Individual movement variability magnitudes are predicted by cortical neural variability

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ABSTRACT

Humans exhibit considerable motor variability even across trivial reaching movements. This variability can be separated into specific kinematic components such as extent and direction, which are thought to be governed by distinct neural processes. Here, we report that individual subjects exhibit different magnitudes of kinematic variability, which are consistent (within individual) across movements to different targets and regardless of which arm (dominant or non-dominant) was used to perform the movements. Simultaneous fMRI recordings revealed that individual subjects also exhibited consistent fMRI variability across movements to different targets when performed with either arm. Cortical fMRI variability of individual subjects predicted their movement extent variability. This relationship was markedly stronger in fMRI responses of posterior-parietal cortex than primary motor cortex, suggesting that individuals with more variable movement planning, exhibit larger kinematic variability. We, therefore, propose that neural and kinematic variability are reliable and interrelated personal characteristics, which may underlie individual motor capabilities.

Keywords: neural variability, movement variability, reaching movement, fMRI, motor control, kinematic variability, motor system

INTRODUCTION

Intertrial variability is a fundamental characteristic of human movements (e.g., Harbourne and Stergiou, 2009). Variability of specific kinematic components such as movement extent and movement direction is thought to be governed by independent neural processes (Gordon et al., 1994a) according to the demands of the examined motor task (Latash et al., 2007; Todorov, 2004). While kinematic variability is detrimental for movement accuracy, it is thought to be critical for motor learning (e.g., Braun et al., 2009; Herzfeld and Shadmehr, 2014; Teo et al., 2011; Wilson et al., 2008). Indeed, it has recently been reported that individuals with higher levels of movement variability exhibit faster motor learning (Wu et al., 2014), thereby suggesting that individuals who consistently behave in a more variable manner may be faster learners.

Intertrial variability is also a fundamental characteristic of neural activity, which is apparent in the variable timing and amplitude of neural responses across trials containing an identical stimulus or task (e.g., Churchland and Abbott, 2012; Dinstein et al., 2015; Faisal et al., 2008; Sauerbrei et al., 2015; Stein et al., 2005). As with kinematic variability, intertrial neural variability also seems to be important for motor learning as demonstrated in studies with songbirds (Kao et al., 2005; Ölveczky et al., 2011; Woolley and Kao, 2015) and primates (Mandelblat-Cerf et al., 2009). Given that neural activity generates behavior, one may expect that intertrial variability in the activity of specific neural populations would generate corresponding intertrial variability in specific kinematic components of movement (e.g., movement extent and/or direction).

Studies that have examined the potential relationship between neural and kinematic variability have proposed three alternative theories. The first theory proposed that kinematic variability during visually guided movements is mostly explained by variability in sensory neural populations. For example, intertrial variability in the initial speed of smooth-pursuit eye movements can be explained by variability in the estimation of target speed in MT neurons (Osborne et al., 2005; for review, see Lisberger and Medina, 2015). In contrast, the second theory has proposed that kinematic variability during reaching movements is generated by variable preparatory (motor planning) activity of premotor and primary motor neurons (Chaisanguanthum et al., 2014; Churchland et al., 2006). Finally, the third theory has suggested that kinematic variability is caused by neural and neuro-muscular variability during actual movement execution (van Beers, 2009; van Beers et al., 2004). Taken together, these studies suggest that distinct neural variability sources are correlated with kinematic variability under different experimental conditions, which include the sensory-motor requirements of the examined motor task (e.g., smooth-pursuit ocular movements versus reaching movements) and the temporal structure of the task (e.g., imposing a delay between movement planning and execution). Notably, most of the electrophysiology studies described above

have focused on the relationship between movement velocity variability (rather than movement extent or direction) and neural variability.

In the current study we examined several outstanding questions regarding kinematic variability, neural variability, and their potential relationship in humans: 1. Do individual subjects exhibit consistent magnitudes of *kinematic variability* regardless of the movements that they are performing (e.g., when using right or left arm)? 2. Do individual subjects exhibit consistent magnitudes of *neural variability* regardless of the movements that they are performing? 3. If so, are between-subject differences in kinematic variability explained by differences in neural variability in specific sensory and/or motor brain areas? Answering these questions is critical for establishing that individual subjects exhibit characteristic kinematic and neural variability magnitudes that may predispose them to exhibit particular motor learning capabilities while also adding new insights regarding the potential relationship between neural variability and kinematic variability.

To answer the questions above and relate the findings with the existing behavioral and electrophysiology literature we quantified intertrial variability of movement direction, peak velocity, and extent across slice (out-and-back) reaching movements. These movements were performed to four peripheral targets with either right or left arm on a touch screen while brain activity was recorded with fMRI. We then quantified fMRI response variability in the primary motor, premotor, parietal, and visual brain areas of each subject and examined whether it was possible to predict between-subject differences in kinematic variability according to neural variability magnitudes in specific brain areas. Note that in our study all movements were performed without visual feedback to preclude the potential influence of neural variability associated with visual input.

RESULTS

***Intertrial kinematic Variability*.**

Subjects exhibited considerable intertrial kinematic variability in their slice (out-and-back) movements to each of the four targets (Figure 1B). We focused our analyses on three kinematic components: direction (at end-point) and extent, which are commonly reported in behavioral studies (Gordon et al., 1994a), and peak

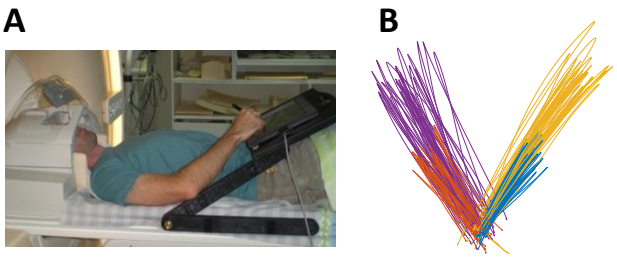

Figure 1. (**A**) *Experimental setup*. (**B**) Representative example of movement paths of one subject. Different colors represent slice movements to the four targets.

velocity, which is commonly reported in electrophysiology studies (Churchland et al., 2006; Cisek, 2006). Note that movement extent and peak velocity are mutually dependent, because peak velocity scales with increasing target distance (Gordon et al., 1994b).

