


RESEARCH

Open Access



Myoelectric interface training enables targeted reduction in abnormal muscle co-activation

Gang Seo¹, Ameen Kishta⁵, Emily Mugler², Marc W. Slutzky^{2,3,4,5*†} and Jinsook Roh^{1*†} 

Abstract

Background: Abnormal patterns of muscle co-activation contribute to impaired movement after stroke. Previously, we developed a myoelectric computer interface (MyoCI) training paradigm to improve stroke-induced arm motor impairment by reducing the abnormal co-activation of arm muscle pairs. However, it is unclear to what extent the paradigm induced changes in the overall intermuscular coordination in the arm, as opposed to changing just the muscles trained with the MyoCI. This study examined the intermuscular coordination patterns of thirty-two stroke survivors who participated in 6 weeks of MyoCI training.

Methods: We used non-negative matrix factorization to identify the arm muscle synergies (coordinated patterns of muscle activity) during a reaching task before and after the training. We examined the extent to which synergies changed as the training reduced motor impairment. In addition, we introduced a new synergy analysis metric, disparity index (DI), to capture the changes in the individual muscle weights within a synergy.

Results: There was no consistent pattern of change in the number of synergies across the subjects after the training. The composition of muscle synergies, calculated using a traditional synergy similarity metric, also did not change after the training. However, the disparity of muscle weights within synergies increased after the training in the participants who responded to MyoCI training—that is, the specific muscles that the MyoCI was targeting became less correlated within a synergy. This trend was not observed in participants who did not respond to the training.

Conclusions: These findings suggest that MyoCI training reduced arm impairment by decoupling only the muscles trained while leaving other muscles relatively unaffected. This suggests that, even after injury, the nervous system is capable of motor learning on a highly fractionated level. It also suggests that MyoCI training can do what it was designed to do—enable stroke survivors to reduce abnormal co-activation in targeted muscles.

Trial registration This study was registered at ClinicalTrials.gov (NCT03579992, Registered 09 July 2018—Retrospectively registered, <https://clinicaltrials.gov/ct2/show/NCT03579992?term=NCT03579992&draw=2&rank=1>)

Keywords: Muscle synergy, Intermuscular coordination, Myoelectric computer interface, Stroke motor rehabilitation

[†]Jinsook Roh and Marc W. Slutzky contributed equally to this project

*Correspondence: msslutzky@northwestern.edu; jroh@uh.edu

¹ Department of Biomedical Engineering, Cullen College of Engineering, University of Houston, 3517 Cullen Blvd, SERC Room 2011, Houston, TX 77204-5060, USA

² Department of Neurology, Northwestern University, 320 E. Superior Ave., Searle 11-473, Chicago, IL 60611, USA

Full list of author information is available at the end of the article

Background

Stroke, the largest cause of long-term disability worldwide, often damages motor pathways in the brain and induces abnormal spatiotemporal patterns of co-activation across arm muscles [1], also called abnormal muscle synergies [2–5]. Using dimensionality reduction methods, such as non-negative matrix factorization (NMF)



or principal component analysis (PCA), several studies characterized the stroke-induced abnormal muscle synergies based on the electromyography (EMG) signals of the arm muscles [6–8]. Commonly observed abnormal muscle synergies after stroke include coupling of activity between elbow flexors and shoulder abductors during isometric torque generation [1, 4] and dynamic reaching [9]. Moreover, stroke induces co-activation of the anterior, middle, and posterior deltoid during the stable force maintaining phase of the isometric reaching task [7]. This co-activation inhibits the ability to flex the shoulder maximally. These abnormal patterns contribute to motor impairment and reduced function after stroke, partially by limiting range of motion during reaching [10, 11]. Thus, targeting these abnormal patterns is a potential new avenue for stroke rehabilitation.

Our previous study developed a myoelectric computer interface (MyoCI) paradigm to reduce abnormal co-activation and thereby impairment [12, 13]. Mugler et al. [13] examined 6 weeks of in-lab MyoCI training in thirty-two chronic stroke survivors with moderate-to-severe impairment. Before the training, each participant went through a screening process to identify the three most abnormally co-activating arm muscle pairs (defined by pairwise correlation coefficients) during free-reaching to targets, placed at waist and shoulder height, in front of and lateral to the impaired limb. After the screening, the participants were randomized to three different training groups (60 and 90 min using isometric activation; 90 min with activation during unrestricted movement). The participants were trained on and learned to activate each identified muscle pair separately for 2 weeks. At the end of the MyoCI training, participants had reduced arm impairment (measured using the Fugl-Meyer Assessment), improved motor function and elbow range-of-motion, and reduced spasticity (measured with the Modified Ashworth Scale). However, it remains unclear how MyoCI training affected intermuscular coordination in the arm in reaching movements.

Here, we investigate to what extent MyoCI training changed intermuscular coordination. We assessed the composition and number of muscle synergies as effects on the more global arm muscle network. Further, we augmented our muscle synergy analysis by developing the disparity index (DI), which measures the disparity between the synergy activation weights of each pair of muscles trained.

Methods

Participants

Thirty-three stroke survivors (15 women; age ranging from 27 to 75 years; mean of 6.5 years since stroke) participated in the original experiment [13]. The time since

stroke was 3.8 ± 6.2 , 4.3 ± 4.1 , and 5.3 ± 3.2 years for 60I, 90I, and 90 M groups, respectively (mean \pm SEM) and ranged from 11 to 314 months. All participants completed the entire 6 weeks of training; 32 completed the 10-week evaluation. An occupational therapist performed the Fugl-Meyer Assessment of the upper extremity (FMA-UE) on the impaired arm to assess the motor impairment of participants. We included adult, chronic stroke survivors (at least 6 months from stroke onset) who had persistent moderate to severe arm impairment (FMA-UE, 8–40/66) and increased arm tone. Full inclusion/exclusion criteria can be found in Mugler et al. [13]. The trial is registered at ClinicalTrials.gov, NCT03579992. The study protocol was approved by the Northwestern University Institutional Review Board, and each participant gave written informed consent prior to eligibility assessment.

Training and assessment paradigm

The MyoCI training involved using EMG envelopes of the targeted muscle pair to move a cursor to different targets in a custom-built game to reduce abnormal co-activation. The cursor started in the bottom left of the screen when the muscles were at rest. EMG amplitudes were multiplied by a gain, such that target distance corresponded to 10–20% of maximum voluntary contraction and then averaged over the previous 50 ms. At each 50-ms time bin, the amplitudes of the targeted muscle pair were mapped to the position of a cursor along the cardinal [horizontal (X) and vertical (Y)] axes, respectively, and the cursor position was determined by a vector sum of these two components [12]. Thus, only activating muscles in isolation would move the cursor along the cardinal axes. Participants trained on three muscle pairs for six sessions each over 2 weeks. We assigned participants pseudo-randomly into three groups: two groups trained isometrically (restraining the arm) for either 60 or 90 min per session (ISO₆₀ and ISO₉₀, respectively) and one group trained without restraining the arm (movement group) for 90 min per session (MVMT). Further details of the training, including specific muscle pairs, are described in our previous study [13].

