Intrusion of pathological synergies does not explain impaired 3D arm movements in subacute stroke

Inbar Avni1,2, Ahmet Arac1, Reut Binyamin-Netser1,2, Shilo Kramer4, John W. Krakauer5,7, Lior Shmuelof1,2

Abstract

It has long been of interest what the contribution of pathological synergies is to abnormal motor control of the arm after stroke. The flexor synergy is defined as unwanted co-activation of flexion at the shoulder and elbow joints. Here we used a video-based, marker-less 3D pose-estimation kinematic model to examine two reaching tasks with different requirements for elbow flexion. Twenty-eight sub-acute (2-12 weeks) post-stroke subjects and sixteen healthy controls performed both a cup to mouth task, requiring shoulder and elbow flexion (within flexor synergy), and a reaching task, requiring shoulder flexion and elbow extension (outside of flexor synergy). Using kinematic analysis of the hand and of elbow/shoulder joint angles, we assessed both overall task performance and intrusion of pathological synergies. Motor impairment, strength and spasticity were measured using established clinical scales. Performance in both tasks was impaired to a similar degree in the patients compared to controls. This lack of performance difference for the in- vs. out-of-flexor synergy tasks was consistent with our finding of no evidence for intrusion of a flexor synergy in the reaching task. Specifically, for the reaching task there was no difference between patients and controls either in time spent within-movement in flexor synergy or in the correlation between shoulder and elbow angles when the shoulder was flexing. A regression analysis indicated that the only significant predictor of poor task performance was degree of weakness. Notably, even though we found no kinematic evidence for post-stroke intrusive flexor synergies, the Fugl-Meyer Assessment (FMA), which was devised to quantify post-stroke synergies, was markedly abnormal. This seeming contradiction is resolved by the observation that abnormal coupling at the shoulder and elbow can occur due to weakness alone, and it is this “synergy mimic” that leads to a low FMA score. The finding that FMA can be abnormal for two qualitatively distinct forms of impaired inter-joint coordination has implications for the interpretation of longitudinal studies that use this single measure. In the sub-acute stage of stroke, intrusion of abnormal synergies is not the reason for impaired reaching.
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**Introduction**

Approximately 80% of stroke survivors experience motor impairments, typically in the form of hemiparesis.\(^1\)\(^2\) Between 50% to 60% of patients with an initial arm paresis, have arm disability at six months\(^3\) and one year.\(^4\) Both motor disability in neurological conditions, which is defined based on the activity and participation levels of the ICF (International Classification of Functioning, Disability and Health),\(^5\) and the process of motor recovery, require a focus on impairment level.\(^1\)

Motor impairments after stroke have multiple components: weakness, reduced motor control or dexterity, sensory loss, spasticity, and intrusion of pathological synergies.\(^1\) These components may be associated with distinct neural substrates and recovery profiles. Indeed, a recent study showed a dissociation between impairments of motor control (dexterity) and the intrusion of synergies.\(^6\) In the clinical setting, a widely used motor impairment measure is the Fugl-Meyer Assessment (FMA), which quantifies abilities of the subjects to make isolated and coordinated joint movements on an ordinal scale.\(^7\) The FMA was designed to emphasize the contribution of pathological synergies, flexor and extensor, to post-stroke limb deficits. For example, in one maneuver, subjects are required to flex the shoulder (0°-90°) while maintaining a straight elbow (0°). In this case, any flexion at the elbow would indicate intrusion of a flexor synergy and lead to a lower score.

