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Muscle synergy patterns as physiological markers of motor cortical damage

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The experimental findings herein reported are aimed at gaining a perspective on the complex neural events that follow lesions of the motor cortical areas. Cortical damage, whether by trauma or stroke, interferes with the flow of descending signals to the modular interneuronal structures of the spinal cord. These spinal modules subserve normal motor behaviors by activating groups of muscles as individual units (muscle synergies). Damage to the motor cortical areas disrupts the orchestration of the modules, resulting in abnormal movements. To gain insights into this complex process, we recorded myoelectric signals from multiple upper-limb muscles in subjects with cortical lesions. We used a factorization algorithm to identify the muscle synergies. Our factorization analysis revealed, in a quantitative way, three distinct patterns of muscle coordination—including preservation, merging, and fractionation of muscle synergies—that reflect the multiple neural responses that occur after cortical damage. These patterns varied as a function of both the severity of functional impairment and the temporal distance from stroke onset. We think these muscle-synergy patterns can be used as physiological markers of the status of any patient with stroke or trauma, thereby guiding the development of different rehabilitation approaches, as well as future physiological experiments for a further understanding of postinjury mechanisms of motor control and recovery.

motor primitive | electromyography | neurorehabilitation | nonnegative matrix factorization | Virtual Reality Rehabilitation System

There has been considerable experimental evidence suggesting that diverse motor behaviors of vertebrates are constructed by a combination of rudimentary building blocks (motor modules) residing in the spinal cord (1–3). The precise mechanism by which the motor cortical areas preside over the orchestration of these modules for movement generation remains largely unknown. To gain some insight into this question, we studied the muscle activation patterns of stroke survivors with cortical lesions of differing severity. Our goal was to gather data not only for unraveling the complexities emerging after cortical outflow is disrupted, but also for providing a perspective upon which principled rehabilitation strategies could be built.

The utilization of factorization algorithms for analyzing muscle activity recorded during motor behaviors has made it possible to decompose myoelectric activation patterns into their building blocks, thereby revealing the modular architecture of the motor system. In the last few years, we and others (2, 3) have pursued this approach to shed light on old questions such as how the motor system circumvents the need to control its large number of degrees of freedom (4) through a flexible combination of motor modules in both animals and humans. Other investigators have used factorization analysis to gain a new understanding of spinal cord functions (5–8), of postural control (9, 10), and of motor development (11, 12).

The factorization analysis that we and others have used models motor modules as groups of muscles activated together (muscle synergies). Each muscle synergy represents a time-

invariant profile of activation across muscles, activated by a time-varying coefficient. When individual synergies, scaled by their coefficients, are summed together, the muscle activation patterns, recorded during movements as electromyographic signals (EMGs), are faithfully reconstructed (Fig. 1).

In this report, we focus on upper-limb muscle synergies of a group of patients with stroke ($n = 31$) with a wide range of unilateral motor impairment (Table S1). To identify muscle synergies, we recorded EMG patterns from both arms during a variety of tasks and reaching movements. We used the non-negative matrix factorization (NMF) algorithm (13) to extract from the EMGs the number of muscle synergies necessary for an 80% R^2 EMG reconstruction and then compared the synergies of the two arms. Our analysis revealed three distinct patterns of muscle synergies, reflecting preservation, merging, and fractionation of the unaffected-arm muscle synergies in the stroke-affected arm, respectively. These patterns manifested themselves to varying degrees in different patient groups, suggesting that they may be used as markers of the physiological status of stroke survivors.

Results

In mildly impaired patients recorded shortly after stroke, we observed that the muscle synergies of the stroke-affected arm were strikingly similar to those of the unaffected arm despite marked differences in motor performance between the arms. For example, in one such patient with an upper-arm Fugl–Meyer (FM) score of 50 (of a maximum score of 66) recorded 2.1 mo poststroke, each of the seven muscle synergies of the affected arm (Fig. 2A, red) could be matched to an unaffected-arm synergy (blue) with a scalar-product similarity of 0.93 ± 0.03 (mean \pm SD). This observation is not only consistent with the conclusion we reached in an earlier study (14), but also compatible with the proposal that muscle synergies are structured in the spinal cord, and after cortical stroke, altered descending commands from supraspinal areas generate abnormal motor behaviors through faulty activations of the spinal modules (14, 15) (see Fig. S4).

