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Evaluation of Muscle Synergy during Exoskeleton-assisted Walking in Persons with Multiple Sclerosis

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Abstract

Objective: Gait deficit after multiple sclerosis (MS) can be characterized by altered muscle activation patterns. There is preliminary evidence of improved walking with a lower limb exoskeleton in persons with MS. However, the effects of exoskeleton-assisted walking on neuromuscular modifications are relatively unclear. The objective of this study was to investigate the muscle synergies, their activation patterns and the differences in neural strategies during walking with (EXO) and without (No-EXO) an exoskeleton.

Methods: Ten subjects with MS performed walking during EXO and No-EXO conditions. Electromyography signals from seven leg muscles were recorded. Muscle synergies and the activation profiles were extracted using non-negative matrix factorization.

Results: The stance phase duration was significantly shorter during EXO compared to the No-EXO condition ($p<0.05$). Moreover, typically 3-5 modules were extracted in each condition. The module-1 (comprising Vastus Medialis and Rectus Femoris muscles), module-2 (comprising Soleus and Medial Gastrocnemius muscles), module-3 (Tibialis Anterior muscle) and module-4 (comprising Biceps Femoris and Semitendinosus muscles) were comparable between conditions. During EXO condition, Semitendinosus and Vastus Medialis emerged in module-5 in 7/10 subjects. Compared to No-EXO, average activation amplitude was significantly reduced corresponding to module-2 during the stance phase and module-3 during the swing phase during EXO.

Conclusion: Exoskeleton-assistance does not alter the existing synergy modules, but could induce a new module to emerge, and alters the control of these modules, i.e., modifies the neural commands indicated by the reduced amplitude of the activation profiles.

Significance: The work provides insights on the potential underlying mechanism of improving gait functions after exoskeleton-assisted locomotor training.

***Index Terms*—Exoskeletons, Multiple Sclerosis, Gait, Muscle Synergy**

I. Introduction

MULTIPLE Sclerosis (MS) is a demyelinating disease of the central nervous system, primarily affecting young adults and occurring three to four times more frequently in women than men [1, 2]. The immune-mediated damage to the myelin sheaths, axons, and neurons, primarily in cortical and subcortical structures disrupts the efficient communication between the central nervous system and peripheral neuromotor components, essential for movement [3]. Motor impairments can be characterized by muscle weakness, selective muscle control, fatigue, abnormal muscle tone, and ataxia. Subsequently, these impairments cause loss of balance and poor gait performance [4], which patients have attributed as being the most restricting consequences of the disease [5]. Specifically, their gait deficit is a major contributor to diminished activities of daily living, decreased quality of life, and loss of employment [6], thereby making gait recovery the major rehabilitation goal.

During walking, reduced hip, knee, and ankle joint motion range, and decreased propulsive force are seen in persons with MS [7, 8] and compensatory strategy such as the co-activation of agonist-antagonist of knee and ankle joint respectively during single and double support phases of gait can be developed. Moreover, the co-activation of agonist-antagonist of

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knee and ankle joint could also be attributed to disturbed balance and reduced gait speed [7]. To promote independent walking in persons with MS, assistive technology such as the robotic exoskeleton could provide an effective solution. Recent preliminary but promising results on the use of wearable robotic exoskeletons for gait assistance have provided a potential for gait realization after MS [9-12]. No study has yet investigated the muscle synergies in persons with MS during exoskeleton-assisted walking and the impact of exoskeleton-assisted walking on neuromuscular coordination in MS remains unclear.

A widely used method to examine neuromuscular adaptation during walking is muscle synergy analysis. The concept of muscle synergies in neuroscience describes the mechanism through which the central nervous system controls the many degrees of freedom of the musculoskeletal system in the human body to produce different movements [13]. It has been suggested that muscle synergy analysis could provide a reliable representation of a person's motor deficits and the degree of adaptability of their motor patterns [14]. As walking is a repetitive process that involves coordination and activation of different muscles with particular activation timing in the gait cycle, it is thus essential to observe the muscle groups functioning in unison during gait. Subsequently, the analysis of combined muscle activity during gait could reveal deficiencies that may be undetermined in individual muscle's electromyography (EMG) analysis. In the context of assisted walking, muscle synergies could reveal the influence of assistive aids on muscle coordination. Specifically, muscle synergy analysis could assist in examining whether the neural command/drive required to activate the muscles has altered (increased or decreased) or there are changes in the contribution of muscles in each synergy module, i.e., due to co-contractions etc. induced by the exoskeleton's assistance.