We computed the coefficient of variation (CV) for extent and peak velocity to examine between-subject differences in movement variability that exceed those predicted by differences in the mean (mean movement extent and peak velocity were correlated with their standard deviations, r = 0.35 and r = 0.53 respectively, across targets and arms; CV was not correlated with mean movement extent and peak velocity, r = -0.18 and r = 0.02, respectively). Intertrial variability in movement direction was not correlated with the mean direction ($r < 0.1$). We, therefore, used the standard deviation (SD) across trials to quantify movement direction variability.

When examining the components in isolation, individual subjects exhibited consistent magnitudes of intertrial variability for each component (Figure 2A&B). Thus, subjects who were, for example, more variable in their movement extents to one target tended to be more variable in their movement extents to all other targets. We quantified this by computing the mean Pearson correlation coefficients across all target pairs for movements performed with the right arm (r = 0.29, 0.41, and 0.39 for movement direction, extent, and peak velocity respectively, $q(FDR) < 0.001$) and left arm (r = 0.46, 0.58, and 0.40 for movement direction, extent, and peak velocity respectively, $q(FDR) < 0.001$). Significant correlations were also evident when comparing the variability magnitudes of each kinematic component across arms (Figure 2C). For example, subjects with more variable movement extents in right arm movements exhibited more variable movement extents in left arm movements as well (r = 0.63, 0.68, and 0.54 for movement direction, extent, and peak velocity, $p < 0.001$).

In line with previous reports (Gordon et al., 1994a), intertrial variability of movement extent and peak velocity were strongly correlated in movements of the right arm ($r = 0.72$, $p < 0.001$; Figure 2D) and left arm ($r = 0.87$, $p < 0.001$; Figure 2E), but variability of movement extent and movement direction (right arm: r = 0.04, p = 0.41; left arm: r = 0.28, p = 0.07) or peak velocity and movement direction (right arm: r = -0.09, p = 0.69; left arm: r = 0.18, p = 0.16) were not. Thus, individuals who exhibited large movement extent and peak velocity variabilities did not necessarily exhibit large movement direction variability and vice versa.

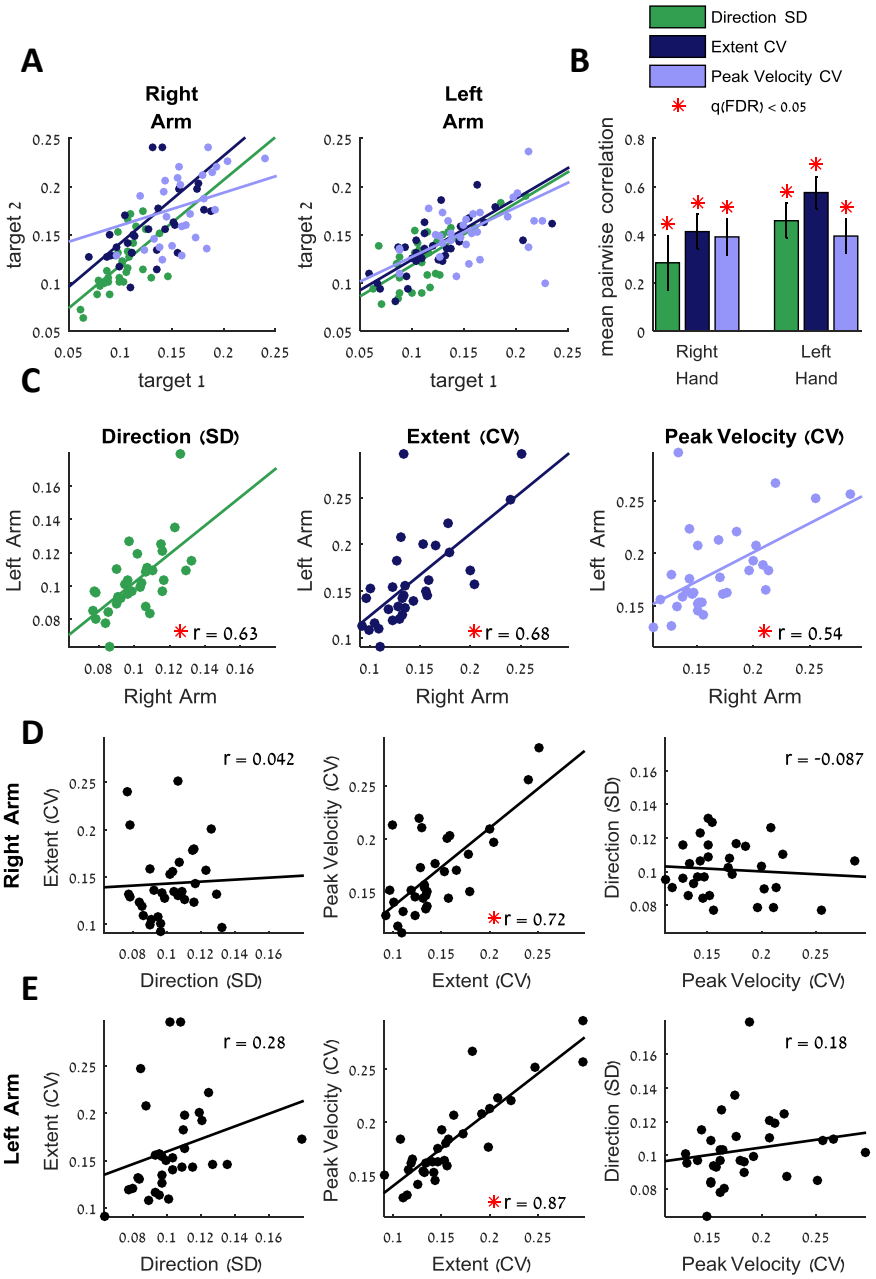

Figure 2. *kinematic variability correlations.* (**A**) Movement direction (standard deviation, SD), movement extent (coefficient of variation, CV), and peak movement velocity (CV) of left and right arm movements toward a pair of targets. Each data point represents the variability of movements of one subject to the two targets. (**B**) Means and SEM of the Pearson correlations of the variability across all pairs of targets. Significant correlations are marked with asterisks. (**C**) Scatter plots of the kinematic variability, averaged across targets, of the right and left arms. Each data point represents variability of movements of a single subject. (**D,E**) Scatter plots of the kinematic variability, averaged across targets, of the right (**D**) and the left (**E**) arms. For all scatter plots: data points represent different subjects; lines represent linear fits. Significant correlations are marked with red asterisks.