In contrast, in subjects with severe motor impairment (FM score ≤ 30), regardless of when the patients were recorded relative to stroke onset, there was much less resemblance between the synergies of the two arms. In the example shown in Fig. 2B, the four synergies extracted from the affected arm (red) could reconstruct the EMG patterns recorded during voluntary movement as effectively as the six synergies extracted from the unaffected arm (blue). This difference in data dimensionality suggests

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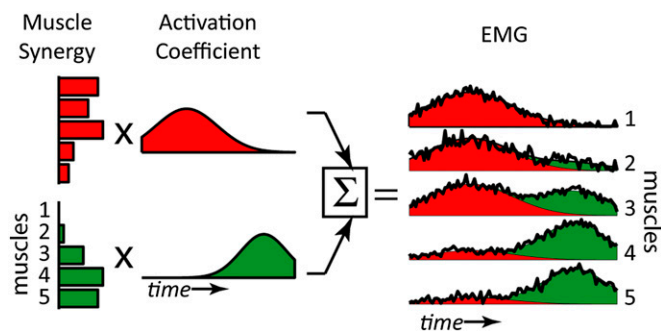


Fig. 1. A schematic illustrating how muscle synergies are linearly combined to generate muscle patterns recorded as electromyographic signals (EMGs). Each of the two muscle synergies shown (red and green bars) is represented as an activation balance profile across muscles (muscles 1–5) and activated, through multiplication, by a time-dependent coefficient. The EMG waveforms resulting from the activations of individual synergies are then summed together to reconstruct the recorded EMGs (black lines). In the schematic, each color in the EMG reconstruction reflects how the waveforms from the synergy coded by the same color contribute to the reconstruction.

that the apparent dissimilarity between the synergies of the two arms may be attributed to a merging of the synergies that were present before stroke in the impaired limb, a merging that

persisted throughout the movement trials. We thus proceeded to investigate this merging systematically with a computational procedure that automatically searched, among the unaffected-arm synergies, those that could be linearly combined to reconstruct each affected-arm synergy (*SI Materials and Methods*). In Fig. 3A, the four synergies *A1–A4* extracted from the affected-arm EMGs (red) were reconstructed by linearly combining two to three synergies from the unaffected arm (blue). Synergy *A1*, for instance, was explained as a combination of *U1* and *U5*; synergy *A2*, of *U2* and *U5*; and so on. The scalar-product similarity between the extracted (red) and reconstructed (pink) synergies for the stroke-affected arm (0.92 ± 0.03) was indeed much higher than the values obtained either by directly matching the synergies of the two arms ($P < 0.03$; 0.78 ± 0.09) (Fig. 2B) or by performing this merging analysis with random unaffected-arm synergies ($P < 10^{-4}$; 0.81 ± 0.02) (Fig. S1).

We applied this merging analysis to the muscle synergies of all other patients and quantified the degree of synergy merging in each patient by calculating the mean number of unaffected-arm synergies found to merge into each affected-arm synergy (thus, in the above example, this number is the average of 2, 2, 3, and 3, corresponding to the numbers for synergies *A1–A4*, respectively, which equals 2.5; a value of 1 corresponds to an absence of merging). We found that this index of synergy merging correlated negatively, and significantly, with the patients' FM scores

