Modulating Inter-Muscular Coordination Patterns in the Upper Extremity Induces Changes to Inter-Muscular, Cortico-Muscular, and Cortico-Cortical Connectivity

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***Abstract*—*Objective:* The changes in neural drive to muscles associated with modulation of inter-muscular coordination in the upper extremity have not yet been investigated. Such information could help elucidate the neural mechanisms behind motor skill learning. *Methods:* Six young, neurologically healthy participants underwent a six-week training protocol to decouple two synergist elbow flexor muscles as a newly learned motor skill in the isometric force generation in upward and medial directions. Concurrent electroencephalography and surface electromyography from twelve upper extremity muscles were recorded in two conditions (As-Trained & Habitual) across two assessments (Week 0 vs. Week 6). Changes to inter-muscular connectivity (IMC), functional muscle networks, cortico-muscular connectivity (CMC), cortico-cortical connectivity (CCC) as well as functional brain network controllability (FBNC) associated with the modulation of inter-muscular coordination patterns were assessed to provide a perspective on the neural mechanisms for the newly learned motor skills. *Results:* Significant decreases in elbow flexor IMC, CMC, and increases in CCC were observed. No significant changes were observed for FBNC. *Conclusion:* The results of this study suggest that modulating the inter-muscular coordination of the elbow flexor muscle synergy during isometric force generation is associated with multiple yet distinct changes in functional connectivity across the central and peripheral perspectives. *Significance:* Understanding the neural mechanisms of modulating inter-muscular coordination patterns can help inform motor rehabilitation regimens.**

***Index Terms*—Brain network, cortico-muscular coherence, inter-muscular coherence, muscle network, muscle synergy, neuromuscular control.**

I. Introduction

VOLUNTARY movement of the upper extremity requires co-activation of several muscles into distinct motor building blocks, also known as muscle synergies [1], which express unique inter-muscular coordination patterns. The habitually expressed patterns of inter-muscular coordination of the upper extremity, as well as their alterations post-stroke, are well understood [2], [3]. The next logical step in the study of inter-muscular coordination patterns is to study the feasibility of modulating or expanding upon the habitually expressed patterns of inter-muscular coordination. As a recent example, the feasibility of altering the composition of the elbow flexor synergy which involves co-activation of brachioradialis and biceps brachii muscles has recently been assessed [4]. Such innovations could be vital in enhancing the effects of motor rehabilitation regimens for patient populations with abnormal inter-muscular coordination patterns such as post-stroke survivors. However, the neural mechanisms underlying how the modulation of inter-muscular coordination is achieved has not been addressed to date.

Assessing the neural drive to muscles via functional connectivity may help explain the process of modulating inter-muscular coordination patterns. Functional connectivity can be taken at the cortico-cortical, cortico-muscular, and inter-muscular levels, each with their own physiological implications. Brain networks, quantified with cortico-cortical connectivity (CCC), indicate the relevant brain regions communicating together during cognitive tasks. Plastic changes to motor, pre-motor, and supplementary motor regions of brain networks [4] after conventional rehabilitation intervention have been implicated in post-stroke survivors,

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as well as their functional brain network controllability (FBNC) [5]. The FBNC is a novel biomarker indicating the ease with which a particular brain region can steer the entire brain network from one initial state to another [6], [7]. Cortico-muscular connectivity (CMC) is another invaluable tool in the study of motor control which quantifies the direct cortico-spinal drive to muscles. The CMC and its alterations have been well documented in the beta-band (β: 13–30 Hz) [8] as biomarkers indicating the integrity and of the cortico-spinal tract [9]. Inter-muscular connectivity (IMC), a similar tool, represents the spectral correlation between muscles and is another metric in the study of common neural drive [10]. IMC in the alpha-band (α: 8–12 Hz) has recently been implicated in the temporal control of muscle synergies [11]. These α-band frequencies have also previously been conjectured to be of subcortical origin [12] which may be related to the reticulospinal drive [13]. IMC in the β-band has also previously been used to assess the common neural drive between muscles of cortico-spinal origin in terms of the functional binding of muscles [8] which is also dependent on the integrity of the corticospinal tract [9], like CMC. The IMC can be further expanded by assessing functional connectivity of several muscles in a muscle network [14]. Muscle networks characterize common neural drive to multiple muscles and were originally conceived to further delve into the physiological explanation of the functional binding of muscles that comprise muscle synergies [15].

Characterizing the changes of common neural drive to synergistic muscles is crucial in understanding the modulation of neuromotor control. Previous studies have not yet studied changes in functional connectivity with respect to myoelectric-signal guided exercises with the aim of introducing newly developed motor skills towards modulating the existing inter-muscular coordination patterns. A similar knowledge gap in can be found in studies looking at the connectivity of muscle networks which have thus far characterized the lower extremity posture [15], and gait [16] of neurologically healthy individuals as well as upper extremity functional connectivity alterations post-stroke [14]. Furthermore, previous studies have identified alterations to inter-muscular coordination [2], [3], CMC [17], and IMC [14] associated with stroke-induced motor impairments, but the changes of CMC and IMC of stroke survivors in regards to modulation of inter-muscular coordination patterns remains unknown. Such information could be valuable for informing physical rehabilitation regimens for stroke survivors.

This study examines the changes of the common neural drive to the elbow flexor synergy associated with modulation of inter-muscular coordination patterns via myoelectric-signal guided exercises at the cortico-cortical, cortico-muscular, and inter-muscular perspectives simultaneously. The CMC was utilized here to assess the direct cortico-spinal drive to the individual elbow flexor synergy muscles. The IMC was assessed to determine any modulation to the shared neural drive among the elbow flexor synergy muscles which may not be captured from the CMC perspective. Lastly, the CCC and FBNC were used to quantify any changes in brain activity associated with the developed strategies that cannot be seen at the IMC or CMC perspectives. This analysis allows for the in-depth review of functional connectivity of the cortico-spinal tract across all levels in the hope of identifying where exactly any changes in functional connectivity may reside. We hypothesized that the shared common neural drive of elbow flexors would decrease as an effect of the motor skill training and be accompanied by changes in the activity of the sensorimotor cortex.