Several studies have investigated the muscle synergies during exoskeleton-assisted walking in healthy persons and in persons with neurological disorders [15-22]. Jacobs *et al.* investigated the muscle synergies during walking with a powered ankle exoskeleton in neurologically intact individuals [15]. Zhu *et al.* investigated the lower limb muscle synergies during walking with an exoskeleton in persons with chronic stroke [23]. Lencioni *et al.* performed muscle synergy analysis in subjects with MS and examined the alteration of the modular control while comparing them with intact subjects [17]. The alterations were attributed to the modifications of activation timing while module composition remain unchanged. Another study comparing muscle synergies of patients with MS and intact control subjects showed changes in both time-dependent activation patterns alongwith alterations of the relative muscle contribution to specific synergy modules in subjects with MS [24]. Typically, four muscle synergy modules have been found in lower limb during walking [17] relating to the different phases of the gait cycle and described as weight acceptance, propulsion, early swing, and late swing [24]. Although numerous studies have investigated muscle synergies in MS, in our knowledge, no study has yet investigated the muscle synergies in persons with MS during exoskeleton-assisted walking and therefore the impact of exoskeleton-assisted gait walking on neuromuscular coordination in MS remains unknown.

Accordingly, the objective of this study was to investigate the lower limb muscle synergies and their respective activation profiles in persons with MS during overground walking, with (EXO) and without (No-EXO) wearing an exoskeleton. Specifically, we investigated whether there is a change in the synergy structures during walking with and without wearing an exoskeleton. We also explored alterations in the spatiotemporal characteristics of the activation profiles.

II. Methods

A. Participants

Ten individuals (8 females, 2 males) with a confirmed diagnosis of MS, mean age: 54.3 ± 12.4 years, mean weight: 70.0 ± 12.0 kg, and mean height 1.7 ± 0.1 m, participated in the study (Table 1). Inclusion criteria were: Age 18 years or older; male or non-pregnant female; ambulatory with assistive devices; with an Expanded Disability Status Scale (EDSS) score between 6.0 and 7.5 inclusive [25]; height between 1.60 and 1.88 m and weight less than 100 kg; able to follow simple 3-step commands and able to understand study procedure and consent form. Exclusion criteria were: History of severe neurologic injuries other than MS, severe comorbidities: active infections, heart, lung, or circulatory conditions, pressure ulcers; documented severe osteoporosis affecting hip and spine; uncontrolled severe spasticity in lower extremities (Modified Ashworth > 3) or uncontrolled clonus; unhealed limb or pelvic fractures; skin issues that prevent wearing the device; range of motion restrictions that would prevent the subject from achieving a normal reciprocal gait pattern or would restrict a subject from completing normal sit to stand or stand to sit transitions; upper extremity strength deficits that limit the ability to balance with a front rolling walker or crutches; heterotopic ossification that resists functional range of motion in lower extremities; contractures (>15° at hips or >20° at knees); psychiatric or cognitive comorbidities resulting in motor planning or impulsivity concerns and Colostomy. The study was approved by the committee for the protection of human subjects at the University of Texas Health Science Center at Houston (HSC-MS-15-0278, May 29, 2015). All subjects provided a written consent for participation. The study was registered on clinicaltrials.gov (Wearable Lower Extremity Exoskeleton to Promote Walking in Persons With Multiple Sclerosis, NCT02519244).

B. Exoskeleton-Assisted Gait Training

To ensure subjects were able to walk with an exoskeleton with minimal assistance from a therapist, all subjects received exoskeleton-assisted training using Ekso® 1.1 exoskeleton (Ekso Bionics, Richmond, CA) for up to 15 sessions. Subjects donned the exoskeleton and participated in individualized treatment sessions that included sit to stand, static and dynamic standing balance, weight shifting, walking, turning, and stand to sit. To facilitate training, the exoskeleton provides the option to tune different parameters such as step height, knee flexion, assistance level, etc. Here the assistance level refers to the torque supplied by the exoskeleton to assist walking. The parameters for gait training were adjusted by the therapist. There was no formal protocol so the adjustments were based on therapist's experience and patients' feedback. For example, the

TABLE I
SUBJECT DEMOGRAPHICS

Subject	EDSS	Gender	Diseases onset (years)	MS Type	Age (years)	Weight (kg)	Height (m)
1	6	F	11	RRMS[a]	32	91	1.65
2	7	F	12	SPMS[b]	45	57	1.68
3	6.5	F	23	PPMS[c]	70	64	1.70
4	6.5	M	9	PPMS	52	61	1.78
5	6.5	F	18	PPMS	58	77	1.70
6	7.5	F	21	RRMS	53	61	1.75
7	6.5	F	10	RRMS	65	68	1.63
8	6.5	M	6	RRMS	40	88	1.83
9	6	F	12	RRMS	61	64	1.55
10	6.5	F	28	SPMS	67	68	1.57
Mean ± SD	6.5 ± 0.4		15.0 ± 7.1		54.3 ± 12.4	70 ± 12	1.68 ± 0.09

[a] Relapsing-Remitting Multiple Sclerosis
[b] Secondary-Progressive Multiple Sclerosis
[c] Primary-Progressive Multiple Sclerosis

parameter 'step height' was adjusted to different values and once the patient felt comfortable during walking with the exoskeleton it was set to that value. Later in training, the main emphasis was on walking. Each training session lasted up to 90 minutes (60 minutes of training with 30 minutes for donning/doffing the device). During the exoskeleton training, Prostep adaptive mode was used. In Prostep adaptive mode, the stepping occurs automatically each time the subjects reach weight shifting targets, i.e., from one leg to another. The gait parameters were adjusted to assist the subject to step, not to correct their gait.

