

Assessing the Usage of Indirect Motor Pathways Following a Hemiparetic Stroke

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Abstract—A hallmark impairment in a hemiparetic stroke is a loss of independent joint control resulting in abnormal co-activation of shoulder abductor and elbow flexor muscles in their paretic arm, clinically known as the flexion synergy. The flexion synergy appears while generating shoulder abduction (SABD) torques as lifting the paretic arm. This likely be caused by an increased reliance on contralesional indirect motor pathways following damage to direct corticospinal projections. The assessment of functional connectivity between brain and muscle signals, i.e., brain-muscle connectivity (BMC), may provide insight into such changes to the usage of motor pathways. Our previous model simulation shows that multi-synaptic connections along the indirect motor pathway can generate nonlinear connectivity. We hypothesize that increased usage of indirect motor pathways (as increasing SABD load) will lead to an increase of nonlinear BMC. To test this hypothesis, we measured brain activity, muscle activity from shoulder abductors when stroke participants generate 20% and 40% of maximum SABD torque with their paretic arm. We computed both linear and nonlinear BMC between EEG and EMG. We found dominant nonlinear BMC at contralesional/ipsilateral hemisphere for stroke, whose magnitude increased with the SABD load. These results supported our hypothesis and indicated that nonlinear BMC could provide a quantitative indicator for determining the usage of indirect motor pathways following a hemiparetic stroke.

Index Terms—Brain-muscle connectivity, hemiparetic stroke, movement impairment, nonlinear analysis.

I. INTRODUCTION

THE human motor system is a highly cooperative network comprised of different groups of neurons. Neural

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connectivity, i.e., the synchronization of neural activity across these groups, is key to the coordination among distant, but functionally related, neuronal groups during the control of movement [1]. After a hemiparetic stroke, damage to the brain increases reliance on indirect motor pathways resulting in motor impairments [2]–[4] and changes in neural connectivity [5]. A hallmark of impairments post hemiparetic stroke is a loss of independent joint control resulting in the abnormal coupling between shoulder abductor and elbow/wrist/finger flexor muscles, known as the flexion synergy [6]. The flexion synergy limits arm/hand function, like reaching and hand opening; and has also been reported to be linked to hyperactive stretch reflexes or spasticity [7], [8].

The flexion synergy appears while generating shoulder abduction (SABD) torques [9], [10] such as when lifting the weight of the arm or more. It is thought to be caused by progressive recruitment of contralesional indirect motor pathways via the brainstem as a function of SABD torque generation following a stroke-induced loss of ipsilesional corticospinal projections [2], [11], [12]. Our previous diffusion tensor imaging (DTI) studies have demonstrated that increased structural integrity of medial reticulo-spinal tracts (MRST – indirect motor pathways for upper limb) in the non-lesioned hemisphere in chronic hemiparetic stroke [11], [13]. However, DTI analysis only shows the structural changes post stroke; it does not reflect the functional use of contralesional indirect motor pathways. A neural connectivity measure that quantifies the recruitment of these indirect motor pathways would be crucial to evaluate post-stroke motor impairments. This measure also allows for the determination of the effect of new therapeutic interventions that aim to reduce such recruitment thus improving paretic arm function.

For decades, researchers investigating neural connectivity of motor pathways focused on linear (iso-frequency) neural coupling between brain (EEG) and muscle activity (EMG), i.e., EEG-EMG coherence [14], by assuming that motor commands from cortex to muscle are linearly transmitted [15]. This linear measurement primarily reflects neural connectivity of direct corticospinal tracts, and reduces at the ipsilesional hemisphere post hemiparetic stroke [5], [16]. However, no enhanced EEG-EMG coherence was found at the contralesional hemisphere during the flexion synergy expression [5], [16], indicating that this measurement may not allow examining the usage of contralesional indirect motor pathways. A plausible reason could be that the neural connectivity of indirect motor pathways is nonlinear [17], [18], showing neural coupling across different frequencies.

Recently, we developed a novel method, namely cross-spectral connectivity, to assess both linear and nonlinear connectivity that cannot be studied by using traditional connectivity methods such as linear coherence [19]. Our neural model simulation indicated that nonlinear connectivity is likely generated by the nonlinear behavior of a synaptic connection and can be cumulatively enhanced across more synapses as in indirect motor pathways [20]. As shown in the simulation, multi-synaptic interactions of indirect motor pathways can lead to more dominant nonlinear connectivity between brain and muscle activity, in comparison to direct corticospinal tracts containing only one/two synapses [20].