To assess the effects of the training on motor impairment, an occupational therapist blinded to the training group evaluated FMA-UE at –2, 0, 2, 6, and 10 weeks relative to the start of training. The occupational therapist was not fully blinded to the number of weeks; they knew when the first evaluation was done, but we did not explicitly tell them the week number of the subsequent sessions. We recorded EMG while each participant performed a reaching task on weeks –2, 0, 2, 4, 6, and 10, relative to the training start. As depicted in Fig. 1, the task consisted of three reaches to each of six targets

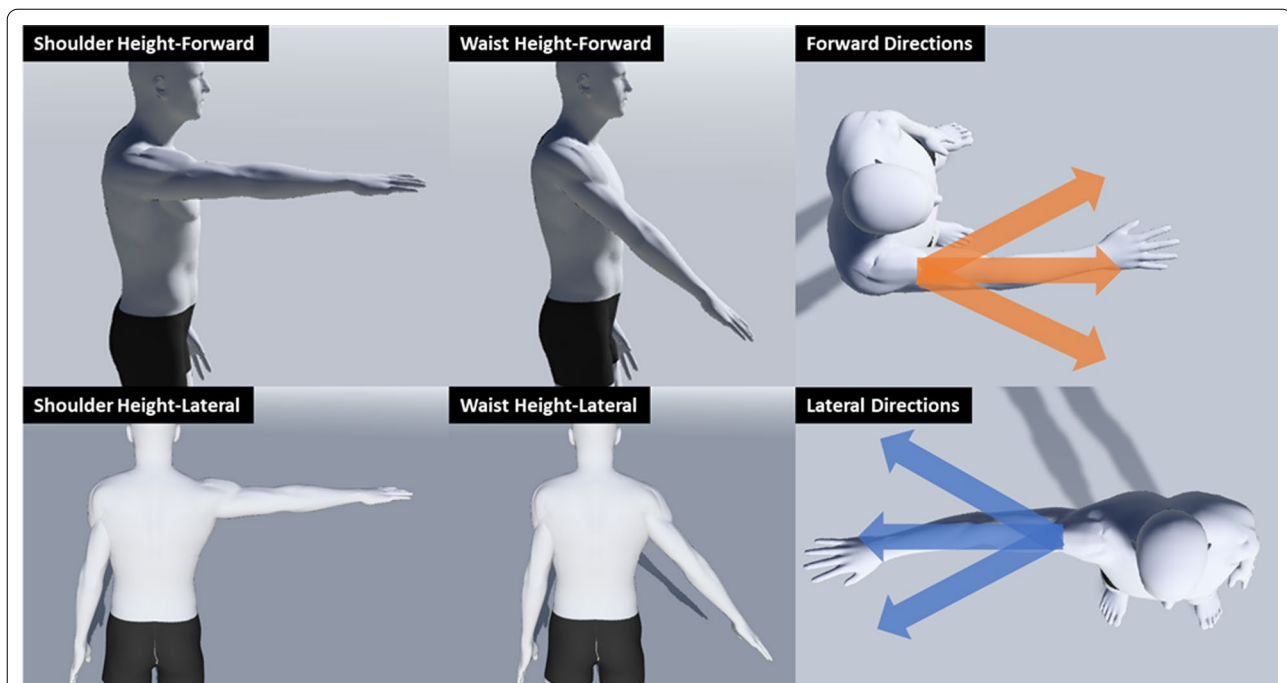


Fig. 1 A reaching task that participants performed to assess the training effects using EMG data. During the motor assessment, participants performed reaches (only away-from-body reaches) three times to each of six targets (approximately 4" in diameter and spaced 1ft apart), placed at the waist and shoulder height, in front of, and lateral to the impaired arm. The participants were asked to bring the arm back to the rest position at the side (elbow extended maximally, shoulder adducted, not flexed nor rotated with the thumb facing anteriorly) after each reach. The arrows indicate three directions of reach at the waist and shoulder height

(approximately 4" in diameter and spaced 1 ft apart), placed at waist and shoulder height, in front of, and then lateral to, the impaired arm (36 reaches, in total, to sample a broad range of reaching directions). The participants were asked to reach to the target as best as they could (self-paced speed) and no adjustments were made for severely impaired survivors. After each reach, participants were asked to bring the arm back to the rest position at the side (elbow extended maximally, shoulder adducted, not flexed nor rotated with the thumb facing anteriorly). The resting period in between each reach was at least 3 s.

EMG recordings

EMGs were recorded to identify muscle targets for the MyoCI training and assess the effects of the training on intermuscular coordination in the arm after stroke. We identified co-activating muscles as targets for training in the study. We defined co-activation as the pairwise correlation coefficient between each pair of EMG envelopes during reaching. Muscle pairs with the largest abnormal co-activation—i.e., not seen in healthy arms during reaching—were selected for the MyoCI training. The selected muscle pairs typically included biceps/anterior

deltoid, anterior/posterior deltoid, and triceps lateral head/posterior deltoid [13].

The skin was prepared by lightly exfoliating and cleaning with alcohol to collect EMG signals. We placed wireless, active EMG electrodes (Trigno, Delsys, Inc.) on the skin over the bellies of 8 muscles on the affected arm: anterior, middle, and posterior deltoids (AD, MD, and PD); biceps brachii (BI), triceps [long (TRIlong) and lateral (TRIlateral) heads]; brachioradialis (BRD); and pectoralis major (PECT). EMG electrodes were placed according to guidelines of the Surface Electromyography for the Non-Invasive Assessment of Muscles—European Community project (seniam.org); a skin marker was used to ensure consistent EMG placement across sessions. EMG was sampled at 1926 Hz.

Participants classification

The 32 participants, who completed both 6 weeks of training and the 10-week evaluation, were divided into two subgroups, responders and non-responders, based on their FMA-UE change after 6 weeks of training. Compared to the mean of the FMA-UE measured at weeks -2 and 0, if the score at week 6 increased by more than 2 points, the participant was considered a responder. For

all analyses, we combined subjects across training groups (ISO₆₀, ISO₉₀, and MVMT).

Data pre-processing and synergy analysis

Before the synergy identification, the raw EMG signals, recorded at weeks $-2, 0, 2, 4, 6,$ and $10,$ were high-pass filtered at 50 Hz, rectified, then low-pass filtered (4th order Butterworth) at 5 Hz to obtain the envelope of the signals [14]. The processed EMG envelope of each muscle was normalized by dividing it by the maximum amplitude over all trials for each week to avoid any bias in synergy extraction toward the muscles with high-amplitude activation. For each subject, the normalized EMG envelopes, which included the entire segment from rest to target and back to rest, were then concatenated across all trials per week to identify one representative set of muscle synergies that counted the entire set of 36 reaches. A Kolmogorov–Smirnov test was used to test the normality of the data distribution, and the data were indeed normal ($\alpha = 0.05$).

To identify the muscle synergies, we applied a non-negative matrix factorization (NMF) to the pre-processed EMG. In the NMF algorithm, the EMG was modeled as a synergy matrix (W) multiplied by the corresponding activation profile matrix (C):

$$EMG_{reconstructed} = W \bullet C \quad (1)$$

The matrix W consisted of N column vectors, each of which described a muscle synergy with eight muscle weights. C was an N by T matrix, denoting activation of N synergies across the trials with T data samples. To estimate the optimal number of synergies that sufficiently reconstructed the spatial characteristics of the EMGs for each participant at each week, the minimum number of synergies that guaranteed the following criteria was identified: the global variance accounted for (gVAF) of the entire dataset greater than 90%, with less than a 5% increase in mean gVAF upon addition of another synergy (diffVAF) [7, 15]. The VAF value was defined based on the ratio between the summation of the squared errors (SSE) and the total sum of the squared with uncentered EMG (SST):

$$VAF = 100 \times \left(1 - \frac{SSE}{SST} \right) \quad (2)$$

For quantifying the changes in the overall composition of muscle synergies between pre- and post-training of each participant, we compared norm synergies (the mean across participants) at the baseline week and week 6 using a similarity index (r -value; between 0 and 1) calculated from the scalar product [16]. The EMG of week 0 was typically used as the baseline EMG, while that of

week -2 was alternatively used for seven subjects to ensure the quality of baseline EMG for further analysis.