C. Assessment Protocol

After training, the subjects performed six-minute walk with an exoskeleton followed by a six-minute walk without an exoskeleton. EMG signals were collected from the Soleus (SO), Medial Gastrocnemius (MG), Tibialis Anterior (TA), Vastus Medialis (VM), Rectus Femoris (RF), Biceps Femoris (BF) and Semitendinosus (ST) from the right leg during walking in both EXO and No-EXO conditions. Disposable, self-adhesive silver/silver chloride (Ag/AgCl) snap electrodes with two circular conductive areas of 1 cm each and an inter-electrode distance of 2 cm were used. To measure the heel contact and toe-off instances, we placed one force sensing resistor at the heel and one at the ball of the foot below the shoe. For the EXO condition, the sensors were placed under the foot of the exoskeleton. Heel contact and toe-off instances were used to segment the stance and swing phases of the gait cycle. All data were recorded using a custom program developed in LabVIEW (National Instruments). EMG signals were collected at 1kHz by the MA300-XVI system (Motion Lab Systems, Inc.). Further data processing and analysis were performed in Matlab (Mathworks, Inc.).

D. Muscle Synergies

EMG recordings from seven muscles including SO, MG, TA, VM, RF, BF, and ST during overground walking in EXO and No-EXO condition at post-training were used for the muscle synergy analysis. EMG and gait event data were collected from subjects while they walked in a rectangular circuit, with the dimensions of 18.3 x 12.2 meters. We only extracted high-quality data of strides during straight-line walking and discarded data from strides during turning. Visual examination of the data was used to determine when turning occurred. We found that when subjects were turning, the heel contact and toe-off events were not consistent with gait phases during straight-line walking; hence, data collected during turning was discarded. Each subject was able to take more than ten strides before turning. Therefore, ten consistent strides were included for muscle synergy analysis.

A representation of the linear envelope of the EMG signals using muscle synergies is shown in Equation (1):

$$\boldsymbol{f}_i(t) = \sum_{j=1}^{n} w_{ij}\,\boldsymbol{c}_j(t) \quad i = 1, \ldots, m; \tag{1}$$

where n represents the number of muscle synergies, m represents the number of muscles, $\boldsymbol{f_i}(t)$ is a row vector that represents the activation level of the i^{th} muscle, w_{ij} is the gain of the j^{th} element of the neural command for the i^{th} muscle, and $\boldsymbol{c}_j(t)$ is a row vector that represents the applied neural command. In this study, each stride is resampled at 1% of the gait cycle to generate 101 points, thus $t = 0 \ldots 100$. The equation can be extended to multiple strides (10 in this case) as follows:

$$\boldsymbol{f_i}(t_k) = \sum_{j=1}^{n} w_{ij}\,\boldsymbol{c_j}(t_k) \quad k = 1 \ldots 10 \tag{2}$$

where $\boldsymbol{f_i}(t_k)$ represents the activation level of i^{th} muscle corresponding to sample instance t of the k^{th} stride, time t, w_{ij} is again the gain of the j^{th} element of the neural command for the i^{th} muscle. We further assume that and all elements of $\boldsymbol{f_i}$, and $\boldsymbol{c_j}$ and each w_{ij} are non-negative, i.e. ≥ 0. Equation 2 can be written in matrix form as follows:

$$\boldsymbol{F} = \boldsymbol{W} \times \boldsymbol{C} \tag{3}$$

Where $\boldsymbol{F}$ is a matrix with dimensions 7×1010, $\boldsymbol{W}$ is a matrix with dimensions $7 \times n$ where n represents the number of muscle synergies and each column of $\boldsymbol{W}$ representing one synergy, and $\boldsymbol{C}$ is a matrix with dimensions $n \times 1010$ and each row of $\boldsymbol{C}$ represents the activation profile of the corresponsing muscle synergy.

E. Muscle Synergy Extraction

Muscle synergy extraction was performed on multiple strides by concatenating the EMG linear envelop matrix from multiple gait cycles. The gait cycle was defined as the instance from heel contact to the heel contact of the right foot. The gait events (heel contact and toe-off) timing were detected using the force-sensing resistors attached below the foot. EMG signals were band-pass filtered (20-450 Hz) with a fourth-order Butterworth filter, rectified, and smoothed with a root-mean-square method with a moving average window of 100 ms. We used the non-negative matrix factorization to extract the muscle synergies. Specifically, we utilized the fast non-negative matrix factorization (FNMF) algorithm developed in [26]. FNMF imposes the non-negativity constraint to extract synergy matrix $\boldsymbol{W}$ as the muscle activation matrix $\boldsymbol{F}$ has all non-negative values. The number of synergies was varied from 2 to 7.

Typically for walking, the minimum number of synergies that explain >90% variance in the overall EMG data is an acceptable criterion for synergy selection [27, 28]. To strengthen this, a local criteria of >75% variability for each muscle was further placed [19, 28, 29]. Therefore, we used the solution that accounted for >90% overall variability and >75% individual muscle variability. The synergy matrix $\boldsymbol{W}$ and neural activation matrix $\boldsymbol{C}$ were used for comparison between the EXO and No-EXO conditions.