In the present study, we investigated the nonlinear vs. linear connectivity between the brain and muscles in hemiparetic stroke during different levels of SABD tasks. We hypothesize that increased usage of indirect motor pathways while activating shoulder abductor muscles will lead to a more dominant nonlinear connectivity between brain and muscle activity when greater levels of SABD torques are required, and thus causes an increased expression of the flexion synergy. To test this hypothesis, we measured scalp EEG, EMG from shoulder abductor muscles as well as flexion synergy elbow torques when eight stroke participants generate 20% and 40% of maximum SABD torque with their paretic arm. By testing the hypothesis, this proof-of-study will provide us with a verified quantitative measure to assess the change to the usage of motor pathways in hemiparetic stroke.

II. MATERIALS AND METHODS

A. Participants and Data Collection

Eight individuals with chronic hemiparetic stroke (age: 64.4 ± 8.0 yrs.) and eight age-matched able-bodied participants (age: 60.1 ± 7.5 yrs.) were included in this proof-of-concept study. The participants were recruited with written informed consent and permission of the Northwestern University institutional review board. All participants with stroke were screened for inclusion by a licensed physical therapist. Inclusion criteria included 1) upper limb paresis, 2) ability to sit and lift the paretic arm without support, 3) an Upper Extremity Fugl Meyer Assessment (UE-FM) [21] 10-40 out of 66 (this is because mildly impaired individuals generally have a reduced expression of the flexion synergy and spasticity), 4) more than one-year post-stroke, and 5) subcortical lesions not extending into sensorimotor cortices. Demographic information for each participant is provided in Table 1.

During the experiment, the participants were seated in a Biodex pedestal attached to a Biodex track (System 3 ProTM., Shirley, NY) with their trunk secured by belt restraints across the chest and abdomen. The tested arm was cast by fiberglass to line up the forearm, wrist, and hand and then rigidly attached to a customized beam connected to a JR3 6-DOF load cell (JR3, Woodland, CA). The test arm of the control participants was matched by the hand dominance of the paretic arm of the stroke participants for a fair comparison: 4 Dominant vs. 4 Non-dominant extremities in both stroke and control groups. The tested upper limb was positioned with 85° shoulder abduction, 45° shoulder flexion, 90° elbow

flexion. The load cell can measure the SABD and elbow flexion (EF) torques generated by the participant simultaneously. The medial epicondyle of the humerus was aligned with the central axis for the rotation of the load cell. The upper limb was positioned with the shoulder at 85° abduction, 45° flexion, and the elbow at 90° flexion angle.

At the beginning of the experiment, the participants were asked to lift the tested arm with their most effort to determine the maximum voluntary torque (MVT) of SABD. The average of three continuous trials without difference larger than 10% of the mean was considered as SABD MVT of the study participant [22]. Similarly, the EF MVT was determined when the arm was fully supported [22].

Then for each trial, the participants were asked to lift the tested arm against 20% (SABD20) or 40% (SABD40) of SABD MVT after receiving an auditory cue and hold for 10 seconds. Visual feedback was provided by a monitor in front of the participant. A red line would rise in proportion to the SABD torque, and the trial started when the target torque was reached. If the SABD torque fell off the 10% error range of the target torque, the participant would be asked to relax and restart the trial after enough rest. Participants performed 25 trials of each level task in total, with 5 trials of one level and shifted to 5 trials of another. The expression of the flexion synergy was quantified as the involuntary synergic elbow flexion torque generated during the SABD, and normalized to the EF MVT [22].

Between trials, participants were asked to relax their arm fully for at least 1 minute. 32-channel EEG was recorded using active electrodes (Biosemi, Inc, Active II, Amsterdam, the Netherlands) mounted on a cap with the 10/20 system. The muscle activity at Intermediate Deltoid of the tested arm was recorded simultaneously by the differential of 2 Biosemi active electrodes with 1 cm inter-electronic distance. All data were sampled at 2048 Hz. The impedance of all electrodes was kept below 25 k Ω during the experiment.