Intertrial fMRI variability

All subjects exhibited robust fMRI responses during the execution of slice reaching movements to the different targets (Figure 3). For each subject, we quantified the fMRI response on each trial in each region of interest (ROI) in the following manner: First, we projected-out (i.e., regressed out) the fMRI time-courses of the ventricles ROI and a gray-matter ROI (containing all gray matter voxels), which may represent fMRI activity that is not necessarily of neural origin (see Methods). Second, we computed the mean fMRI response in each ROI to each target (Figure 4A) and used it in a general linear model analysis to estimate the amplitude of response (i.e., beta value)

for each trial/movement in the experiment (Figure 4B). Third, we quantified intertrial fMRI variability by computing the standard deviation of beta values across trials to each of the targets (Figure 4B&C).

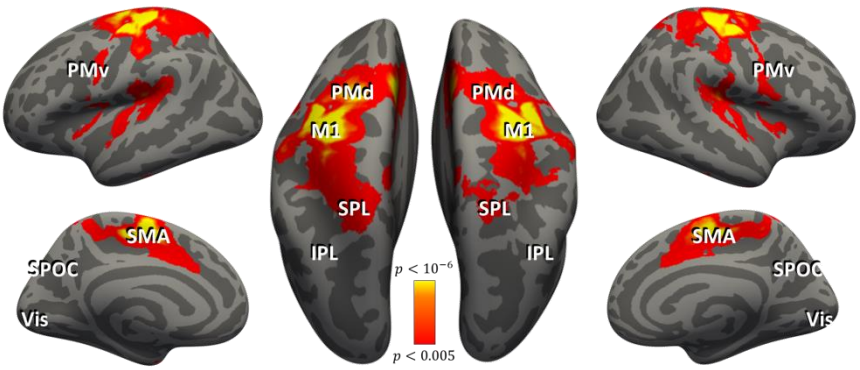

Figure 3. *Regions of interest*. Cortical areas that exhibited larger responses during arm movement are shown in red/orange. Results calculated across all subjects (random-effects GLM) and displayed on inflated hemispheres of a template brain. The general locations of the selected ROIs are outlined in circles (actual ROIs were anatomically and functionally defined in each subject). ROIs: Primary motor cortex (M1), dorsal premotor cortex (PMd), ventral premotor cortex (PMv), supplementary motor area (SMA), inferior parietal lobule (IPL), superior parietal lobule (SPL), superior parieto-occipital cortex (SPOC), and the visual cortex (Vis).

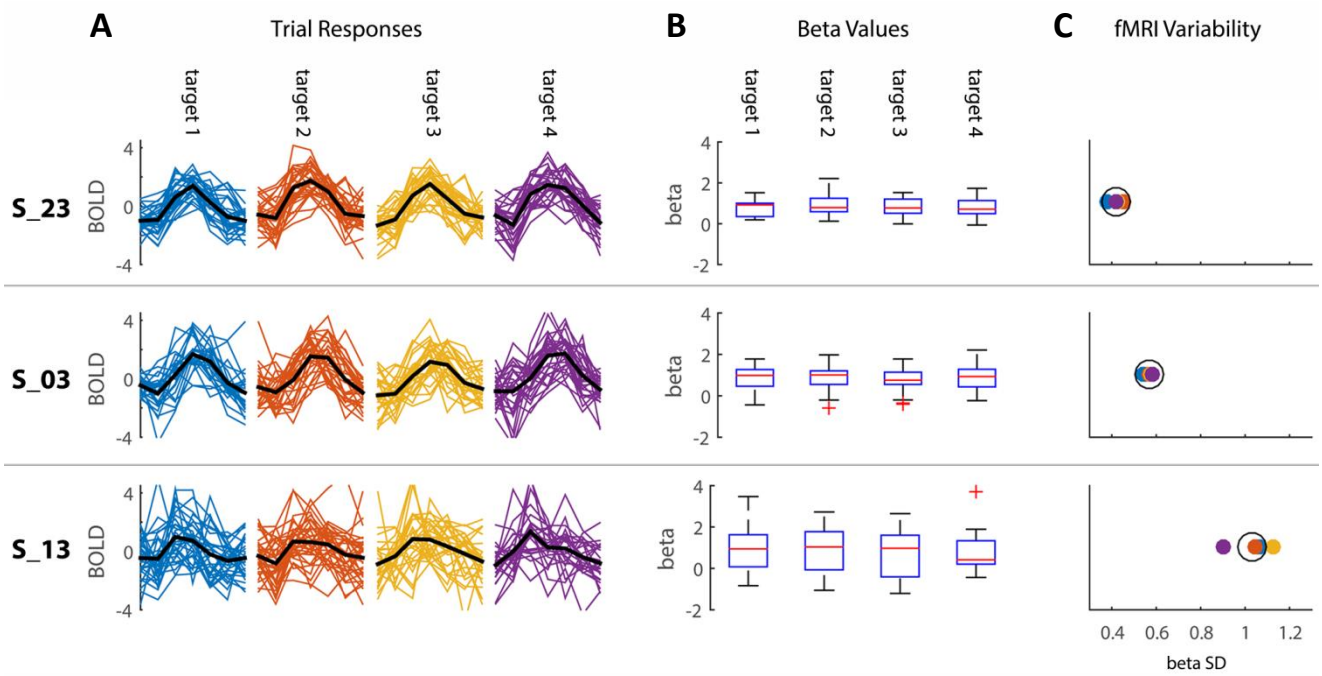

Figure 4. *fMRI Variability*. Methods for quantifying the fMRI variability presented over left M1 of 3 example subjects during right arm movements. (**A**) Trial responses of the mean time course across voxels in the ROI in z-scored BOLD signal units, color coded for the different targets (same colors as in figure 1B). (**B**) Boxplots of the beta values of all trials (a boxplot per subject per target, in same order as in A). (**C**) fMRI variability (measured as standard deviation over the beta values of all trials) for each subject to each target (color code is the same as in A). The averaged variability of each subject across targets is plotted as a black circle.

Intertrial fMRI variability was correlated across all pairs of targets in most of the examined ROIs (Figure 5). Hence, subjects who exhibited more variable brain responses when moving to one

target also exhibited more variable brain responses when moving to other targets. During right arm movements all ROIs in the left hemisphere, except SPOC, and all ROIs in the right hemisphere, except SPOC and PMd, exhibited significant pair-wise correlations across targets (q(FDR) < 0.05) and similar results were also apparent for left arm movements (data not shown).