II. MATERIALS AND METHODS

A. Participant Recruitment

Six young, neurotypical female participants (26.67 ± 3.50 years of age) without any history of muscular or orthopedic injuries in the upper extremity completed the entire six weeks of the training. As a part of the recruitment process, the participants were pre-screened based on their inter-muscular coordination patterns identified during an isometric reaching task. Only the participants who were unable to intentionally decouple the coactivation of their naturally coupled elbow flexor muscles were selected for the study. Participants were instructed to use their dominant arm to perform both the training and the assessment task (five right-handed; one left-handed). All participants provided informed consent in accordance with the Declaration of Helsinki, with the approval of the Institutional Review Board of the University of Houston and the Korean Advanced Institute of Science and Technology. The study was registered at the Clinical Research Information Service (CRiS) of Korea National Institute of Health (KCT0005803).

B. Experimental Setup

To conduct the training and assessment, the KAIST Upper Limb Synergy Investigation System (KULSIS) was used [18]. Electromyograms (EMG) from twelve major upper extremity muscles were collected with a wireless EMG recording system (Trigno Avanti Platform; Delsys Inc., Natick, MA). The following UE muscles were recorded at a sampling rate of 1 kHz with bandpass filtering (20–450 Hz) and amplification (x1000): brachioradialis (BRD), biceps brachii (medial head; BI), triceps brachii (long and lateral heads; TRIlong and TRIlat), deltoids (anterior, middle, and posterior fibers; AD, MD, and PD), pectoralis major (clavicular fibers; PECT), trapezius (upper, middle, and lower fibers; TRPU, TRPM, and TRPL), and infraspinatus (INFRA). In accordance with the guidelines of surface EMG electrode placement [19], the wireless EMG sensors were positioned on the muscle bellies. To ensure precise and consistent sensor placement throughout the training period, a long-sleeve compression shirt, specifically customized to feature an aperture at the location of each muscle's belly, was made per participant. For the electroencephalogram (EEG) recording, a 32-channel EEG system (ActiCHamp; Brain Products GmbH, Munich, Germany) was used. The data recorded through each channel at a sampling rate of 1 kHz was labeled in accordance with the international 10–20 system. Throughout the recording period, the impedances of EEG electrodes were maintained below 10 kΩ.

The main PC (PC1) simultaneously recorded the three-dimensional end-point forces and the EMG signals (Fig. 1).

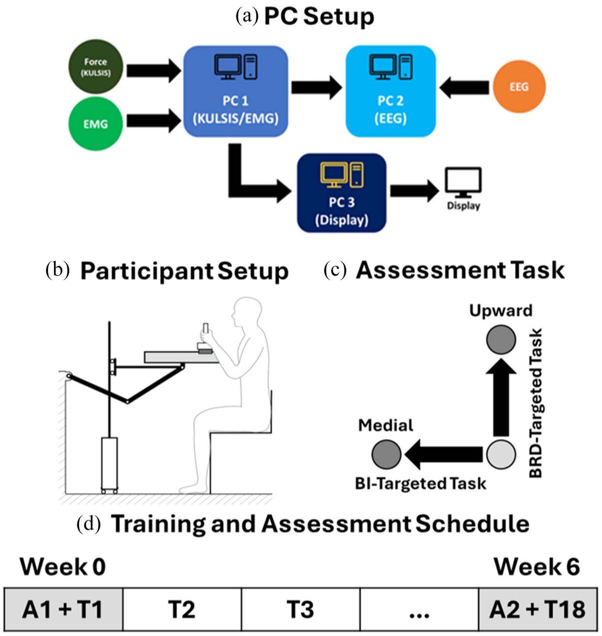


Fig. 1. (a) Experimental setup. The main computer (PC1), which acquires the force and EMG signals, controls the system for the training and the assessment. PC2 and PC3 receive a trigger signal from PC1 for EEG recording and task information for display, respectively. (b) Participant Setup. Participants were seated comfortably while holding a gimbal handle. (c) Assessment task. Participants were asked to move a digital cursor on a 2D screen with newly learned motor skills to target brachioradialis and biceps brachii activity separately. (d) Training and assessment schedule. Participants underwent 3 training sessions per week lasting at least 1 hour.

Synchronization of the force and EMG signals was achieved using an internal clock controlled by a custom-made LabView (National Instruments, Austin, TX) software on PC1. Concurrently, a separate PC (PC2) collected the EEG signals using BrainVision Recorder (Brain Products GmbH, Munich, Germany) software. The EEG data was time-locked to the EMG and force data using a trigger signal delivered by the PC1. Additionally, PC1 communicated with PC3 via User Datagram Protocol (UDP) to display task information, guiding participants during the training.

C. Experimental Protocol

The training aimed at the development of new inter-muscular coordination pattern in the upper extremity through modulating a naturally coupled elbow flexor muscle pair, BRD and BI. As reported in our previous publication [20], the training consisted of total of 18 sessions, 3 sessions per week (at least one day of break was given in between two sessions), and 1 hour per session (3 blocks of 15 minutes-long training with 5 minutes of break in between). During the training, the participants were sitting on a seat and holding the handle attached to the KULSIS with their dominant hand. The height and the position of the seat were adjusted to align the shoulder level to the handle and maintain the elbow flexion angle at 90°. To ensure the isometric condition, the upper body was constrained with a harness belt fixed to the seat. For the training, the participants were instructed to modulate the activations of BRD and BI, which were mapped to the vertical and horizontal movement of the cursor, to match the target randomly appeared either in upper or lower corner of the display within a given period (7 s). No fixed number of targets was given. The participants were instead asked to match the targets as many as possible during the 1-hour session. Fig. 2 illustrates a representation of a participant utilizing the KULSIS device, along with the functional connectivity analyses later described.