There are experimental approaches to the study of upper limb synergies that go beyond the FMA. EMG recordings during 2D isometric movements of the upper limb in stroke subjects have shown abnormal flexor and extensor muscle co-activation patterns.\(^8\)-\(^10\) Alternatively, more naturalistic tasks have been devised that require movements in and out of synergy and so can differentially bring out abnormal coupling between the shoulder and elbow.\(^11\)-\(^12\) Zackowksi and colleagues examined 3D kinematics in 18 chronic stroke participants and showed that their
performance was less impaired in the task that could be done within flexor synergy compared to the task that could not. In addition, they showed that subjects could not flex their wrist, elbow or shoulder joints in isolation,\textsuperscript{11} as a result of enslaving the other joints. They concluded that one of the main sources of impairment in 3D reaching in patients with chronic stroke is intrusion of the flexor synergy. A study using a similar task design to Zackowski and colleagues, but in the early sub-acute stage of stroke, obtained the opposite result: weakness was the dominant source of the reaching impairment rather than failure to individuate single joints.\textsuperscript{13} Here we sought to test directly for flexor-synergy intrusion during 3D functional arm movements in the sub-acute stroke period.

Materials and methods

Participants

Participants with either an ischemic or a hemorrhagic stroke (which was confirmed by imaging) were recruited by the Negev lab (a collaborative initiative of Ben-Gurion University and Adi Negev Nahalat Eran in Israel), between 2019 and 2022. Research protocols for both stroke and healthy participants were approved by Sheba Hospital Helsinki Committee and Ben-Gurion University Human Subjects Research Committee, respectively. Only participants who were able to give informed consent were recruited. Additional inclusion criteria were: 1) Intact cognitive and motor control abilities before the incidence, and 2) Sufficient active movement of the arm. Subjects were excluded if they had a history of physical or neurological conditions that interfered with either the study procedures or the assessment of motor function (e.g., severe arthritis, severe neuropathy, Parkinson's disease).

We analyzed data from 28 stroke subjects in the sub-acute stage (2-12 weeks post-stroke, aged 65.9 ± 10.4) (Table 1), and 16 healthy controls (aged 68.8 ± 3.5). Motor FMA was collected from all participants, as well as impairment measures of spasticity (Modified Ashworth Scale) and strength (grip dynamometer).
Table 1 Characteristics of participants in the sub-acute phase after stroke

<table>
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<th>Subject number</th>
<th>Age at stroke</th>
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<th>Paretic side</th>
<th>Stroke type</th>
<th>Weeks post stroke</th>
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Experimental design

Two tasks were recorded: a cup-to-mouth task that required shoulder and elbow flexion, and a reaching task that required shoulder flexion and elbow extension. In the cup-to-mouth task, participants were instructed to perform simulated cup-to-mouth motion from a side table to their mouth, holding a plastic cup in their hand (taken from an ARAT kit). In the reaching task, participants were instructed to perform upward and forward reaching movements towards a suspended target. The instruction was to perform 10 iterations in each task. To compare the two tasks, in the cup-to-mouth task, only the movement segments of reaching from table to mouth were examined.

In order to quantify movement, we used a novel approach for analyzing marker-less, 3D kinematics (DeepBehavior)\(^4\) with a convolutional neural network algorithm (OpenPose)\(^5\) that was trained to detect 57 key points in the human body in each video frame (Figure 1).
Figure 1 **Kinematics of the human arm and body performing two different 3D tasks.** 3D body estimation of individual subjects performing the tasks: blue lines are connecting the model’s joints positions and the movements trajectories are marked by black lines (each subject performed 10 repetitions of the task). Trajectories are shown for two subjects: a healthy control subject (left column) and a stroke subject (right column) performing the cup-to-mouth task (top row) and the reaching task (bottom row).

### Recording setup

The tasks were recorded using a custom-made system comprising of two high-speed cameras (150 frames per second, 1280x1024 pixels, Blackfly S Color 1.3 MP USB3 camera with a Fujinon 1.5MP 6mm C Mount lens), set on a custom-designed aluminum camera holder with a 66° angle between their axes. In this setup, cameras were positioned 120 cm in front of the subject, at a height of 95 cm, and placed at a set 45° angle towards the subject, which allowed us to produce the 3D kinematic data of 57 body key points. In the cup-to-mouth task, participants faced the cameras at a 45° angle with the moving arm closer to the camera lenses, and a side table with an empty cup placed to their side. In the reaching task, participants were recorded from the frontal angle while facing the cameras and reaching up towards a suspended object (~1.5 m above ground). Each participant attempted to perform 10 iterations of each task.
in each hand (in separate blocks). Stroke subjects that were only able to partially execute these tasks were included in the analyses if minimal movement of the paretic arm was detected at least twice in each task. During the recordings, no markers were placed on the subjects as the analysis algorithm enables marker-less detection of joint positions.