To determine the significance of the similarity, we generated 1000 sets of 1 by 8 random synergy vectors consisting of randomly selected muscle weights of synergies identified in the study, and we performed the dot product of all possible pairs of random synergies [7, 17]. If the similarity between two muscle synergies exceeded the 95th percentile of the similarity indexes of random synergies (similarity threshold = 0.86), we considered the two muscle synergies statistically similar. We used the same method to quantify the inter-subject variability of synergy composition within a group. The norm synergy at each week was compared with its corresponding synergy of each participant using the dot product.

Disparity index (DI) analysis

To explore the training effects on the synergies, the relative change in the muscle activation weights (W) of trained muscle pairs within a synergy between the baseline week and week 6, post-training, was computed. The synergies were extracted from EMG envelopes concatenated across all trials for each week, and each trial included the entire reaching segment from rest to target and back to rest. Therefore, the weights represent the activation patterns of arm muscles that can be combined to characterize the inter-muscular coordination during the entire set of 36 reaches. At the baseline week, we selected the trained muscle pair whose muscle weights ($m1_{base}$ and $m2_{base}$, for the first and second muscles of the pair, respectively) within a synergy exceeded a co-activation threshold level ($Th_{CoA} = \frac{1}{\sqrt{8}} = 0.35$). Th_{CoA} was determined based on the normalized weight of each muscle within a synergy if all eight muscles were equally activated. Using the selected $m1_{base}$ and $m2_{base}$, we quantified the disparity index (DI) of a muscle pair at the baseline (DI_{base}) as:

$$DI = \sqrt{\left(m1 - \frac{m1 + m2}{2}\right)^2 + \left(m2 - \frac{m1 + m2}{2}\right)^2} \quad (3)$$

A DI value represents how much the pair of muscle weights diverged from their co-activation level, i.e., the mean of their weights. Therefore, a higher DI value indicated a lower level of co-activation of the muscle pair. After identifying $m1_{base}$ and $m2_{base}$ within a synergy and calculating DI_{base} , we obtained the weights of the same muscles in a corresponding synergy at week 6 ($m1_{wk6}$ and $m2_{wk6}$) to calculate their disparity index (DI_{wk6}). The selection of the corresponding synergy vector at week 6 was based on the similarity score calculated from the scalar product. Once DI_{base} and DI_{wk6} of the trained

muscle pair were obtained, we calculated the change in the weight disparity ($\Delta DI_{\text{post-training}} = DI_{\text{wk6}} - DI_{\text{base}}$) to quantify the training effect on the co-activation of the trained muscle pair (Fig. 2). If more than one synergy at the baseline week contained both $m1_{\text{base}}$ and $m2_{\text{base}}$ exceeding Th_{CoA} , the synergy with the smallest weight disparity between the two muscles was considered the representative synergy for the co-activation of the given muscle pair. That is, we chose the synergy with the most co-activation between the muscle pair because that was what we aimed to counteract with the MyoCI training. To summarize, as depicted in Fig. 2, the algorithm selects the representative weights of each trained muscle pair from the baseline week (pre-training), which exceed the co-activation threshold and have minimal disparity, and compares them with the corresponding weights obtained from week 6 (post-training) using the DI method.

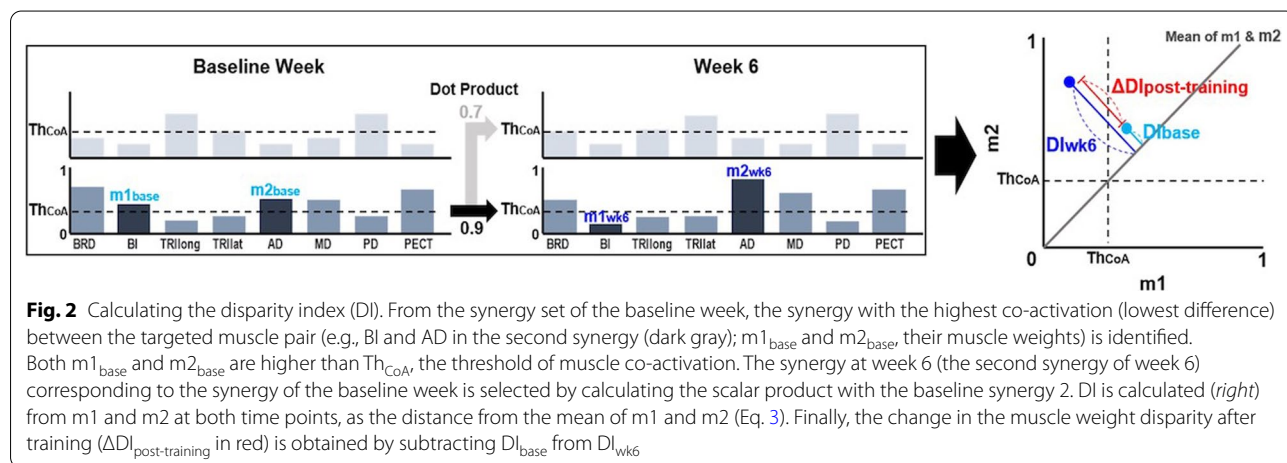
We measured the significance of the change in DI after six weeks of training in three different ways. First, we compared $\Delta DI_{\text{post-training}}$ with the 95% confidence interval of baseline variation, which we computed using 1000 bootstrap samples of the pre-training ΔDI values obtained from the entire participants at week 0 and week -2 ($\Delta DI_{\text{pre-training}} = DI_{\text{wk0}} - DI_{\text{wk-2}}$). To validate whether

the Th_{CoA} level influenced the results, we compared $\Delta DI_{\text{post-training}}$ with the bootstrapped $\Delta DI_{\text{pre-training}}$ calculated using twenty different thresholds set at 5–100% of Th_{CoA} (in increments of 5%). Second, we computed the $\Delta DI_{\text{post-training}}$ for the trained muscle pair and for all possible pairwise combinations of untrained muscles. Third, we computed the significance of the difference in the distributions of DI_{base} and DI_{wk6} of all trained muscle pairs regardless of their initial weights (no Th_{CoA} applied) using a two-tailed t-test ($\alpha = 0.05$).

