# Scale-Invariant Movement Encoding in the Human Motor System

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#### SUMMARY

How does the human motor system encode our incredibly diverse motor repertoire in an efficient manner? One possible way of encoding movements efficiently is to represent them according to their shape/trajectory without regard to their size, by using neural populations that are invariant across scale. To examine this hypothesis, we recorded movement kinematics and functional magnetic resonance imaging (fMRI) while subjects wrote three letters in two different scales. A classification algorithm was trained to identify each letter according to its associated voxel-by-voxel response pattern in each of several motor areas. Accurate decoding of letter identity was possible in primary motor cortex (M1) and anterior intraparietal sulcus (aIPS) regardless of the letter's scale. These results reveal that large, distributed neural populations in human M1 and aIPS encode complex handwriting movements regardless of their particular dynamics and kinematics, in a scale-invariant manner.

#### INTRODUCTION

Handwriting is one of the most exciting achievements of the human motor system, requiring extreme dexterity and precision. A remarkable feature of handwriting is that the geometrical shape of an individual's handwriting remains consistent across different scales and even when executed with different effectors (van Galen and Teulings, 1983; Raibert, 1977; Wright, 1990). These findings have been interpreted as evidence for a hierarchical organization of motor control (Bernstein, 1935; Georgopoulos, 1990; Wright, 1990) where movements are first planned according to their path/geometry and then translated into precise kinematics and dynamics (Viviani and Flash, 1995). Such a structured organization is thought to enable efficient encoding of our vast and diverse motor repertoire. But how exactly is this hierarchal motor control implemented by neural populations in different motor system areas?

Common descriptions of the motor system's hierarchy suggest that the anterior intraparietal sulcus (aIPS) and adjacent parietal regions are high-level areas, which contain neural populations that plan future movements (Snyder et al., 1997) and encode movements according to their abstract intentions or goals (Hamilton and Grafton, 2006). In contrast, primary motor cortex (M1) is often described as a low-level area containing neural populations that encode instantaneous dynamic (Evarts, 1968; Kakei et al., 1999) and/or kinematic (Georgopoulos et al., 1982; Moran and Schwartz, 1999) movement variables, which govern the moment-by-moment execution of movements. It is important to note, however, that this view is mostly based on studies with nonhuman primates who were trained to perform simple movements such as applying a static force (Kakei et al., 1999), moving a single joint (Cheney and Fetz, 1980), or performing straight reaching movements toward peripheral targets (Georgopoulos et al., 1982). Studies that have employed more elaborate movements have challenged this view and suggested that M1 neurons encode more complex time-evolving trajectories (Hatsopoulos et al., 2007; Hocherman and Wise, 1991) or goal-directed actions (Graziano et al., 2002a) in a manner that is invariant to specific movement details. These later studies suggest that the hierarchical organization of the motor system is less distinct than originally proposed.

In the current study we focused on a particular aspect of hierarchical motor control: invariance to movement scale. Subjects wrote three different letters at two different scales and did not receive any visual feedback of their moving hand, while we recorded their brain activity with fMRI and their movement kinematics via a touch screen. Writing the same letter at different scales alters the executed movement dynamics (e.g., relative activity of proximal versus distal muscles and joints [Lacquaniti et al., 1987]) and kinematics (e.g., average movement speed and duration [Wright, 1990]) but retains the movement's relative shape. Multivariate classification analyses revealed that it was possible to accurately decode both the identity and the scale of each executed letter according to its associated voxel-byvoxel response patterns in M1 and aIPS. Most importantly, it was possible to accurately decode the identity of each letter regardless of its scale (i.e., training the classifier on small movements enabled accurate decoding of large movements and vice versa). We interpret these results as evidence for the existence of large distributed neural populations in M1 and aIPS that encode the shape of a movement in a relatively abstract manner, regardless of its precise scale. These results challenge descriptions of a strict hierarchy in which M1 is a low-level brain area concerned only with encoding instantaneous movement dynamics. Instead, these findings support descriptions of more distributed, abstract (scale-invariant) movement encoding across multiple levels of the motor hierarchy.





#### Figure 1. Experimental Setup and Design

(A) Kinematics were recorded with an MRI-compatible digitizing tablet. Subjects viewed a back-projected screen through a tilted mirror, which prevented any visual feedback of the movements.
(B) Each trial began with an auditory instruction indicating the letter and scale to be executed (e.g., "large n"), which was followed by the fixation cross turning green (subject had 4 s to write the letter), then red (subject had 4 s to return to a starting point), and then black (subject had 4–8 s of rest).

large and small scales were indeed strongly correlated (correlation values: a, s, n = 0.93, 0.96, 0.94, averaged across subjects, SEM: 0.015, 0.007, 0.011) (Figure S1 available online).

## Univariate Analysis and ROI Selection

A whole-brain statistical parameter map (SPM) analysis showed that the typical

#### RESULTS

Subjects wrote three lowercase letters (either a, s, or n) in large or small scales (1:2 ratio) without any visual feedback during several hundred trials. Movement kinematics were recorded with a touch screen and brain activity was recorded by fMRI (Figure 1).

#### **General Movement Parameters**

Subjects were successful in keeping a scaled ratio of ~1:2 between small and large movements despite the lack of visual feedback. Mean letter size (measured by path length) of large and small a, s, and n equaled 32.0, 22.6, 32.2 cm, and 13.1, 10.5, 13.0 cm, respectively (SEM: 1.91, 1.13, 1.82 and 0.88, 0.69, 0.76) (Figure 2A). Each large letter was executed with significantly faster speed and longer duration than the equivalent small letter (paired t tests, Bonferroni corrected p < 0.001, Figures 2B and 2C).

#### **Similarity of Path Shape**

Path shape was similar across trials of the same letter regardless of size (Figure 3). Shape similarity was assessed separately for each subject via the Procrustes transformation (see Experimental Procedures). The Procrustes distance is an index with a range of 0–1 that is used to compare pairs of movement paths while ignoring their velocity, absolute position, orientation, and scale (a distance of zero indicates absolute shape identity). The Procrustes distances between trials of the same letter were small, regardless of their scale (mean < 0.1 for all three letters, averaged across subjects, SEM < 0.004), indicating that the shape of each letter across trials and scales was highly similar. For comparison, the Procrustes distances across trials containing different letters were much larger (mean = 0.43, pooled across letters and subjects, SEM 0.02).

We also assessed the correlation between velocity profiles of same letter identity across scales after normalizing their duration. Normalized velocity profiles of the same letter written in cortical and subcortical motor areas responded robustly during letter-writing trials (Figure 4). We used the functional responses of each subject to identify eight motor regions of interest (ROIs) individually in each subject: left primary motor cortex (M1), left anterior intraparietal sulcus (aIPS), left dorsal premotor cortex (dPM), left ventral premotor cortex (vPM), supplementary motor area (SMA), left putamen (PTM), right cerebellum (CRB), and left insular cortex (INS). These motor ROIs were defined based on a combination of anatomical and functional criteria (see Experimental Procedures). Two control ROIs that did not exhibit activation during movement execution were also identified: left orbito-frontal cortex (OFC) and an out-of-brain region (Out of brain). Because motor control is clearly lateralized, all ROIs were selected in the contralateral left hemisphere (movements were performed with the right hand), apart for the ipsilateral right cerebellum ROI (Nitschke et al., 1996). Anatomical landmarks and sizes of all ROIs are listed in Table 1.