B. Data Analysis

1) *Preprocessing*: EEG and EMG data were preprocessed using EEGLAB. Raw EEG data were band-pass filtered between 1 and 100 Hz and notch filtered between 58 to 62 Hz (to remove line noise) with a zero-phase shift filter. Independent Component Analysis (ICA) algorithm was applied on filtered EEG to remove artifacts caused by movement and eye-blinks. Raw EMG data were band-pass filtered between 20 and 100 Hz and notch filtered between 58 to 62 Hz with a zero-phase shift filter, rectified, and normalized to the peak rectified EMG obtained during maximum SABD. Then all data were segmented into 1 s epochs with 250 ms overlapping. EEG signal was examined to remove bad channels and epochs with artifacts.

2) *Laterality Index of EEG Power*: The signal power of task-related brain activity at each EEG channel was estimated by the average of root-mean-square across all epochs (13 epochs/trial \times 25 trials in total). The Laterality Index was then be computed to indicate hemispheric dominance of brain activity: $LI = (CS - IS)/(CS + IS)$, where CS

is the sum of estimated signal power over the contralateral/ipsilesional sensorimotor areas, and IS is the sum over ipsilateral/contralesional sensorimotor areas. $LI > 0$ indicates the contralateral/ipsilesional dominance, $LI < 0$ the ipsilateral/contralesional dominance.

3) *EEG-EMG Connectivity and N-L Index*: We computed the EEG-EMG connectivity (separating its nonlinear vs. linear parts) during shoulder abduction to investigate flexion synergy related neural connectivity by using our cross-spectral connectivity (CSC) method [19]. The CSC is a nonlinear extension of the classical (linear) coherence (used in the corticomuscular coherence), based on high-order spectra for distinguishably measuring nonlinear (cross-frequency, $n \neq m$) and linear (iso-frequency, $n = m$) connectivity between signals:

$$CSC = \frac{|S_{XY}(f_X, f_Y)|}{\sqrt{S_{XX}^n(f_X) S_{YY}^m(f_Y)}}$$

where f_X and f_Y are frequencies of EEG and EMG, n and m are integers following $n:m = f_X:f_Y$, and $S_{XX}^n(f_X)$ is the n -th order auto-spectra. The algorithm traverses all the frequencies between 1-100Hz for EEG (f_X) and 20-100Hz for EMG (f_Y), and finds frequency pair with a common factor greater than 1 [19]. The linear part of our results obtained by this method, when $n = m$, is comparable to the commonly used corticomuscular coherence. To compare the dominance of nonlinear vs. linear connectivity, we define the nonlinear-over-linear index (N-L Index): $N-L \text{ Index} = (SN-SL) / (SN+SL)$, where SL is the sum of linear connectivity over contralateral/ipsilesional sensorimotor areas, SN is the sum of nonlinear connectivity over ipsilateral/contralesional sensorimotor areas. So, nine electrodes over the sensorimotor area on each side of the brain were included in this calculation, which are FC1, FC3, FC5, C1, C3, C5, CP1, CP3, CP5 on the left side and FC2, FC4, FC6, C2, C4, C6, CP2, CP4, CP6 on the right side. $N-L \text{ Index} > 0$ indicates greater nonlinear connectivity, $N-L \text{ Index} < 0$ indicates greater linear connectivity. This definition is in line with our previous study for comparing linear and nonlinear connectivity in able-bodied individuals [23].

4) *Statically Analysis*: We applied the Shapiro-Wild test [24] and Levene's F-test [25] to verify the normality and homoscedasticity to allow parametric analysis. Student's two-sample one-tailed paired t-test was applied to compare the group means for 20% SABD vs. 40% SABD levels within stroke participants, and Student's two-sample two-tailed paired t-test was applied to compare that within control participants. Student's two-sample one-tailed t-test was applied to compare the group means of stroke vs. control at the same level of SABD. When the group is heteroscedastic and parametric analysis was not applicable, Welch's two-sample one-tail (paired) t-test was applied. A significance level of 0.05 was used for all the tests in this paper.

III. RESULTS

Shown in all participants suffering from a hemiparetic stroke, the expression of the flexion synergy enhanced with increased SABD load (see Figure 1, paired t-test: 0.0003).