To assess the changes in the muscle and brain activities after the 6 weeks of training, the participants performed a three-dimensional force matching task under the same isometric condition applied to the training at Week 0 (pre-training) and Week 6 (post-training) of the training period. The assessment consisted of two targets, upward and medial targets, and 10 trials per target were given in a random order. The target directions were empirically determined based on the observation that generating isometric force in upward and medial directions tended to induce the isolated BRD or BI activation, respectively. The targeted force magnitude which determined the distance between the center of the force space, where the forces were calibrated to zero, and the target was set to 40% of each participant's maximum lateral force (MLF) as described in the previous study [20]. After 3 s of baseline period, the participants navigated a force-driven cursor towards the target and remained in a logical radius (30% of the targeted force magnitude) of the target for 10 s within a given period (20 s). In between each trial, the participants rested for 30 s.

The isometric force matching assessment was performed in two different conditions: 1) Habitual and 2) As-Trained. The participants were instructed to use their habitual motor strategies to perform the isometric force matching task in the Habitual condition. In the As-Trained condition, the participants intentionally utilized the motor strategies they acquired from the training to match the force target. Specifically, the participants were instructed to use their BRD activation strategy for the upward target matching and BI activation strategy for the medial target matching. For the As-Trained condition at Week 0, the verbal instructions empirically designed to help induce isolated activation of BRD and BI were given prior to the task.

D. Signal Pre-Processing

EEG signals were processed using EEGLAB [21]. EEG signals were band-passed between 1–50 Hz, visually inspected for artifacts, and subjected to independent component analysis (ICA) to remove ocular artifacts contaminating the EEG signals. EEG signals were re-referenced to the common average of all electrodes for CMC analysis and re-referenced separately to the Surface Laplacian Estimate reference for CCC and FBNC analyses. EEG signals were then segmented according to the trial duration of EMG signals to facilitate the CMC analysis. Both EEG and EMG signals were standardized to zero-mean and unit-variance to prevent any amplitude biases in the subsequent spectral analyses. Lastly, concatenated EEG and EMG signals were further segmented into 1s segments for all connectivity

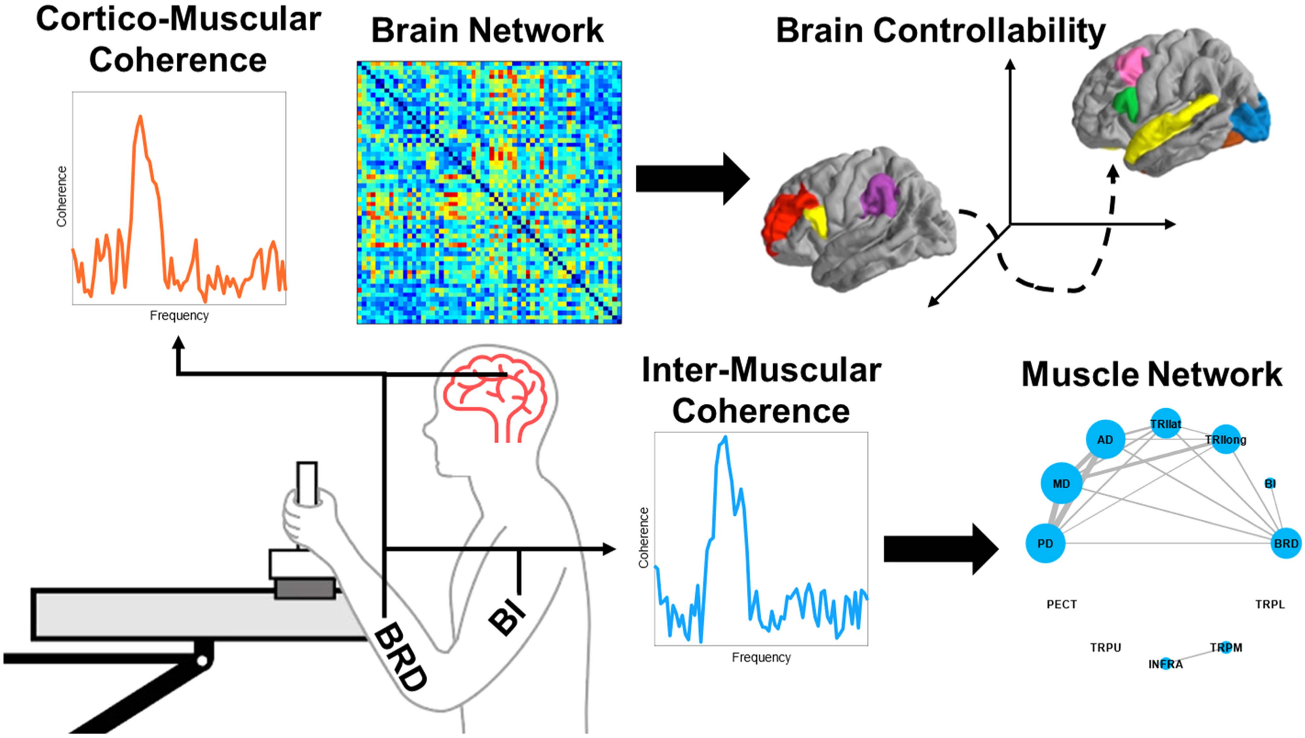


Fig. 2. Representative figure illustrating a subject using the KULSIS device. The functional connectivity analyses performed at the cortico-cortical level (brain networks and controllability), cortico-muscular level (cortico-muscular coherence), and inter-muscular level (inter-muscular coherence and muscle networks) are depicted.

analyses. All subsequent functional connectivity analyses were performed using the Fieldtrip toolbox [22]. All subsequent graph theory analyses were done with the Brain Connectivity Toolbox [23].

E. Muscle Synergy Analysis

To identify muscle synergies from the recorded EMG signals, the raw EMG data of each trial were pre-processed through DC offset removal, rectification, and a 4th order Butterworth low-pass filter with a cutoff frequency at 10 Hz. The pre-processed data were then segmented based on the force onset (a point where the force exceeded 4 standard deviations of the resting state amplitude) and offset (a point where the task was terminated). Following the segmentation, all the trials (10 upward targets and 10 medial targets) for each condition were further concatenated and normalized to have a unit variance.