All motor cortical and subcortical ROIs exhibited significantly stronger fMRI responses during execution of large letters than during execution of small letters, except vPM (paired t tests, Bonferroni corrected p < 0.05) (Figure S2).

#### **Classification of Letter Scale**

An initial step in assessing scale invariance is to identify the response components that are associated with movement scale. Because the mean response of most motor system ROIs was significantly larger during execution of large letters (Figure S2), we first tested whether the overall mean ROI response amplitude enabled accurate decoding of letter scale. Randomly selected groups of three trials from each letter and scale were averaged to create exemplars/samples with better signal-to-noise ratio for the classification procedures (see Experimental Procedures). We trained a classifier to distinguish letter scale on exemplars belonging to each letter separately (within-letter classification) and tested it by a "leave one out" cross-validation scheme. We

Scale-Invariant Movement Encoding





Figure 2. General Movement Parameters

(A) Path length was approximately twice as large for the large letters than for the small letters. (B) Mean speed was significantly higher for the

large letters.

(C) Movement duration was significantly longer for the large letters.

Black bars, large-scale movements; white bars, small-scale movements. All results are averaged across trials and across subjects. Error bars, SEM across subjects. Asterisks: Bonferroni corrected p < 0.001.

also performed an equivalent analysis across letters (across-letter classification) where we trained the classifier with exemplars of two letters and tested the ability to decode movement scale on trials of the third letter. It was possible to decode the scale of a letter from the corresponding mean ROI amplitude with significant above-chance accuracy in all motor ROIs except for vPM (Figures 5 and S3): M1 (within letter, 66%–82%; across letters, 59%-79%), aIPS (65%-76%; 62%-74%), dPM (64%-68%; 59%-68%), SMA (67%-76%; 64%-74%), PTM (60%-66%; 58%-66%), CRB (64%-72%; 60%-71%), and INS (62%-70%; 58%-66%). Randomization analyses were performed to determine whether the decoding accuracy in each ROI was significantly above chance (see Experimental Procedures).

We next performed the same classification analyses on the voxel-by-voxel response patterns of single exemplars after de-meaning each trial such that the mean response across the ROI equaled zero. The point of this analysis was to determine whether small and large movements differed not only in their mean responses, but also in their voxel-by-voxel response patterns. Classification of de-meaned response patterns yielded significantly above-chance decoding accuracy of scale, both within-letter and across-letters, in all motor ROIs (Figures 5 and S3): M1 (within letter, 83%-92%; across letters, 76%-89%), aIPS (84%-88%; 77%-87%), dPM (73%-82%; 71%-81%), vPM (64%-75%; 68%-75%), SMA (78%-87%; 73%-84%), PTM (62%-67%; 62%-69%), CRB (78%-84%; 69%-78%), and INS (67%-79%; 70%-77%). The ability to decode letter scale across letters (i.e., when training the classifier on two letters and testing it on another) suggests that each scale was associated with a scale-specific voxel-by-voxel response pattern, which was similar across letters.

Specific movement-scale response components were, therefore, evident in both the mean ROI response and the de-meaned voxel-by-voxel pattern of all motor system ROIs (except for vPM).

#### **Classification of Letter Identity**

We performed equivalent classification analyses to determine whether it was possible to decode letter identity from the responses of different motor ROIs. Classifier training and testing was performed separately for large-scale movements and small-scale movements (within-scale classification) and also across scales (across-scale classification). Using the mean ROI amplitudes to decode letter identity yielded accuracy measures that were indistinguishable from chance in all ROIs except for the decoding of large letter identities in M1 (Figures 6 and S4). This revealed that letter identity, unlike letter scale, could not be accurately identified according to mean ROI responses.

Using the voxel-by-voxel response patterns of each ROI, however, revealed significant above-chance decoding accuracies of letter identity when assessing small and large exemplars separately: M1 (68%, large; 61%, small), aIPS (61%; 52%), dPM (53%; ns), vPM (49%; ns), SMA (58%; 47%), PTM (43%; ns), CRB (53%; 50%), and INS (49%; 47%) (Figures 6 and S4). Most importantly, decoding letter identity across scales, by training the classifier on large letters and testing on small letters and vice versa, also revealed significant above-chance accuracies in both directions, but only in M1 (51%, large to small; 56%, small to large), aIPS (43%; 46%), and INS (43%; 43%).

To dissociate letter-specific and scale-specific response components, we performed a final classification analysis after regressing-out the scale-specific response patterns. For each ROI, we extracted the mean response pattern across all largescale trials from each large-scale trial and the mean response pattern across all small-scale trials from each small-scale trial. This manipulation reduced scale-decoding accuracies in all ROIs to chance levels, yet slightly improved letter-identity decoding in aIPS and M1 (Figures 6 and S4). The accuracy of letter-identity decoding remained significantly above chance when performed separately for small and large letter exemplars in M1 (64%, large; 57%, small), aIPS (57%; 52%), SMA (55%; 47%), CRB (50%; 50%), and INS (45%; 45%) and when performed across small and large letter exemplars in M1 (56%, large to small; 57%, small to large), aIPS (50%; 51%), and SMA (46%; 46%).

M1 and aIPS were, therefore, the only two motor system areas that exhibited robust above-chance decoding accuracies of letter identity in all within-scale and across-scale analyses. These results suggest that the letter-specific responses in these areas were invariant to the scale of the executed movement/letter, and therefore extracting all scale-related modulations from the voxel-by-voxel responses did not alter their letter-decoding accuracies.

#### **Pattern Correlation Analysis**

A complementary correlation analysis was conducted to further establish whether letters of similar identity but different size shared similar response patterns. We averaged across trials to compute the mean response pattern of each letter in each scale and correlated patterns across scales. Voxel-by-voxel response patterns of a letter written in small and large scales were significantly correlated across letters with the same identity, but not



#### Figure 3. Similarity of Path Shape across Trials and Scales for Three Representative Subjects

Top: Movement traces of single trials (small letters, light orange; large letters, light blue) and their means (darker colors) after performing the Procrustes transformation on single trials, separately for each scale.

Bottom: Mean movement traces after performing the Procrustes transformation across scales. Each panel represents a single subject. Note the clear consistency in shape across trials and scales.

across letters with different identities, in M1, aIPS, and SMA (randomization test, p < 0.001). INS showed marginally significant correlation values (p < 0.01). All other ROIs exhibited correlation values that were not significant (Figures 7 and S5). Statistical significance of the correlation values was again assessed by a randomization test.

#### **Searchlight Analysis**

A whole-brain searchlight analysis was performed to identify letter-encoding regions without defining a priori regions of interest (Kriegeskorte et al., 2006). This enabled us to explore decoding accuracies in the entire brain while using smaller ROIs (27 voxels per searchlight ROI as opposed to ~300 voxels in the predefined ROIs), which were less prone to over-fitting issues given the small number of samples in each condition (~42 trials per letter at each scale). We performed equivalent letter-classification analyses to those described above for the predetermined ROIs in each of the searchlight ROIs. This included within-scale and across-scale letter classification analyses. The significance of decoding accuracies in each voxel was assessed by a t test across subjects (see Experimental Procedures).

