Stability of muscle synergies for voluntary actions after cortical stroke in humans

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Production of voluntary movements relies critically on the functional integration of several motor cortical areas, such as the primary motor cortex, and the spinal circuitries. Surprisingly, after almost 40 years of research, how the motor cortices specify descending neural signals destined for the downstream interneurons and motoneurons has remained elusive. In light of the many recent experimental demonstrations that the motor system may coordinate muscle activations through a linear combination of muscle synergies, we hypothesize that the motor cortices may function to select and activate fixed muscle synergies specified by the spinal or brainstem networks. To test this hypothesis, we recorded electromyograms (EMGs) from 12–16 upper arm and shoulder muscles from both the unaffected and the stroke-affected arms of stroke patients having moderate-to-severe unilateral ischemic lesions in the frontal motor cortical areas. Analyses of EMGs using a nonnegative matrix factorization algorithm revealed that in seven of eight patients the muscular compositions of the synergies for both the unaffected and the affected arms were strikingly similar to each other despite differences in motor performance between the arms, and differences in cerebral lesion sizes and locations between patients. This robustness of muscle synergies that we observed supports the notion that descending cortical signals represent neuronal drives that select, activate, and flexibly combine muscle synergies specified by networks in the spinal cord and/or brainstem. Our conclusion also suggests an approach to stroke rehabilitation by focusing on those synergies with altered activations after stroke.

Successful execution of voluntary movements relies on the functional integration of many different parts of the CNS. Multiple motor cortical areas in the frontal lobe of the brain, including the primary motor cortex (M1), the cingulate, premotor, and supplementary motor areas, produce descending neural signals destined for the spinal interneurons and motoneurons (1, 2), which in turn activate different muscles to result in purposeful motor behaviors. The critical roles of these cortical areas in motor control underlie the clinical observation that lesions of the frontal lobe after ischemic or hemorrhagic events severely affect generation of voluntary movements.

How the motor cortical areas specify appropriate descending neural commands for a particular voluntary action has remained elusive to date. The tacit assumption over the last 40 years had been, and to a certain extent still is, that one could discern the functions of cortical neurons, and particularly M1 neurons, based on the correlation of their activities with some parameters of movement. Beginning with the original investigations of Evarts (3), neural correlates have been found for virtually every parameter examined, such as force, direction, and speed of movement, end point position, joint motion, and muscle activation (4–10). At present, a growing number of investigators are becoming aware of how this plethora of correlations makes it difficult to understand how the spinal circuitries can still manage to interpret these mixed descending cortical signals for diverse motor tasks.

An additional factor compounding the difficulty of deciphering the nature of descending motor activities is the fact that the motor cortical areas need to coordinate the actions of a large number of muscles with thousands of motor units in the limbs for even the simplest movements. Given the complexity of the dynamic relationship between any joint motions and their required joint torques, and the considerable redundancy in joint actions across muscles, how the motor system coordinates the activations of so many degrees of freedom has remained obscure. Presumably, the CNS copes with this apparent difficulty of coordination with a certain simplifying control strategy. Elucidating the nature of such a strategy and understanding how it can be implemented by the motor cortices and spinal cord has remained two highly important questions in neuroscience.

Recently, there has been some experimental evidence suggesting that the CNS may circumvent the computational complexities of motor control by generating motor commands through a linear combination of motor synergies (11–14), each of which activates a group of muscles as a single unit. Such muscle coactivations facilitate control by reducing the number of degrees of freedom needed to be specified. Here, instead of viewing cortical activities as encoding certain movement parameters, we ask the question of whether cortical signals represent neuronal drives that select, activate, and combine in a flexible way muscle synergies specified by networks in the spinal cord and/or brainstem. We investigated this question with muscle recordings from stroke patients having unilateral lesions in the frontal lobe, which severely impair motor performance by interfering with descending neural commands for the spinal cord or brainstem. We recorded electromyograms (EMGs) from multiple muscles of both the unaffected and the stroke-affected arms and used suitable computational methods both for extracting muscle synergies from the EMGs, and for comparing the synergies of the two arms.