Using a non-negative matrix factorization method, the concatenated EMG data were reconstructed as a linear combination of muscle synergy composition matrix (time-invariant; the number of muscle synergies by the number of recorded muscles) and muscle synergy activation coefficient matrix (time-variant; the number of recorded muscles by the number of data points) as described in the earlier studies [24], [25], [26], [27], [28], [29], [30]. The optimal number of muscle synergies was selected based on the global variance-accounted-for (gVAF) value (the percentage of the variance of the raw EMG that can be explained by the EMG reconstructed with a given number of synergies). For the muscle synergy analysis in this study, the number of muscle synergies that guaranteed gVAF greater than 90% while the difference in gVAF acquired by adding an additional synergy was less than 3% was defined as the optimal number of muscle synergies. Muscle synergies were identified for each participant at each week and condition. To characterize the changes in the muscle synergies which particularly BRD and BI were mainly involved in, the disparity index (DI) analysis [29] was applied. The DI analysis quantified how much the activation weights of the targeted muscle pair within a muscle synergy were deviated from the co-activation level of the muscle pair. Therefore, the increase in the DI value indicates a decrease in the co-activation of a targeted muscle pair. Further details of the DI analysis are reported elsewhere [29].

F. Cortico-Muscular and Inter-Muscular Connectivity Analyses

CMC and IMC were calculated using the magnitude-squared coherence. Magnitude-squared coherence C_{xy} was calculated by normalizing the square of the absolute value of the cross-spectral power density of two signals, P_{xy}, with the auto-power spectral density of the same two signals, P_{xx} and P_{yy} (1).

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)\,P_{yy}(f)} \tag{1}$$

A multi-taper approach using discrete prolate spheroidal sequence tapers was utilized with 3 tapers per data segment resulting in a 4 Hz smoothing box (± 2 Hz). Magnitude-squared coherence was subsequently converted to Z-scores [8], [14],

[31] by taking the hyperbolic tangent of the square root, C_{xy}, and dividing that by the square root of 1 divided by 2 times the number of windows, L, used in the magnitude-squared coherence calculation (2).

$$Z_{xy}(f) = \frac{\tanh^{-1}\left(\sqrt{C_{xy}(f)}\right)}{\sqrt{\frac{1}{2L}}} \tag{2}$$

After the Z-score conversion, connectivity values at or above 1.65 exceeded the 95% confidence interval. Connectivity values for the BRD-BI muscle pair were averaged in the α-band and β-band, and connectivity values for CMC in the β-band were averaged. The coherence between the C3 electrode position and the BRD and BI muscles were used for CMC analysis. The C3 electrode position was chosen as it is commonly used to represent the primary motor cortex at the sensor-level perspective [32].

G. Muscle Network Analysis

Muscle networks were created by taking the average of the Z-score coherence in the α-band and β-band across all muscle pairs and applying an absolute threshold of 1.65 for significant connections [31], [33], [34]. The threshold on Z-score coherence was only applied on the adjacency matrix of muscle networks prior to graph theory analysis and did not affect the previously described IMC analysis of BRD-BI muscles. In muscle networks individual muscles are considered as nodes and the band-average connectivity between nodes are considered as connections. This methodology is an update and simplification to our previous applications [14]. Namely, there is no dependency on the stability of the non-negative matrix factorization which can vary depending on the complexity of the coherence. Standardizing the number of networks across participants provides a simpler one-to-one comparison akin to traditional brain network analyses.

H. Brain Connectivity Analysis

CCC was calculated using the weighted phase lag index (wPLI) as it is known for its robustness to instantaneous zero-phase noise interactions [35]. For this reason, wPLI was chosen instead of magnitude-squared coherence for CCC which is dependent on the instantaneous phase and would have been biased due to volume conduction effects. The wPLI is a connectivity metric which quantifies the non-zero phase lag/lead relationship between two signals. The wPLI is bounded between 0 and 1 signifying a more random or a more consistent phase relation between two signals, respectively. The wPLI is calculated with an extra normalization step after calculating the phase lag index (the absolute of the sign of the imaginary component of the complex, non-diagonal component of the cross-spectrum of two signals, $\Im$). The wPLI then normalizes the cross-spectrum with the magnitude of the imaginary component (3).

$$wPLI = \frac{|E\{\Im(Z)\}|}{E\{|\Im(Z)|\}} \tag{3}$$

Brain networks were created from the average wPLI of the α-band [4] and thresholded to the top 40% of highest connections. Brain networks were then characterized by global efficiency. The global efficiency is calculated as the inverse of the shortest path length and is understood as the network's ability for parallel information transferring and integrated processing [36]. Global efficiency was chosen as the graph theory measure to confirm if any training-specific effects of the entire brain network were evident, since CMC and FBNC were already employed at the C3 location representing the primary motor cortex.

I. Functional Brain Network Controllability Analysis

The brain networks were then used to calculate the FBNC using modal controllability. Modal controllability is the ease with which a particular brain region can help steer the entire brain state into a different yet difficult-to-reach brain state [5], [6], [7], [37], [38], [39], [40]. A higher value of modal controllability indicates a stronger influence of a node on the entire brain network, whereas a smaller value of modal controllability reflects a minimal influence of the node on the entire brain network. FBNC of the C3 electrode position was implemented to consider the primary motor area cortex as done for the CMC analysis. Raw modal controllability scores were then converted to ranks. Modal controllability is derived from the functional brain network adjacency matrix, A, and its eigenvectors v, and eigenvalues λ.

$$MC = \sum_{j=1}^{N} \left(1 - \lambda_j^2(A)\right) v_{ij}^2 \tag{4}$$

J. Statistical Analyses

All measures were statistically analyzed in SPSS via a repeated-measured Analysis of Variance (RANOVA) to test for main effects and interactions between independent variables. Sphericity was assessed via Mauchly's test. Normality of residuals was confirmed with the Shapiro-Wilk test. Two-way RANOVA (Condition: As-Trained vs. Habitual; Assessment; Week 0 vs. Week 6) was used to analyze the DI, global efficiency of brain networks, and FBNC. Three-way RANOVA (Condition: As-Trained vs. Habitual; Assessment; Week 0 vs. Week 6) was used to analyze α-band IMC and global efficiency of muscle networks. Four-way RANOVA (Condition: As-Trained vs. Habitual; Assessment: Week 0 vs. Week 6; Direction: Upward vs. Medial; Muscle: BRD vs. BI) was used to analyze the CMC. Lastly, beta-band IMC was analyzed with the Friedman test because the assumption of normality of residuals was not met.