Left M1 and left aIPS were the two regions with the highest decoding accuracies across all classification analyses (significant within-scale decoding shown in light blue and overlap of significant within-scale and across-scale decoding shown in red in Figure 8). These results are consistent with the previous ROI analysis and demonstrate that accurate letter decoding was mostly confined to these two motor ROIs. Moreover, the use of different selection criteria for the ROIs and a different classification algorithm in the searchlight analysis demonstrate the robustness of the results and conclusions across multiple methodological choices.

#### DISCUSSION

Our results reveal that it is possible to accurately decode both the identity (Figures 6, 7, 8, and S4) and the scale (Figures 5

and S3) of written letters from their associated fMRI response patterns in multiple motor system areas. Writing each letter generated a letter-selective voxel-by-voxel response pattern, which was similar across small and large scales such that it was possible to accurately identify an executed letter regardless of its scale in M1 and aIPS. This scale invariance was robustly apparent only in M1 and aIPS across classification (Figure 6) and correlation (Figure 7) analyses in predefined ROIs as well as when performing an unrestricted searchlight analysis throughout the entire cortex (Figure 8). Note that subjects did not receive any visual feedback of their hand throughout the experiments, thereby eliminating the possibility that analyzed response patterns were visually evoked.

We interpret these results as strong evidence for the existence of distributed neural populations in M1 and aIPS that encode letter-writing movements in a scale-invariant manner. We hypothesize that these findings are not limited to handwriting movements and suggest that efficient motor control is achieved in part through the use of scale-invariant neural populations in human M1 and aIPS. The existence of similar scale invariance in M1 and aIPS responses challenges the common description of a strict motor system hierarchy where M1 is a "low-level" area that encodes only instantaneous dynamics and kinematics.

#### **Dissociating Letter Scale and Letter Identity**

Writing a particular letter at different scales involves generating different movement dynamics (e.g., activation of proximal versus distal muscles and joints [Lacquaniti et al., 1987]) and kinematics (movement speed and duration [Figure 2]) while retaining the letter's abstract shape/geometry (Figure 3). Comparing letter-specific response patterns across different scales, therefore, offers a useful manipulation for dissociating response characteristics that change with scale from those that are scale invariant.

Writing letters at different scales altered fMRI responses in two ways. First, all motor ROIs (except for vPM) exhibited significantly larger mean responses when writing large in comparison to small letters (Figure S2). This overall amplitude difference



#### Figure 4. Activations during Letter Writing

Orange indicates areas that exhibited significantly larger response amplitudes during letter writing than rest across all subjects. Results are displayed on inflated hemispheres (left) as well as on two horizontal slices (right) of an exemplar subject. White ellipses outline the general location of selected ROIs: left primary motor cortex (M1), left anterior intraparietal sulcus (aIPS), left dorsal premotor cortex (dPM), left ventral premotor cortex (vPM), supplementary motor area (SMA), left putamen (PTM), right cerebellum (CRB), and left insular cortex (INS). Two control ROIs that did not exhibit activation during movement execution were also identified: left orbito-frontal cortex (OFC), and an out-of-brain region (Out of brain). All ROIs, except for the two control ROIs, were selected separately in each subject.

enabled accurate decoding of letter scale on single exemplars (Figures 5 and S3). Second, larger movements exhibited different voxel-by-voxel response patterns from small movements. This enabled accurate decoding of letter scale from de-meaned response patterns of single exemplars (Figure 5). In fact, it was possible to decode scale across different letters by training a scale classifier on exemplars of two letters and decoding scale on exemplars of the third letter. This suggests that response patterns differed consistently between all small and large letters, regardless of letter identity, and presents evidence for the existence of distributed neural populations that encode movement scale in a shape-invariant manner. Note that movement scale and mean speed were tightly coupled in the current experiment (Figure 2), such that scale-specific responses may equally represent speed-specific responses.

The main purpose of this study, however, was to investigate scale invariance rather than scale selectivity. More specifically, we set out to identify particular motor system areas that exhibit both letter selectivity (i.e., a unique response to each letter) and scale invariance (i.e., similarly unique responses to each letter across different scales). Writing different letters did not alter the overall mean response amplitude in motor ROIs. However, letter selectivity was apparent in the voxel-by-voxel response patterns of several motor areas, where it was possible to accurately decode the identity of the executed letter on single exemplars (Figures 6 and S4). Letter selectivity and scale invariance was robustly apparent in M1 and aIPS where training a classifier on large letters enabled accurate decoding of small letters and vice versa (Figures 6 and 8). Decoding accuracies were similar before and after removing all scale-specific responses from single exemplar response patterns (Figure 6). This suggests that distributed neural populations in M1 and aIPS encode movement shape in a scale-invariant manner. Furthermore, this suggests that the fMRI response patterns associated with letter identity and letter scale were dissociable and that independent neural responses generated the voxel-by-voxel responses associated with letter shape and scale.

When discussing letter selectivity we do not mean to imply that populations of motor neurons are uniquely dedicated to encoding single letters. Instead, M1 and aIPS neural populations may encode particular segments or primitives of handwriting movements (Hatsopoulos et al., 2007; Polyakov et al., 2009), possibly based on directional vectors (Georgopoulos et al., 1982), which are summed by the sluggish hemodynamic response to present a unique fMRI response pattern for each letter. Regardless of how neural populations encode the precise movement segments that are combined into handwriting movements, the critical finding is that these segments are encoded independently of their size/scale.

Whereas shape is probably encoded by shape-selective neural populations, independent neural encoding of scale/speed may be achieved in several different ways. Movement scale could be encoded by gain modulation of the entire population. In such a scheme, the discharge rate of neurons in M1 and aIPS would be consistent with a multiplicative process where neurons show shape/directional tuning but the amplitude of the tuning curve scales with movement amplitude or speed (Moran and Schwartz, 1999; Paninski et al., 2004). Alternatively, movement shape and scale could be encoded by entirely separate neural populations (Desmurget et al., 2004) or by sequential encoding in the same neural populations (Fu et al., 1995). Our results suggest that larger movements are indeed associated with an increase in the entire ROI responses (Figure S2), which is compatible with gain modulation. The observed change in the voxel-by-voxel response pattern, however, suggests the recruitment of scale-encoding neural populations that are entirely separate or partially overlapping with shape-encoding populations. Our findings could, therefore, be compatible with a combination of all three proposed implementations.

