, duration, or speed). The portion of the variance in the peak fMRI activity explained by each parameter was estimated by calculating the effect-size (eta-squared) per subject and ROI (that is, three eta-squared values were calculated for each subject and ROI, over voxels). Next, four types of analysis were performed on the eta-squared data. First, to check whether the assignment of activity according to each of the three parameters differed from chance, a permutation test was performed by shuffling the peak activity (1,000 times) and randomly assigning them into four groups, for each subject and ROI. Three eta-squared values were then calculated from each random assignment, and compared to the eta-squared calculated from the non-random assignment. Namely, the number of cases in which the eta-squared calculated from the randomly assigned data was equal to or smaller than the eta-squared calculated from the correctly assigned data plus one (i.e., plus the correct assignment) was divided by the total number of calculations: P equals the number of cases in which $[(\text{random-assignment } \eta^2 \leq \text{non-random assignment } \eta^2) + 1] / (1,001)$. This yielded, for each subject and ROI, three P -values for testing the hypothesis that brain activity was modulated by the corresponding kinematic parameter. The three eta-squared values calculated from the correctly assigned peak activity data (namely according to the three parameters) were used for the subsequent analyses. The second analysis included repeated measures ANOVA with ROI and Parameter as the dependent within subject variables, testing whether there is a main effect of regions, and especially whether there is an interaction effect between regions and parameters, suggesting that regions differ in their preferred parameter(s) encoding. Third, within each ROI, a 1-way ANOVA was performed on the eta-squared values calculated from the 3 non-random assignments over subjects, to see if there is a preferred parameter that explained the largest portion of variance in the fMRI activity (across subjects). If the effect-sizes differed between the three models, post-hoc t -tests were performed and corrected for multiple comparisons. Lastly, 1-way ANOVAs were performed between regions, per parameter, to test whether the strength of parameter

preference varied across regions. The last three analysis steps were repeated twice: once for our primary ROIs, M1, and lobule V of the cerebellum, and once for our secondary analysis including all five ROIs. Because the number of subjects varied between ROIs, missing data were replaced by the group average per ROI. The results were nearly identical when missing samples were fully removed.

Movement Analysis

Wrist position was measured online and recorded throughout the experiment using LabVIEW (National Instruments, Austin, TX; sampling rate 1 KHz) and then analyzed using Matlab R2009a (MathWorks, Natick, MA; Fig. 2d left, kinematic behavior of representative subject #1). The momentary first time derivative (speed) was calculated offline (Fig. 2d right). Peak-amplitude (maximal wrist flexion), total movement duration, and peak-speed during the flexion movement, were calculated for each trial, and averaged over trials of the same condition per subject. Values for each subject and group means are presented in Figure 2e.

Electromyographic (EMG) Control

Muscle activity could have potentially confounded the brain activity that is attributed to the kinematic parameters in a systematic manner. Therefore, EMG recordings from the wrist flexion agonist, the flexor carpi radialis (FRC), were conducted out of the scanner (6 of the 12 subjects who participated in the main imaging experiment). Electrodes for monitoring electrocardiography (Unomedical, Great Britain) were used with a $\times 1,000$ gain; data were passed through a 10 KHz low-pass filter, rectified (taking absolute values), smoothed by a moving root mean square window of 75 ms, and sampled at 1 KHz. During the EMG measurements, subjects used the same apparatus used in the scanner, while lying on a bed with their eyes closed and their arms supported by cushions. A wide metal half-cylinder was attached to the bed above the subjects' upper-body to mimic the position and atmosphere of the scanner. Wrist position was simultaneously recorded to ensure consistent behavior during the fMRI experiment and the EMG control.

EMG profiles from all trials were aligned to the beginning of the chirp sound (namely "Go" signal). The average EMG profile was then integrated (IEMG) separately for each condition (from 1 s before the "Go" signal until 3 s after this signal). IEMG data were analyzed in the same manner as the β values.