F. Statistical Analysis

Descriptive analysis was performed to describe gait speed, stance phase duration (expressed as a percentage of the gait cycle), training sessions, and the number of synergies. Values are expressed as mean ± standard deviation. We used paired sample t-test to compare the average activation profiles between the EXO and No-EXO conditions during the stance phase and swing phase. We utilized the scalar-product similarity to compare the structure of the muscle synergy modules between the EXO and No-EXO condition. In addition we also used paired sample t-test to compare the indivual muscles comprising the modules between the EXO and No-EXO conditions. P-values < 0.05 were considered statistically significant.

III. Results

Subjects completed up to 15 sessions (average number of sessions: 12.8 ± 2.0) of exoskeleton-assisted training and post-training assessment protocol that included walking during EXO and No-EXO conditions. We extracted the muscle synergies and the neural activation signals using the FNMF algorithm from the EMG signals of 7 muscles collected during the EXO- and No-EXO conditions.

A. Gait Speed Across Conditions

On average, the subjects walked at 0.31 ± 0.05 m/s during EXO condition and 0.35 ± 0.18 m/s during No-EXO condition (Fig. 1). Six subjects walked at a higher speed during EXO compared to the No-EXO condition while four subjects showed a higher walking speed during the No-EXO condition compared to the EXO condition. No significant difference was found in the averaged gait speeds between the two conditions.

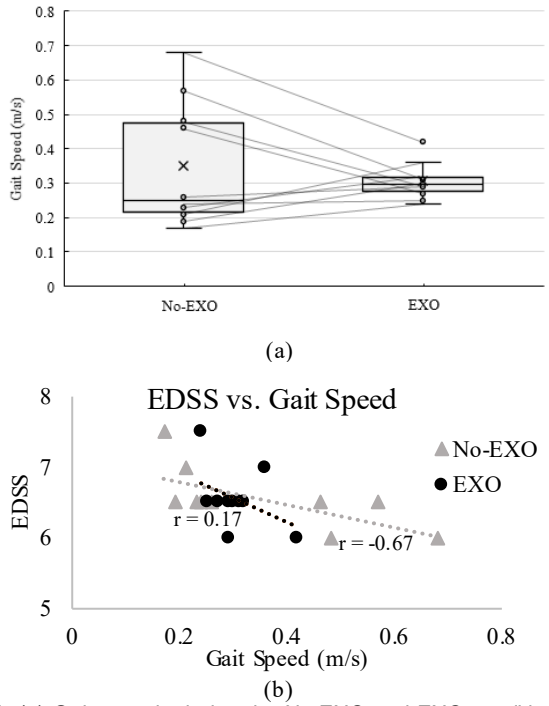

Fig. 1. (a) Gait speeds during the No-EXO and EXO condition. Less variability in gait speed is visible during the EXO condition primarily due to the limitation in speed achieved by the exoskeleton. The variability during EXO reflects the subjects' faster weight shifting causing the Ekso to move faster. (b) Correlation between Expanded disability scale score (EDSS) and gait speeds across conditions. Strong correlation was found between the gait speed and EDSS in the No-EXO condition. Black circles represent the EXO condition. Grey triangles represent the No-EXO condition.

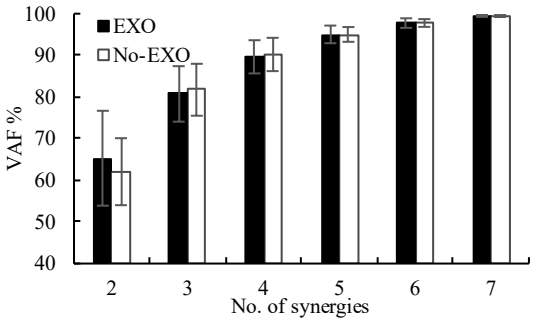

Fig. 2. Total variability accounted for (VAF) based on the number of synergies extracted using FNMF. VAF% represents the precision of reconstruction of the EMG signals from the corresponding synergies and is defined as 100% X uncentered Pearson correlation coefficient. VAF gradually increased with an increase in the number of synergies. Larger VAF values indicate that the analysis more closely accounted for the variability in the activation patterns.

While the speed variability in the EXO condition was dependent on how quickly the subjects shifted their weight from one leg to the other, correlation analyses showed that the gait speed in the No-EXO condition was strongly negative correlated with EDSS score (r=-0.67) and height (r=-0.70) and the gait speed in the EXO condition was negative correlated with EDSS score (r=-0.41) and height (r=-0.21). Moreover, strong positive correlations were observed between the Body-Mass-Index and gait speed in both the No-EXO (r=0.76) and EXO condition (r=0.61).