#### **Kinematics of Handwriting**

In agreement with previous studies (Edelman and Flash, 1987; van Galen and Teulings, 1983; Viviani and Terzuolo, 1982), we report remarkable geometrical similarity across letters written on different trials and at different scales (Figure 3). These findings have often been interpreted as evidence for a hierarchical organization of motor control where movements are first planned according to their path/geometry and then translated into precise kinematics and dynamics (Viviani and Flash, 1995). Scale invariance is, therefore, a characteristic that would be expected

Table 1. Mean ROI Talairach Coordinates and Size				
	Talairach Coordinates			ROI Size
ROI Name	x	Ŷ	Ζ	# Functional Voxels
L M1	-34.15 (2.39)	-26.43 (4.40)	54.93 (1.42)	338.4 (26.4)
L alPS	-32.61 (3.39)	-47.80 (3.25)	50.78 (5.96)	346.1 (30.7)
L dPM	-24.12 (1.13)	-8.48 (1.30)	58.73 (0.93)	265.1 (39.0)
L vPM	-47.49 (1.84)	2.29 (3.11)	30.30 (1.39)	264.4 (14.7)
SMA	-1.11 (1.47)	-7.39 (3.35)	54.99 (2.20)	344.4 (17.6)
L PTM	-22.27 (1.40)	0.39 (1.78)	6.48 (1.59)	317.7 (22.5)
R CRB	19.90 (4.02)	-48.38 (3.16)	-18.51 (2.89)	313.9 (31.0)
L INS	-43.85 (2.70)	-2.97 (7.89)	9.98 (3.84)	353.7 (20.2)
OFC	-14.22 (0)	46.34 (0)	1.80 (0)	317 (0)
Out of brain	-54.18 (0)	52.06 (0)	56.71 (0)	363 (0)

#### SD across subjects shown in parentheses.

Anatomical landmarks: M1, hand knob in the left central sulcus; aIPS, rostral part of the left IPS; dPM, junction of the left precentral sulcus and superior frontal sulcus; vPM, junction of the left precentral sulcus and inferior frontal sulcus; SMA, medial walls of the left and right hemispheres, anterior to the precentral gyrus; PTM, left putamen of the basal ganglia; CRB, anterior lobe of the right cerebellum; INS, left insular cortex; OFC, left orbitofrontal cortex.

in the higher levels of such a motor hierarchy. Our results reveal that scale invariance is similarly evident in aIPS and M1 responses, which are often thought to embody distinct levels in the motor hierarchy.

#### **Movement Encoding in M1**

Theories regarding the function of M1 neural populations have evolved over the years to suggest that M1 neurons encode increasingly more elaborate movement features. Early electrophysiology studies suggested that M1 neurons encode the amount of force applied by specific muscles (Evarts, 1968), and later studies suggested that M1 neurons encode end-point movement kinematics such as direction (Georgopoulos et al., 1982), speed (Moran and Schwartz, 1999), and amplitude (Fu et al., 1995). More recent electrophysiology studies have suggested that M1 neurons encode more abstract geometrical movement segments/primitives (Hatsopoulos et al., 2007; Hocherman and Wise, 1991; Polyakov et al., 2009) as well as complex goal-directed actions in nonhuman primates (such as bringing the hand toward the mouth from different initial positions) (Graziano et al., 2002a; Overduin et al., 2012). Recent fMRI studies in humans presented evidence for directional selectivity in M1 in straight reaching movements (Eisenberg et al., 2010), partially invariant to movement amplitude (Fabbri et al., 2012). Our results extend these previous studies by demonstrating that distributed neural populations in human M1 encode complex handwriting movements in a scale-invariant manner that is independent of specific dynamics and joint kinematics. Taken together, these findings are slowly transforming our appreciation of the substantially more "high-level" role that M1 neural populations play within the motor system hierarchy. Such high-level motor commands may be translated to specific



### Figure 5. Decoding Accuracies of Letter Scale in M1, aIPS, and Control ROIs

Bars show classification accuracy results, averaged across letters and subjects. Decoding accuracy was computed for each ROI, separately for each letter (a, dark blue; s, blue; n, cyan) and across letters (trained on a and s, red; a and n, orange; s and n, yellow). Classification and decoding was performed once using the mean ROI amplitudes (top) and again using the de-meaned voxel-by-voxel response patterns (bottom). Solid line indicates chance level (50%, two decoding possibilities). Dashed line marks p < 0.001 (randomization analysis, Bonferroni corrected). Error bars, SEM across subjects. Asterisks: significant above-chance decoding accuracies (see also Figure S3).

muscle synergies by downstream projections, facilitating the executed movement (Overduin et al., 2012).

#### **Movement Encoding in aIPS**

The aIPS and adjacent parietal areas are commonly described as high-level sensory-motor areas involved in movement planning (Snyder et al., 1997), sensory-motor integration (Cui and Andersen, 2007), and action observation (Rizzolatti and Sinigaglia, 2010). Electrophysiology studies in nonhuman primates focusing on movement kinematics have reported that single neurons in anterior intraparietal areas exhibit directional tuning during hand movements (Kalaska et al., 1983) and that population vectors from small neural ensembles enable decoding of elaborate movement trajectories (e.g., when drawing geometrical shapes [Averbeck et al., 2005]). Recent fMRI classification (Gallivan et al., 2011) and adaptation (Fabbri et al., 2012) studies have demonstrated that aIPS responses exhibit similar directional selectivity in humans. Although it may be expected that a highlevel motor area like aIPS would exhibit movement-specific responses that are invariant to scale, our study provides actual evidence for this.

With respect to handwriting, several studies have previously reported that parietal areas respond robustly when subjects perform handwriting movements (Menon and Desmond, 2001), regardless of the effector used to execute the movement (Rijntjes et al., 1999). These studies, however, utilized univariate analyses to examine the response amplitude of each motor area and were unable to identify and compare letter-specific responses, which require assessment of voxel-by-voxel patterns.



## Figure 6. Decoding Accuracies of Letter Identity in M1, aIPS, and Control ROIs

Decoding accuracy was computed for each ROI, separately for each scale (large, dark blue; small, cyan) and across scales (trained on large, red; trained on small, yellow). Classification and decoding was performed once using the mean ROI amplitudes (top), again using the de-meaned voxel-by-voxel response patterns (middle), and finally using voxel-by-voxel response patterns after regressing-out the mean scale patterns (bottom). Solid line indicates chance level (33%, three decoding possibilities) and dashed line marks p < 0.001 (randomization analysis, Bonferroni corrected). Error bars, SEM across subjects. Asterisks: significant above-chance decoding accuracies (see also Figure S4).

Our results, therefore, present a considerable advance in revealing how writing movements are encoded by neural populations in the aIPS.

#### **Movement Encoding in Other Brain Areas**

We focused our discussion on M1 and aIPS because these were the only two brain areas that exhibited robustly significant scale invariance across all classification, correlation, and searchlight analyses. Two other brain areas, however, exhibited significant or marginally significant responses in most of the same analyses: the supplementary motor area (SMA) and insular cortex (INS). Both the SMA (Fried et al., 1991; Wymbs and Grafton, 2013) and insular cortex (Fink et al., 1997) are involved in movement planning and execution. Although previous studies have reported that SMA neurons encode movement direction in straight reaching movements (Tankus et al., 2009), encoding of more complex movements, such as those inherent in handwriting, has not been thoroughly studied. Here, both areas exhibited above-chance decoding accuracies for single letters when assessed within each scale separately (Figure S4). The ability to decode letter identity across scales, however, was less clear. Although SMA and insular cortex exhibited above-chance decoding in some



Figure 7. Correlation Values between Response Patterns of Different Size Letters in M1, aIPS, and Control ROIs

Black dots, correlation between same letter identities, across different sizes, averaged across letters and subjects. Gray triangles, correlation between different letter identities, across different scales, averaged across letters and subjects. Dashed lines mark p < 0.001 (randomization analysis, Bonferroni corrected). Error bars, SEM across subjects. Asterisks: significant above-chance correlation values (see also Figure S5).

across-scale classification analyses (Figure S4), neither of these areas exhibited significant above-chance decoding accuracies across scales in the searchlight analysis (Figure 8).