Results

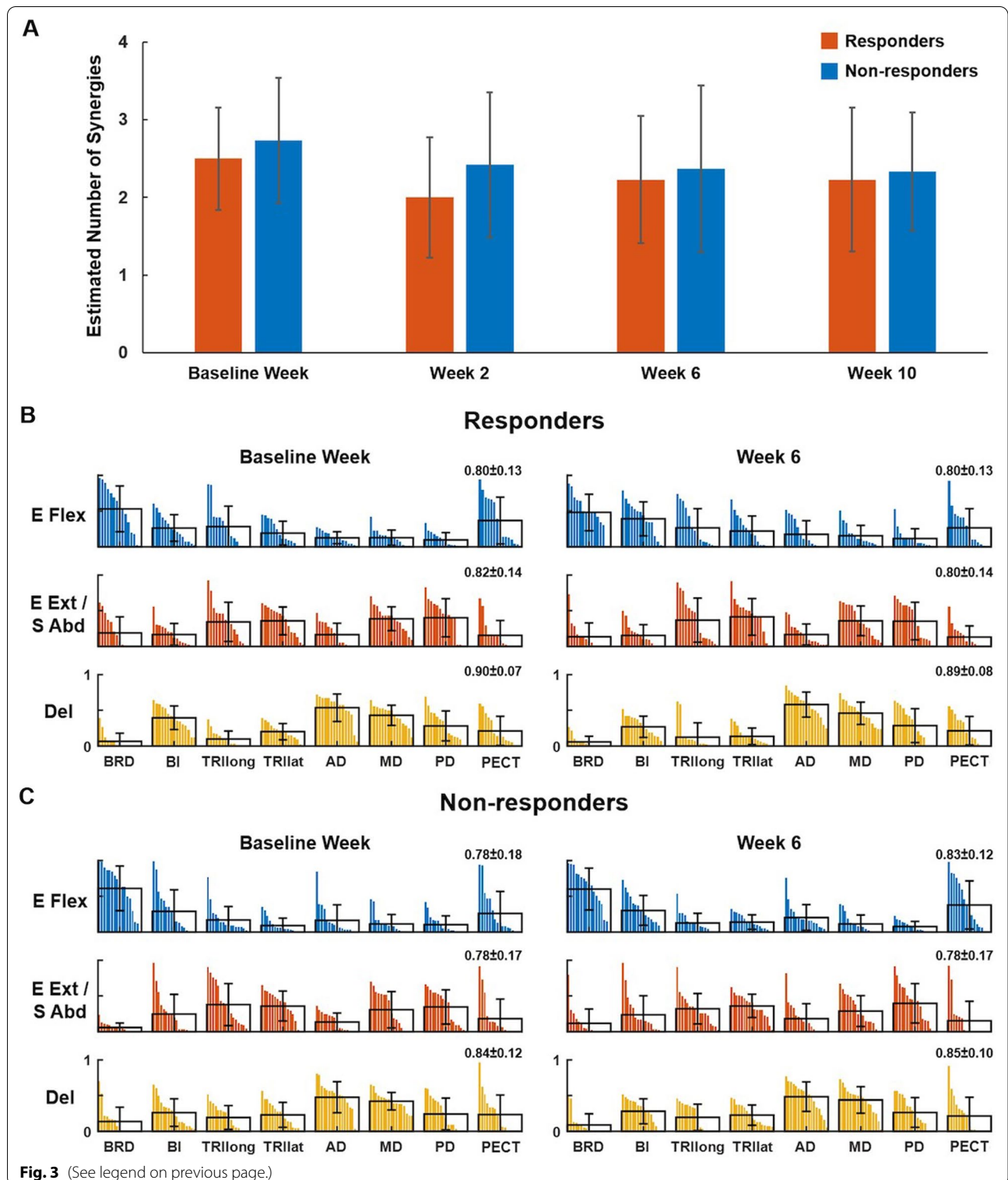
Estimation of the number of synergies and overall synergy composition

Based on the level of improvement in the motor impairment (FMA-UE) after the training, 15 and 17 participants were categorized as responders and non-responders, respectively. Typically, two to four synergies were identified from the EMGs of each participant before, interim, and after the MyoCI training in both responder and non-responder groups (Fig. 3A). The average number of synergies across all participants and weeks was 2.41, indicating that three synergies predict most of the total EMG variance in both groups and across weeks. Overall,



(See figure on next page.)

Fig. 3 The number and composition of muscle synergies in responders and non-responders. **A** Estimation of the number of synergies identified across weeks including pre-training (Baseline week), interim (week 2), post-training (week 6), and retention (week 10) in the responder and non-responder groups. The number of synergies did not differ between the two groups nor across weeks in each group. **B, C**, The mean and SD of muscle weights, superimposed on the distribution of the muscle weights of responders (**B**, $n = 15$) and non-responders (**C**, $n = 17$), per each of three synergies identified in pre- and post-training (Baseline week and week 6, respectively). The muscle weights per muscle were displayed in descending order. Eight muscles included: brachioradialis (BRD); biceps brachii (BI); triceps (long (TRIlong) and lateral (TRIlal) heads); anterior, middle, and posterior deltoids (AD, MD, and PD); and pectoralis clavicular fiber (PECT). The synergies were characterized as (1) E Flex: elbow flexors, (2) E Ext/S Abd: elbow extensors, and 3) Del: three heads of the deltoid. The r -value next to each muscle synergy indicates the scalar products between the norm synergy (the mean across the subjects) and its corresponding synergy of each participant (mean \pm SD)



no consistent pattern of change in the number of muscle synergies was observed after the training in each group. The number of synergies did not change significantly

from the baseline to week 6 (change in responders (n=15): -0.27 , $p=0.37$; non-responders (n=17): -0.37 , $p=0.19$, one-way ANOVA). Compared to the