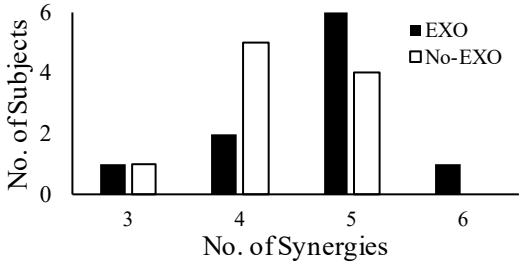

Fig. 3. Histogram of number of muscle synergies during the EXO and Wo-EXO conditions. Four or fewer modules were required to account for cycle-by-cycle variability from 7 unilateral leg muscles during No-EXO condition in 6/10 subjects. At least 5 modules were required to account for cycle-by-cycle variability in 7/10 subjects during EXO condition.

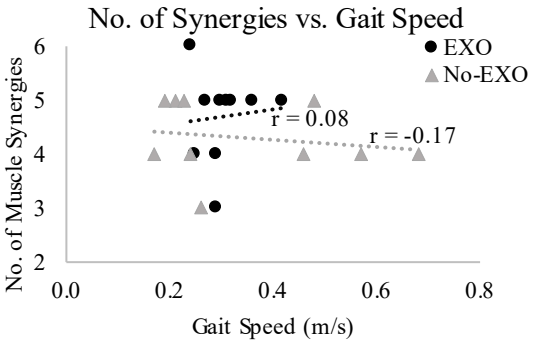

Fig. 4. Correlation between number of muscle synergies and gait speeds across conditions. Weak correlation was found between the gait speed and number of extracted muscle synergies in the No-EXO condition. Grey triangles represent the No-EXO condition.

B. Extraction of Muscle Synergies

The overall variance accounted for (VAF) with the different number of muscle synergies for the two conditions is shown in Fig. 2. VAF is a similarity matrix that is often used to quantify the similarity between the two patterns [30]. Specifically, VAF is defined as 100% X uncentered Pearson correlation coefficient [30]. Unlike the standard Pearson correlation coefficient (*r*), which focuses only on matching the shape of the patterns, VAF quantifies for both the shape and magnitude of the measured and reconstructed patterns. VAF increased with an increase in the number of muscle synergies.

Paired sample t-test revealed no significant differences in the VAF between the two conditions for the same number of modules (as shown in Fig. 2). This suggests that the exoskeleton usage during walking may not have influenced the muscle coordination complexity. However, the distribution of the modules between the two conditions varied considerably across subjects as shown in Fig. 3. When looking across subjects between the two walking conditions, four or fewer modules were required in 6/10 subjects in the No-EXO condition. On the contrary, five or more modules were required in 7/10 subjects during the EXO condition. The results further indicated that 4 subjects had more modules and one subject had fewer modules in the EXO condition compared to the No-EXO condition, and 5 subjects had no change in the module number between two conditions.

C. Number of Modules Across Subjects

The number of modules and the gait speeds for each subject across the two conditions are shown in Fig. 4. The average number of modules was 4.7 ± 0.8 in the EXO condition, and 4.3 ± 0.7 in the No-EXO condition. No significant difference was found in the number of extracted modules between two conditions. Individually, six subjects walked with a greater speed during the EXO condition compared to the No-EXO condition and five of these six subjects showed no change in the number of modules between the two conditions. The remaining four subjects walked slower with EXO compared to No-EXO condition and three of these four subjects showed a greater number of modules during the EXO condition. Moreover, the correlation analysis showed that the number of modules was weakly negative correlated (r=-0.17) with walking speed in the No-EXO condition.

There was no correlation between the number of synegies and EDSS score in the No-EXO condition (r=-0.05), whereas moderately positive correlation was observed between the number of synergies and EDSS score (r=0.51) in the EXO condition.

D. Muscle Modules Between Conditions

The synergy extraction algorithm provides the synergies and the activation matrices. However, the synergies are not arranged in any specific order. After extracting the muscle synergies for each subject we next arranged them to their respective modules. This was performed by calculating the dot product similarity between the extracted muscle synergies of the same label. The synergy with the highest weight of RF and VM muscle (knee extensors) was assigned to the first module. The synergy with the highest weight of MG and SO (ankle plantar flexors) was assigned to the second module. The synergy with the highest weight of TA (ankle dorsiflexor) was assigned to the third module. The synergy with the highest weight of BF and ST (the knee flexors) were assigned to the fourth module. The dot product similarity ensured that all synergies of all subjects were sorted accordingly. A representative set of muscle synergy modules across subjects and the activation profiles corresponding to each synergy module are presented in Fig. 5.