**Impairment and functional measures**

FMA,\(^7\) Action Research Arm Test (ARAT),\(^16\) spasticity (Modified Ashworth Scale, MAS)\(^17\) and strength (grip dynamometer) scores were collected from all participants. Neither MAS nor strength scores were collected when the arm was either flaccid or the subject couldn’t perform power grip.

**Data analysis**

The recordings resulted in two synchronized videos from two cameras. Each video was passed through the OpenPose algorithm to detect joint positions. Then, the corresponding 2D positions of joints from each video were stereo-triangulated to obtain the estimated 3D position.\(^18\) To do this, a prior calibration using a checkerboard was obtained. This resulted in a list of 3D positions of all joints. These data were smoothened using a Savitzky-Golay filter with a window size of 57 and a polynomial degree of 3. Then, the joint tangential velocities were calculated. Movements were segmented based on the wrist velocity profiles (movement start and end were defined based on the crossing point of 10% of the peak velocity). Peak velocity detection and segmentation were automatic but verified and adjusted manually. The main performance measures were extent, defined as the radial 3D position at the end of reaching/cup-to-mouth task compared to the start position, movement duration and peak velocity.

Joint angle data was calculated using an intrinsic (anatomical) coordinate system (angle calculated in relation to a specific joint; shoulder flexion angle is defined as the angle in degrees between the ipsilateral elbow joint, ipsilateral shoulder joint and contralateral shoulder, projected onto the horizontal plane – defined by the torso and shoulder vectors created by the 3D model of the subject; elbow extension angle is defined as the angle in degrees between the ipsilateral wrist, elbow and shoulder joints).

Flexor synergies were quantified based on the angular velocity of the elbow and shoulder joints, in two ways: 1) flexor synergy proportion was calculated as the time spent while simultaneously flexing the elbow and shoulder, divided by the total time of the movement, and
2) Flexor synergy strength was the Pearson’s correlation coefficient of the shoulder flexion and elbow extension angles, during the largest segment in the movement that the shoulder was flexing. To deal with the skewed distribution of this measure, we performed a Fisher transformation by calculating the inverse hyperbolic tangent (arctanh) of the correlation coefficients. Data analysis was performed using a custom written code in MATLAB.19

**Statistical analysis**

One and two-way ANOVA analyses were performed to assess the differences in kinematic measures between groups (control, non-paretic stroke and paretic stroke) and across tasks, respectively. Additionally, between group differences were assessed using two sample, two-tailed, t-tests with unequal variance. Cohen’s d was used to assess effect sizes of differences between groups and Bayes Factor was calculated to describe the strength of evidence for the alternative hypothesis vs the null hypothesis.

Furthermore, the contribution of different impairment measures (spasticity, strength and coordination) to performance measures (e.g. smoothness and extent), in the data of stroke participants, was assessed using a linear regression analysis. Statistical analysis was performed via MATLAB19 and JASP.20

**Power analysis**

Based on the final sample containing 28 stroke participants and 16 age matched controls, the power to identify significant differences across groups (three groups: controls, non-paretic arm measures and paretic arm measures of the stroke group), in a one-way ANOVA assuming a medium effect size of $f=0.4$ across groups, is 86%. Furthermore, our correlation analysis has a power of 84% to identify an effect of $\rho=0.5$. The multiple linear regression analysis, have a power of 78% to identify an effect of $R^2 = 0.5$ with 4 predictors in the model. Statistical power was computed using G*power version 3.1.9.4.21

**Data availability**

Raw data was collected at Ben-Gurion University and Adi Negev Nahalat Eran in Israel. Derived data supporting the findings of this study is available from the corresponding author on request.
Results

Performance was abnormal in both 3D arm tasks

To test for a possible effect of a flexor synergy on arm movements after stroke, we had subjects perform a reaching task that required flexion at the shoulder and extension at the elbow (movement outside of flexor synergy), and cup-to-mouth task, that required flexion at the shoulder and elbow (movement within flexor synergy) (Fig. 1 and Supp Fig. 1 and 2).