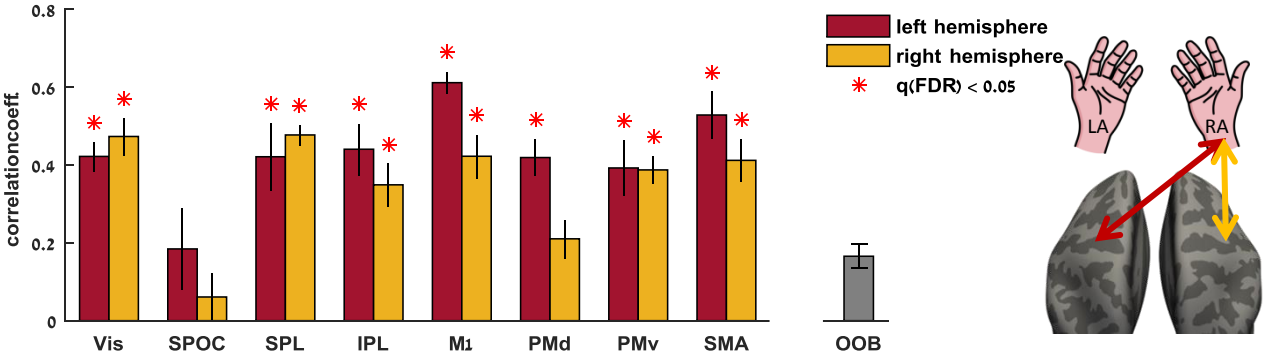

Figure 5. *fMRI Variability correlations*. Mean fMRI variability correlations across all pairs of targets during right arm movements within each ROI contralateral (contra) and ipsilateral (ipsi) to the moving arm. Significant correlations are marked with asterisks. Significant correlations are marked with red asterisks.

Most importantly, fMRI variability was also correlated across movements performed with the right and left arms (q(FDR) < 0.05; Figure 6). This was evident in two complimentary analyses: 1) fMRI variability was significantly correlated (r > 0.39, q(FDR) < 0.05) across left and right arm movements in each of the left hemisphere ROIs (Figure 6, red bars) except for M1 (similar results were also apparent in the right hemisphere ROIs). 2) fMRI variability was significantly correlated (r > 0.39, q(FDR) < 0.05) across left and right arm movements in all contralateral ROIs (e.g., variability in left M1 during right arm movements was significantly correlated with variability in right M1 during left arm movements, Figure 6, purple bars), except for Vis, IPL, and PMv. Thus, individual subjects who exhibited more variable fMRI responses in most of the motor ROIs while moving their right arm also exhibited more variable responses in that ROI and/or in the contralateral ROI when moving their left arm.

To determine whether these correlations were due to differences in measurement noise across subjects, we examined intertrial variability in 8 ROIs located outside the brain (one ROI in each corner of the scanned volume). fMRI variability magnitudes were not significantly correlated across trials with movements to different targets (r < 0.17, q(FDR) > 0.2) or movement performed with different arms (r <0.3, q(FDR) > 0.07). This demonstrates that the results above were not generated by potential between-subject differences in MRI scanner noise.

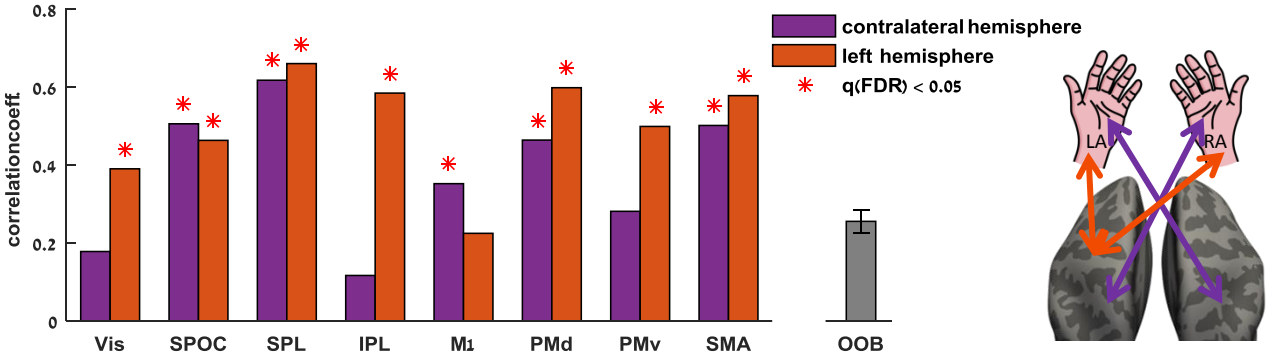

Figure 6. *fMRI Variability correlations*. Neural variability correlations across movements of the right and left arms, compering variability both in the same ROI (left/right) and in ROIs with contralateral to the moving arm. Significant correlations are marked with red asterisks.

Relationship between kinematic and fMRI variability

Subjects with larger intertrial fMRI variability exhibited larger intertrial extent variability (i.e., subjects with "noisier" brain responses exhibited "noisier" movement extents; Figure 7A&B). The strongest and most significant correlation was apparent between movement extent variability and fMRI variability in ipsilateral IPL ($r = 0.51$, $q(FDR) < 0.05$ for right arm movements, and $r = 0.53$, $q(FDR) < 0.01$ for left arm movements). For left arm movements a significant correlation with movement extent variability was also apparent in the contralateral (right) IPL ($r = 0.51$, $q(FDR) < 0.01$). There were no significant correlations between fMRI variability and movement direction or peak velocity variability in any of the examined ROIs.

To demonstrate the specificity of these results to the examined cortical ROIs, we performed the same analysis with fMRI responses extracted from the ventricles ROI and two ROIs located outside the brain. In both cases the correlations were small and non-significant ($r < .25$, $q(FDR) > 0.2$).

In an additional analysis we examined whether between-subject differences in kinematic variability could be better explained by combining fMRI variability measures across different sets of ROIs. Specifically, we performed a partial least squares regression analysis that attempted to explain between-subject differences in variability of movement direction, extent, or peak velocity using predictors from either parietal (bilateral SPL and IPL) or motor (bilateral M1 and PMd) ROIs (Figure 7C). Intertrial fMRI variability in posterior parietal cortex explained 23% of the between-subject differences in extent variability for right arm movements and 29% for left arm movements, while intertrial variability in motor cortices (bilateral M1 and PMd) explained only 8% and 6% of the between-subject differences in extent variability for right and left arm movements respectively. In order to ensure no contribution of head motion to this correlations we repeated the analysis after Regressing-out head motion variability (calculated as SD over time of each of the six parameters

obtained by rigid body correction of head motion; three translations and three rotations) from the fMRI variability of each subject in each ROI. This approach revealed equivalent results (Figure 7D). These results were, therefore, not generated by potential between-subject differences head motion magnitudes.