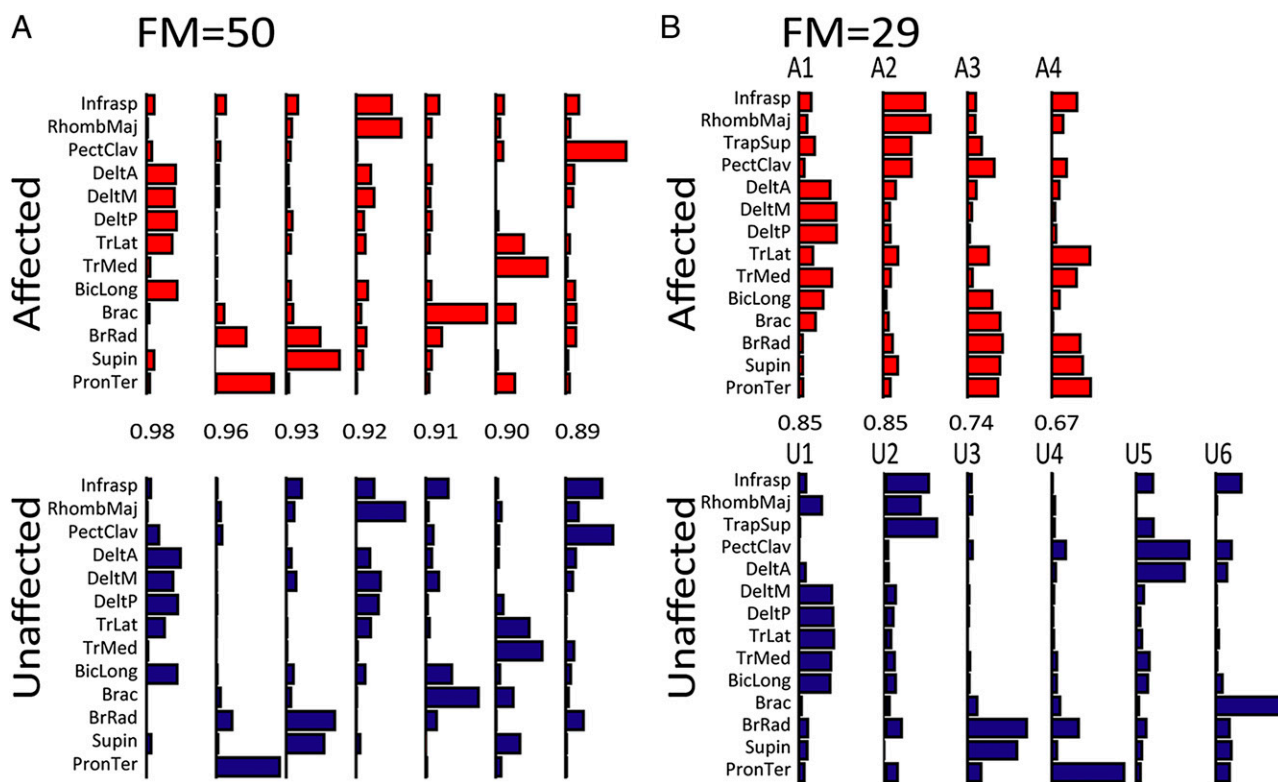


Fig. 2. Preservation of muscle synergies in a mildly impaired patient with stroke but not in a severely impaired patient. (A) The muscle synergies extracted from the EMGs of the stroke-affected (red) and unaffected (blue) arms of a mildly impaired patient with stroke with a Fugl–Meyer (FM) score of 50. For both arms, seven muscle synergies were sufficient for an EMG reconstruction R^2 of $\sim 80\%$. Each affected-arm synergy was matched to an unaffected-arm synergy giving the highest scalar-product similarity value, shown in between each synergy pair. All seven pairs had high similarity values (0.89–0.98), suggesting preservation of the normal muscle synergies in the stroke-affected arm of this patient. (B) The muscle synergies of a severely impaired stroke patient with FM score of 29. For this subject only four synergies were needed for reconstructing the affected-arm EMGs (synergies *A1–A4*) whereas six were needed for the unaffected arm (synergies *U1–U6*). The similarity values between the synergies of the two arms were lower (0.67–0.85), but the affected-arm synergies tended to have activation components in more muscles than the unaffected-arm synergies (e.g., compare *A3* with *U3* and *A4* with *U4*). This observation suggests that the apparent dissimilarity between the synergies of the two arms may be due to merging of the unaffected-arm synergies in the stroke-affected arm. Infraspin, infraspinatus; RhombMaj, rhomboid major; TrapSup, trapezius superior; PectClav, clavicular head of pectoralis major; DeltA, anterior part of deltoid; DeltM, medial part of deltoid; DeltP, posterior part of deltoid; TrLat, lateral head of triceps brachii; TrMed, medial head of triceps brachii; BicLong, long head of biceps brachii; Brac, brachialis; BrRad, brachioradialis; Supin, supinator; PronTer, pronator teres.