A synergy module is the simplest structure that stores the relative activation of muscles during a motor task. Typically, all muscles that activate together will occur in the same synergy module. An activation profile represents the strength of the estimated neural command required to activate its corresponding synergy module. In Fig. 5, the synergy module-1 is composed of the knee extensors, VM and RF. The synergy module-2 primarily involves the activation of the ankle plantar flexors, SO and MG. The synergy module-3 involves ankle dorsiflexor, TA. Synergy module-4 mainly comprised of the knee flexors, BF and ST. We found a high similarity between the first four muscle synergies using the dot product between the EXO and No-EXO condition (module 1: *0.82*; module 2: *0.89*; module 3: *0.89*; module 4: *0.81*). The similarity between the fifth modules of the two conditions was weak (*0.54*). There were some differences between the muscle compositions in the fourth module. In the No-EXO condition, BF and ST contributed similarly, whereas in the EXO condition the contribution of ST was significantly lower than BF ($p<0.05$). The synergy module-5 was different in the two conditions. In the No-EXO condition, the module-5 occurred in 4 subjects

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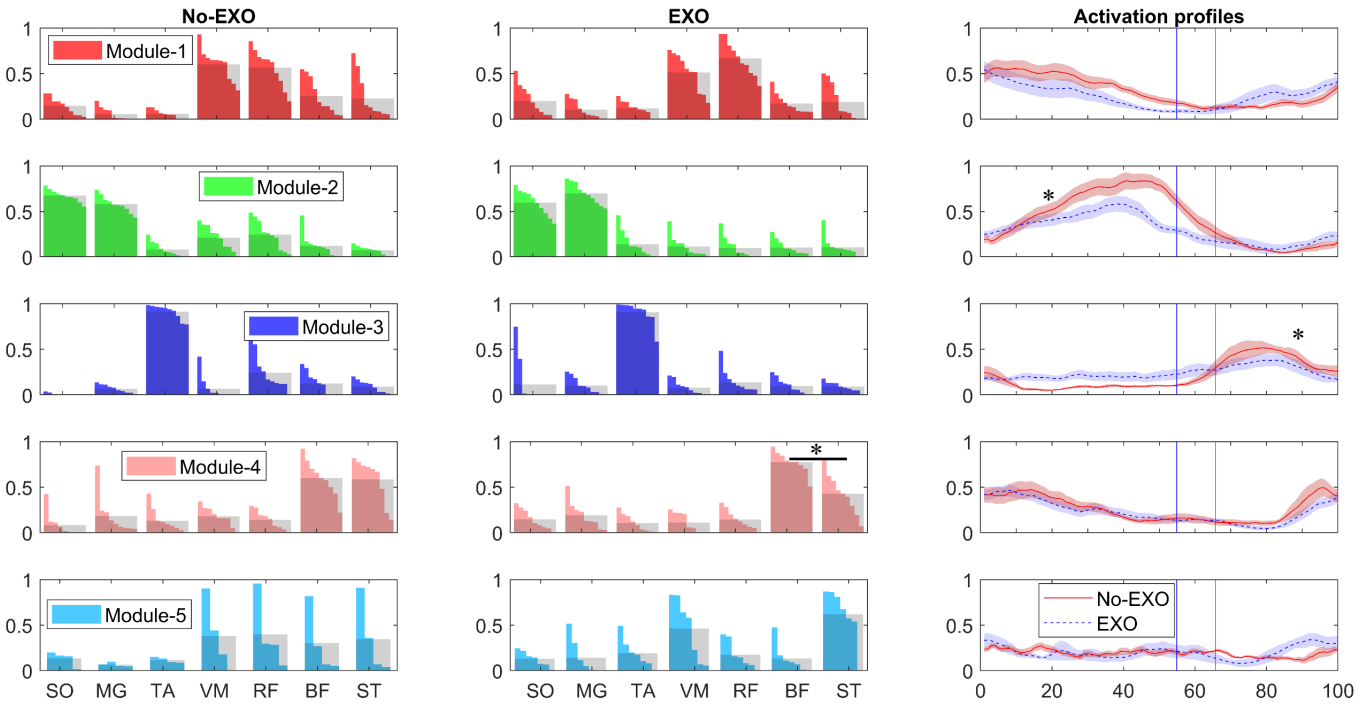

Fig. 5. Muscle synergy modules during the No-EXO (left panel) and EXO (middle panel) condition and activation profiles (right panel). In the left and middle panel, each gray shaded bar (wider) represents the average of the bars (narrower) that represent each subject. Please note, synergy modules 1, 2, and 3 have 10 narrow bars each in No-EXO and EXO condition for each muscle, synergy module 4 has 9 bars in No-EXO and EXO conditions, and module 5 has 7 bars in EXO condition and 4 bars in No-EXO condition. Each bar represents one subject. In the right panel, the solid red and dashed blue lines represent the mean of the activation profiles during EXO and No-EXO conditions, respectively. The blue shaded region represents the standard error of the activation profile during No-EXO condition. The light red shaded region represents the standard error of the activation profile during EXO condition. The vertical red and blue lines represent the average divide between the stance and swing phases in the No-EXO and EXO condition respectively. * denotes significant difference ($p<0.05$).

with each subject showing the presence of one muscle in an extra synergy module. The module-5 in the 4 subjects was mainly composed of one muscle as follows: subject 2 (BF), subject 5 (VM), subject 8 (RF), and subject 9 (ST). However, in the EXO condition, module-5 mainly comprised of VM and ST. The Ekso assitances (EXO condition) facilitated more subjects (7/10) to develop a 5th synergy module and its composition (mainly consisting of VM and ST) is much more consistent across subjects compared to the No-EXO condition.