Furthermore, intertrial fMRI variability in posterior parietal cortex explained 13% and 16% of the between-subject differences in peak velocity variability for right and left arm movements respectively, as well as 14% and 9% of the movement direction variability. Intertrial fMRI variability in motor cortices explained 4% and 6% of the between subject differences in peak velocity variability for right and left arm movements respectively, as well as 11% and 3% of the movement direction variability.

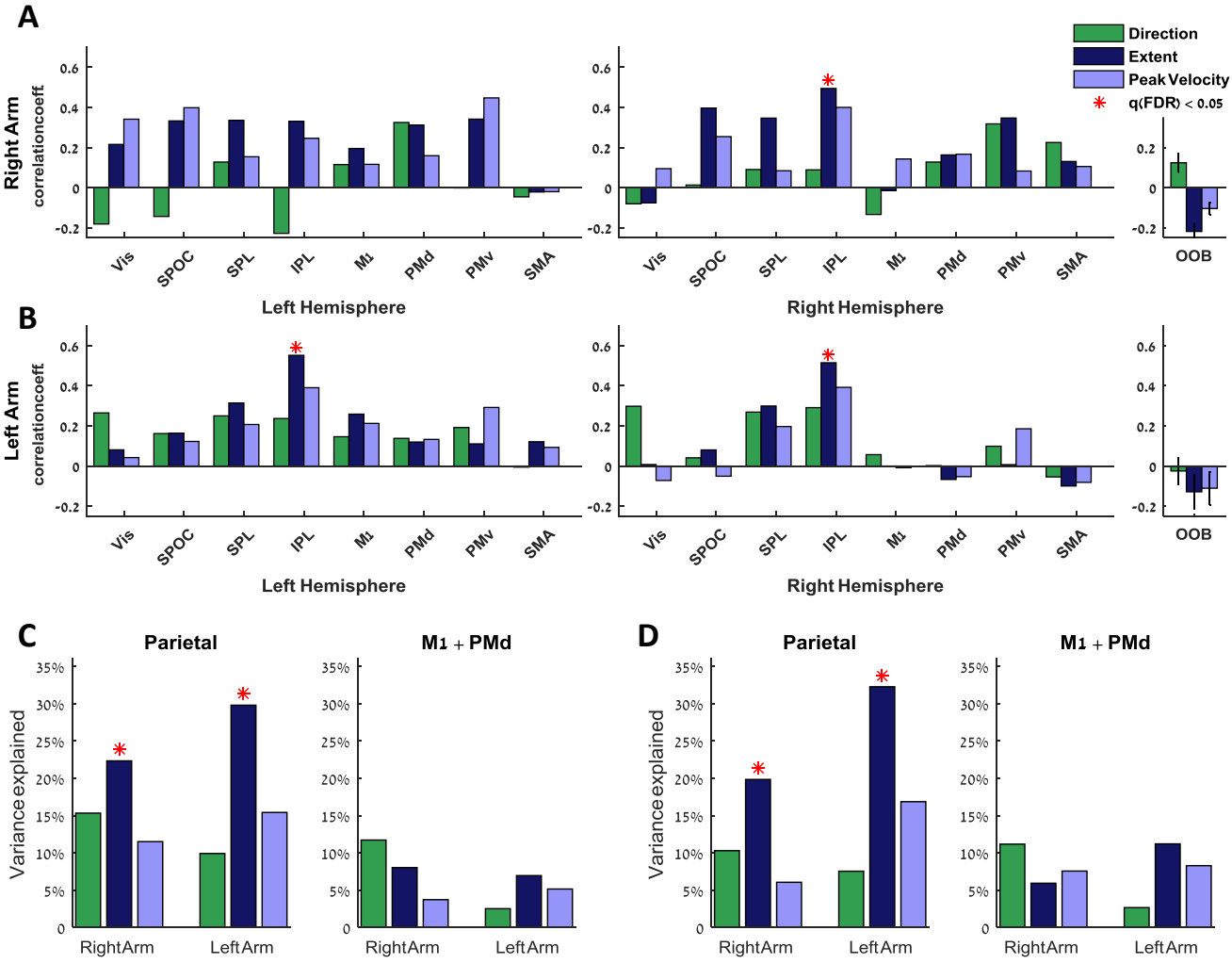

Figure 7. *Kinematic–fMRI Variability correlations*. Pearson correlation coefficients between the variability of the kinematic variables and the neural variability of the different ROIs during right (**A**) and left (**B**) arm movements (green: SD of movement direction; dark and light blue: CVs of extent and peak velocity, respectively). (**C**) Variance explained in the across subjects differences in kinematic variability by Partial Least Squares regression of neural variability in sets of ROIs – parietal (bilateral SPL and IPL), frontal (bilateral M1 and PMd). (D) Variance explained by PLS (same as C) after regression out of the variance explained by head movements. Significant correlations are marked with red asterisks.

Searchlight analysis

In a final analysis we used a whole-brain searchlight approach (Kriegeskorte et al., 2006) to map the correlations described above across the entire cortical surface so as not to restrict the analysis to a-priori ROIs. We used a volumetric searchlight cube of 125 functional voxels in the cortical gray matter segmented within the native space of each subject. For each searchlight cube, we calculated the intertrial neural variability (in the same way we did for each ROI, as described above) and then registered the resulting variability maps of all subjects to a common inflated brain. We calculated Pearson correlation coefficients to estimate the relationship between intertrial fMRI variability and movement extent variability across subjects. The searchlight map revealed complementary results to those described above and demonstrated that significant positive correlations between fMRI variability and movement extent variability were mostly apparent in bilateral parietal cortex (Figure 8). Equivalent maps examining the relationship between fMRI variability and peak velocity or movement direction variability did not yield any significant correlations and are, therefore, not presented. Note that the searchlight map is highly symmetric across hemispheres and is relatively similar across movements of the right (Figure 8, Red) and left (Figure 8, Blue) arms.