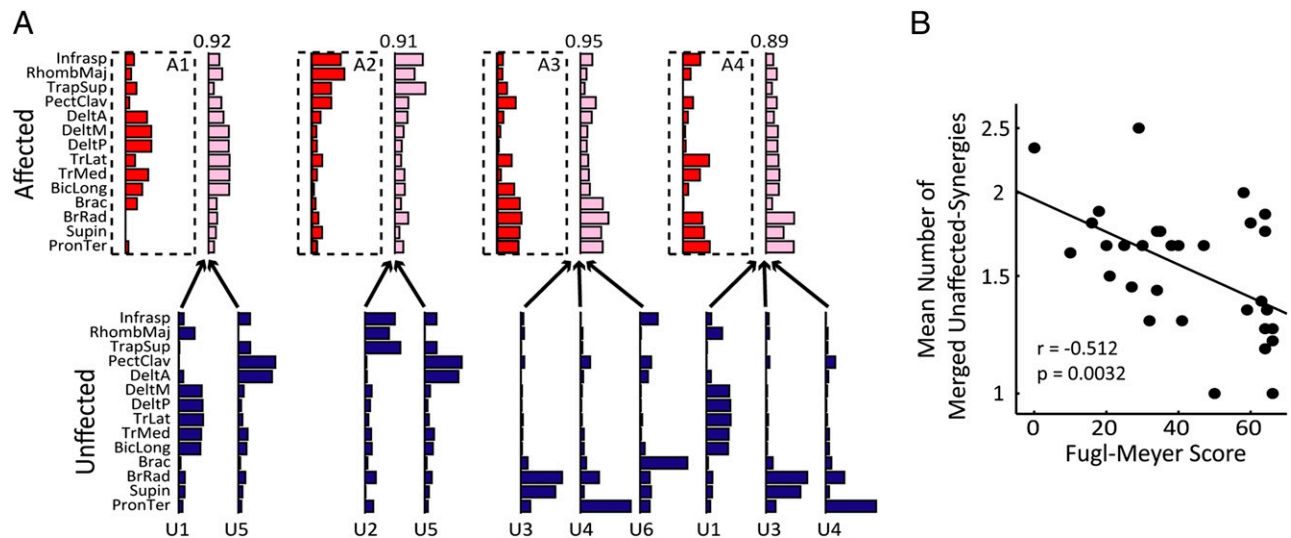


Fig. 3. The stroke-affected arm muscle synergies of severely impaired patients explained as merging of unaffected-arm synergies. **(A)** We devised a computational procedure that systematically finds the subset of unaffected-arm synergies that can be linearly combined to reconstruct each affected-arm muscle synergy. Each affected-arm synergy from the example shown in Fig. 2B (red, A1–A4) was reconstructed by merging two to three unaffected-arm synergies (blue, U1–U6). Synergy A1, for instance, could be reconstructed by combining U1 and U5; synergy A2, by combining U2 and U5; and so on. The reconstructed affected-arm synergies (pink), when compared with the synergies extracted from the affected-arm EMGs (red), yielded high similarity values (0.89–0.95, shown between each extracted and reconstructed synergy pair for the affected arm). **(B)** We derived an index quantifying the degree of synergy merging by calculating the mean number of unaffected-arm synergies found merging into each affected-arm synergy. When calculating this average, we included in our statistic only those affected-arm synergies that could be well reconstructed as a combination of unaffected-arm synergies (scalar product >0.75). Across all patients ($n = 31$), we found a significant, negative correlation between our index of synergy merging (in log scale) and the FM score ($r = -0.512$, $P = 0.0032$). Thus, the more impaired the patient with stroke, the more likely that an affected-arm synergy represents a merging of multiple unaffected-arm synergies.

(Fig. 3B; $r = -0.51$, $P < 0.01$); thus, the more severe the impairment, the more likely it is that an affected-arm synergy represents a merging of multiple unaffected synergies. Further statistical tests confirmed that the degree of merging of unaffected-arm synergies varied with the FM score [three-way ANOVA, $F(1, 30) = 8.0$, $P < 0.01$], but not with poststroke duration ($F = 0.01$, $P > 0.9$) or with the side affected by the stroke ($F = 0.90$, $P > 0.3$) (Fig. S2).

Whereas our model of synergy merging has enabled us to reconstruct the affected-arm muscle synergies in most patients with good fidelity, in some subjects, particularly the chronic survivors, there was a portion of affected-arm synergies that could not be well explained by any combination of merging (Fig. 4A and Fig. S3). For instance, in one chronic stroke survivor (poststroke duration of 450.7 mo), whereas one of the six synergies extracted from the affected-arm EMGs could be very well reconstructed (Fig. 4B, synergy A1; scalar product of 0.91), the rest could be only moderately well or poorly reconstructed (A2–A6; scalar product of 0.71–0.81). It occurred to us that the affected-arm synergies that could not be explained as a merging were in fact fractionations of unaffected-arm synergies. Using a computational procedure, we identified affected-arm synergies A2 and A3 as fractionations of one unaffected-arm synergy (Fig. 4C, U1) and A4, A5, and A6 as fractionations of another (U3).