RESULTS

Kinematic Behavior Differed between Conditions

Twelve right-handed subjects performed right-wrist flexion and extension movements in a rapid event-related

fMRI study (Fig. 2a) in which three kinematic parameters were manipulated: movement amplitude, duration, and speed (Fig. 2b). Four movement conditions were included to establish whether regions in the motor system encode single or rather a mix of nondirectional kinematic parameters (see Methods and Fig. 2b,c). Online kinematic recordings during the experiment indicated that subjects performed the movements as instructed (Fig. 2d,e), with shorter movement amplitudes in conditions I and III relative to conditions II and IV (Fig. 2d,e left); shorter movement duration in conditions I and II relative to conditions III and IV (Fig. 2d,e middle); and fast movements in condition II, slow movements in condition III, and intermediate speeds in conditions I and IV (Fig. 2d,e right). Subjects completed all trials as instructed, and therefore no trials were removed.

Five ROIs along the motor system were selected as the most consistent regions responsive to wrist movements across subjects, irrespective of kinematics (Table I). The ROIs were defined individually for each subject (see Methods), including M1 ($n = 12$; Fig. 4), right anterior cerebellum (primarily lobule V; $n = 10$; Table II and Fig. 5), left SMA ($n = 12$), left putamen in the BG ($n = 12$), and left AIP ($n = 8$) in the parietal cortex. Table I also reports the number of subjects for whom the selected ROI was significant, per region. Linear regression was used to estimate the average activity time course (β values) for each condition at each time point in each voxel.

Primary Analysis: Different Preferential Encoding in M1 and Cerebellum

We first focused on M1 and the cerebellum, as the two regions lower in the motor hierarchy, traditionally thought to encode movement-related parameters. Despite the overall similarity in the patterns of the time-courses between left M1 and right lobule V of the cerebellum (Fig. 3a,b), a clear difference was observed in the peak time-courses between these two regions, indicating different contributions of the various kinematic parameters (Fig. 3c,d). Group data shows that in both regions, activity peaked 6 s after the beginning of the trial for all conditions. At that time point, the four conditions can be accurately grouped according to their level of peak activity. However, different grouping characteristics describe the peak activity levels in these two regions. In M1 (Fig. 3a,c), the two conditions of higher amplitude movements (conditions II, IV) yielded comparable significant activity, whereas the two conditions with lower amplitude movements (conditions I, III) yielded a (similar) weaker activity. That is, peak activity differed according to the amplitude of the movement ($F_{(3,33)} = 9.6$, $P \ll 0.001$, 1-way ANOVA; $P < 0.01$, post-hoc paired t -tests, corrected for multiple comparisons, in which conditions I and III (and II and IV) did not differ significantly one from the other, whereas significant differences were observed within all other

Figure 3.

Peak activity patterns differed between M1 and cerebellum. (a,b) Normalized group activity (β values) over time in M1 (a) and cerebellum (b; mean and SEM over subjects) calculated by linear regression (0, trial onset). Peak activity, 6 s after the beginning of trials, marked by a dashed square and shown as bar graphs in (c,d). (c,d) Peak activity (mean and SEM over subjects) significantly differed between conditions. In M1 (c), conditions II and IV, sharing the same high amplitudes but having different speeds and durations, elicited similar activity strengths, stronger than those elicited by conditions I and III ($P \ll 0.001$, 1-way ANOVA, corrected for multiple comparisons, see text). In the cerebellum (d), condition II, characterized by the highest speed, elicited the strongest activity; condition III, having the lowest speed, elicited the weakest activity; and conditions I and IV, which share an intermediate peak speed (while having different amplitudes and durations) resulted in intermediate activity levels ($P \ll 0.001$, 1-way ANOVA, corrected for multiple comparisons, see text). (e,f) In each voxel within an ROI, conditions were ranked by the activity they elicited at the time of peak activity. The percent

of voxels in the ROI for which each condition was in each rank was then calculated and averaged over subjects. P -values represent results from Kruskal-Wallis non-parametric tests on the conditions' rank, over subjects, corrected for multiple comparisons. (e) M1. (f) Cerebellum. Note, that the first rank (the strongest activity) accorded to movement amplitude and movement speed, in M1 and the cerebellum, respectively. (g,h) Effect-size (eta-squared) is calculated from three independent models, each dividing the data according to one manipulated kinematic parameter: amplitude, duration, and speed. Error bars: 95% confidence limits. P -values, from post-hoc contrasts, corrected for multiple comparisons. Activity in both M1 and the cerebellum was most strongly modulated by different single parameters. (g) M1. It should be noted that the largest effect-sizes was for the amplitude, whereas the duration and speed had significantly smaller and similar effect-sizes. (h) Cerebellum. Here, the largest effect-size was obtained for speed, while amplitude and duration exhibited similar and smaller effect-sizes.

pairs). In lobule V of the cerebellum, however, peak activity levels can be divided into three categories, according to the peak speed of the flexion movement: condition II with the highest speed led to the strongest activity; condition III with the lowest speed elicited the weakest activity; and conditions I and IV, which share an intermediate peak speed, resulted in an intermediate activity level (Fig. 3b,d; $F_{(3,33)} = 19.7$, $P \ll 0.001$, 1-way ANOVA; $P < 0.005$, post-hoc paired t -tests, corrected for multiple comparisons in which conditions II and III each differed significantly from all other conditions, while conditions I and IV did not differ significantly one from the other).