Results

Overview. For this study we recruited eight patients having moderate-to-severe unilateral ischemic stroke in the frontal lobe (Table 1) and six healthy subjects serving as controls. As demonstrated by the patients’ Fugl-Meyer and Ashworth scores (Table 1), the motor functions in the affected arms of all patients were impaired to varying degrees. For every patient, trajectories of the affected arm in most of the seven tasks that we examined also differed noticeably from those of the other arm in kinematic features such as movement speed (slower in the affected) and range of joint motions (more restricted in the affected). After we recorded EMGs of 12–16 upper arm and shoulder muscles from both arms of the subjects, we performed a series of EMG analyses to systematically compare the muscle synergies expressed by the unaffected and stroke-affected arms of the patients that we recruited. The nonnegative matrix factorization


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(NMF) method (15) was used to decompose the recorded EMGs into a linear combination of nonnegative synergies (Fig. 1). After our earlier study (16), extraction of muscle synergies was performed in two stages. In stage I, synergies were extracted from the EMGs of each arm separately for a first estimation of the number of synergies composing the data of each arm. In stage II, synergies shared between the two arms and those specific to each arm were extracted simultaneously from the pooled dataset comprising data recorded from both arms; this data pooling maximizes the data variability used during synergy extraction and thus allows the potential discovery of additional shared synergies. Similarity between the synergies of the two arms was quantified using the cosine of principal angles, which indicate the dimensionality of the subspace shared between the spaces spanned by the synergy sets of the two arms.

**Interarm Similarity of Muscle Synergies.** In both stages of our analyses, we found that in most patients the muscle synergies for the unaffected arm and those for the stroke-affected arm were strikingly similar. As an example, Fig. 2 shows muscle synergies extracted separately from each arm of patient 2, a patient with a fronto-temporo-parietal stroke involving both primary motor cortex and basal ganglia. In both arms of this patient, a linear combination of five synergies was sufficient for explaining a decent fraction of data variation in 12 recorded muscles (unaffected, \( R^2 = 75.5\% \); stroke-affected, \( R^2 = 75.7\% \)). After paring each unaffected-arm synergy (Fig. 2A) with its most similar
affected-arm synergy (Fig. 2B), it became apparent that the two synergy sets matched extremely well. The scalar product values between these pairs of synergies, ranging from 0.804 to 0.958, were well above the baseline average scalar products (0.327 to 0.665) between random vectors generated by shuffling vector components across those very same synergies (95% C.I., 1,000 trials). Of the five principal angles between these two synergy sets (Fig. 2C), the cosines of four were greater than the threshold value that we selected for dimensionality determination (see Materials and Methods), indicating that the subspace shared between the two synergy sets could be spanned by at least four synergies common to both arms. Similar results were obtained from the EMGs of other patients (Table 2, columns 3–5). In eight patients, we found, on average, 6.75 ± 0.74 synergies specific to the paralyzed arm. Similarly, numbers of muscle synergies identified for each arm in two stages of analyses

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number of recorded muscles</th>
<th>Unaffected arm</th>
<th>Stroke-affected arm</th>
<th>Shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Patient 2</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Patient 3</td>
<td>12</td>
<td>6</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Patient 4</td>
<td>16</td>
<td>7</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Patient 5</td>
<td>16</td>
<td>8</td>
<td>5</td>
<td>4</td>
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<td>Patient 7</td>
<td>14</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Patient 8</td>
<td>13</td>
<td>8</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

HS1, HS2, HS3, HS4, HS5, and HS6 refer to healthy subjects.

EMG Reconstructions. We demonstrate here, with several examples from patient 5 (Fig. 4), how complex differences between the EMGs of the unaffected and stroke-affected arms may be captured as differences in the activation amplitude or duration of synergies shared between the two arms. In this patient, the lateral head of triceps brachii, medial head of triceps brachii, long head of biceps brachii, and posterior part of deltoid displayed more activations in the stroke-affected arm in the reaching-with-single-constraint task, but fewer activations in shoulder circumduction. Such differences were explained by NMF through a larger activation of synergy 3 (Fig. 4A, B) for the affected arm in the former task, and a smaller activation of the same synergy in the latter (Fig. 4C, D). Similarly, in another task, reaching with double constraints, the larger-amplitude EMG bursts of the superior trapezius, infraspinatus, and teres major in the affected arm were attributed by NMF to an increased activation of a single synergy in the affected limb (Fig. 4B, D). These examples show that changes in the activations of many muscles after a stroke lesion may be more compactly described as changes in the recruitment pattern of a few fixed muscle synergies.