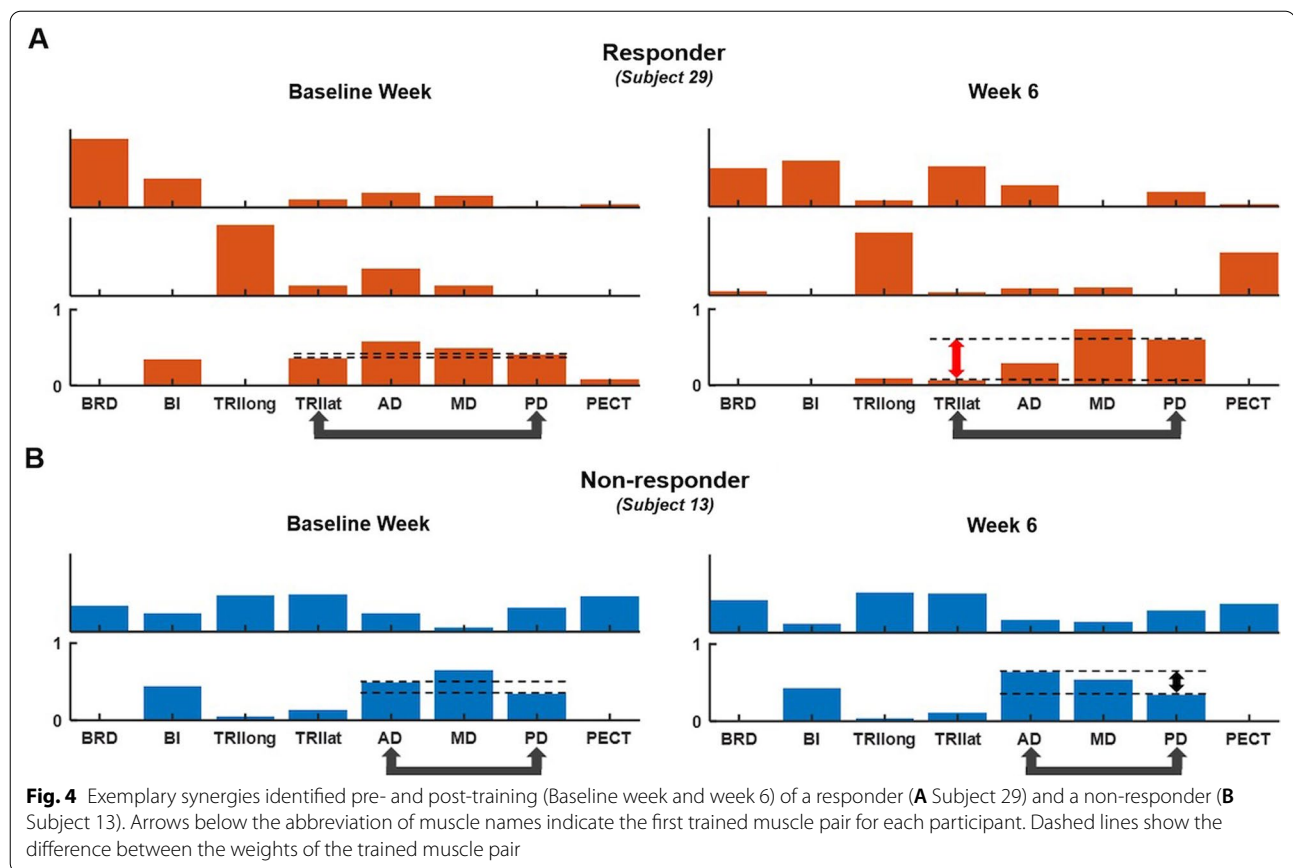


Fig. 4 Exemplary synergies identified pre- and post-training (Baseline week and week 6) of a responder (**A** Subject 29) and a non-responder (**B** Subject 13). Arrows below the abbreviation of muscle names indicate the first trained muscle pair for each participant. Dashed lines show the difference between the weights of the trained muscle pair

baseline week, the number of synergies was preserved in 40.6% ($n = 13$) of all participants, decreased in 37.5% ($n = 12$), and increased in 21.9% ($n = 7$). Among responders, the number of synergies was preserved in 46.7% ($n = 7$), reduced in 33.3% ($n = 5$), and increased in 20.0% ($n = 3$). Among non-responders, 35.3% ($n = 6$) showed no change in synergy number, 41.2% ($n = 7$) decreased, and 23.5% ($n = 4$) increased.

The composition of three muscle synergies extracted from each participant at each week was distinctive with the dominant muscle weights but with inter-subject variability. The synergies consisted of (1) two elbow flexors (BRD and BI) with PECT, (2) two elbow extensors (TRl long and TRl lat) and shoulder abductor/extensor (MD and PD), and (3) three heads of the deltoid (AD, MD, and PD) with BI for both responders and non-responders (Fig. 3B and C, respectively). On average, the similarity (r -value) of three norm synergies (the mean of clustered synergies; Fig. 3B and C) between pre- (baseline week) and post-training (week 6) was 0.98 ± 0.01 and 0.99 ± 0.01 for responders and non-responders, respectively. The high similarity values indicated no significant change [i.e., r -value > the similarity threshold (0.86); $p < 0.05$] in the group-wise overall composition of muscle

synergies due to the MyoCI training. However, when the norm synergy per group and week was compared with its corresponding synergy of each participant, inter-subject variability of synergy composition within the same group was observed (Figs. 3B and C). The mean r -value of each synergy was lower than the similarity threshold (0.86; $p < 0.05$), indicating substantial inter-subject variability of the synergy composition [responders: 0.84 ± 0.11 (baseline week), 0.83 ± 0.12 (week 6); non-responders: 0.80 ± 0.15 (baseline week), 0.82 ± 0.13 (week 6)]. Also, the same result was obtained even when extracting only two, instead of three, synergies ($p < 0.05$). In terms of the activation profile, regardless of the number of synergies extracted (two or three), there was no clear pattern of change in the mean magnitude of coefficients observed in both groups ($p > 0.05$). Overall, the observations motivated us to develop a more precise way to quantify potential changes in a pair of muscle weights within a synergy, trained in the MyoCI protocol.

Weights of the trained muscle pairs within a synergy changed with MyoCI training

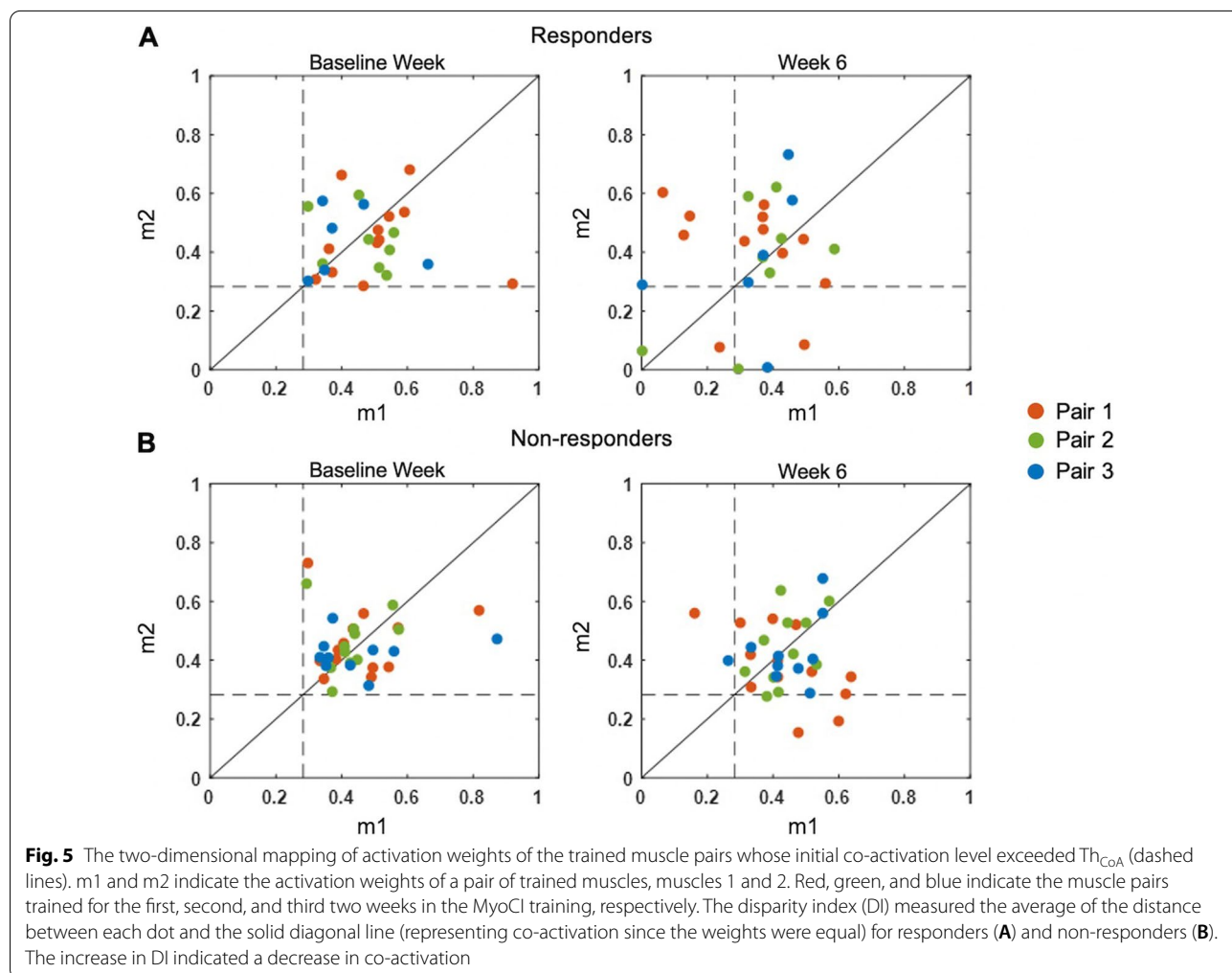
The MyoCI training modulated the weights of trained muscle pairs within a synergy in responders, not in