Another important motor area, the cerebellum, showed significantly accurate within-scale but not across-scale letter decoding. This suggests that movement-specific responses were different across scales, which would be expected in cases where movement shape and scale are encoded simultaneously (Fu et al., 1997). Note, however, that the lack of accurate across-scale decoding is a null result, which may be due to different reasons and should be interpreted cautiously.

#### **Potential Pitfalls**

Classification is an exceptionally useful analysis for assessing the selectivity of fMRI response patterns, but it suffers from a worrisome potential pitfall: overfitting. The ability of a classifier to accurately separate voxel-by-voxel responses into distinct groups depends on the number of voxels being considered and the number of exemplars available from each group. In situations where there are more voxels (features) than exemplars, as is the case in our ROI analysis (typically  $\sim$ 300 voxels and  $\sim$ 14 exemplars per condition), the classification algorithm may arbitrarily separate the training exemplars into meaningless groups by overfitting the large number of features. In such a situation the classification algorithm will generalize poorly to independent data. To ensure that our results were not prone to classification overfitting, we validated classification performance by either a leave-one-out validation procedure (when performing withinscale decoding) or by validating the classification with entirely independent data (when performing across-scale decoding). To ensure that the reported decoding accuracies were not artificially inflated or biased in any way, we also performed exactly the same classification and decoding procedures in two control



#### Figure 8. Whole-Brain Searchlight Analyses for Letter Identity

Voxels with decoding accuracies that were significantly above chance (>33%) across subjects are marked on an inflated left hemisphere of one of the subjects. Light blue indicates voxels that showed significant decoding accuracies for letter identity (p < 0.001) in both within-scale classification analyses (overlap of large-scale and small-scale decoding); red indicates voxels that showed significant decoding accuracies for letter identity (p < 0.001) across all analyses: within and across scale.

ROIs, which did not respond during movement execution and were, therefore, not expected to exhibit accurate letter decoding (Figure 6). Analyses in these ROIs consistently exhibited chance-level decoding accuracies. In addition, we also performed a searchlight classification analysis with small ROIs, which contained fewer voxels (27 voxels per ROI) than exemplars (~42 per condition) and were, therefore, less prone to overfitting problems. This analysis revealed equivalent results (Figure 8).

When considering our findings and conclusions it is important to note that the precise relationship between fMRI responses and neural activity is a topic of active research and debate. Although fMRI responses are strongly correlated with local neural activity (Mukamel et al., 2005), there are situations where this relationship may be less consistent (Logothetis, 2008). Studying encoding principles of motor neural populations by fMRI is, therefore, subject to the limitations of this neuroimaging technique.

#### Implications for Models of Motor Control

We propose that shape-selective and scale-invariant encoding is a general organizational principle of neural populations in M1 and aIPS, which enables the efficient encoding of the vast human motor repertoire. The dissociation we observed is in agreement with previous behavioral studies that presented evidence for an independent encoding of movement direction and movement amplitude (Gordon et al., 1994; Messier and Kalaska, 1997). We assume that the letters used in the current study are faithful representatives of movements more generally and hypothesize that scale invariance would be evident in M1 and aIPS responses during the execution of other well-learned movements. Nevertheless, further studies are necessary to test this assumption.

The results presented here, along with those of several previous studies (Averbeck et al., 2005; Graziano et al., 2002a; Hatsopoulos et al., 2007; Kalaska et al., 1983), suggest that the commonly described hierarchical organization of the motor system may require modification. The current textbook description of the motor system proposes that abstract motor intentions encoded by neural populations in high-level brain areas including premotor and parietal cortices are transformed into precise moment-by-moment encoding of kinematics and dynamics in M1. The existence of similar scale-specific and scale-invariant responses in M1 and aIPS suggest that at least some neural populations in both of these areas share similar encoding properties and perform similar motor control computations, making the hierarchical distinction between these areas less clear and supporting alternative organizational models of the motor system, which propose a more distributed network of movement encoding (e.g., Graziano et al., 2002b).

#### **EXPERIMENTAL PROCEDURES**

#### Subjects

Eleven healthy right-handed subjects (4 males; mean age, 28, SD 3) participated in one training session, which introduced the task and setup, and one scanning session. All subjects provided written consent and were paid for their participation in the study. The IRB committees at Sheba Medical Center and Weizmann Institute approved the experimental procedures.

#### **Experimental Setup and Design**

Subjects lay supine in the scanner bore and viewed a back-projected screen through an angled mirror, which prevented any visual feedback of their hand. An MRI-compatible digitizing tablet (MAG Design and Engineering) was placed over the subject's waist to track their hand movements (Figure 1A). Subjects wrote three different English lowercase letters (a, s, and n) in two different sizes (ratio of ~1:2). Each trial began with an audio instruction indicating the letter and scale to be executed. A fixation cross on the screen turned green and subjects had 4 s to execute the letter. The cross then turned red for 4 s, indicating that subjects should return their hand to the starting position. Finally, the cross turned black for a randomized intertrial interval (the rest period) of 4–8 s, indicating that the subjects should hold their hand still at the starting position (Figure 1B). Subjects were trained to perform the task during a separate training session. The fMRI session included 6 scans, each containing 7 trials of each letter at each scale (i.e., 42 trials of each condition in total).

#### **Movement Recording and Analysis**

Kinematic data were recorded at 100 Hz and smoothed via a fourth-order Butterworth low pass filter with 5 Hz cut-off. Movement onset and offset were determined as the time at which velocity exceeded and fell below 10% of the maximum velocity, respectively. Movement duration, length of path, reaction time, and mean speed were computed for each trial. Trials containing erroneous movements (wrong letter or wrong size) or movements with duration, path length, or reaction time that were three standard deviations below or above the median of trials were discarded from the analysis. On average, 3.3% (SD 1.1%) of the trials from each subject were discarded.

#### **Similarity of Path Shape**

We used the Procrustes transformation to assess letter similarity across trials and scales (Goodall, 1991). Because trials had different durations and velocities, we first resampled the hand position data such that each trial contained 500 positions of equal distance. This enabled us to compare movement shape across trials with normalized velocity and duration. For each subject, we computed an average movement shape across all trials of each condition by the Generalized Procrustes Analysis (Wright, 1990) and superimposed single trials onto the estimated average shape by linearly transforming (translating, rotating, and scaling) them, such that the sum of squared distances between each trial and the average shape was minimized. The Procrustes distance was then computed as:

$$R^{2} = \sum_{i=1}^{n} (y_{i} - x_{i})^{T} (y_{i} - x_{i})$$

where *x* is the current trial's transformed shape, *y* is the average shape, and *x<sub>i</sub>* and *y<sub>i</sub>* are the coordinate vectors of the *i*th point in the two shapes. The Procrustes distance ( $R^2$ ) was normalized such that it equaled a value between 0 and 1, where 0 implied a perfect geometrical match between the single trial and mean. Similarity across scales was assessed by computing the Procrustes distance between the two average shapes of each letter across scales. These analyses were completed for each subject separately and then averaged across subjects.