Discussion

We believe that the results that we obtained from analyzing EMGs of stroke patients have provided us with important clues concerning the nature of the descending cortical signals for generating voluntary movements. The muscle synergies that we identified were similar not only between the normal and affected arms (Fig. 2 and Table 2) but also across subjects (Fig. 3). This is a striking result, given that the patients that we studied had stroke lesions over different cortical locations (Table 1). Such a robustness of the muscle synergies across arms and cortical lesion types suggests that these synergies are structured most likely by neuronal networks downstream of the neocortex, such as the spinal interneuronal circuits and/or neurons in the brainstem nuclei. Descending signals from the motor cortical areas activate these networks organizing each synergy, which in
The above conclusion that stroke lesions may impair movements by interfering with synergy activations suggests an approach to neurorehabilitation for stroke patients by focusing on those muscle synergies whose activation pattern is altered after stroke. The insight of cortical signals as representing neuronal drives for synergies also might open up new avenues for ongoing endeavors of using cortical signals to control prosthetic devices.

**Materials and Methods**

**Subjects.** Eight patients (patients 1–8, mean age = 60.1) with unilateral ischemic stroke in the frontal lobe were recruited from the San Camillo Hospital, Venice, Italy. Magnetic resonance imaging was used to verify lesion extent and location in every patient (Table 1). The sensorimotor status of each patient was evaluated using both the Fugl-Meyer scales—measuring range of movements—and the Ashworth scales for measuring muscle spasticity—including scores for five different muscles (Table 1). All patients had received various amounts of physical rehabilitation therapy before recording. In addition, six healthy subjects (healthy subjects 1–6, mean age = 66.7) with no history of neurological disorder were recruited to serve as controls. All procedures were approved by the Ethics Committee of the San Camillo Hospital before experiments.

**Tasks and EMG Recordings.** Both the stroke patients and the control subjects were asked to perform, with each arm, seven motor tasks involving the
shoulder and elbow joints: simple upward reaching, shoulder abduction, forward reaching across a single spatial constraint, upward reaching across two spatial constraints, hand pronation, shoulder circumduction, and moving along a path together with hand pronation. The tasks examined for both arms were identical, except that their trajectories were mirror images of each other. As the subject performed each task, EMG activities were collected at 1,000 Hz from 12–16 upper arm and shoulder muscles of each arm (Biopac Systems). The recorded muscles included triceps brachii, lateral and medial heads; biceps brachii, short and long heads; deltoid, anterior, medial, and posterior parts; superior trapezius; rhomboid major; brachioradialis; supinator; brachialis; pronator teres; pectoralis major, calvicular head; infraspinatus; and teres major. Electrodes for each muscle were placed according to guidelines of the Surface Electromyography for the Non-Invasive Assessment of Muscles—European Community project (SENIAM) and Delagi et al. (34). For every task, EMGs of 10–11 trials were collected for each arm. For every trial, data collected from 0.5 s before movement onset to 1.0 s after movement offset were stored in a computer and subsequently analyzed offline using customized software written in Matlab (The MathWorks).

**EMG Preprocessing.** The collected EMGs were high-pass-filtered with a window-based finite impulse response filter (50th order, cutoff of 50 Hz) to remove motion artifacts, rectified, low-pass-filtered (50th order, cutoff of 20 Hz) to remove noise, and then integrated over 25-ms intervals to capture envelopes of EMG activity. To correct for interarm EMG-amplitude differences arising from differences in electrode placement and to ensure that subsequent extraction of muscle synergies from the EMGs would not be biased against low-amplitude muscles, data from each arm and each muscle were normalized to a suitable maximal value. This value was found by first calculating the median trial maximum across all trials of every task, and then identifying the maximum of these medians across all tasks. Taking the median (instead of the maximum amplitude) ensures that the above normalization is robust against occasional high-amplitude spikes arising from noise.

**Extracting Muscle Synergies.** Muscle synergies and their corresponding activation coefficients were extracted from the EMGs using the NMF algorithm (15). The NMF models the activities of the recorded muscles as a linear combination of several muscle synergies, each activated by a time-dependent activation coefficient (Fig. 1). To compare the muscle synergies identified from the stroke-affected arm with those from the unaffected arm, we used the two-stage analytic paradigm that we have proposed previously (16, 17). Briefly, in stage I, synergies were extracted separately from the EMGs of each arm. A first estimate of the number of synergies underlying each arm was obtained based on a cross-validation procedure (see Estimating the Number of Muscle Synergies, and the similarity between the synergies of the two arms was assessed using principal angles (see Synergy Similarity). In stage II, we pooled the data of the unaffected and stroke-affected arms and used the
method described in Cheung et al. (16) to search for synergies shared by the two arms, synergies specific to the unaffected arm, and synergies specific to the stroke-affected arm simultaneously from the pooled dataset. The stage-II analysis enables NMF to fully use the data variability present in the EMGs of both arms for discovering the maximum number of shared synergies while allowing arm-specific synergies to be extracted. Readers are referred to our previous article (16) for a detailed description of how the stage-II analysis was implemented.