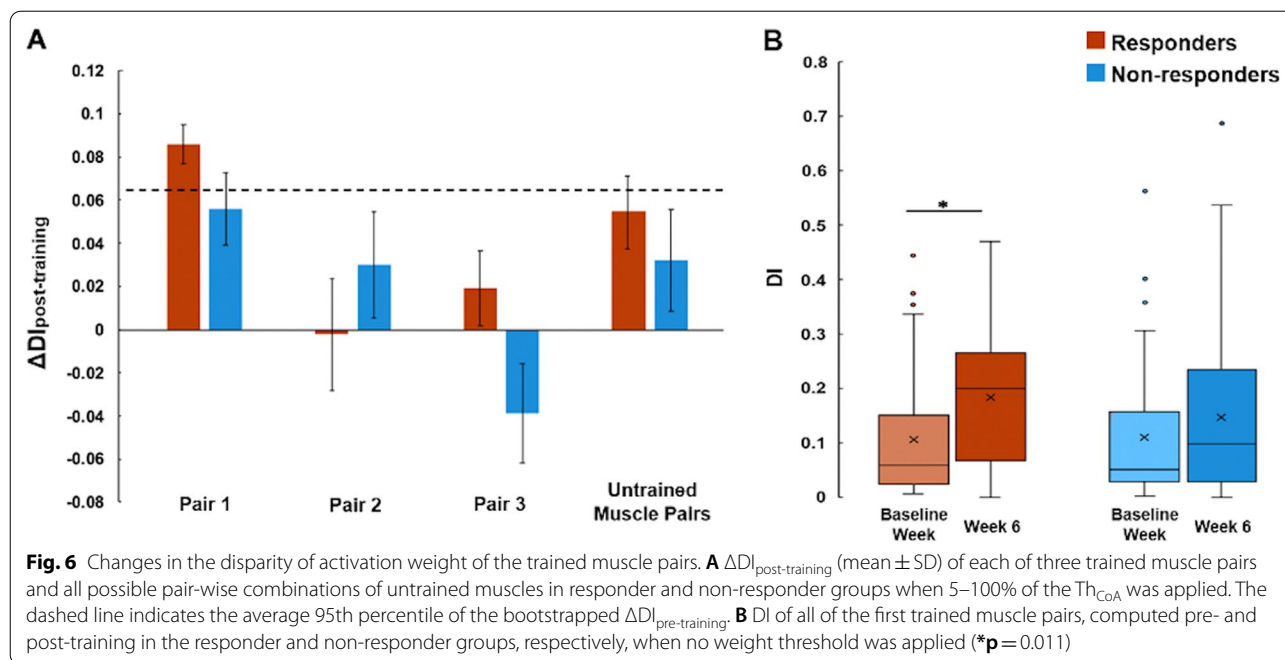
non-responders. Figure 4A shows an example of these patterns for a representative responder; the relative weights of the first trained muscle pair, the TR1lat and PD, in the synergy noticeably changed after the training. This finding signifies a reduction in co-activation of the first muscle pair. The decrease in co-activation was not typically observed in non-responders (Fig. 4B). These results suggest that the MyoCI training, which aimed to decrease the abnormal co-activation of a pair of muscles, increased the disparity of weights of the trained muscle pair within a given synergy in responders but not in non-responders.

Before MyoCI training (baseline), the mean DI, computed with Th_{CoA} applied, of all three targeted muscle pairs was comparable between responders and non-responders (Fig. 5; $DI_{R-base} = 0.091 \pm 0.095$, $DI_{NR-base} = 0.074 \pm 0.076$; $p = 0.33$, t-test). After the training (week 6), only the responders showed an increase in DI compared to baseline ($\Delta DI_R = 0.044 \pm 0.11$, $p = 0.046$; $\Delta DI_{NR} = 0.018 \pm 0.11$, $p = 0.10$; t-test), which implied

a decrease in co-activation of the trained muscle pair within the synergy in general. Interestingly, in both groups of participants, the first trained muscle pair, which initially had the highest abnormal co-activation (pair-wise correlation) among the three pairs, demonstrated the most reduction in co-activation due to MyoCI training ($\Delta DI_{R-pair1} = 0.073 \pm 0.13$, $\Delta DI_{NR-pair1} = 0.055 \pm 0.14$; $\Delta DI_{R-pair2} = 0.002 \pm 0.055$, $\Delta DI_{NR-pair2} = 0.011 \pm 0.092$; $\Delta DI_{R-pair3} = 0.042 \pm 0.14$, $\Delta DI_{NR-pair3} = -0.021 \pm 0.065$; Fig. 5). However, only the responders showed a significant reduction of DI in the first pair ($p = 0.016$, t-test).

This result was not influenced by the level of Th_{CoA} because $\Delta DI_{post-training}$ was comparably similar while the threshold was varied systematically (5–100% of Th_{CoA} with an increment of 5%). Among the three pairs of muscles trained, only $\Delta DI_{R-pair1}$ in responders exceeded the 95th percentile level of $\Delta DI_{pre-training}$ regardless of the level of Th_{CoA} ($p = 0.0025$; Fig. 6A). In particular, the participants in the movement-based training group showed a greater $\Delta DI_{post-training}$ value of the first trained muscle





pair than the isometric training groups ($p=0.0029$ for comparing MVMT to ISO_{60} ; $p<0.001$ for comparing MVMT to ISO_{90} , ANOVA). For non-responders, the ΔDI of the first pair did not significantly change ($p=0.12$). Similar results were observed when there was no threshold, Th_{CoA} , applied. These findings mean that, even when the DIs of all of the first trained muscle pairs across participants were considered regardless of their level of initial co-activation, the responder group demonstrated a statistically significant increase in the mean DI at week 6 ($p=0.011$; Fig. 6B).

Discussion

In this study, we investigated the effect of MyoCI training on intermuscular coordination using muscle synergy analysis. The number of synergies identified during reaching ranged from two to four and did not change due to the training. The overall composition of muscle synergies also did not change. However, there was a notable change, within individual synergies, in the disparity of muscle weights of the trained muscles in responders to the training. While not all muscle pairs changed their co-activation, the muscle pairs with the largest abnormal co-activation before training showed the largest reduction in coupling after training, especially in the movement-based training group. These results suggest that our MyoCI paradigm did, in fact, allow participants to decouple the targeted muscle pairs (particularly the most abnormally co-activating, muscle pair 1), which, in turn, was correlated with improved movement. The fact that the

training only changed the behavior of the trained muscles suggests that the CNS is capable of making highly fractionated changes in motor control, even after a stroke-causing severe impairment.

Our prior study showed that MyoCI training might reduce arm impairment in moderately and severely impaired stroke survivors [13]. That study found some reduction in pairwise correlations of the trained muscles during reaching in the movement group, but not in the isometric groups. This study, which looked at the within-synergy weights of the trained muscles, found increased disparity (reduced co-activation). Thus, the more comprehensive approach to intermuscular coordination using muscle synergy analysis revealed changes that were not seen in the simpler, pairwise correlation analysis.

In this study, we found no consistent pattern of change (e.g., merging or fractionation) observed in the overall composition of the synergy sets. Few studies have characterized the number of muscle synergies after stroke, as compared to unimpaired limbs, as having three different patterns: preservation, merging, and fractionation of unimpaired synergies [9, 18, 19]. More severe impairment after stroke correlated with having fewer synergies (merging) [18, 20] or fewer muscle networks [21]. This observation suggests that we might expect to see fractionation of synergies (greater number of synergies) with improved function from MyoCI training. However, the current MyoCI paradigm was customized for each individual's pattern of muscle co-activation, meaning that different muscle pairs were targeted for different

participants. This inter-subject variability may have resulted in a diverse effect on the synergy composition across participants, given the variation in initial co-activation of muscles trained. Moreover, no clear pattern of change in the activation profile was observed due to the inconsistency of the pattern of change in the number and the composition of muscle synergies that arose from the high inter-subject variability.