It is important to note that group data do not emerge from averaging over different patterns, but rather reflect single-subject activity patterns that were very similar

across subjects (M1: Fig. 4; cerebellum: Fig. 5). Moreover, in both regions and for each subject, peak activity significantly differed between conditions, indicating their different contributions to the BOLD response (repeating the analysis described above at the single subject level: $P \ll 0.001$, 1-way ANOVA, M1, per subject; $P < 0.0005$, 1-way ANOVA, cerebellum, per subject; peak activity ranked according to movement amplitude in 10/12 subjects in M1, and according to movement speed in all 10/10 subjects in lobule V of the cerebellum).

The effects seen in M1 and lobule V of the cerebellum at the single-subject level could have emerged from a small number of voxels (outliers) with a stronger activation response, as activity was averaged over all voxels per ROI. To investigate this possibility, a nonparametric method

Figure 4.

Activity patterns in M1 were similar across individual subjects, and activity strength reflected movement amplitude. Data from 12 individual subjects. For each subject: **Top:** M1 ROI is presented in cyan on a coronal slice, the center-of-mass is marked by a white cross, and the Talairach coordinates of the center-of-mass are provided underneath (left hemisphere is shown on left side). **Bottom left:** Activity level, showing the sequential unnormalized regression (β) values as a function of time. **Bottom-right:** Peak activity, 6 s from the beginning of trials, after

normalizing the maximal raw-beta to be 1. Noteworthy is a consistent movement amplitude effect for individual subjects (with the exception of subjects 4, 12), as the two conditions involving high-amplitude movements (II green, IV magenta) elicit stronger activity than the two conditions involving low-amplitude movements (I red, III blue). The effect of the different conditions is significant in all subjects (per subject: $P \ll 0.001$, 1-way ANOVA, indicating different activity strengths between conditions).

was used to study activity at the voxel level by ranking conditions according to the activity strength that they elicited within each voxel (see Methods). Then, the percentage of voxels within the ROI for which each condition was in each rank was calculated and averaged over subjects (Fig. 3e,f), providing insight into activation patterns at the sub-ROI scale. In M1, the rank-order of peak beta values was ordered according to movement amplitude, significantly differing from the null hypothesis stating that all values are the same regardless of condition (Kruskal-Wallis nonparametric test over subjects, $P \ll 0.0001$). Similarly, the speed effect found in lobule V of the cerebellum did not emerge from a few outliers either, as the rank-ordered activity elicited by each condition per voxel also ranked according to the speed of movement (Kruskal-Wallis nonparametric test over subjects, $P \ll 0.001$). Thus, the results were confirmed at the voxel level and are therefore not the outcome of a few outlying voxels.

As already noted, the four experimental conditions were generated by varying levels of three kinematic parameters (Fig. 2b). This design facilitated a direct comparison of the contributions of the various parameters to

the fMRI signal during the different conditions. Because such an analysis should consider the interdependency between the manipulated parameters, the dataset of peak activity was split in three different ways, each time according to a different parameter (movement amplitude, movement duration, or movement speed). The portion of the variance explained by each parameter was assessed by calculating the effect-size, denoted by eta-squared, from three independent models (see Methods). To check whether a given parameter yielded an above-chance effect, permutation tests were performed comparing eta-squared values computed from the observed data with eta-squared values computed from resampling the data wherein the labels of the conditions were randomly shuffled. This was done separately for each parameter, ROI, and subject (Methods). Splitting M1 activity according to each of the manipulated kinematic parameters significantly explained peak activity variance in all or most subjects ($P < 0.05$, permutation test, significant in 12, 9, and 10 out of 12 subjects for movement amplitude, duration, and speed, respectively). Thus, each of the three manipulated kinematic parameters significantly affected activity

Figure 5.