**Estimating the Number of Muscle Synergies.** The NMF algorithm requires the number of synergies composing the dataset to be determined a priori. We identified the number of synergies by first plotting the EMG reconstruction $R^2$ against the number of extracted synergies (from one to the number of recorded muscles). From this $R^2$ curve, we sought to select, with the following steps, a “correct” number of synergies that is more interpretable than those found by ad hoc methods previously proposed (e.g., refs. 12, 16, and 27). In our stage-I extractions (see Extracting Muscle Synergies), we extracted synergies from both the collected EMGs and unstructured EMGs generated by randomly shuffling the original dataset across time and muscles. This allowed us to plot from both the collected EMGs and unstructured EMGs generated by randomly testing data were used for plotting the steps, a “correct” number of synergies that is more interpretable than those identified the number of synergies by first plotting the EMG reconstruction against the number of extracted synergies (from one to the number of recorded muscles). From this curve, we sought to select, with the following steps, a “correct” number of synergies that is more interpretable than those found by ad hoc methods previously proposed (e.g., refs. 12, 16, and 27). In our stage-I extractions (see Extracting Muscle Synergies), we extracted synergies from both the collected EMGs and unstructured EMGs generated by randomly shuffling the original dataset across time and muscles. This allowed us to plot two $R^2$ curves, one for the original unshuffled EMGs and another for the random EMGs denoting the baseline $R^2$ values expected from chance. The $R^2$ curve for the random data invariably increases from 0 to $\approx 100\%$ with an almost constant slope. We then define the “cusp” of the original $R^2$ curve to be the point at which the curve’s slope drops below 75% of the slope of the baseline $R^2$ curve. The number of synergies at this cusp—or the number beyond which any further increase in the number of extracted synergies yields an $R^2$ increase smaller than 75% of that expected from chance—may then be regarded as a reasonable choice for the number of synergies composing the dataset. When we implemented the above procedure, we also randomly chose half of the EMG episodes for synergy extraction and another half for testing the extracted synergies. The average $R^2 (n = 10)$ denoting the fit quality to the testing data was used for plotting the $R^2$ curve. The slope of the curve was obtained by fitting each point and both of its neighboring points to a straight line using least squares.

Similarly, our stage-II extractions require the numbers of shared synergies and of synergies specific to each arm extracted from the pooled datasets to be specified beforehand. We initiated all stage-II extractions with the datasets’ stage-I estimates of the numbers of synergies. Then, we successively increased the number of shared synergies, starting from one, until the specific synergies for each arm became dissimilar (as assessed by principal angles; see Synergy Similarity) from those for the other arm. If the stage-I estimates for the two arms were unequal, then we further increased the number of synergies in the arm with the smaller number, one by one but with this number not exceeding the number of synergies in the other arm, until such further increases did not yield more shared synergies. This way, the number of shared synergies recoverable was maximized.

**Synergy Similarity.** Similarity between the synergy sets for the unaffected and stroke-affected arms was first assessed using the scalar product. We further quantified synergy similarity by estimating the dimensionality of the subspace shared between the spaces spanned by the synergy sets of the two arms. This estimation was achieved by computing the principal angles (35) between those two sets of synergy vectors and then finding the number of principal angles whose cosines were greater than a suitable threshold. This threshold was obtained by corrupting either synergy set with Gaussian noise ($\mu = 0, \sigma = 0.1$) for 1,000 times and then finding the minimum cosine of the principal angle between each of these corrupted synergy sets and the original uncorrupted set. The 2.5th percentile of the resulting set of 1,000 minimum cosine values was then selected as the threshold for determining the dimensionality of the shared subspace.

**Clustering Synergies.** Muscle synergies of all of the healthy subjects and stroke patients were categorized respectively into clusters for comparison of synergies across subjects. This clustering analysis was performed using the Matlab statistics-toolbox functions pdist (Minkowski option, $p = 3$), linkage (Ward option), and cluster.

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