In 18 of the 31 subjects, our procedure identified two or more synergies for the impaired arm as fractionations of one or multiple unaffected-arm synergies. Within this group of subjects, the percentage of affected-arm synergies found to be fractionations correlated strongly with poststroke duration (Fig. 4D; $r = 0.66$, $P < 0.004$).

Discussion

The muscle synergies extracted by the factorization algorithm from the EMGs of multiple tasks (Figs. 2–4) have allowed us to reveal, in a quantitative way, distinct myographic patterns

reflecting the physiological processes that occur following cortical damage. These patterns vary as a function of both the severity of motor impairment and the temporal distance from stroke onset. Whether they also depend on the anatomical location of the lesion would require further analysis of the magnetic resonance imaging data of our subjects.

In our analysis, we have compared the muscle synergies of the stroke-affected arm with those of the unaffected arm of the same subject. The patterns of muscle synergies we have revealed rely on the assumption that the unaffected-arm synergies are themselves not changed by either the stroke lesions or the elapse of time after stroke. This assumption is supported by an earlier observation that the unaffected-arm synergies in patients with stroke are similar to the ones identified in the arms of healthy control subjects (14).

Central to the present investigation is the use of a factorization algorithm (NMF) to extract muscle synergies from the EMGs of multiple muscles. The factorization procedure essentially performs a dimensionality reduction by grouping the muscles that tend to covary in the dataset into individual synergies (Fig. 1). The set of extracted muscle synergies may thus be viewed as a compact representation of the most salient features embedded within the variability present in the EMG dataset. The use of an algorithm provides an objective and efficient means to identify, from large, high-dimensional EMG data recorded from multiple tasks, basic muscle groupings that are not necessarily obvious from visual inspection of the raw data or simple correlation analysis between the EMGs of muscle pairs. Importantly, an earlier study has shown that different linear factorization algorithms (except principal component analysis) produced similar synergies in both simulated and experimental datasets (16). This result supports that the extracted synergies are likely not artifacts contingent upon the assumptions of NMF, but reflect structures of the motor modules used by the motor system for movement control.