Activity patterns in the cerebellum were similar between individual subjects, and activity strength reflected movement speed. Data from 10 individual subjects, depicting the location of peak activity in the cerebellum. Figure organization is the same as of Figure 4. Note the consistent peak speed effect for all individual subjects, as the condition involving high-speed movements (II, green) elicited the strongest activity; the condition involving

low-speed movements (III, blue) elicited the weakest activity; and the conditions involving intermediate speeds (I, red and IV, magenta) elicited intermediate activity levels. The effect of the different conditions was significant for all subjects (per subject: $P \ll 0.001$, 1-way ANOVA, indicating different activity strengths between conditions).

in M1, indicating that M1 encodes all three parameters above chance. A similar analysis was performed for the cerebellum data. Here, splitting the peak activity data according to each manipulated kinematic parameter significantly explained activity variance in all subjects ($P < 0.05$, permutation test, significant 10 out of 10 subjects for movement amplitude, duration, or speed). That is, in lobule V of the cerebellum as in M1, each manipulated kinematic parameter significantly affects the activity, indicating that lobule V encodes each of the kinematic parameters tested above chance.

Given that all eta-squared values were significantly larger than chance, we asked whether the encoding of the parameters differed within each region, indicating a preferred parameter, as well as whether the encoding differed between the two regions. For this analysis, we conducted repeated-measures ANOVA with within-subject factors Region and Parameter. We found a significant Region $\times$ Parameter interaction ($F_{(2,22)} = 28.8$, $P \ll 0.001$), as well as a significant Parameter main effect

($F_{(2,22)} = 9.3$, $P < 0.005$), suggesting that these two regions differ in the way they encode the tested kinematic parameters. Next, we asked whether the variance in peak activity is explained by the different parameters as measured by comparing the eta-squared values from the three independent models over subjects using 1-way repeated-measures ANOVAs per ROI. Both regions were found to encode the three movement parameters differently (Fig. 3g,h; M1: $F_{(2,22)} = 25.7$, $P \ll 0.001$; lobule V of the cerebellum: $F_{(2,22)} = 11.3$, $P < 0.001$). Post-hoc contrasts (corrected for multiple comparisons) show a preference for one single parameter in both M1 and the cerebellum. Specifically, movement amplitude described the largest portion of variance in the fMRI signal from M1 ($P < 0.0005$ comparing the amplitude model to each of the other models; and $P > 0.05$ between the duration and speed models). Speed of movement explained the largest portion of variation in the cerebellar peak activity ($P < 0.001$ comparing the speed model to each of the other models; and $P > 0.05$ between the amplitude and duration models).

Figure 6.

Peak activity patterns in SMA, BG, and AIP did not show preferential encoding for any kinematic parameter. (a, c, e) Peak activity, 6 s after the beginning of trials (same analysis as in Fig. 3c,d), did not differ between conditions. (b, d, f) Parameter analysis

(same analysis as in Fig. 3g,h). Noteworthy is the overlap of the 95% confidence limits of the effect-sizes of the three kinematic parameters, indicating the lack of preferential encoding ($P > 0.05$, 1-way ANOVA).

Secondary Analysis: Nonpreferential Encoding in Other Motor Regions

We next wished to test whether regions along higher levels of the motor hierarchy are similarly primarily sensitive to single kinematic parameters or rather show mixed encoding of kinematic parameters. We therefore repeated the analytical procedures described thus far with ROIs in the SMA, BG, and AIP, all significantly involved in the task, as evident from peak activations (Fig. 6a,c,e). However, as opposed to M1 and the cerebellum, there was no difference in the peak-activity elicited by the four conditions in any of these regions ($F_{(3,33)} = 3.4$, $P = 0.05$; $F_{(3,33)} = 0.95$, $P = 0.4$; and $F_{(3,33)} = 3.3$, $P = 0.07$; SMA, BG, and AIP, respectively; 1-way repeated measures ANOVAs per ROI), pointing to a lack of preferential parameter encoding within each of these regions (Fig. 6b,d,f). These effects were also evident in the rank order analyses of peak values, which did not deviate from random levels. We reran the repeated measures ANOVA, with within-subject factors of Region and Parameter, this time using all five ROIs. We found a significant Region $\times$ Parameter interaction ($F_{(8,88)} = 3.6$, $P < 0.005$), and significant Parameter main effect ($F_{(2,22)} = 6.96$, $P < 0.05$), as well as significant Region main effect ($F_{(4,44)} = 3.2$, $P < 0.05$), suggesting different parameter encoding between the five ROIs. Post-hoc analyses revealed a significant difference in amplitude encoding between the five regions ($F_{(4,44)} = 6.8$, $P \ll 0.001$), and post-hoc contrasts showed that amplitude encoding was larger in M1 than in lobule V of the cerebellum, BG,