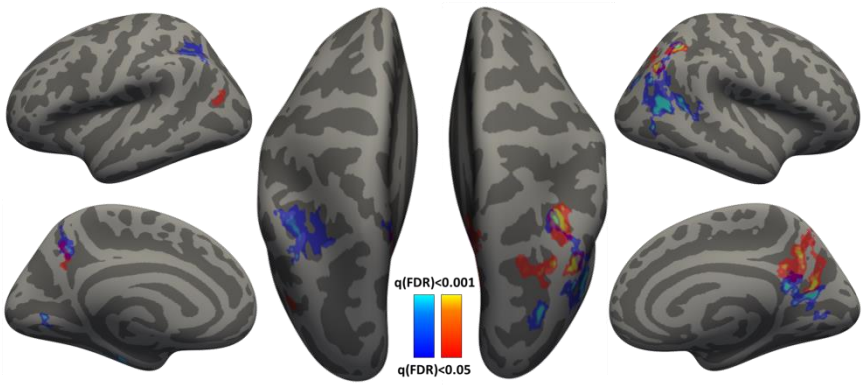

Figure 8. *Searchlight analysis* displaying cortical areas with significant correlations between movement extent variability and fMRI variability across subjects. Results for right (red) and left (blue) arm movements are presented on the inflated cortical anatomy of a single subject. Correlation significance was determined based on student t-test (FDR corrected).

Alternative sources of fMRI variability

Between subject differences in fMRI variability can be generated by several non-neural sources that need to be considered. First, previous studies of fMRI variability have reported that the strength of the mean fMRI response was correlated with the magnitude of intertrial variability across subjects (Ferri et al., 2015; He, 2013). To measure intertrial fMRI variability in individual subjects independently of their mean response, we estimated intertrial variability with respect to the mean hemodynamic response function (HRF) apparent in each ROI of each subject (see methods). This enabled us to compute the relative fMRI variability with respect to the actual HRF as opposed to using a canonical HRF that assumes an identical shape and amplitude across subjects. Indeed, when

using this method, intertrial fMRI variability was not correlated with mean fMRI response in any of the ROIs ($r < 0.15$, $p > 0.1$).

Second, head-motion artifacts can generate fMRI variability across trials. To ensure that such differences were not behind our findings, we regressed-out estimated head-motion parameters from the fMRI activity of each voxel in the brain before performing the analyses (see methods). Furthermore, we estimated head motion magnitude in each of the subjects by computing the variability of head motion over time. There were no significant correlations between head motion variability and their fMRI variability estimates in any of the examined ROIs ($r < .3$, $p > 0.1$). Finally, regressing-out head motion variability from fMRI variability did not change the results of the main analysis (Figure 7D). This ensured that the results were not due to potential head motion differences across subjects.

Third, we regressed-out the mean fMRI time-courses of the lateral ventricles and an ROI containing all gray-matter voxels (sometimes called the global component). These time-courses represent fMRI changes that may be associated with changes in respiration, blood pressure, and other non-neural origins.

DISCUSSION

When examining specific kinematic variables (i.e., movement extent, peak velocity, or direction), subjects exhibited consistent variability magnitudes which were correlated across movements to different targets when performed with either arm (Figures 2). For example, individuals with relatively larger movement extent variability tended to exhibit larger variability regardless of target location or arm used to perform the movement. Analogous findings were also apparent in fMRI response variability of specific cortical regions (Figures 4&5). Subjects with larger fMRI response variability tended to exhibit larger variability regardless of target location and of arm used to perform the movement. Most importantly, fMRI variability magnitudes in parietal cortex explained a considerable portion of between-subject differences in movement-extent variability (23-29%), while fMRI variability in primary motor or premotor cortices explained a much smaller portion (6-8%, Figure 7&8). We speculate that intertrial variability in the activity of brain areas that plan movements may generate movement-extent variability in a target and effector invariant manner, potentially predisposing individual subjects to exhibit different motor capabilities.

Two important strengths of the current study are: 1) By quantifying variability across movements to multiple targets, which were performed by either right or left arm, we were able to

generalize conclusions across targets and effectors. 2) By simultaneously recording kinematic and whole-brain fMRI data, we were able to determine the relative contribution of fMRI variability magnitudes in specific brain areas to the variability of specific kinematic components. Together, these strengths enabled us to carry out the first study to ever examine the relationship between kinematic and cortical response variability in humans.

Neural sources of kinematic variability

Previous theories have suggested that intertrial kinematic variability is predominantly generated by the variable activity of sensory neural populations (Osborne et al., 2005; for review, see Lisberger and Medina, 2015), premotor and primary motor neural populations involved in motor planning (Chaisanguanthum et al., 2014; Churchland et al., 2006), or by neuro-muscular variability that characterizes actual movement execution (van Beers, 2009; van Beers et al., 2004). It is entirely possible, however, that different sources of neural variability generate kinematic variability under different experimental conditions, such that behavioral motor variability would embody the sum of multiple neural variability sources (for review see Faisal et al., 2008). With this in mind, neural variability in a particular brain area is likely to explain a certain proportion of kinematic variability. Furthermore, neural variability in different brain areas may generate variability in different kinematic components of movements (e.g., movement extent versus movement direction).

Our results indeed demonstrate that about a quarter of the between-subject differences in movement extent variability are explained by individual neural variability differences in parietal cortex, which is thought to play a dominant role in the planning of reaching movements (Cohen and Andersen, 2002). This finding resonates with previous electrophysiology reports that claim that variability in neural activity during preparation for movement in primary motor and dorsal premotor cortex is correlated with peak movement velocity (Chaisanguanthum et al., 2014; Churchland et al., 2006). While previous electrophysiology studies did not examine neural variability in parietal areas, our results suggest that it will be fruitful to extend these studies to areas such as IPL which may have even stronger correlations with the intertrial kinematic variability than that already reported in M1 and PMd (Figure 7).

It may seem surprising that correlations between kinematic variability and fMRI variability were remarkably weak in primary motor cortex given that M1 is thought to be the last brain area in the motor hierarchy that sends out the motor command to the muscles (e.g., Shadmehr and Krakauer, 2008). In humans, however, only 30% to 40% of the axons in the corticospinal tract originate from neurons in the primary motor cortex, while the rest originate from the premotor, supplementary motor, and posterior parietal cortices (Kandel et al., 2013). This means that neural variability in parietal regions may potentially generate kinematic variability downstream of M1, in spinal motor circuits. A potentially interesting analogy can be found in songbirds where a specific nucleus (the

lateral magnocellular nucleus of anterior nidopallium – LMAN) has evolved to inject direct neural variability into the motor circuits that control singing in order to enable juvenile birds to learn through trial and error (Ölveczky et al., 2011).