#### **MRI Acquisition and Preprocessing**

MRI data were acquired with a Siemens 3T Trio MRI scanner located at the Weizmann Institute of Science in Rehovot, Israel. Blood oxygenation leveldependent (BOLD) contrast was obtained with a T2\* sensitive echo planar imaging (EPI) pulse sequence: repetition time (TR) 2,000 ms, 32 slices, 3\*3\*4 mm voxels. High-resolution anatomical volumes were acquired with a T1 weighted 3D-MPRAGE pulse sequence (1\*1\*1 mm). MRI data were preprocessed with the Brain Voyager software package (Brain Innovation) and custom software written in MATLAB (MathWorks). Functional scans were subjected to slice scan-time correction, 3D motion correction, and temporal high-pass filtering with a cutoff frequency of two cycles per scan. Functional images were aligned with the high-resolution anatomical volume by trilinear interpolation. Anatomical and functional images were then transformed to the Talairach coordinate system (Talairach and Tournoux, 1988). No additional spatial smoothing was performed.

#### **Univariate Analysis and ROI Selection**

Statistical parameter mapping (SPM) analysis was used to identify brain areas with significantly larger response amplitudes during letter writing (across all conditions) than rest. The expected fMRI responses were modeled with a canonical hemodynamic response function (Boynton et al., 1996) and a linear regression analysis was used to estimate response amplitudes for each voxel in each of the movement conditions. Results were combined across subjects by a random-effects analysis, and a false discovery rate (FDR) of q = 0.01 was used to address the multiple comparisons problem (Genovese et al., 2002).

Eight motor system regions of interest (ROIs) were defined for each subject separately. We used an automated MATLAB script to identify adjacent voxels exhibiting the strongest activation across all movements within a radius of ~12 mm around particular anatomical landmarks (see Figure 4 and Table 1) (using smaller ROIs of ~100 functional voxels gave similar results in the subsequent classification analyses). Two control ROIs that did not exhibit any motor activation in any of the subjects were defined as well. The first included voxels located in the orbito-frontal cortex (OFC) and the second included voxels outside the brain (Out of brain).

#### **Estimating fMRI Response Patterns**

The response of each voxel in each ROI was estimated for each trial by averaging the BOLD percent signal change at time points 3, 4, and 5 (6, 8, and 10 s) after movement onset. These time points corresponded to the peak of the movement-evoked hemodynamic response in all motor ROIs (Figure S2). The resulting spatial response pattern of each trial can be described mathematically as a multidimensional vector containing the response amplitudes of the ROI voxels. We used these vectors, as well as the mean ROI amplitudes (across all voxels), for the subsequent classification and correlation analyses.

#### **Classification of Scale by Mean Responses**

The mean ROI amplitude for each trial was computed by averaging the responses of all the voxels in the ROI. We then averaged random groups of three trials from the same letter and scale to improve the signal-to-noise ratio of the exemplars used for classification. This decreased the number of exemplars we had for each condition from ~42 to ~14, but also decreased the amount of noise inherent in each exemplar. A binary SVM linear classifier (Matlab R2011b, Bioinformatics Toolbox) was then trained to separate the responses of large and small letters and a discrimination function was computed separately for each letter (within-letter scale decoding). The classifier was trained on all but one large and one small exemplar and classification accuracy was then tested by decoding the left-out exemplars. Training and testing was repeated for each available exemplar to compute a decoding accuracy, which represented the proportion of left-out exemplars that were accurately decoded as small or large. This procedure was performed 100 times, while averaging the trials in different random groups of 3 and the resulting decoding accuracies were averaged. Because there were two possible decoding options (small or large), chance-level decoding accuracy was 0.5.

We also performed an equivalent analysis across letters (across-letter scale decoding) where we trained the classifier to discriminate between large and small exemplars of two letters and tested the classifier's ability to decode scale in exemplars of the third letter. In this case the classifier was trained on all available exemplars of two letters and decoding accuracy was tested by decoding all exemplars of the other letter. Chance-level decoding was 0.5 in this analysis as well.

Decoding accuracies were computed for each ROI and each subject separately. We then compared decoding accuracies across the different ROIs to a statistical significance threshold to determine which ROIs exhibited abovechance decoding of letter scale.

#### **Classification of Scale by Normalized Voxel-by-Voxel Responses**

Identical analyses were performed with the voxel-by-voxel response patterns of each ROI. Here, instead of training and testing the classifier with a single value per exemplar (mean ROI amplitude), we used the multidimensional vector corresponding to the voxel-by-voxel responses of each exemplar. The vector of each trial was first de-meaned by subtracting the ROI mean from each voxel. This normalization was performed to ensure that accurate decoding of scale was due to differences in voxel-by-voxel response patterns and not to differences in the mean ROI amplitudes. All classification analysis details were identical to those described above.

#### **Classification of Letter Identity**

We performed equivalent classification analyses to those described above to test whether it was possible to accurately decode the identity of the letter associated with each exemplar. These analyses were performed first with mean response amplitudes and then with de-meaned voxel-by-voxel response patterns. All procedures were identical to those described above except that here we had three classes ("a," "s," and "n") and employed a "one-versus-one" approach to solve the multiclass problem (Hsu and Lin, 2002). We trained three binary classifiers to distinguish between pairs of letters identity is "a"), it had to be successfully decoded by the two relevant binary classifiers (e.g., both a-n and a-s classifiers). Because there were three decod-ing outcomes, chance level in these analyses was 0.33.

Classification of letter identity was performed first within each scale by training and testing the classifiers on exemplars of the same scale and by using a leave-one-out validation scheme. In a second analysis we also tested decoding accuracies across scales. Here the three binary classifiers were trained on all exemplars of one scale and then their accuracy was tested by decoding all exemplars of the other scale.

#### **Regressing out Scale-Specific Response Patterns**

A final classification analysis of letter identity was conducted after "regressing out" all scale-specific information from each trial's response pattern (see Haxby et al., 2001). We computed the mean voxel-by-voxel response pattern of all small trials, performed a regression analysis between this multidimensional vector and the multidimensional vector of each small trial, and retained the residuals of each small trial for further analyses. This procedure was conducted before randomly averaging trials to exemplars and ensured that there was no correlation between the mean small response pattern and the trials used for classification. The same was done for the large-scale trials using the mean voxel-by-voxel pattern of all large-scale trials. Indeed, attempting to decode scale from these regressed out exemplars was below chance level. All classification procedures for decoding letter identity using the scale regressed out exemplars were identical to those described above.