Subjects were generally successful in performing the task, however the movements of the stroke subjects were slower and shorter, showed increased jerkiness, and sometimes involved compensations. To go beyond observation, performance on the two tasks was quantified by measuring the peak velocity, movement duration and movement extent for each subject.

A significant main effect of group (control, non-paretic and paretic) was found in all performance measures: movement duration (Fig. 2A), peak velocity (Fig. 2B) and extent (Fig. 2C), in both tasks (Table 2).

The inferior performance was seen when comparing the paretic side with the performance of control subjects in all measures and tasks. When comparing the performance of the non-paretic side with the performance of the age-matched control subjects, no significant differences were observed in most of the measures of the cup-to-mouth task (peak velocity and extent: \( P > 0.20 \)), and in the extent of the reaching task (\( P = 0.10 \)). Movement duration and peak velocity of the reaching task showed significant differences between the controls and non-paretic groups (\( P < 0.02 \)) (Fig. 2 & table 2).

Additionally, in the two-way ANOVAs, interaction between group and task was not significant for all measures (\( P > 0.07 \)). Thus, patients were impaired compared to controls on both tasks and did not seem to have greater difficulty on the reaching tasks, which was the one expected to suffer from intrusion by a flexor synergy.

Table 2 Statistical analysis of kinematic measures

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<th>Kinematic measure</th>
<th>One-way ANOVA for group effect</th>
<th>t-test for stroke (paretic side) vs. controls effect</th>
<th>t-test for stroke (non-paretic side) vs. controls effect</th>
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Figure 2 Kinematic measures of performance are impaired in both the reaching and cup-to-mouth tasks after stroke. (A) Scatter plots of movement duration, (B) peak velocity and (C) extent in each group, for both tasks. Each triangle represents the values of the measure for a single participant across all individual movement in the task. Horizontal lines represent averages. Significant differences across groups are denoted by asterisks (* = P < 0.05, ** = P < 0.01, *** = P < 0.001, two sample t-test with unequal variance).

There was no evidence for intrusion of flexor synergies

Although the impairment was not increased in tasks that required movements outside the pathological synergy, intrusion of synergies could still contribute to the motor impairment in the reaching task, and even in the cup-to-mouth task. To examine for this, we measured the time spent within flexor synergy during movement by identifying the segments in which both the shoulder and elbow were flexing (flexor synergy), based on their angular velocities (see Fig. 3A). In neurotypical individuals, the percentage of time spent in flexor synergy will reflect the amount of flexion-flexion pattern that is required by the task. Indeed, in the cup-to-mouth task, subjects spent a greater percentage of time in a flexor synergy (mean±std: 70.03 ± 15.1) than in the reaching task (mean±std: 18.75 ± 11.6). While the proportion of time spent in flexor synergy was highly affected by the task (F(1, 84) = 276.2, P = 0), this measure was not greater in the stroke participants (cup-to-mouth task: F(2, 69) = 2.41, P = 0.10; reaching task: F(2, 69) = 0.1, P = 0.90) (Fig. 3B).