To account for this diversity, we designed DI analysis to focus on the training effect on each individual's muscle synergies, particularly those most relevant to the targeted muscle pairs. Previous studies showed that conventional synergy analysis can be misleading [22, 23]. When synergies are identified from a small subset of muscles, the conventional method using the VAF and its preset threshold for synergy identification can overestimate VAF, which affects the estimation of the number of synergies and the corresponding synergy composition [22]. This overestimation can lead to ignoring important features embedded in the residual muscle activities [23]. DI analysis captured a consistent change in synergy activation weights in the responders that was not identified by conventional synergy analysis. DI thus complements conventional synergy analysis. However, the current DI method is limited to reflecting the change in the disparity between weights of a muscle pair only.

Only a few recent studies have investigated the effects of rehabilitation training on potential changes in the number and/or composition of muscle synergies and/or their activation profiles in stroke survivors [11, 24, 25]. Two small studies showed that EMG feedback could reduce co-activation between agonist and antagonist muscles during training in stroke participants [26, 27]. While this finding aligns with our overall result, these studies did not assess the more global picture of arm intermuscular coordination. Pierella et al. [28] showed that improved arm function in the subacute stage, coinciding with exoskeleton training, correlated with an increase in muscle synergy number and similarity to non-stroke controls in some of the participants. Two other studies showed some evidence of post-stroke synergies becoming more like those of unimpaired arm movement due to different rehabilitation strategies [29, 30]. However, other studies showed unclear relationships between improved motor outcomes and either the number of muscle synergies or similarity between impaired and unimpaired synergies [31, 32]. Notably, these last two studies are pilot studies that included participants with only mild to moderate impairment.

One of the characteristics of human upper limb movements is that they can be highly fractionated—i.e., we can precisely control the activation of individual

joints and even single muscles. This is thought to be due to the precise connections of the corticospinal tract to small pools of motoneurons [33]. The presence of abnormal co-activation after stroke means that less fractionated movements are possible; this is thought to be due to corticospinal tract damage and higher reliance on the reticulospinal tract after stroke [34–37]. Here, we showed that MyoCI training enabled stroke survivors to improve arm function not by changing entire synergies but rather by reweighting the activities of just those muscles that were targeted. This finding indicates that even severely impaired stroke survivors are capable of fractionated changes in movement control. This, in turn, suggests that some corticospinal tract functions may have remained in our responders to MyoCI. Alternatively, it is possible that plastic changes occurred at the spinal cord level. While we unfortunately did not directly examine the corticospinal excitability (e.g., with transcranial magnetic stimulation) or cortico-reticulospinal responses such as StartReact [36, 38], we hope to examine this in future studies to determine the extent to which this change is dependent on corticospinal tract changes. Regardless of the exact mechanism, MyoCI training enabled highly precise targeting of changes in muscular coordination.

This study did have some limitations. The muscle synergies were not investigated in the arms of neurologically intact persons or in the ipsilesional arm of stroke survivors. Therefore, the comparison of synergies was made only within the stroke-impaired arm. Moreover, since the total number of analyzed muscles affects synergy analysis [22], further testing is important to examine whether the results remain consistent when more than eight arm muscles are examined. We are testing this in a follow-up, sham-controlled study with a wearable version of the MyoCI [39]. Further, some muscles may co-activate normally at different times. Overall, we selected those muscle pairs for training that were typically not synergistic in multiple activities of daily living, in particular reaching, i.e., those that showed significantly less co-activation in age-matched, able-bodied individuals performing the same reaching task. Lastly, there is no widely accepted definition of “co-activation” in terms of the weight of muscle within a synergy, which makes it unclear how best to quantify the degree of co-activation. The proposed DI method focuses on the change in weight disparity of a muscle pair to quantify the change in pair-wise co-activation level. This approach simplifies the quantification of change in co-activation. However, other factors, such as the change in the mean weight of a muscle pair, could be also considered in future studies to interpret the

training effect on the intermuscular coordination more comprehensively.

Conclusions

In conclusion, we demonstrated that the MyoCI paradigm improved the upper extremity motor impairment of the stroke survivors by rebalancing the muscle weights of trained muscles within muscle synergies. While there was no consistent pattern of change in the number and composition of muscle synergies after MyoCI training, the DI analysis captured the increase in weight disparity of trained muscle pairs within a synergy in the responders. Although not every muscle pair was decoupled, the results imply that MyoCI training can target abnormal co-activation, particularly of the most abnormally co-activating muscle pair. Further, MyoCI can enable functional improvement in people with severe impairment from stroke, even years after the stroke occurs.

Abbreviations

MyoCI: Myoelectric computer interface; DI: Disparity index; FMA-UE: Fugl-Meyer Assessment of the upper extremity.

Acknowledgements

We would like to thank Zachary Wright for assistance with the MyoCI software, and Kathy Kopka for assistance with outcome evaluations.

Author contributions

GS completed the data analysis and interpretation and made significant contributions to manuscript writing. AK helped to analyze the data. EM executed the experiments and collected the data. MS and JR designed the study, helped analyze and interpret results, and wrote the manuscript. All authors read and approved the final manuscript.

Funding

This research was supported in part by National Institutes of Health Grants (R21NS084069, R01NS099210, and UL1TR001422 for MS) and American Heart Association Grant (17SDG33670561 for JR).

Availability of data and materials

The data used in this study may be made available by the corresponding author upon a reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Northwestern University Institutional Review Board, and each participant gave written informed consent prior to eligibility assessment.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author details

¹Department of Biomedical Engineering, Cullen College of Engineering, University of Houston, 3517 Cullen Blvd, SERC Room 2011, Houston, TX 77204-5060, USA. ²Department of Neurology, Northwestern University, 320 E.

Superior Ave., Searle 11-473, Chicago, IL 60611, USA. ³Department of Neuroscience, Northwestern University, Chicago, IL, USA. ⁴Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, IL, USA. ⁵Department of Biomedical Engineering, Northwestern University, Evanston, IL, USA.