Finally, it is important to note that we and all previous electrophysiology studies on the topic measured variability only in the kinematics of the movement and not in the dynamics of the executed movements. It is highly possible that intertrial variability in movement dynamics (i.e., muscle activation), which are not necessarily captured in measures of kinematic variability, may be explained by intertrial neural variability in specific brain areas.

Decomposing neural variability

Neural variability can be decomposed into different spatial and temporal components using measures from different types of neuroimaging and electrophysiological techniques (Dinstein et al., 2015). When studying variability with fMRI, it is possible to simultaneously quantify intertrial variability in multiple different brain areas, but the temporal resolution of this measure is limited by the sluggish nature of the hemodynamic response (Heeger and Ress, 2002). This means that one can estimate a single fMRI response amplitude per trial (in each voxel or ROI) and then quantify intertrial variability across response amplitudes (Figure 4), but estimating intertrial variability in the timing of the response is not possible. Furthermore, since fMRI is not a direct measure of neural activity, but rather a measure of hemodynamic changes over time, intertrial variability in the function of neuro-vascular coupling mechanisms will be an inherent part of the fMRI intertrial variability measure.

This limits the ability to measure neural variability with fMRI and, therefore, limits the ability to relate neural variability and behavioral variability measures. With this in mind it is impressive that we were able to identify a consistent relationship between fMRI variability and movement extent variability which was similarly evident in movements of right and left arm (Figure 7 & 8). We speculate that stronger relationships may be revealed with direct measures of human neural activity such as ECOG recordings in patients who are candidates for epilepsy surgery.

Hemispheric lateralization

While arm movements are clearly generated and controlled by neural activity in the contralateral hemisphere (Penfield and Boldrey, 1937), we found significant correlations between movement extent variability and neural variability in both the contralateral and ipsilateral hemispheres. We speculate that neural variability in both hemispheres may, therefore, have an impact on the accuracy and reliability of arm movements. Several animal studies have indeed shown that M1 neurons are modulated by ipsilateral arm movements (Cisek et al., 2003; Donchin et al.,

1998; Mehring et al., 2003) and could even continuously represent ipsilateral limb position (Ganguly et al., 2009). Furthermore, previous human fMRI studies by us and others found directional tuning of arm movement (Fabbri et al., 2010; Haar et al., 2015) and finger-specific activity patterns across many levels of the cortical motor hierarchy in the ipsilateral hemisphere (Diedrichsen et al., 2013). The ipsilateral neural variability correlations, demonstrated in the current study, emphasize the relationship between the neural activity in the contralateral and the ipsilateral hemisphere, as well as the relevance of the ipsilateral neural activity to motor performance.

Variability and motor learning

Individual kinematic and neural variability intensities are likely to predispose individual subjects to exhibit different motor learning capabilities. While variability is clearly detrimental for movement accuracy, previous behavioral studies have reported that subjects who exhibited larger task-relevant movement variability were faster learners (e.g., Herzfeld and Shadmehr, 2014; Teo et al., 2011; Wu et al., 2014). Since a considerable portion of the differences in movement variability between subjects can be explained by the differences in their neural variability in motor planning areas, we speculate that individuals with larger neural variability in motor planning areas may be faster learners. A study relating neural variability with learning rates is, therefore, highly warranted.

Conclusions

The motor control literature has a long history of examining kinematic intertrial variability across movements to understand how the brain encodes movements and learns to perform new movements. This is the first study to examine how such kinematic variability may be associated with cortical intertrial variability in human subjects. Our results demonstrate that kinematic and cortical variabilities are stable individual traits, which appear consistently across movements to different targets when performed by either right or left arms. Furthermore, these variabilities are related such that subjects with larger neural variability in parietal motor areas exhibited larger variability in their movement-extents. We believe that these results represent an important first step for understanding how neural variability may generate movement variability in humans and, thereby, predispose individuals to exhibit distinct movement accuracy levels and different motor learning capabilities.

METHODS

Subjects. 32 right-handed volunteers with normal or corrected-to-normal visual acuity (15 women and 17 men, aged 22-36 (25.6±2.5)) participated in the present study. The Soroka Medical Center Internal Review Board approved the experimental procedures and written informed consent was obtained from each subject.

Experimental Setup and Design. Subjects lay in the scanner bore and viewed a back-projected screen through an angled mirror, which prevented any visual feedback of their arm and hand. An MRI-compatible digitizing tablet (Hybridmojo LLC, CA, USA) was placed over the subject's waist and used to track their arm movements (Figure 1A). Subjects performed slice (out-and-back) reaching movements from a central target to four peripheral targets differing in their directions and extents (Figure 1B) and did not receive any visual feedback of their arm location during movement. Each trial started with the presentation of a peripheral target for one second. Four seconds after the target disappeared, the central target changed from red to green, indicating that the movement should be performed by moving the stylus pen on the tablet. Subjects had one second to complete the movement after which the center target turned red and remained red for the entire inter-trial-interval (ITI), which lasted six seconds. There was no post-trial visual feedback or knowledge-of-results. All subjects preformed three experiments with each arm, each lasted 9 minutes and contained 11 movements to each of the four targets.

Movement Recording and Analysis. Kinematic data were recorded at 200 Hz. Trials with a reaction time of more than 1 second, trials with a movement angle error $>30^{o}$ (at peak velocity or end point), and trials with movement length that was <50% or >200% of the target distance were discarded from further analysis. Trials containing correction movements (i.e., velocity profiles with more than two peaks) were also removed. On average approximately 8% (std 3%) of the trials were discarded for each subject. There was no significant difference in the number of discarded trials between the two arms.

We quantified intertrial variability for each of three kinematic components: movement direction, movement extent, and peak movement velocity. Movement extent and peak velocity variabilities were normalized by their respective means so as to compute the coefficient of variation (CV). This was necessary, because the variability of these kinematic components scales with their mean (speed-accuracy trade-off; Schmidt et al., 1979). Movement direction variability was quantified by the standard deviation (SD) across trials. Each of these measures was computed for each target and each subject separately and then averaged across targets to compute a single extent, peak velocity, and direction variability measure for each subject.