#### **Statistical Significance of Decoding Accuracies**

A randomization analysis was used to assess whether the decoding accuracy in each ROI was larger than that expected by chance (Stelzer et al., 2013). We performed identical classification analyses to those described above except

that here we randomly shuffled movement identities across trials and split them into artificial groups of equivalent sizes before training and testing the classifiers on scale or identity. We ran this analysis 100 times for each subject separately, reshuffling the identity of the trials each time, yielding 100 chance decoding accuracies for each subject. We next performed a bootstrap analysis in which we randomly sampled (with replacement) a single chance decoding accuracy from each subject and averaged across all subjects to get a mean chance decoding accuracy across subjects. This procedure was repeated  $10^5$ times and yielded a "null" distribution of  $10^5$  mean decoding accuracy was considered significantly higher than chance level if it exceeded the 1/10 percentile (i.e., p value < 0.001).

This analysis was performed separately when assessing decoding accuracies using the mean ROI responses and the voxel-by-voxel response patterns. When decoding letter identity by mean ROI amplitudes or voxel-by-voxel response patterns, all ROIs generated similar null distributions with a mean of ~0.33 and a statistical threshold (p < 0.001, Bonferroni corrected) of ~0.54 and ~0.42, respectively. When decoding letter scale by mean ROI amplitudes or voxel-by-voxel response patterns, all ROIs generated similar null distributions with a mean of ~0.54 and ~0.42, respectively. When decoding letter scale by mean ROI amplitudes or voxel-by-voxel response patterns, all ROIs generated similar null distributions with a mean of ~0.5 and a statistical threshold (p < 0.001, Bonferroni corrected) of ~0.62 and ~0.61, respectively.

#### **Pattern Correlation Analysis**

Correlation was used to assess the similarity of response patterns across scales (see Haxby et al., 2001). We computed the mean response pattern across all trials from each letter (separately for each size) and assessed the correlation between the small and large mean response patterns. In this analysis we used the voxel-by-voxel response patterns generated after regressing out of the scale-specific response patterns as described above. The resulting correlation coefficients were pooled across same letters (i.e., large a and small a, large n and small n, and large s and small s) and across different letters (i.e., large a and small s, large a and small n, large s and small n, etc.), and averaged across subjects. Statistical significance was assessed via a randomization test where the same correlation analysis was performed after randomly shuffling movement identities (within each scale) across 200 repetitions. This yielded 200 chance correlation coefficients for each subject in each ROI. We next performed an equivalent bootstrap analysis to create a "null" distribution and assess statistical significance of the actual correlation values. Different ROIs generated slightly different null distributions with a mean of 0 and a statistical threshold of  $\sim$ 0.1–0.3 (p < 0.001 Bonferroni corrected).

#### **Searchlight Analysis**

A "searchlight" analysis (Kriegeskorte et al., 2006) was used to identify cortical areas with voxel-by-voxel responses that yielded above-chance decoding of letter identity, without defining a priori regions of interest. In this analysis, classification was performed with a linear classification algorithm called LDA-shrinkage (linear discriminant analysis, with a shrinkage estimator for the covariance matrix) implemented in the SearchMight toolbox for Matlab (Pereira and Botvinick, 2011). The analysis included selecting ROIs with 26 functional voxels surrounding a central voxel, performing classifier training and testing steps using the response pattern of this group of voxels, and attributing a decoding accuracy to the central voxel. In this analysis we did not regress out the scale-specific response nor did we average groups of trials into exemplars (i.e., all ~42 trials per condition were used). Gray matter masks were constructed with the Brain Voyager software package and the classification was performed separately for each gray matter voxel.

Note that searchlight analyses may result in a false inflation of the regions marked as informative, because a voxel may be marked as informative in situations where decoding accuracy was based on responses of neighboring voxels and not the center voxel. However, when using small searchlight ROIs as done here, this effect is relatively small (Stelzer et al., 2013).

With this method, we generated three decoding accuracy maps for each subject. The first map described the accuracy of letter decoding when assessing only large trials, the second map described the accuracy of letter decoding when assessing small trials, and the third described the accuracy of letter decoding when assessing classification across scales (i.e., when classifying letters of one scale and decoding letters of the other scale). Spatial smoothing

was applied to each subject's classification accuracy maps, using a lowpass filter with a Gaussian width of 5 voxels at half height. Statistical significance of decoding accuracies for each voxel was computed by a t test across subjects, testing whether the decoding accuracies were significantly different from chance (p < 0.001). Voxels with significant decoding accuracies in both within-scale tests (i.e., above-chance decoding in both large-scale and small-scale classification analyses) and voxels with significant decoding accuracies in both within-scale tests and across-scale test (i.e., above-chance decoding in large-scale, small-scale, and across-scale classification analyses) are presented on an inflated brain of one of the subjects (light blue and red, respectively, in Figure 8).

#### SUPPLEMENTAL INFORMATION

Supplemental Information includes five figures and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2013.10.058.

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#### REFERENCES

Averbeck, B.B., Chafee, M.V., Crowe, D.A., and Georgopoulos, A.P. (2005). Parietal representation of hand velocity in a copy task. J. Neurophysiol. *93*, 508–518.

Bernstein, N. (1935). The problem of interrelation of co-ordination and localization. Arch. Biol. Sci. *38*. Reproduced in Whiting, H.T.A., ed. (1984). Advances in Psychology, volume 17 (Amsterdam: North-Holland), pp. 77–119.

Boynton, G.M., Engel, S.A., Glover, G.H., and Heeger, D.J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. J. Neurosci. *16*, 4207–4221.

Cheney, P.D., and Fetz, E.E. (1980). Functional classes of primate corticomotoneuronal cells and their relation to active force. J. Neurophysiol. 44, 773–791.

Cui, H., and Andersen, R.A. (2007). Posterior parietal cortex encodes autonomously selected motor plans. Neuron 56, 552–559.

Desmurget, M., Grafton, S.T., Vindras, P., Gréa, H., and Turner, R.S. (2004). The basal ganglia network mediates the planning of movement amplitude. Eur. J. Neurosci. *19*, 2871–2880.

Edelman, S., and Flash, T. (1987). A model of handwriting. Biol. Cybern. 57, 25–36.

Eisenberg, M., Shmuelof, L., Vaadia, E., and Zohary, E. (2010). Functional organization of human motor cortex: directional selectivity for movement. J. Neurosci. *30*, 8897–8905.

Evarts, E.V. (1968). Relation of pyramidal tract activity to force exerted during voluntary movement. J. Neurophysiol. *31*, 14–27.

Fabbri, S., Caramazza, A., and Lingnau, A. (2012). Distributed sensitivity for movement amplitude in directionally tuned neuronal populations. J. Neurophysiol. *107*, 1845–1856.

Fink, G.R., Frackowiak, R.S.J., Pietrzyk, U., and Passingham, R.E. (1997). Multiple nonprimary motor areas in the human cortex. J. Neurophysiol. 77, 2164–2174.

Fried, I., Katz, A., McCarthy, G., Sass, K.J., Williamson, P., Spencer, S.S., and Spencer, D.D. (1991). Functional organization of human supplementary motor cortex studied by electrical stimulation. J. Neurosci. *11*, 3656–3666.