Participants suffering from a hemiparetic stroke show a lower Laterality Index (see Figure 2) in comparison to the

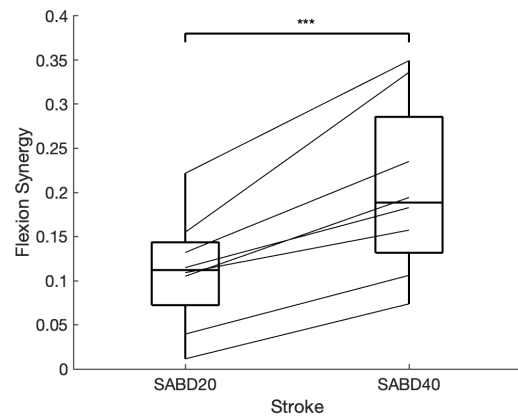


Fig. 1. Flexion synergy of hemiparetic stroke participants with different level of shoulder abduction. The expression of the flexion synergy was quantified as the involuntary synergic elbow flexion torque during the SABD, and normalized to the EF MVT. On each box, the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Paired t-test was applied. * for p-value < 0.05 , ** for p-value < 0.01 and *** for p-value < 0.001 .

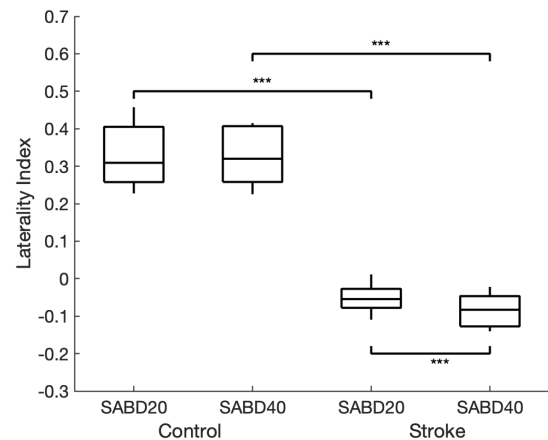


Fig. 2. Laterality index for control and stroke subjects with different level of shoulder abduction. Two-sample t-test was applied across groups with same level of SABD, and paired t-test was applied among groups with different levels of SABD. * for p-value < 0.05 , ** for p-value < 0.01 and *** for p-value < 0.001 .

able-bodied controls (two-sample t-test p-value < 0.00001 for both SABD20 and SABD40), indicating a more dominant contralesional brain activity in hemiparetic stroke during the SABD tasks. Meanwhile, a higher N-L index (see Figure 3) is shown in the stroke participants as compared to the able-bodied controls (two-sample t-test p-value < 0.00001 for both SABD20 and SABD40), indicating a more dominant nonlinear BMC in hemiparetic stroke. When the stroke participants were lifting their paretic arm more as increasing their SABD load from 20% to 40% MVT, the Laterality Index significantly decreased from -0.052 with SD 0.038 to -0.085 with SD 0.046 (paired t-test p-value = 0.0004), and the N-L index significantly increased from 0.276 with SD 0.062 to 0.375 with SD 0.054 (paired t-test p-value = 0.0016). No such significant changes were shown in the able-bodied controls when they were increasing the SABD load with the same amount.

IV. DISCUSSION

Recruitment of contralesional indirect motor pathways post-stroke is thought to be the cause of the expression of flexion

TABLE I
PARTICIPANT DEMOGRAPHICS

Controls					Stroke					
Participant	Age	Gender	Dominant Arm	Tested Arm	Participant	Age	Gender	Years Post-stroke	UE-FM	Paretic/ Tested Arm
P ₁	60-65	M	R	R	P ₁	45-50	M	9	30	L
P ₂	75-80	M	L	R	P ₂	70-75	M	16	13	L
P ₃	55-60	M	R	L	P ₃	55-60	M	11	19	L
P ₄	55-60	F	R	L	P ₄	60-65	M	4	26	L
P ₅	60-65	F	R	R	P ₅	65-70	F	2	24	L
P ₆	60-65	M	R	R	P ₆	70-75	F	16	8	R
P ₇	60-65	M	R	R	P ₇	60-65	M	6	40	R
P ₈	45-50	M	R	L	P ₈	70-75	M	25	12	L
Mean \pm std.	60.1 \pm 7.5	-	-	-	Mean \pm std.	64.4 \pm 8.0	-	11.1 \pm 7.1	21.5 \pm 10.0	-