MRI acquisition and preprocessing. Imaging was performed using a Philips Ingenia 3T MRI scanner located at the Ben-Gurion University Brain Imaging Research Center. The scanner was equipped with a 32 channel head coil, which was used for RF transmit and receive. Blood oxygenation level-dependent (BOLD) contrast was obtained using a T2* sensitive echo planar imaging (EPI) pulse sequence (TR = 2000 ms; TE = 35 ms; FA = 90^{o}; 28 slices; voxel size of 2.6*2.6*3 mm and with 0.6 mm gap). Anatomical volumes were acquired with a T1-weighted sagittal sequence (TR = 8.165 ms; TE = 3.74 ms; FA = 8^{o}; voxel size of 1*1*1 mm).

MRI data were preprocessed with the Freesurfer software package (http://surfer.nmr.mgh.harvard.edu, Fischl, 2012) and FsFast (Freesurfer Functional Analysis Stream). Briefly, this process includes removal of non-brain tissue and segmentation of subcortical, gray, and white matters based on image intensity. Individual brains were registered to a spherical atlas which utilized individual cortical folding patterns to match brain geometry across subjects. Each brain was then parcellated into 148 cortical ROIs using the Destrieux anatomical atlas (Destrieux et al., 2010). Functional scans were subjected to motion correction, slice-timing correction and temporal high-pass filtering with a cutoff frequency of two cycles per scan. Functional scans were registered to the high-resolution anatomical volume. No additional spatial smoothing was performed. Preprocessed data was imported into MATLAB (R2015a, *MathWorks Inc.* USA), and all further analysis was performed using custom software written in matlab.

Identification of regions of interest. Visual and motor regions of interest (ROIs) were defined a priori according to a combination of anatomical and functional criteria in the native space of each subject. We identified 8 commonly reported visual, visuomotor, and motor ROIs (Barany et al., 2014; Gallivan et al., 2011; Haar et al., 2015; Vesia and Crawford, 2012) by selecting 100 continuous functional voxels with the strongest activation during movements to the four targets that were located in the following anatomical areas:

- Primary motor cortex (M1) - anterior bank of the central sulcus in the hand knob area.
- Dorsal premotor cortex (PMd) - Junction of superior frontal sulcus and precentral sulcus.
- Ventral premotor cortex (PMv) - Junction of inferior frontal sulcus and precentral sulcus.
- Supplementary motor area (SMA) - Medial wall of the superior frontal gyrus, anterior to the central sulcus, posterior to the vertical projection of the anterior commissure.
- Inferior parietal lobule (IPL) - Dorsal portion of the angular gyrus and the middle segment of the intraparietal sulcus.
- Superior parietal lobule (SPL) - Anterior portion of the superior parietal lobule, superior to the IPS and slightly posterior to the postcentral sulcus.
- Superior parieto-occipital cortex (SPOC) - Superior portion of the parieto-occipital sulcus.
- Early visual cortex (Vis) - Occipital pole and calcarine sulcus

We defined 8 additional ROIs outside the brain (one ROI in each corner of the scanned volume). Those ROIs were used in control analyses to assess measurement noise during the scan of each subject.

Time course analysis. To ensure that our estimates of intertrial fMRI variability were not generated by head motion, respiration, and blood flow artifacts, we removed the following components from the fMRI time-course of each cortical voxel, through linear regression: (1) six head motion parameters obtained by rigid body correction of head motion (three translations and three rotations), (2) fMRI time-course from the lateral ventricles, and (3) the mean fMRI signal of the entire cortex (i.e., global component). In addition, we normalized the time-course of each voxel to a mean of zero and unit variance (i.e., Z-score). This ensured that overall time-course variance was equal across subjects such that our measure of inter-trial fMRI variability captured only task-related trial-by-trial variability differences across subjects rather than variability associated with the entire scanning session.

Intertrial fMRI variability. We extracted the mean hemodynamic response in each ROI of each subject by computing the mean across trials to each target. We then used this subject specific and target specific hemodynamic response function (HRF) to quantify how fMRI responses of single trials differed from their mean. We built a general linear model (GLM) with a row for every time-point and a column for every trial. Each column contained a delta function at trial onset, which was convolved with the relevant target specific hemodynamic response function. This enabled us to estimate a response amplitude associated for each trial using multiple regression. Intertrial fMRI variability for each target and each ROI was estimated as the standard deviation across beta values of all trials to the same target.

Previous studies have reported that when using a canonical HRF to estimate intertrial variability, the strength of the mean fMRI response is positively correlated with intertrial variability (Ferri et al., 2015; He, 2013). This is problematic, because it does not allow for a clear separation of the two measures and separate assessment of the behavioral relevance of each. By quantifying intertrial variability with respect to each subject's HRF, specifically in each ROI (rather than using a canonical HRF), we were able to entirely discount the mean HRF amplitude and shape from our analysis – yielding a pure measure of individual intertrial variability.

Correlations. We used Pearson correlation coefficients to assess whether individual kinematic variability magnitudes were correlated across targets, arms, and different kinematic components. Equivalent analyses were performed to examine whether individual fMRI variability magnitudes (in each of the examined ROIs) were correlated across targets and arms as well as between the variability of each kinematic component and fMRI variability in each ROI. We assessed the statistical significance using a permutation tests. We randomly shuffled the variability values of

the different subjects in each correlation analysis and computed the correlation. This process was repeated 5000 times to generate 5000 correlation values that represented a distribution of correlations expected by chance (null distribution). For the true (un-shuffled) value to be considered significant, it had to surpass the 97.5th percentile of the null distribution (i.e., the equivalent of a $p < 0.05$ value in a two-tailed t-test). We used the false discovery rate (FDR) correction (Benjamini and Hochberg, 1995; Yekutieli and Benjamini, 1999) to correct for the multiple comparisons across target pairs and across ROIs.

Searchlight analysis. In addition to the ROI analysis, we used a searchlight analysis (Kriegeskorte et al., 2006) to map the correlations between fMRI variability and kinematic variability (i.e., movement extent, peak velocity, or direction) throughout the entire cortex. Clusters of 125 functional voxels were defined using a cube with an edge length of 5 voxels around each gray matter voxel in the native space of each subject. fMRI variability was calculated for each cluster of voxels, as described above in the ROI analysis. After computing the variability map of each subjects, all maps were transformed to a standard cortical surface using Freesurfer, and correlation analysis between kinematic and fMRI variabilities were performed for each kinematic measure using movements performed by either right or left arm. This yielded six correlation maps (three kinematic variables and two arms). A student t-test was used to determine the significance of the correlation across subjects in each vertex. We used FDR correction to correct for the multiple comparisons performed across vertices (Storey, 2002).

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