and AIP ($P < 0.0005$, $P < 0.0005$, and $P < 0.005$, Bonferroni corrected), with a trend for being larger than in the SMA ($P = 0.06$). All other contrasts were not significant ($P > 0.22$). Speed encoding also differed between regions ($F_{(4,44)} = 7.12$, $P \ll 0.001$). The largest speed effect was seen in lobule V: larger than in M1 ($P < 0.001$, Bonferroni corrected), and to a lesser degree larger than BG and AIP ($P < 0.01$, $P < 0.05$, respectively, not corrected), but not larger than in SMA ($P = 0.19$). Weakest speed encoding was in M1: smaller than in lobule V of the cerebellum ($P < 0.001$, Bonferroni corrected), and to a lesser degree than SMA and AIP ($P < 0.05$, $P < 0.01$, respectively, not corrected), though not different than speed encoding in the BG ($P = 0.54$). Lastly, speed encoding was larger in SMA than in the BG ($P < 0.05$, not corrected). Duration encoding did not differ between any of the regions ($F_{(4,44)} = 1.5$, $P = 0.23$).

Contribution of Muscle Force

To test whether muscle activity could have systematically affected the brain activity attributed to the kinematic parameters, EMG was recorded from the FRC muscle of six of the subjects who participated in the main imaging experiment (Methods; Fig. 7). Brain activity patterns were similar between the EMG-subgroup and the entire group, indicating that this subgroup constitutes a good representation of the entire cohort of subjects. EMG patterns were similar across subjects (Fig. 7b). The two conditions of higher-amplitude movements (conditions II, IV) yielded

Figure 7.

EMG activity. EMG was recorded from the FCR muscle while six subjects repeated the experiment. **(a)** EMG from one subject (thick line—average over trials, thin lines—SEM). **(b)** IEMG calculated separately from each condition. Data from individual subjects are shown

as dotted gray lines and the group average (and SEM) as a thick black line. **(c)** Parameter-analysis (as in Fig. 3g,h) for the IEMG. Amplitude explained the larger portion of the variance in the EMG signal more than the two other manipulated parameters.

comparable stronger integrated EMG (IEMG) activity than the two conditions with lower-amplitude movements (conditions I, III; Fig. 7b; $P \ll 0.001$, 1-way-ANOVA over conditions and subjects, corrected for multiple comparisons). Parameter analysis applied to IEMG data indicated that the main parameter affecting IEMG activity was movement amplitude ($F_{(2,10)} = 14.9$, $P < 0.001$, 1-way-ANOVA over parameters and subjects Fig. 6c; $P < 0.01$ comparing the amplitude model to the duration model, and $P \ll 0.001$ comparing the amplitude model to the speed model; $P > 0.05$ between the duration and speed models; corrected for multiple comparisons). Thus, muscular force was more strongly affected by movement amplitude than by movement duration or speed, which by themselves did not differ in the effect they had on muscular force.

DISCUSSION

Our objective here was to test whether regions in the motor system are preferentially modulated by single nondirectional kinematic parameters or rather a mixture of parameters. We found converging evidence supporting dissociation in preferential parameter encoding along the motor system, based on BOLD signal in a well-controlled wrist-movement task. Specifically, M1 showed preferential encoding of movement amplitude, and activity in the anterior lobe of the cerebellum (lobule V) was preferentially modulated by movement speed. Conversely, SMA, BG, and AIP did not show preferential modulation by any specific parameter, but rather a mixture of all kinematic parameters tested to a similar extent.