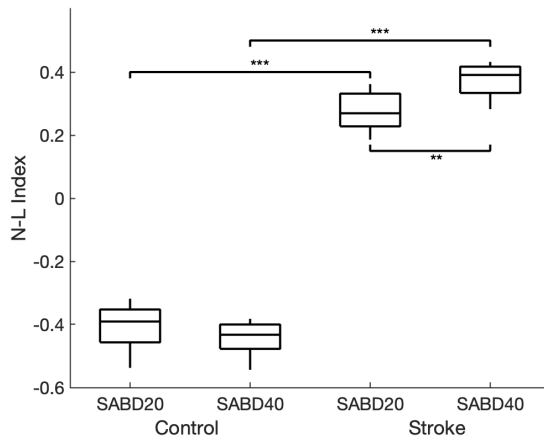


Fig. 3. N-L index for control and stroke subjects with different level of shoulder abduction. Two-sample t-test was applied across groups with same level of SABD, and paired t-test was applied among groups with different levels of SABD. * for p-value < 0.05, ** for p-value < 0.01 and *** for p-value < 0.001.

synergy in chronic hemiparetic stroke [2]. Quantitative measurement of the use of indirect motor pathway is essential to evaluate the motor impairments and guide the target intervention that aims to reduce the expression of flexion synergy. Traditional linear coherence was not able to completely capture brain-muscle connectivity because of the accumulation of nonlinearity after the motor command passing through multiple synapses in the indirect motor pathways via the brain stem [20]. By applying our cross-spectral connectivity (CSC) method, we, for the first time, assessed both linear and nonlinear brain-muscle connectivity (BMC) at different SABD levels (20% vs. 40%) in chronic hemiparetic stroke, as compared to the healthy controls. We found that nonlinear connectivity is dominant as N-L index > 0 in hemiparetic stroke, indicating that individuals with a hemiparetic stroke tend to use more the indirect, multi-synaptic motor pathways, when they were performing the SABD tasks, due to the damage to their direct corticospinal tract. Furthermore, the laterality index < 0 indicates that the recruited indirect motor pathways are from the contralesional hemisphere (ipsilateral to the paretic arm). This result is in line with our recent imaging work using diffusion tensor imaging (DTI) demonstrated that damage to the corticospinal tract can lead to the increased structural integrity of indirect motor pathways (e.g., the medial reticulospinal

tract) at the non-lesioned side [13] in chronic hemiparetic stroke.

The N-L index increases when the stroke participants were performing a higher level SABD task (40%) while the laterality index decreases. This is likely because the use of contralesional indirect motor pathways increases with the SABD level since a higher level SABD task requires more effort of contralesional indirect motor pathways to compensate for the lost function of the direct corticospinal tract.

In healthy controls, the linear connectivity is dominant N-L index < 0 and it is mainly from the contralateral hemisphere as the laterality index > 0. This result is in line with previous studies showing the healthy controls are mainly using the direct, contralateral corticospinal tract for motor control of upper limb muscles [17], [18] and, therefore, showing the dominance of the contralateral, linear BMC [14], [23].

We did not find statistical correlation between clinical scores with the indexes. This may be due to the limited sample size in this study. We plan to apply the proposed method to a larger population to examine the potential statistical correlation between clinical scores with the indexes in the future.

V. CONCLUSION

The applied cross-spectral connectivity method allows the assessment of both linear and nonlinear brain-muscle connectivity that cannot be quantified by using conventional connectivity methods such as coherence which only assesses linear brain-muscle connectivity. The results in this study support our hypothesis that increased usage of contralesional indirect motor pathways leads to a more dominant nonlinear connectivity between brain and muscle activity as reflected by an increased N-L index. As such, this study, for the first time, provides a sensitive metric (i.e., N-L index) to quantitatively determine the usage of indirect motor pathways and its link to the expression of flexion synergy. The obtained knowledge and the proposed measures are essential for future studies examining how the recruitment of indirect motor pathways can be minimized by using more targeted interventions, such as physical [26] and pharmacological [27] methods we recently proposed to promote the use of remaining corticospinal resources from the lesioned hemisphere post hemiparetic stroke.

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