III. RESULTS

A. De-Coupling the Co-Activation of Elbow Flexor Synergy Muscles

Alterations to the co-activation of the elbow flexor synergy were identified after the myoelectric-signal guided exercises. The participants exhibited noticeable improvements in the training sessions through faster cursor movements, lower

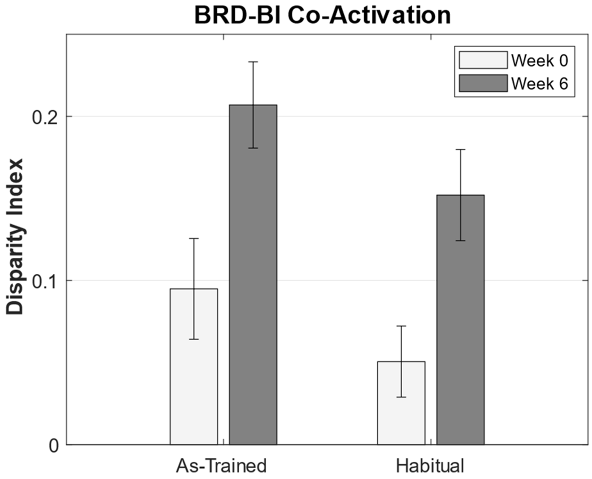


Fig. 3. BRD-BI DI values across both assessments (week 0 and week 6) and conditions (as-trained and habitual). BRD-BI DI values increase after the training for both as-trained and habitual conditions. Error bars: ± 1 standard error of the mean.

path lengths of cursor movements, and greater number of successfully matched targets after just two weeks of training for the BI-activated trials in the As-Trained condition. Similarly, BRD-activated trials in the As-Trained condition saw consistent trends with increases in the number of matched targets and cursor movement speed and decreased completion time and path length. Readers are referred to [20] for more detailed discussion on the task performance during the training sessions.

At Week 0, two muscle synergies on average were identified across the participants for both As-Trained and Habitual conditions, and this optimal number of muscle synergies was conserved even after six weeks of training. While no significant change in the number of muscle synergies was observed, the composition of muscle synergies, in terms of the disparity between BRD and BI muscle weights, was altered after training (Fig. 3). RANOVA did not find any significance for the main effect of Condition ($F = 2.212$, $p = 0.197$), or the interaction between Condition and Assessment ($F = 0.023$; $p = 0.885$). However, a significant main effect was identified for Assessment ($F = 77.126$, $p < 0.001$). Specifically, the disparity index was significantly increased from Week 0 to Week 6. Ultimately, these results indicate a reduction in the BRD-BI coactivation across assessments irrespective of the As-Trained and Habitual conditions.

B. Reducing the Inter-Muscular Connectivity of Elbow Flexor Synergy Muscles

Alterations to the α-band IMC of the elbow flexor synergy were identified after the myoelectric-signal guided exercises. Significant main effects were identified with RANOVA for Condition ($F = 9.896$, $p = 0.026$), Assessment ($F = 30.446$, $p = 0.003$), and Direction ($F = 9.074$, $p = 0.03$). Significant interactions were identified for Condition$*$Assessment ($F = 6.987$, $p = 0.046$), and Assessment$*$Direction ($F = 8.35$, $p = 0.034$). The As-Trained condition was found to have greater α-band IMC as compared to the Habitual condition. The α-band IMC was also found to significantly decrease from Week 0 to Week 6. The Upward direction isometric task had greater α-band IMC as compared to the Medial direction isometric task.

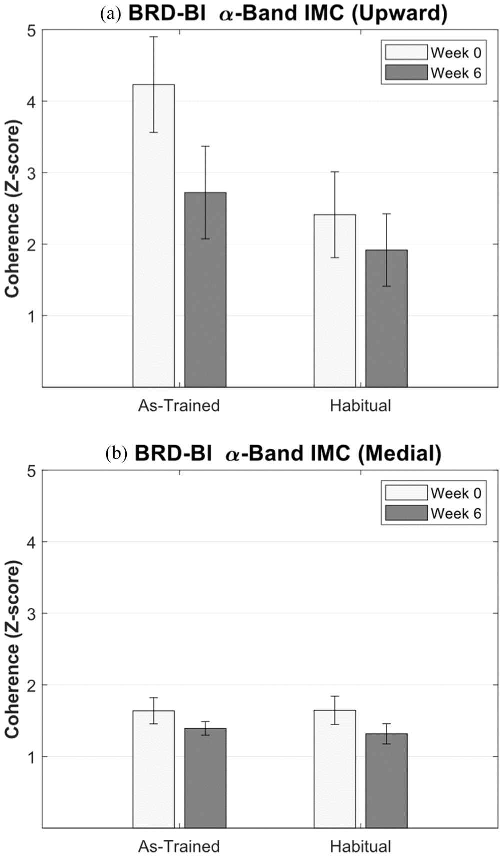


Fig. 4. BRD-BI IMC values in the α-band across both assessments (week 0 and week 6) and conditions (as-trained and habitual). Error bars: ± 1 standard error of the mean.