Out of the three tested kinematic parameters, activity in M1 was largely modulated by movement amplitude and to a lesser extent by movement speed and duration. This finding is consistent with a limited number of studies that examined neuronal modulation of movement amplitude in M1, including electrophysiological studies of arm reaching [Churchland et al., 2006; Fu et al., 1995] or wrist flexion-

extension [Kurata, 1993; Riehle and Requin, 1989] in primates, as well as fMRI studies of human finger-flexion [Waldvogel et al., 1999]. Still, scale-invariant encoding in M1 has also been reported [Kadmon Harpaz et al., 2014]. In contrast to M1, BOLD signal in lobule V of the cerebellum was largely invariant to movement amplitude, consistent with an earlier fMRI study [Lewis et al., 2003] reporting cerebellar encoding of movement speed, but not movement amplitude and directional-change.

The effect of speed modulation was complementary to the effect of movement amplitude modulation, as movement speed most strongly affected the fMRI signal in lobule V of the cerebellum, but not in M1. Preceding kinematic studies in primates found that M1 encodes movement velocity [Johnson et al., 1999; Stark et al., 2007], yet this activity typically correlated with the direction of the velocity vector and not with its magnitude (namely speed) [although see Aflalo and Graziano, 2007; Churchland et al., 2006; Moran and Schwartz, 1999]. Based on electrophysiological studies, speed modulation was expected to be indistinguishable in M1 BOLD signal, because pure speed modulation of M1 neurons has not been observed [Johnson et al., 1999; Stark et al., 2007], has weak instantaneous correlations with neuronal activity [Aflalo and Graziano, 2007], and has an equal distribution of positive and negative modulations of neuronal firing [Johnson et al., 1999] averaging-out at the population level.

However, the involvement of the cerebellum in speed control has been well established in primates [Coltz et al., 1999; Mano and Yamamoto, 1980; Roitman et al., 2005] and humans [Ivry and Diener, 1991; Lewis et al., 2003; Turner et al., 1998], consistent with the results reported here. First, cerebellar cells are sensitive to velocity magnitude (speed) in addition to the direction of velocity [Coltz et al., 1999; Roitman et al., 2005]. Second, the average firing rate and modulation depth of cerebellar cells more frequently increases rather than decreases with faster speed [Roitman et al., 2005], a property which may be expected to be reflected in positive modulation of the fMRI signal.

Third, movement speed (and not movement amplitude or directional-change), positively correlates with cerebellar activity in human imaging studies [Lewis et al., 2003; Turner et al., 1998; Wenzel et al., 2014]. Fourth, there is even evidence for perceptual sensitivity to speed in the cerebellum, as cerebellar patients show impairments in making perceptual judgments regarding the speed of moving visual stimuli but not their position [Ivry and Diener, 1991].

Unlike in M1 and the cerebellum, activity higher in the motor hierarchy, namely in the SMA, AIP, and BG, was affected by a mixture of all three manipulated parameters. Mixed published results pertaining to SMA exist, linking this region to both movement speed [Tankus et al., 2009] and amplitude [Waldvogel et al., 1999], but also to higher-level aspects of movement, such as the order of forthcoming movements in complex motor sequences [Gerloff et al., 1997]. AIP, on the other hand, has been implicated in the encoding of movement direction rather than movement amplitude [Davare et al., 2015]. More generally, parietal cortex has a role in the integration of information for upcoming movements [Andersen and Buneo, 2002; Stark and Zohary, 2008]. In line with this role, in the current task AIP could have been involved in the transformation of the auditory instructions into a general motor plan, which was not limited to one single parameter in the current task. Finally, the BG have been linked to the control of movement amplitude [Desmurget et al., 2004; Turner and Anderson, 1997], speed [Singh and Bötzel, 2013], and velocity [Anderson and Horak, 1985], but also to an extensive array of motor-related functions, including selection of action, on-line error correction, movement rate, force, motor control, and motor learning [Gurney et al., 2001; Lawrence, 2000; Prodoehl et al., 2009; Taniwaki et al., 2003]. Consistent with this diverse functional profile, our data did not reveal selective activation in the putamen in response to movement amplitude or any other specific kinematic parameter. Note that while movement speed, velocity and rate [Anderson and Horak, 1985; Singh and Bötzel, 2013; Taniwaki et al., 2003] were previously associated with activity in the globus pallidus rather than putamen (striatum), the anatomical proximity between these regions and the limited fMRI spatial resolution, could have contributed to the nonpreferential activation currently observed. Future studies using ultra-high field MRI [Duyn, 2012; Harel, 2012], and/or sophisticated multivariate techniques for detecting representational similarities and dissimilarities in populations of voxels [Diedrichsen and Kriegeskorte, 2017] may possibly allow to detect more consistent spatial patterns that are preferentially tuned to kinematic parameters within these regions and other regions in the motor system.