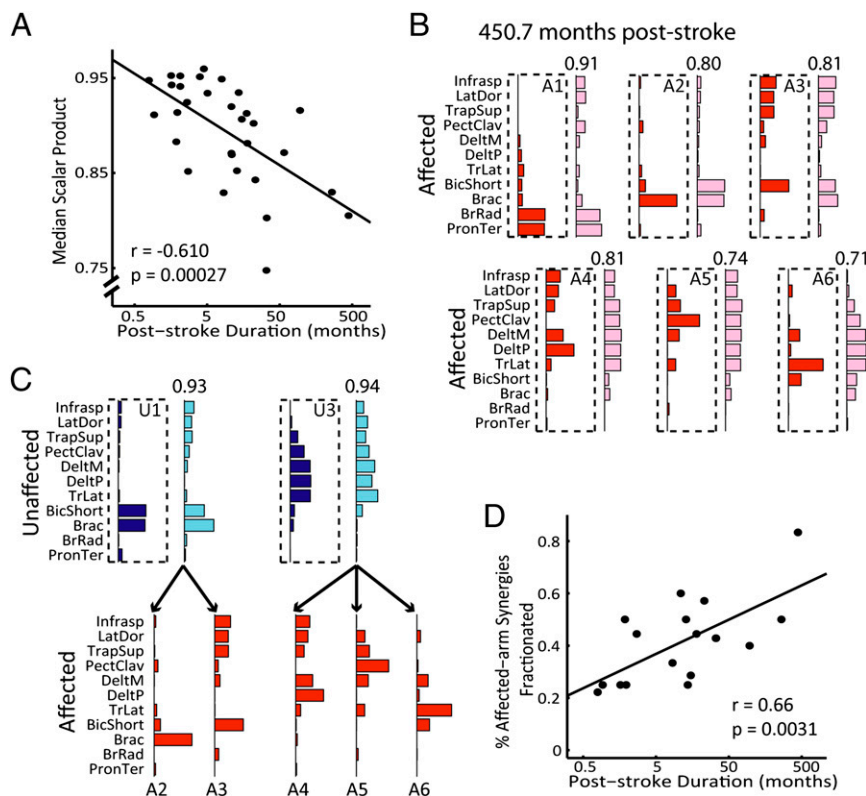


Fig. 4. The stroke-affected arm muscle synergies of chronic patients explained as fractionations of unaffected-arm synergies. (A) Some of the affected-arm synergies from the chronic patients in our dataset could neither be directly matched to an unaffected-arm synergy nor be explained as a merging of multiple unaffected-arm synergies. In fact, the median scalar-product similarity value between the extracted and reconstructed (via the merging model) affected-arm synergies decreased with the subjects' poststroke duration (in log scale) ($r = -0.610$, $P = 2.7 \times 10^{-4}$). (B) The muscle synergies of a very chronic patient (poststroke duration = 450.7 mo) extracted from the affected-arm EMGs (red, A1–A6) and their corresponding reconstructions by merging unaffected-arm synergies (pink). Of these six synergies, only one could be well reconstructed (A1). (C) The affected-arm synergies that could not be well reconstructed by the merging model in B (A2–A6) could instead be explained as fractionations of unaffected-arm synergies. Our computational procedure identified synergies A2 and A3 to be fractionations of synergy U1 for the unaffected arm, and A4–A6 as fractionations of synergy U3. The affected-arm synergies identified as fractionations (red) could in fact be linearly combined to result in reconstructions of their corresponding unaffected-arm synergies (cyan) that matched very well to the synergies extracted from the unaffected-arm EMGs (blue) (scalar product = 0.93–0.94). (D) Within the group of subjects in whose affected-arm synergies fractionations were observed ($n = 18$), the percentage of affected-arm synergies identified to be fractionations of unaffected-arm synergies increased with the subjects' poststroke duration (in log scale) ($r = 0.66$, $P = 0.0031$).

Our factorization procedure has identified three basic patterns of muscle synergies. In cases of mild-to-moderate impairment ($FM > 30$), we observed that the synergies in the affected and unaffected arms were similar even though the muscle activation patterns were different (Fig. 2A). This observation indicates that the output of spinal modules can still be retrieved by the factorization procedure. However, as reflected by the differences in the activation coefficients of these preserved synergies between the two arms (Fig. S4), the machinery for activating synergies, presumably under cortical control, has faltered after stroke. It is the failure of activating the synergies in a correct way that generates abnormal motor behaviors.

In cases of severe impairment ($FM \leq 30$), we observed a different pattern of muscle synergies. In the affected arm, multiple synergies appeared to merge (Fig. 2B). As a consequence of this merging, the EMGs of the affected arm could be reconstructed with fewer synergies (Fig. S5). This merging of muscle synergies we observed is compatible with the poststroke "cocontractions" of muscles described in the literature (17–20) and a previous report of motor-module fusion in the affected lower limb of stroke survivors (21). In fact, in our data certain combinations of muscle synergies were observed to merge more frequently than others across patients (Fig. S6). The merging of these specific muscle synergies could potentially account for the previously

observed poststroke couplings of shoulder and elbow actions (22), which could in turn lead to a reduction in the range of joint motion.

Whereas the former two patterns are related to the severity of motor impairment, the third pattern we identified emerged only after years from the initial injury. In a subset of patients with chronic stroke, a portion of the synergies in the affected arm appeared to be fractionations of the synergies observed in the unaffected arm (Fig. 4C), and this fractionation process tended to increase the number of synergies required for adequate description of the affected-arm EMGs (Fig. S5). It remains to be verified whether fractionation is an adaptive process triggered in response to the poststroke motor impairment. For instance, an increased flexibility of controlling the shoulder and upper-arm muscles provided by synergy fractionation could compensate for impaired motions of the more distal joints resulting from stroke (17).

Even though we present here the preservation, merging, and fractionation of muscle synergies as three distinct poststroke responses, we note that two or all three of these responses could be present simultaneously in the same subject (Fig. S7). The extent to which each of these three responses manifests itself in the stroke-affected arm could therefore serve as a precise and quantifiable marker of the physiological status of the patient at any given time.