With respect to the significant interactions, the α-band IMC for the As-Trained condition in Week 0 was significantly greater than that of the Habitual condition ($p = 0.016$). However, there was no significant interaction at the Week 6 assessment. Lastly, the Week 0 assessment had a significantly greater α-band IMC for the Upward direction task versus the Medial direction task ($p = 0.012$). No significant interaction was identified at the Week 6 assessment. The Friedman test did not identify any significance for the β-band IMC ($\chi^2 = 7.778$, $p = 0.353$). The BRD-BI elbow flexor connectivity is visualized in Fig. 4. These results, in conjunction with the changes in disparity indices, indicate that the level of BRD-BI co-activation and α-band IMC are both reduced after the six-week training. The importance of α-band with respect to inter-muscular coordination is in line with prior studies (suggesting perhaps a greater role of spinal versus corticospinal drive), and the observed decreases match our hypothesis.

C. Inter-Muscular Connectivity Beyond the Elbow Flexor Synergy Remains Unchanged

The global inter-muscular connectivity, depicted by muscle networks, appeared to remain unchanged after the myoelectric-signal guided exercises. With respect to the global efficiency of

TABLE I
GLOBAL EFFICIENCY OF MUSCLE NETWORKS

Frequency Band	Assessment	Condition	Direction	Global Efficiency
α	Week 0	As-Trained	Upward	2.321 (0.583)
			Medial	2.32 (0.803)
		Habitual	Upward	1.984 (0.535)
			Medial	2.514 (0.642)
	Week 6	As-Trained	Upward	2.141 (0.515)
			Medial	2.644 (0.517)
		Habitual	Upward	1.949 (0.512)
			Medial	2.533 (0.697)
β	Week 0	As-Trained	Upward	2.293 (0.36)
			Medial	2.555 (0.618)
		Habitual	Upward	2.038 (0.471)
			Upward	2.562 (0.406)
	Week 6	As-Trained	Medial	2.327 (0.484)
			Medial	2.802 (0.507)
		Habitual	Upward	1.962 (0.415)
			Medial	2.547 (0.426)

Values tabulated as mean (standard deviation).

TABLE II
CORTICO-MUSCULAR COHERENCE

Muscle	Assessment	Condition	Direction	Coherence (Z-score)
BRD	Week 0	As-Trained	Upward	1.112 (0.313)
			Medial	0.962 (0.296)
		Habitual	Upward	1.6 (0.336)
			Medial	1.135 (0.298)
	Week 6	As-Trained	Upward	1.212 (0.475)
			Medial	1.268 (0.548)
		Habitual	Upward	1.166 (0.356)
			Medial	1.161 (0.387)
BI	Week 0	As-Trained	Upward	1.236 (0.252)
			Medial	1.145 (0.427)
		Habitual	Upward	1.558 (0.468)
			Upward	1.279 (0.167)
	Week 6	As-Trained	Medial	1.298 (0.528)
			Medial	1.434 (0.421)
		Habitual	Upward	1.327 (0.356)
			Medial	1.056 (0.288)

Values tabulated as mean (standard deviation).

muscle networks calculated from α-band frequencies, RANOVA did not identify any significance for Condition (F = 2.066, p = 0.21) or Assessment (F = 0.065, p = 0.809). However, significant main effects were discovered for Direction (F = 26.145, p = 0.004). Additionally, significant interactions were present for Condition∗Direction (F = 12.186, p = 0.017) and Assessment∗Direction (F = 8.47, p = 0.033). The global efficiency was significantly greater in the Medial direction as compared to the Upward direction. Global efficiency of α-band muscle networks during upward isometric force production was found to be significantly greater in the As-Trained condition versus the Habitual condition (p = 0.05). No significance was identified in the medical direction. Lastly, the global efficiency of α-band muscle networks during medial isometric force production was significantly greater than that of the upward isometric force production across both Weeks 0 and 6 (p = 0.026, p = 0.003, respectively).

Global efficiency of β-band muscle networks displayed similar results. RANOVA identified significant main effects for Condition (F = 0.9579, p = 0.027) and Direction (10.997, p = 0.021), but not Assessment (F = 0.247, p = 0.64). There were no significant interactions across factors. The global efficiency of β-band muscle networks was significantly greater in the As-Trained condition as compared to the Habitual condition. Global efficiency was also found to be significantly greater in the Medial direction as compared to the Upward direction.

Table I shows the global efficiency of muscle networks. These results indicate that the global muscle network connectivity remained unaffected across assessments but were different across conditions and directions of isometric force production. These results suggest the effects of the targeted myoelectric-signal guided exercises are localized to the elbow flexor synergy, not the entire muscle network, and that the global functional connectivity is task-dependent.

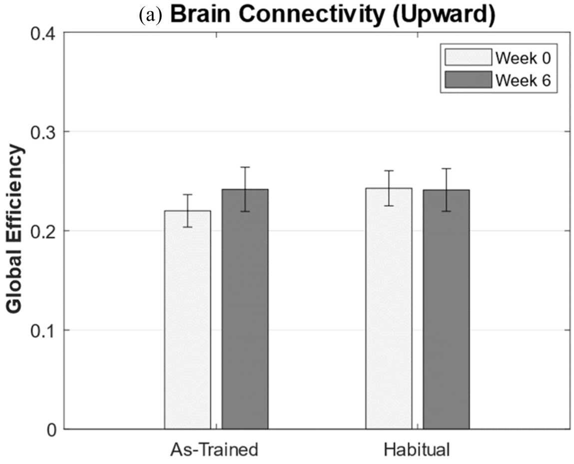
D. Decreased Cortico-Muscular Connectivity of the Elbow Flexor Synergy

The CMC of elbow flexors was decreased, as seen in Table II. RANOVA did not identify significance for any main factors. However, a significant interaction was observed for Assessment∗Direction (F = 9.998, p = 0.025). The CMC of the Upward direction was significantly decreased from Week 0 to Week 6 ($p < 0.001$), but not for the Medial direction (p = 0.301). This would suggest that the direct cortico-spinal drive to the elbow flexor synergy muscles is selectively modulated after the six-week training.

E. Increased Global Efficiency of Brain Networks

The connectivity of brain networks, quantified by global efficiency, was not significantly modulated after the six weeks of training. No significant main effects were identified across any of the main factors. However, a significant interaction effect was discovered for Assessment∗Direction (F = 9.867, p = 0.026). Global efficiency of brain networks for the Medial direction saw a significant increase from Week 0 to Week 6 (p = 0.026). No such significance was identified for the Upward direction (p = 0.48). These results suggest that there is a selective change in information exchange across the entire brain network that was dependent on the direction of isometric force generation. The global efficiency of brain networks is displayed in Fig. 5.