Received: 29 October 2021 Accepted: 2 June 2022

Published online: 01 July 2022

References

- Dewald JP, Pope PS, Given JD, Buchanan TS, Rymer WZ. Abnormal muscle coactivation patterns during isometric torque generation at the elbow and shoulder in hemiparetic subjects. *Brain*. 1995;118(Pt 2):495–510.
- Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain*. 1951;74(4):443–80.
- Beer RF, Dewald JPA, Dawson ML, Rymer WZ. Target-dependent differences between free and constrained arm movements in chronic hemiparesis. *Exp Brain Res*. 2004;156(4):458–70.
- Ellis MD, Holubar BG, Acosta AM, Beer RF, Dewald JPA. Modifiability of abnormal isometric elbow and shoulder joint torque coupling after stroke. *Muscle Nerve*. 2005;32(2):170–8.
- Tresch MC, Cheung VC, d'Avella A. Matrix factorization algorithms for the identification of muscle synergies: evaluation on simulated and experimental data sets. *J Neurophysiol*. 2006;95(4):2199–212.
- Cheung VCK, d'Avella A, Tresch MC, Bizzi E. Central and sensory contributions to the activation and organization of muscle synergies during natural motor behaviors. *J Neurosci*. 2005;25(27):6419–34.
- Roh J, Rymer WZ, Perreault EJ, Yoo SB, Beer RF. Alterations in upper limb muscle synergy structure in chronic stroke survivors. *J Neurophysiol*. 2013;109(3):768–81.
- Reisman DS, Scholz JP. Aspects of joint coordination are preserved during pointing in persons with post-stroke hemiparesis. *Brain*. 2003;126(Pt 11):2510–27.
- Cheung VCK, Turolla A, Agostini M, Silvoni S, Bennis C, Kasi P, et al. Muscle synergy patterns as physiological markers of motor cortical damage. *Proc Natl Acad Sci U S A*. 2012;109(36):14652–6.
- Chae J, Yang G, Park BK, Labatia I. Muscle weakness and cocontraction in upper limb hemiparesis: relationship to motor impairment and physical disability. *Neurorehabil Neural Repair*. 2002;16(3):241–8.
- Hong YNG, Ballekere AN, Fregly BJ, Roh J. Are muscle synergies useful for stroke rehabilitation? *Curr Opin Biomed Eng*. 2021;19(100315): 100315.
- Wright ZA, Rymer WZ, Slutzky MW. Reducing abnormal muscle coactivation after stroke using a myoelectric-computer interface: a pilot study. *Neurorehabil Neural Repair*. 2014;28(5):443–51.
- Mugler EM, Tomic G, Singh A, Hameed S, Lindberg EW, Gaide J, et al. Myoelectric computer interface training for reducing co-activation and enhancing arm movement in chronic stroke survivors: a randomized trial. *Neurorehabil Neural Repair*. 2019;33(4):284–95.
- Rose W. Electromyogram analysis. Online course material. University of Delaware. Retrieved July, 2011 Jul;5:2016.
- Roh J, Beer RF, Lai A, Rho M, Karvelas KR, Nader AM, et al. The effects of selective muscle weakness on muscle coordination in the human arm. *Appl Bionics Biomech*. 2018;2018:5637568.
- Roh J, Lee SW, Wilger KD. Modular organization of exploratory force development under isometric conditions in the human arm. *J Mot Behav*. 2019;51(1):83–99.
- Roh J, Rymer WZ, Beer RF. Robustness of muscle synergies underlying three-dimensional force generation at the hand in healthy humans. *J Neurophysiol*. 2012;107(8):2123–42.
- Clark DJ, Ting LH, Zajac FE, Neptune RR, Kautz SA. Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. *J Neurophysiol*. 2010;103(2):844–57.
- Park J-H, Shin J-H, Lee H, Roh J, Park H-S. Alterations in intermuscular coordination underlying isokinetic exercise after a stroke and their implications on neurorehabilitation. *J Neuroeng Rehabil*. 2021;18(1):110.
- Hesam-Shariati N, Trinh T, Thompson-Butel AG, Shiner CT, McNulty PA. A longitudinal electromyography study of complex movements in post-stroke therapy. 2: changes in coordinated muscle activation. *Front Neurol*. 2017;8:277.

21. Houston M, Li X, Zhou P, Li S, Roh J, Zhang Y. Alterations in muscle networks in the upper extremity of chronic stroke survivors. *IEEE Trans Neural Syst Rehabil Eng.* 2021;29:1026–34.
22. Steele KM, Tresch MC, Perreault EJ. The number and choice of muscles impact the results of muscle synergy analyses. *Front Comput Neurosci.* 2013;7:105.
23. Barradas VR, Kutch JJ, Kawase T, Koike Y, Schweighofer N. When 90% of the variance is not enough: residual EMG from muscle synergy extraction influences task performance. *J Neurophysiol.* 2020;123(6):2180–90.
24. Taborri J, Agostini V, Artemiadis PK, Ghislieri M, Jacobs DA, Roh J, et al. Feasibility of muscle synergy outcomes in clinics, robotics, and sports: a systematic review. *Appl Bionics Biomech.* 2018;2018:1–19.
25. Rossi S, Artemiadis PK, Roh J, Agostini V. Muscle synergies: use and validation in clinics, robotics, and sports. *Appl Bionics Biomech.* 2018;2018:6345256.
26. Jian C, Deng L, Liu H, Yan T, Wang X, Song R. Modulating and restoring inter-muscular coordination in stroke patients using two-dimensional myoelectric computer interface: a cross-sectional and longitudinal study. *J Neural Eng.* 2020;18(3): 036005.
27. Marin-Pardo O, Phanord C, Donnelly MR, Laine CM, Liew S-L. Development of a low-cost, modular muscle-computer interface for at-home telerehabilitation for chronic stroke. *Sensors (Basel).* 2021;21(5):1806.
28. Pierella C, Pirondini E, Kinany N, Coscia M, Giang C, Miehlbradt J, et al. A multimodal approach to capture post-stroke temporal dynamics of recovery. *J Neural Eng.* 2020;17(4): 045002.
29. Niu CM, Bao Y, Zhuang C, Li S, Wang T, Cui L, et al. Synergy-based FES for post-stroke rehabilitation of upper-limb motor functions. *IEEE Trans Neural Syst Rehabil Eng.* 2019;27(2):256–64.
30. Irastorza-Landa N, García-Cossio E, Sarasola-Sanz A, Brötz D, Birbaumer N, Ramos-Murguialday A. Functional synergy recruitment index as a reliable biomarker of motor function and recovery in chronic stroke patients. *J Neural Eng.* 2021;18(4): 046061.
31. Ambrosini E, Parati M, Peri E, De Marchis C, Nava C, Pedrocchi A, et al. Changes in leg cycling muscle synergies after training augmented by functional electrical stimulation in subacute stroke survivors: a pilot study. *J Neuroeng Rehabil.* 2020;17(1):35.
32. Tropea P, Monaco V, Coscia M, Posteraro F, Micera S. Effects of early and intensive neuro-rehabilitative treatment on muscle synergies in acute post-stroke patients: a pilot study. *J Neuroeng Rehabil.* 2013;10(1):103.
33. Shinoda Y, Yokota J, Futami T. Divergent projection of individual corticospinal axons to motoneurons of multiple muscles in the monkey. *Neurosci Lett.* 1981;23(1):7–12.
34. Zaimi B, Edgley SA, Soteropoulos DS, Baker SN. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain.* 2012;135(Pt 7):2277–89.
35. McPherson JG, Chen A, Ellis MD, Yao J, Heckman CJ, Dewald JPA. Progressive recruitment of contralesional cortico-reticulospinal pathways drives motor impairment post stroke: dynamic cortical laterality and arm function post stroke. *J Physiol.* 2018;596(7):1211–25.
36. Choudhury S, Shobhana A, Singh R, Sen D, Anand SS, Shubham S, et al. The relationship between enhanced reticulospinal outflow and upper limb function in chronic stroke patients. *Neurorehabil Neural Repair.* 2019;33(5):375–83.
37. Karbasforoushan H, Cohen-Adad J, Dewald JPA. Brainstem and spinal cord MRI identifies altered sensorimotor pathways post-stroke. *Nat Commun.* 2019;10(1):3524.
38. Honeycutt CF, Kharouta M, Perreault EJ. Evidence for reticulospinal contributions to coordinated finger movements in humans. *J Neurophysiol.* 2013;110(7):1476–83.
39. Hung N-T, Paul V, Prakash P, Kovach T, Tacy G, Tomic G, et al. Wearable myoelectric interface enables high-dose, home-based training in severely impaired chronic stroke survivors. *Ann Clin Transl Neurol.* 2021;8(9):1895–905.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