To further test for intrusion of a flexor synergy, we analyzed the motion of the elbow when the shoulder was flexing. Our assumption was that if abnormal synergy patterns interfered in the movement, then this would mostly take place in the parts of the movements in which the shoulder was actively flexing, enslaving the elbow in flexion. We therefore identified in each task the longest segment of shoulder flexion and calculated the Pearson’s correlation coefficient on the angular trajectories of the shoulder and elbow during that segment (Fig. 3C). This measure, termed ‘flexor synergy strength’ will reflect the extent of shoulder flexion and elbow flexion dependency, and is expected to be positive in tasks requiring mostly flexion and flexion, and negative in tasks requiring flexion and extension. Indeed, in the control subjects, flexor synergy strength was higher in the cup-to-mouth task (mean±std: 2.14 ± 0.40) than in the reaching task (mean±std: -1.34 ± 0.82). Nevertheless, no difference in synergy strength were observed between groups (cup-to-mouth task: F(2, 69) = 1.54, P = 0.22; reaching task:
\[ F(2, 69) = 0.68, \ P = 0.51 \). These two analyses show no evidence for intrusion of flexor synergies to the paretic arm during these two 3D tasks.

**Figure 3 Intrusion of flexor synergies measures.** A: Shoulder and elbow angular trajectories of two hemiparetic subjects (left and middle) and a control subject (right), in both tasks: cup-to-mouth (top) and the reaching task (bottom). Gray areas represent the time points in which both joints were flexing, based on which the proportion of time spent in flexor synergy was calculated (flexor synergy proportion). Horizontal black lines represent the longest segment identified of shoulder flexion. Based on this segment, Pearson’s correlation coefficient on the angular trajectories of the shoulder and elbow was calculated (flexor synergy strength). Angular trajectories are averaged across all individual movement in the task. B: Scatter plot of the percentage of time spent within flexor synergy movement pattern in each group. C: Scatter...
plot of the correlation coefficient measured only in segments of shoulder flexion in each group. Correlation coefficient measured only in segments of shoulder flexion. Each triangle represents the values of the measure for a single participant. Significant differences across groups are denoted by asterisks (* = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$, two sample t-test with unequal variance).

The lack of group differences in the intrusion measures in the reaching task indicates that the average sub-acute stroke participant does not suffer from intrusion of synergies and that intrusion of synergies cannot account for the performance impairments. Nevertheless, pathological synergies may appear in some of the subjects. To examine if our cohort includes subjects that show intrusion of synergies, we searched for subjects that show a total flexion of their elbow during the reaching movement (that required a substantial extension of the elbow). Two stroke subjects flexed their elbow in the reaching task (Fig. 4). Notably, these subjects also had low FMA scores (S2 FMA = 40, S17 FMA = 34). One of the subjects showed increased proportion of shoulder/elbow flexion during the movement with increased strength (S2), consistent with the predicted pathological coordination pattern, but the other did not show increased coupling, and his elbow flexion occurred when his shoulder was not flexing (S17, Fig. 4B-C).

**Figure 4** Analysis of total elbow flexion during the reaching task. Scatter plot of the total elbow flexion during the reaching task in each group (A) and shoulder and elbow angular trajectories of two hemiparetic subjects (B and C). Angular trajectories are averaged across all individual movement in the task. Each triangle represents the values of the measure for a single participant. Significant differences across groups are denoted by asterisks (* = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$, two sample t-test with unequal variance).
Another concern is that the sample of 28 subjects contained a large group of subjects with only mild to moderate motor impairments (14 subjects have a FMA score that is higher than 59, see Table 1). The lack of indications of intrusion of synergies and small effect size in some of the analyses may therefore be a result of the specific sample and could not generalize to more severe cases (Fig. 3). To address this concern, we repeated the same analysis steps only for a sub-sample of stroke subjects with lower FMA scores (FMA < 60, n = 14, mean FMA of 47.29). When comparing flexor synergy intrusion across groups, no group differences were observed (Fig. 5A-B; P > 0.05), indicating that even in more severe cases of hemiparesis, pathological synergies are not observed.

Figure 5 Analysis for the sub-sample of 14 subjects with lower FMA scores. Scatter plot of the percentage of time spent within flexor synergy in each group (left) and flexor synergy strength (right). Each triangle represents the values of the measure for a single participant. Significant differences across groups are denoted by asterisks (* = P < 0.05, ** = P < 0.01, *** = P < 0.001, two sample t-test with unequal variance).