(a) **Brain Connectivity (Upward)**



(b) **Brain Connectivity (Medial)**

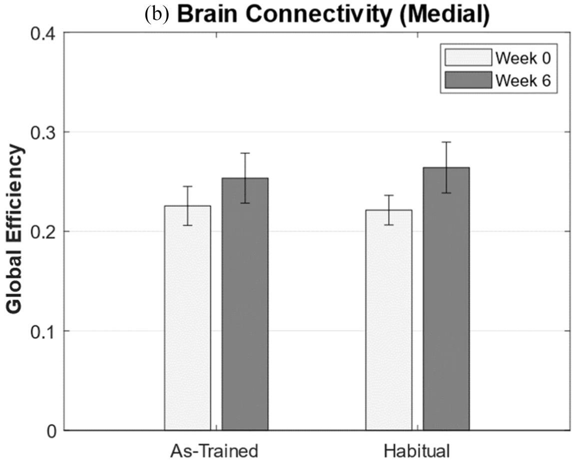
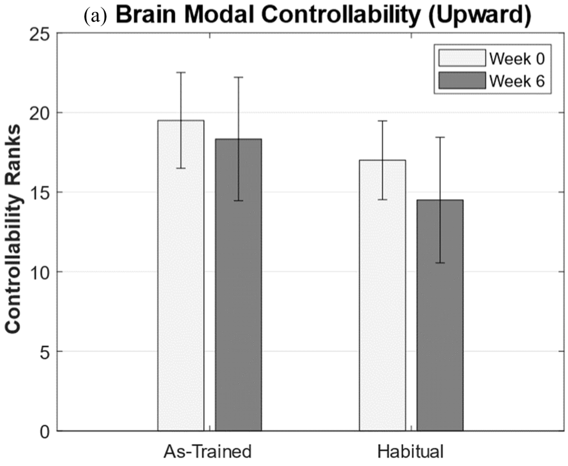


Fig. 5. Global efficiency of brain networks across both assessments (week 0 and week 6) and conditions (as-trained and habitual). Significant increases of global efficiency were detected in the medial force output across both conditions. Error bars: ± 1 standard error of the mean.

(a) **Brain Modal Controllability (Upward)**



(b) **Brain Modal Controllability (Medial)**

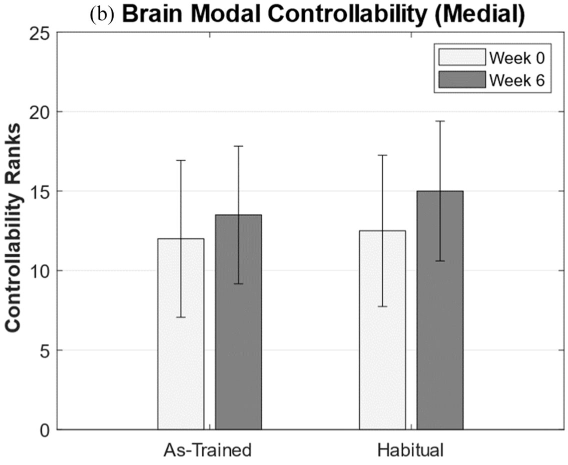


Fig. 6. Modal controllability for the C3 position across both assessments (week 0 and week 6) and conditions (as-trained and habitual). Error bars: ± 1 standard error of the mean.

F. Modal Controllability of the Motor Cortex Remains Unchanged

The FBNC of the motor cortex was not modulated after the six-week training. No main effects were identified for Condition ($F = 0.311$, $p = 0.601$), Assessment ($F = 0.002$, $p = 0.964$), or Direction ($F = 2.658$, $p = 0.164$). No significant interaction of main factors was identified either. The FBNC is shown in Fig. 6. These results suggest that the capability to push the entire brain network into a different yet difficult-to-reach brain state after training as compared to before the training did not change in a meaningful way.

IV. DISCUSSION

This study assessed the changes in functional connectivity across the sensorimotor cortex and muscles associated with the modulation of inter-muscular coordination patterns induced by newly learned motor skills requiring the decoupling of two synergist muscles of the upper extremity for the first time. One of the initial studies focusing on the cortical modulation of motor control and muscle synergies established that the task modulation of β-band IMC was associated with differential recruitment of divergent corticospinal pathways contributing to correlated muscle activities [41]. However, previous study also identified that there was a relationship between the feedforward nature of task modulation β-band IMC and the feedback nature of target-dependent visual responses related to task-relevant errors ultimately contributing to emergence of task-specific muscle synergies, Subsequently, studies have focused on modulating connectivity during bimanual motor tasks [42], context-dependent modulation of connectivity during initiation and maintenance of force generation [43], isometric maximal strength training [44], short-[45] and long-term [46] motor skill learning, and even modulation of connectivity induced by audio-visual rhythms [47]. However, none of these studies have characterized the baseline connectivity between the motor cortex and synergist muscles as well as their changes associated with long-term motor training at the timescale presented in this study. Recently, one study has investigated the IMC, CMC, and even cortico-synergy coherence in upper limb force generation with an experimental protocol most similar to that of the current study [48]. That study [48] discovered that α-band IMC was much greater between muscles within a synergy than otherwise, which is in agreement with previous findings [11], [14]. Interestingly, they also found that significant cortico-synergy coherence was identified but not CMC between the motor cortex and synergy muscles, suggesting a distributed control of synergies at the cortical level rather than individual control of muscles. While this study did provide further evidence suggesting the cortical modulation of muscle synergies, it did not investigate the modulation of the inter-muscular coordination patterns of muscle synergies through motor skill training, which this study reports.