Fu, Q.G., Flament, D., Coltz, J.D., and Ebner, T.J. (1995). Temporal encoding of movement kinematics in the discharge of primate primary motor and premotor neurons. J. Neurophysiol. *73*, 836–854.

Fu, Q.-G., Flament, D., Coltz, J.D., and Ebner, T.J. (1997). Relationship of cerebellar Purkinje cell simple spike discharge to movement kinematics in the monkey. J. Neurophysiol. *78*, 478–491.

Gallivan, J.P., McLean, D.A., Smith, F.W., and Culham, J.C. (2011). Decoding effector-dependent and effector-independent movement intentions from human parieto-frontal brain activity. J. Neurosci. *31*, 17149–17168.

Genovese, C.R., Lazar, N.A., and Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage *15*, 870–878.

Georgopoulos, A.P. (1990). Neurophysiology of reaching. In Attention and Performance XIII, M. Jeannerod, ed. (Hillsdale: Erlbaum), pp. 227–263.

Georgopoulos, A.P., Kalaska, J.F., Caminiti, R., and Massey, J.T. (1982). On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. J. Neurosci. *2*, 1527–1537.

Goodall, C. (1991). Procrustes methods in the statistical analysis of shape. J. R. Stat. Soc., B *53*, 285–339.

Gordon, J., Ghilardi, M.F., and Ghez, C. (1994). Accuracy of planar reaching movements. I. Independence of direction and extent variability. Exp. Brain Res. *99*, 97–111.

Graziano, M.S., Taylor, C.S., and Moore, T. (2002a). Complex movements evoked by microstimulation of precentral cortex. Neuron *34*, 841–851.

Graziano, M.S., Taylor, C.S., Moore, T., and Cooke, D.F. (2002b). The cortical control of movement revisited. Neuron *36*, 349–362.

Hamilton, A.F., and Grafton, S.T. (2006). Goal representation in human anterior intraparietal sulcus. J. Neurosci. 26, 1133–1137.

Hatsopoulos, N.G., Xu, Q., and Amit, Y. (2007). Encoding of movement fragments in the motor cortex. J. Neurosci. 27, 5105–5114.

Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L., and Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science *293*, 2425–2430.

Hocherman, S., and Wise, S.P. (1991). Effects of hand movement path on motor cortical activity in awake, behaving rhesus monkeys. Exp. Brain Res. 83, 285–302.

Hsu, C.-W., and Lin, C.-J. (2002). A comparison of methods for multiclass support vector machines. IEEE Trans. Neural Netw. *13*, 415–425.

Kakei, S., Hoffman, D.S., and Strick, P.L. (1999). Muscle and movement representations in the primary motor cortex. Science 285, 2136–2139.

Kalaska, J.F., Caminiti, R., and Georgopoulos, A.P. (1983). Cortical mechanisms related to the direction of two-dimensional arm movements: relations in parietal area 5 and comparison with motor cortex. Exp. Brain Res. *51*, 247–260.

Kriegeskorte, N., Goebel, R., and Bandettini, P. (2006). Information-based functional brain mapping. Proc. Natl. Acad. Sci. USA *103*, 3863–3868.

Lacquaniti, F., Ferrigno, G., Pedotti, A., Soechting, J.F., and Terzuolo, C. (1987). Changes in spatial scale in drawing and handwriting: kinematic contributions by proximal and distal joints. J. Neurosci. *7*, 819–828.

Logothetis, N.K. (2008). What we can do and what we cannot do with fMRI. Nature 453, 869–878.

Menon, V., and Desmond, J.E. (2001). Left superior parietal cortex involvement in writing: integrating fMRI with lesion evidence. Brain Res. Cogn. Brain Res. *12*, 337–340. Messier, J., and Kalaska, J.F. (1997). Differential effect of task conditions on errors of direction and extent of reaching movements. Exp. Brain Res. *115*, 469–478.

Moran, D.W., and Schwartz, A.B. (1999). Motor cortical representation of speed and direction during reaching. J. Neurophysiol. 82, 2676–2692.

Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., and Malach, R. (2005). Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. Science *309*, 951–954.

Nitschke, M.F., Kleinschmidt, A., Wessel, K., and Frahm, J. (1996). Somatotopic motor representation in the human anterior cerebellum. A high-resolution functional MRI study. Brain *119*, 1023–1029.

Overduin, S.A., d'Avella, A., Carmena, J.M., and Bizzi, E. (2012). Microstimulation activates a handful of muscle synergies. Neuron *76*, 1071–1077.

Paninski, L., Fellows, M.R., Hatsopoulos, N.G., and Donoghue, J.P. (2004). Spatiotemporal tuning of motor cortical neurons for hand position and velocity. J. Neurophysiol. *91*, 515–532.

Pereira, F., and Botvinick, M. (2011). Information mapping with pattern classifiers: a comparative study. Neuroimage 56, 476–496.

Polyakov, F., Stark, E., Drori, R., Abeles, M., and Flash, T. (2009). Parabolic movement primitives and cortical states: merging optimality with geometric invariance. Biol. Cybern. *100*, 159–184.

Raibert, M.H. (1977). Motor Control and Learning by the State-Space Model (Tech. Rep. Al-TR-439). (Cambridge: MIT).

Rijntjes, M., Dettmers, C., Büchel, C., Kiebel, S., Frackowiak, R.S.J., and Weiller, C. (1999). A blueprint for movement: functional and anatomical representations in the human motor system. J. Neurosci. *19*, 8043–8048.

Rizzolatti, G., and Sinigaglia, C. (2010). The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. Nat. Rev. Neurosci. *11*, 264–274.

Snyder, L.H., Batista, A.P., and Andersen, R.A. (1997). Coding of intention in the posterior parietal cortex. Nature *386*, 167–170.

Stelzer, J., Chen, Y., and Turner, R. (2013). Statistical inference and multiple testing correction in classification-based multi-voxel pattern analysis (MVPA): random permutations and cluster size control. Neuroimage *65*, 69–82.

Talairach, J., and Tournoux, P. (1988). Co-Planar Stereotaxic Atlas of the Human Brain. (New York: Thieme Medical Publishers).

Tankus, A., Yeshurun, Y., Flash, T., and Fried, I. (2009). Encoding of speed and direction of movement in the human supplementary motor area. J. Neurosurg. *110*, 1304–1316.

van Galen, G.P., and Teulings, H.L. (1983). The independent monitoring of form and scale factors in handwriting. Acta Psychol. (Amst.) 54, 9–22.

Viviani, P., and Flash, T. (1995). Minimum-jerk, two-thirds power law, and isochrony: converging approaches to movement planning. J. Exp. Psychol. Hum. Percept. Perform. *21*, 32–53.

Viviani, P., and Terzuolo, C. (1982). Trajectory determines movement dynamics. Neuroscience 7, 431-437.

Wright, C.E. (1990). Generalized motor programs - Reexamining claims of effector independence in writing. In Attention and Performance XIII, M. Jeannerod, ed. (Hillsdale: Erlbaum), pp. 294–320.

Wymbs, N.F., and Grafton, S.T. (2013). Contributions from the left PMd and the SMA during sequence retrieval as determined by depth of training. Exp. Brain Res. *224*, 49–58.