Arm inter-joint coordination was abnormal due to weakness

Taken together, the evidence presented so far indicates that the impairments in 3D arm movements in the sub-acute stroke phase were not attributable to intrusion of a flexor synergy. This leads to the question: What drives the motor impairments of the subjects that are seen in the kinematic analysis and in the FMA scores?

To answer this, the video for each subject was watched by a neurologist (JWK) and two occupational therapists (RBN, SD). The dominant problem noted by the clinicians was weakness-induced compensatory movements around the shoulder. Specifically, weakness was
evident in the difficulty subjects had anteriorly flexing the shoulder and extending the elbow to its full capacity (Fig. 6). Compensatory abduction and hiking of the shoulder led to internal rotation of the arm, with the result that the elbow fell into flexion (Fig. 6A). Weakness was also apparent in wrist drop (Fig. 6A). Thus, the flexion pattern observed at the shoulder and elbow was due to a combination of weakness and compensation for weakness, that mimicked a flexor synergy to sufficient degree to lead to an abnormal FMA score. In addition, the clinicians noted evidence for muscle adhesion and scapula impingement.

Figure 6 Examples of subjects performing the reaching task. Two subjects are presented at the end of the upward motion in the reaching task, demonstrating their difficulty in performing the task. Movies depicting the 3D model of the subjects performing the task are also available in the supplementary material (Supp Mov. A and B, corresponding to each of the subjects presented in this figure).

Finally, to evaluate the differential contribution of impairment measures to performance, we applied a regression analysis with kinematic measures as the dependent variable and strength, spasticity, and synergy measures as independent variables. The results were consistent with the clinical observations: the only significant predictor of performance in the reaching task was weakness (extent: $P = 0.015$; peak velocity: $P = 0.041$) (Table 3).

Table 3 Regression analysis of impairment measures

<table>
<thead>
<tr>
<th>Kinematic measure</th>
<th>Spasticity (MAS)</th>
<th>Strength (dynamometer grip)</th>
<th>Flexor synergy strength</th>
<th>Flexor synergy proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>beta</td>
<td>std</td>
<td>p</td>
<td>beta</td>
</tr>
<tr>
<td>Peak velocity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cup-to-mouth</td>
<td>0.07</td>
<td>0.11</td>
<td>0.83</td>
<td>0.42</td>
</tr>
<tr>
<td>Reaching</td>
<td>-0.0</td>
<td>0.17</td>
<td>0.97</td>
<td>0.57</td>
</tr>
</tbody>
</table>
**Discussion**

We sought to examine the contribution of intrusion of pathological flexor synergies to reaching impairments in the arm in the sub-acute stroke period using a novel marker-less pose-estimation approach. We were not able to find any evidence for intrusion of the flexor synergy as a contributor to impaired kinematic performance on either of two functional tasks requiring 3D arm movements. Abnormal FMA scores in the sub-acute stage were attributable instead to compensatory movements at the shoulder combined with extensor weakness at the elbow.

Studies in the second half of the 20th century that attempted to formally characterize changes in the post-stroke arm paretic phenotype over the time-course of recovery noted that in addition to reduced strength, stroke survivors also suffer from obligatory flexor and extensor synergies.\(^{22,23}\) The Fugl-Meyer Assessment (FMA)\(^7\) was designed, in part, to capture such intrusion by synergies. The FMA correlates with other measures of synergies\(^6,8,9\) and is abnormal in acute, sub-acute and chronic stroke.\(^{24,25}\) The contribution of synergies to abnormal movements in the setting of post-stroke paresis can also be quantified using kinematics.\(^{11,26}\)