This study has several advantages and some disadvantages. This type of study benefits heavily from the multi-modal brain and muscle signals and analyses to give a more complete account of neural drive through cortico-cortical, cortico-muscular, and inter-muscular perspectives. Quantifying CMC and IMC can help to confirm the functional binding of muscles in motor control [8]. Furthermore, using connectivity as a metric to investigate effects of modulating inter-muscular coordination is physiologically relevant. Corticospinal drive in β-band frequencies to muscles has already been well established in the literature [8], [9] and several publications have suggested the involvement of α-band in the common neural drive to co-active muscles with sub-cortical involvement [11], [49], [50]. The disadvantage of this study is the relatively small sample of participants ($n = 6$). The six-week training protocol is a relatively long time and requires consistency and compliance from participants. A full dataset for one participant takes six weeks to generate, assuming there are no obstacles to a consistent training schedule or participant dropout. In fact, the consistency of training in motor tasks has been suggested to be a factor in the consolidation of motor skills and IMC [51]. Another point to consider is that the experimental design was only concerned with de-coupling BRD and BI. However, how this de-coupling occurs specifically was not able to be controlled for.

The decoupling of synergist muscle co-activation is associated with a reduced common α-band neural drive as determined by IMC. The importance of the α-band in IMC between agonist muscles has been documented in neurologically healthy persons [11], [14] as well as its deficits under pathophysiologic conditions [9], [14], [52]. The results of this study appear to align with [11] in that α-band IMC was greater in magnitude in the As Trained condition when the BRD and BI muscles were co-active as a muscle synergy and decreased significantly when participants utilized the newly developed motor skill from the six-week training. Furthermore, the fact that significance was identified in the α-band and not the β-band for IMC may suggest that the modulation of inter-muscular coordination required to decouple the co-activation of BRD & BI does not rely on the modulation of the cortico-spinal drive but rather a neural drive sub-cortical in nature. Additionally, modulating the inter-muscular coordination of two synergist elbow flexor muscles does not appear to have large-scale changes in IMC across the upper extremity as seen through the global efficiency of the entire muscle network. These results are consistent with the local changes in BRD-BI co-activation as shown with the disparity indices as well as the preservation of baseline muscle synergy composition for the rest of the upper extremity muscles identified previously [20]. The myoelectric-signal guided exercises were designed exclusively with the intention of de-coupling BRD and BI, which appears to be the case.

While the IMC of elbow flexor muscle synergy was changed in general after modulating the inter-muscular coordination patterns, changes were also identified from the CMC but only for one of the directional tasks. These two findings alone provide an interesting perspective into the neural mechanisms by which modulating inter-muscular coordination patterns in neurologically healthy individuals may occur. These results would suggest that the neural drive which was changed because of the modulation of inter-muscular coordination patterns may not be entirely cortical in origin, since only α-band was implicated for IMC and β-band for CMC. However, a previous study [48] identified significant α-band IMC for muscles within a given synergy as well as significant cortico-synergy coherence, but noted non-significant CMC. While these results help to provide some perspective into the neural control of modulating muscle synergy co-activation, understanding the mechanisms and neural origins of muscle synergies still remains to be answered fully.

The modulation of the global efficiency of brain networks may be an indicator of motor skill acquisition. A prior study [53] on diffusion-tensor imaging observed that the global efficiency of brain networks from high skill-level athletes was significantly greater than that of ordinary individuals. However, the lack of changes to the FBNC of the motor cortex (as represented by the C3 position) were unexpected, seeing as frequency power within α-band have been shown to be involved with motor learning [54], but there has been some support to suggest the role of the parietal lobe in motor function recovery in motor imagery-based brain computer interfaces [55]. The importance of the motor cortex in context of modulating inter-muscular coordination patterns may prove to be more prevalent under the presence of neurological damage (i.e., stroke) such has been reported elsewhere [4], [5], [56].

The modulation of neural drive to upper extremity muscles targeted by myoelectric-signal guided exercises may involve corticospinal and spinal common input to varying degrees. As has been shown before, there is a strong relationship between inter-muscular coordination patterns derived from muscle synergy analysis and the strength of inter-muscular connectivity in the α-band [11], [14], [31]. This frequency range has been attributed to most likely be of subcortical origin in nature [8], [13]. Additionally, the contribution of β-band common input at the cortico-muscular and inter-muscular perspectives is well documented in literature [8], [9], [31], [47]. The DI of BRD-BI and α-band IMC of BRD-BI during isometric force generation were altered without any changes to CMC. These results would suggest that the modulation of BRD-BI inter-muscular coordination are associated with changes in common spinal neural drive to BRD and BI while still preserving the non-BRD/BI inter-muscular coordination patterns and global connectivity of the rest of the upper extremity muscles.

The results of this study have implications for future studies intending to observe the post-stroke effects of modulating inter-muscular coordination on CMC and IMC. Stroke patients typically express altered inter-muscular coordination between their deltoids as an abnormal muscle synergy [2], [3] as well as reduced α-band and β-band IMC [14], [57]. This more clinically relevant and abnormal muscle synergy, if modulated to approximate neurologically healthy behavior, could be a more impactful motor rehabilitation strategy. Additionally, the activity of the premotor cortex as well as connectivity of bilateral primary motor cortices has been shown to improve after 4 weeks of standard rehabilitation intervention [4]. Such changes may be expected to be observed in stroke patients undergoing motor skill training as presented in this study. The efficacy of such a clinically relevant and personalized motor rehabilitation could be monitored by quantifying the inter-muscular coordination, CMC, and IMC of the targeted muscles. Our future work will focus on repeating this study with post-stroke survivors to validate the changes of functional connectivity reflected in neurologically healthy individuals.

V. CONCLUSION

Inter-muscular coordination patterns of young, neurologically healthy individuals were modulated through newly learned motor skills involving the decoupling of two synergist elbow flexor muscles. Results suggested that the α-band IMC of elbow flexors was reduced along with a decrease of CMC in one of the directional tasks, and an increase in global efficiency of brain networks. No significant changes to muscle network connectivity or FBNC were identified. Future studies are necessary to validate these findings in a larger cohort as well as to determine the same outcomes in a patient population suffering from motor impairment such as post-stroke survivors.

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