There is a large body of evidence pointing to the role of the cerebellum in interval timing. In our task, however, duration seems to emerge from the specific demands requiring to choose particular kinematic profiles,

determined by speed-amplitude combinations. Specifically, the task design and verbal instructions indicating movement speed and amplitude but not movement duration (e.g., “fast near” and “fast far”), sweep sounds dictating movement speed, and physical constraints bounding movement amplitude, created specific speed-amplitude combinations that resulted in different movement durations. Thus, movement duration might not have been encoded directly, but rather emerged from the combination of these other parameters. Indeed, evidence for preferential modulation of movement duration was not found in any of the regions.

Possible Confounding Factors

Despite the specific context and well-controlled single-joint movements that were performed during the task, additional factors could have affected the results. First, various control requirements may account for the cerebellar sensitivity to speed. Fast movements as the ones performed in the task require active braking (i.e., stopping), demanding greater coordination of agonist-antagonist muscles. Evidence from cerebellar patients, who have difficulty in properly stopping fast movements, point to the role of the cerebellum in precise coordination of agonist-antagonist muscles [Hallett et al., 1991; Hore et al., 1991]. Moreover, the cerebellum has also been associated with the control of stability [Haruno et al., 2012], and fast movements create greater instabilities such as interaction torques which could potentially account for the speed effects observed here. However, we used single-joint movements to minimize confounds arising during multijoint movements (stronger presence of interaction torques and cocontraction of multiple muscles [Haruno et al., 2012]), therefore simplifying inverse dynamics by eliminating the need for the motor system to compensate for these torques [Hollerbach and Flash, 1982].

Second, although force was not directly manipulated in the task, it could have varied between conditions [Spraker et al., 2012]. Even in single-joint movements, like the wrist flexion included here, dynamic forces may not be separable from movement kinematics, as the joint torques themselves depend on position, velocity and acceleration, and on joint impedance parameters (i.e., stiffness, viscosity and inertia). Previous studies [Haruno et al., 2012; Spraker et al., 2012] have found scaling of cerebellar BOLD signal with force and also reported EMG activity in association with each of the three kinematic parameters currently manipulated, including speed [Carpentier et al., 1996; Schmidt et al., 1988; Sherwood et al., 1988], movement amplitude [Buneo et al., 1994; Kurata, 1993; Sherwood et al., 1988; Waldvogel et al., 1999] and movement duration [Buneo et al., 1994; Carpentier et al., 1996; Schmidt et al., 1988]. Therefore, we had no a-priori prediction regarding the relative effects of the manipulated kinematic parameters on the IEMG in the current task. The data indicated that while movement duration and speed may have contributed to the IEMG, muscular activity was largely

determined by movement amplitude, corroborating previous wrist motion results [Charles and Hogan, 2012].

More generally, despite using a highly constrained single-joint movement task, we cannot completely reject the possibility that the activation patterns found here do not actually reflect the encoding of additional or alternative movement-related and contextual parameters. These may include muscle force, sensory (auditory, proprioceptive) input, or acceleration [Ganesh et al., 2008; Kakei et al., 1999; Reznik et al., 2015; Stark et al., 2007]. Importantly, we are not claiming here that movement amplitude is encoded solely in M1, and that movement speed is only encoded in lobule V of the cerebellum, or that they are planned independently. On the contrary, we show that each of the regions involved in the encoding of wrist movements in this task encodes all of the tested kinematic parameters. Thus, our result suggests that the encoding of each kinematic parameter involves interactions between multiple brain regions working together as a distributed network to control movements and successfully fulfill the purpose of the motor system to produce precise movements, supported by strong functional connections between the tested regions [Celnik, 2015; Krienen and Buckner, 2009]. However, even within these networks, there are regions that preferentially control one parameter over others, suggesting some level of specificity within nodes in the network.

Taken together, the current results support the notion of a large-scale network of brain regions that work together to control and produce precise movements. Beyond its mechanistic implications, this emerging heterogeneous control framework may have translational implications, for instance when designing brain-computer interfaces where simultaneous recordings from different parts of the motor system may be in place.

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AUTHOR CONTRIBUTIONS

ASI: Conception and design, data acquisition, data analysis, writing the manuscript. ED: data analysis, writing the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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