Using kinematic analysis, it is possible to determine the relative contributions of negative signs, such as loss of dexterity and weakness, and positive signs, such as intrusion of pathological synergies, to the overall arm motor control deficit. Levin (1996) showed that inter-joint coordination deficits during 2D planar arm movements in subjects with chronic stroke were invariant to reaching direction, suggesting that intrusion of synergies is not a major contributor to 2D post-stroke reaching impairment.\(^{26}\) In contrast, Zackowski and colleagues showed intrusion of synergy by demonstrating greater deficits in 3D reaching requiring movement outside the flexor synergy than within the flexor synergy in chronic stroke. They supported this conclusion by also showing that subjects could not make isolated movements of the individual movements.\(^{11}\) Wagner and colleagues examined reaching in the acute post-stroke stage (all subjects were tested withing two weeks of their stroke), using a similar individuation paradigm. In this case, the weakness measures had greater contribution to the kinematic deficits than the individuation measure, thereby supporting reduced synergy intrusion.\(^{13}\)
Our results in subjects in the early and late sub-acute stroke stage are consistent with those reported by Wagner and colleagues, namely we also did not see evidence for intrusive flexor synergies. This finding raises a critical question: What is the basis of the abnormal FMA score at this stage post-stroke? Notably, subjects were not assessed with the FMA in the study by Wagner and colleagues, but it is well established that the FMA is abnormal in acute stroke and it was in our study, too. As stated in the results, a low FMA score can be obtained through weakness-induced dis-coordination between the shoulder and elbow. Thus, despite the synergy-measurement rationale for the FMA, it can also be scored low because of weakness alone. Various studies have shown that the FMA correlates with weakness. This correlation is not just because weakness and synergies arise from a common lesion but also because weakness-induced joint coupling can look like a neural synergy. Thus, it appears that the FMA can be abnormal for two reasons: weakness-induced synergy mimics and true neural synergies. Based on our results and previous ones, we suggest that abnormal neural synergies, perhaps attributable to upregulation of the reticulospinal tract (RST) and loss of its regulation by a compromised corticospinal tract (CST), only start to be expressed as patients transition into the chronic phase of stroke.

These results, along with previous ones, have several implications. First, they emphasize the importance of going beyond clinical scales and towards characterization of neurological deficits with fine-grained kinematic analyses. Second, they suggest that the meaning of an abnormal FMA qualitatively changes as a function of post-stroke stage: progressing from weakness-induced joint coupling to true neural synergies. This is very important as it implies that a change in the FMA early after stroke has a very different mechanistic basis as compared to a similar change in the chronic stage. Indeed, this may explain why interventions can fail to improve the FMA in the sub-acute stage but nevertheless do so in the chronic stage. For example, in two trials that sought to intervene with extra neurorehabilitation within the first two to three weeks after stroke, the FMA did not improve beyond the spontaneous recovery seen in the control group. In contrast, adding extra therapy in chronic patients can change the FMA. Third, the fact that weakness plays such an important role in the motor control deficits in the acute and sub-acute stages post-stroke may be the reason that the RST, which is critical to the generation of large forces gets upregulated. Essentially, a weakness problem gets replaced by a synergy problem. Novel interventions, likely best instigated at the acute and subacute stages, are going to be needed to mitigate this zero-sum game trade-off.
Limitations

One potential limitation of this study is that our sample included subjects with only a mild level of impairment (34-66) (50% of the stroke group). These subjects may dilute the effect of intrusion of synergies if they are expressed more in more severe paresis. While the results held in a sub-sample containing 14 subjects with lower FMA scores (34-58), replication of the results in larger datasets with a broader range of impairment is required. It should be noted however, that in a recent study of sub-acute post-stroke subjects, we could not find evidence of upregulation of the RST, which is consistent with the findings presented here.38

Finally, the novel measure of inter-joint synergy we used here, derived from marker-less 3D kinematics, will need further testing and validation.

References


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**Supplementary material**

Supplementary figure 1 Shoulder and elbow angles of the dominant hand of controls in the reaching task.
Supplementary figure 2 Shoulder and elbow angles of the paretic hand of sub-acute patients in the reaching task.