E. Activation Profiles

We compared the spatiotemporal characteristics of the activation profiles between the EXO and No-EXO conditions during the stance and swing phases of the gait cycle. We first compared the duration of the stance and swing phases during the gait cycles of the two conditions. The stance phase lasted for a significantly higher percentage (65.7 ± 5.4 %) of the gait cycle in the No-EXO condition compared to the stance phase in the EXO condition (54.9 ± 3.5 %, $p < 0.001$).

In general, the amplitudes of the activation profiles in the EXO condition were lower in magnitude than the activation profiles in the No-EXO condition. However, significant differences were only observed in two activation profiles in module-2 and module-3. The average normalized activation amplitude during the stance phase was significantly greater during the No-EXO condition compared to the EXO condition ($p < 0.05$) in module-2 (Fig. 5 right panel), indicating that the exoskeleton assistance reduced the activation of SO and MG during the stance phase. There was no significant difference between activation amplitudes of the two conditions in the stance phase of module 3. During the swing phase, the average normalized activation amplitude was significantly greater in the No-EXO condition compared to the EXO condition ($p < 0.05$) in module-3.

IV. Discussion

A. Summary

We investigated the muscle synergies and their corresponding activation profiles in persons with MS during walking with and without an exoskeleton. For the majority of subjects, four to five synergies were required to explain the variability in the EMG patterns in both EXO and No-EXO conditions. We found similarities in the first four modules extracted between the two conditions. The major difference between the EXO and No-EXO condition occurred in module-5. In the No-EXO condition, the module-5 occurred in four subjects but was inconsistent in terms of the composition. In the EXO condition, the module-5 was much more consistent and was mainly composed of VM and ST muscle. In addition, we observed differences in the amplitude of the activation profiles, typically used to represent neural commands, between the two conditions. Furthermore, the muscles' coordination complexity, indicated by the number of modules, was independent of gait speed across this sample. The plausible explanation for the

similarities in muscle synergies and the observed differences in the activation profiles are provided next.

B. Activation Profiles

Based on our findings, the amplitudes of the activation profiles in module-2 and module-3 were significantly reduced in EXO condition compared to No-EXO conditions. It has been previously reported that persons with MS show increased co-activation of the module-2 and module-3 compared to healthy subjects [7, 17]. This alteration in activation profile could be attributed to two mechanisms: 1) the adaptation after the neurologic damage and 2) the environmental requirement [17]. During training, the exoskeleton settings (i.e., knee flexion angle, step height, etc.) were adjusted based on needs of the subjects to ensure that the exoskeleton only provided assistance as needed during gait. While it may be difficult to reverse the effect of neurological damage to alter the activation of modules, our results indicate that a change in environment is introduced and it could explain the alteration in the activation of module-2 and module-3.

Therefore, the differences could be further explained by this particular device's design which, 1) the passive footplate maintains the subject's ankle to 90 degrees and provides passive assistance and support at the ankle joint particularly during toe-off, thereby acting as an ankle-foot orthosis, and 2) the assistance from the device's hip and knee actuators effectively assist the subjects performing stepping and clearing the foot from the ground.

Specifically, the activation profiles corresponding to the second synergy module (ankle plantar-flexors, SO and MG), activates in mid-late stance phase and it is associated with body support, forward propulsion, and swing initiation. Persons with MS have difficulty in maintaining a proper balance during stance phase due to muscle weakness and have to put in extra effort to propel the impaired limbs forward during pre-swing. When walking with an exoskeleton, these module-2 associated tasks were largely compensated or assisted by the robotic assistance (from the hip and knee powered actuators), resulting activation reduction in module-2 during mid-late stance phase.

The module-3 mainly consists of TA (ankle plantarflexor) and activates in early swing and at heel contact among healthy subjects, and is associated with toe ground clearance during swing and smooth heel contact [16, 31]. The TA module only has one activation peak around mid-swing in No-EXO condition (a little bit later than healthy subjects), indicating that persons with MS have difficulty lifting up their foot from the ground swiftly due to hamstring weakness and they often have to put in extra effort to minimize the toe dragging by activiating the dorsiflexor (TA)/module-3. When walking with an exoskeleton, the assistance from the Ekso's hip and knee actuators, which drive the subject's limb to a larger hip and knee flexion angles and the passive footplate that maintains the subject's ankle to 90 degrees, clear the foot from the ground and prevent the toe from dragging.

C. Muscle Synergies Between EXO and No-EXO Condition

We observed no significant difference in the average number of modules (muscle coordination complexity) between the EXO and No-EXO conditions. However, there was a weak correlation in the number of synergies between the two conditions. Specifically, the number of extracted muscle modules in individuals during the EXO and No-EXO condition could be dependent on the gait speed between the two conditions. All but one subject with higher gait speed during the EXO condition showed no difference in the number of synergies between the two conditions. On the contrary, the subjects with lower gait speed in the EXO condition showed increased number of modules during EXO condition compared to No-EXO condition. The change in the number of modules for subjects with lower speed during EXO condition could be due to the subjects adapting to the slower walking speed offered by the exoskeleton, thereby the altered motor control resulted in a different number of muscle synergies.