At this point it would be hazardous to speculate upon the neural mechanisms underlying both merging and fractionation of

muscle synergies. The motor system is a complex, integrated system with ascending and descending pathways working in ways that defy simple hierarchical descriptions. Even though the lesions are cortical, the merging and fractionation might be dependent on either neural changes at the cortical level (23) or other processes at the brainstem or spinal cord levels unmasked by the cortical lesions (17). Although it is premature to advance any concrete hypothesis on the origin of these three patterns of muscle synergy, we believe a description of these patterns is nonetheless important because the patterns provide physiological markers that can be used for shedding light on the complex processes that follow accidents involving the cortical motor system.

With animal models, the use of these markers, in conjunction with conventional physiological and behavioral techniques, may provide an understanding of how cortical and subcortical processes interact to produce the motor patterns observed in patients with stroke. A more challenging task, however, is to develop more effective rehabilitation procedures on the basis of the data provided by our factorization analysis. At the very least, the observation of merging and fractionation of muscle synergies should prompt the development of different therapeutic approaches. In the long run, the markers we have identified might be profitably used for assessing the efficacy of any existing or new rehabilitation therapies by providing physiological information on how they affect the dynamics of motor recovery from cortical lesions. Finally, these markers may represent a step toward the establishment of customized therapies tailored to the conditions of individual patients.

Materials and Methods

Subjects. Thirty-one stroke survivors were recruited from the San Camillo Hospital, Lido di Venezia, Italy ($n = 21$) and the Spaulding Rehabilitation Hospital, Boston ($n = 10$). All patients studied suffered from a mostly unilateral cortical and subcortical lesion resulting from either an ischemic or a hemorrhagic stroke (Table S1). All procedures were approved by the Ethics Committees of the San Camillo Hospital, Spaulding Rehabilitation Hospital, and Massachusetts Institute of Technology. All participants gave informed consent before experimentations.

Behavioral Tasks and EMG Recordings. Each subject was asked to perform multiple upper-limb tasks with each of the two arms so that the muscle patterns from the stroke-affected arm could be compared with those from the unaffected arm of the same subject. At San Camillo, the motor behaviors tested consisted of seven virtual-reality tasks (10–11 trials per task). At

Spaulding, subjects were asked to perform a point-to-point reaching task consisting of ballistic movements from an initial position to 1 of 12 possible targets in 3D space, and then from the target back to the initial position (3–4 trials per target). As the subject performed the tasks, EMG activities of 10–16 shoulder, upper-arm, and forearm muscles of each arm were collected using surface bipolar electrodes.

Extracting Muscle Synergies. Muscle synergies were extracted from filtered, rectified, integrated, and variance-normalized EMGs of each arm of each subject using the NMF algorithm (13). The NMF models the activities of the recorded muscles as a linear combination of time-invariant muscle synergies, each activated by a time-varying activation coefficient (Fig. 1). To identify the number of muscle synergies composing the EMGs, we successively increased the number of synergies extracted from one to the number of muscles recorded and selected the minimum number of synergies required for a cross-validated EMG-reconstruction R^2 of 80%. Because the synergies and their coefficients extracted from the data may represent a local extremum on the R^2 surface, we repeated the synergy extraction 50 times and selected the solution giving the highest R^2 for further analyses.

Merging and Fractionation of Muscle Synergies. We investigated whether the observed muscle synergies in the stroke-affected arm could be explained as multiple synergies merging together by modeling each affected-arm synergy as a linear combination of the set of unaffected-arm synergies. The coefficients of this linear combination were identified through a standard nonnegative least-squares procedure (SI Materials and Methods). For every affected-arm synergy, an unaffected-arm synergy was defined to contribute to the merging if its associated coefficient was >0.2 . Note that in this model, each unaffected-arm synergy could contribute to the merging of more than one affected-arm synergy.

In addition, we investigated whether two or more affected-arm synergies could be fractionations of any unaffected-arm synergy by modeling each unaffected-arm synergy as a linear combination of the set of affected-arm synergies. Thus, the fractionation model is equivalent to the one obtained by swapping the roles of the unaffected- and affected-arm synergies in the merging model. Because each affected-arm synergy could not simultaneously be fractionations of more than one unaffected-arm synergy, we imposed the additional constraint in the least-squares optimization that each affected-arm synergy could contribute to the reconstruction of at most one unaffected-arm synergy.

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