It has been shown that the central nervous system employs a flexible control of activation of the muscle synergies to regulate walking speed [32]. Therefore, any change in walking speed is likely caused by the modulation of the neural activation signal. Interestingly, 4/10 subjects had decreased speed of walking during EXO condition whereas the remaining 6/10 had an increased speed of walking during the EXO condition compared to No-EXO condition. Despite the difference in gait speed changes during walking with EXO, the assistance from the exoskeleton was a dominant factor in the control of activation of muscle synergies. If this had not been the case then increased activation of muscle synergies would have been observed during increase in gait speed and vice versa. It could be argued that this variability in gait speed could bias the interpretation of the muscle synergies. However, Clark *et al.* have suggested that the primary goal of non-negative matrix factorization is to identify the commonalities in a complex data set, thus the inter-subject differences, particularly in gait speed, could be ignored when interpreting the results [33].

Although gait speed had no impact on the number of synergies, the EDSS did have an impact on muscle synergies during the EXO condition. This is supported by the positive correlation between the EDSS score and number of muscle synergies during the EXO condition. Subjects with higher EDSS scores required more synergies during the EXO condition. Although the sample size was small (10 subjects) the correlation between EDSS and muscle synergies during the EXO condition indicates the impact of the exoskeleton assistance on modulating the muscle synergies. In the No-EXO condition there was no correlation between the EDSS score and number of synergies.

In addition to the number of modules, we observed that the module-4 showed a reduced contribution of ST compared to BF in the EXO condition. This also validates the higher contribution of ST in module-5 in the EXO condition. In the No-EXO condition, there was no difference between the activation level of BF and ST. The ST muscle is primarily involved in knee flexion and knee internal rotation during flexion. The exoskeleton assistance mainly contributes to movement in the sagittal plane, thereby imposing movement restrictions in the transverse plane. Subsequently, this restriction limits any joint rotation, particularly the knee joint rotation. The resistance to joint rotation probably increases activation of the muscles contributing to the joint rotation, while reducing the contribution in the flexion synergy, i.e.,

module-4. Kinematic analysis of the exoskeleton-assisted walking in future studies could validate this point.

We observed the appearance of a 5th synergy module in seven subjects during the EXO condition. Although the amplitude of the activation profile corresponding to the 5th synergy is lower than the amplitude of activation profiles corresponding to the first four modules, the 5th module indicates a co-activation of VM and ST muscles. The co-activation could occur to provide joint stability. The co-activation of VM and ST could also be due to the fact that exoskeleton's design limits the internal and external rotation of the knee as only the knee extension and flexion is typically modelled [34]. It is well documented that the knee rotates internally and externally during various phases of the gait [35]. While this constraint caused the ST muscle to not activate as much as BF in module-4, the constraint caused ST and VM to activate during the gait cycle as one of the function of these muscles is internal rotation of the knee. In No-EXO condition, four subjects required a 5th synergy module. The peak values of VM, RF, BF, and ST in the module-5 appeared in separate subjects indicating a separation of synergy modules for those particular subjects. Merging of motor modules has been associated with reduced locomotor performance in stroke subjects [33]. Unlike the merging of muscle synergies after stroke, some subjects in this study have shown the separation of some muscles in multiple synergy modules, thereby increasing the total number of synergies. Only one subject, subject-3, showed a merger of modules, i.e., three synergy modules were sufficient to capture the neuromuscular information characterizing the gait in the two conditions. This indicates that unlike after stroke, the reduced locomotor performance in persons with MS may not be characterized by a reduced number of modules. To validate this, further research is required with a larger cohort of MS population and a broader distribution based on EDSS scores or other measures of locomotor performance.

The muscle synergy analysis indicates that improvement in walking due to exoskeleton assistance could be due to the reduction of the neural activations. Walking becomes more demanding after MS as people with MS fatigue much quickly. While we did not observe a big influence of exoskeleton assistance on muscle synergy changes, there was significant alteration in the neural activations that suggest that patients with MS may have found exoskeleton-assisted walking less demanding. We found in the previous study [12] from our group that gait speed improved over short distances and there was reduced metabolic expenditure indicating less fatigue.

As this is the first study exploring muscle synergies during exoskeleton-assisted gait in MS population, here we compare it with the results from our previous study in stroke. First, the key difference between MS and stroke is that the effect of stroke is present only on one side of the body. However in MS, both sides of the body are affected. In the recent study from our group in stroke subjects [16], we consistently found a merger of modules on the paretic side and 3 synergies were present during No-EXO walking. Exoskeleton-assisted did provide a more normative gait pattern and the merged modules were separated during exoskeleton-assisted walking. The number of muscle synergies in MS have been shown to be similar to those in healthy subjects [17]. Second, we did observe an alteration in the activation profiles in the stroke study and alterations in activation profiles were also observed this study. There was difference in timing of activation profiles, particularly an influence caused by the longer swing phase duration during EXO condition.

D. Comparison of No-EXO Synergy Analysis with Previous Studies

We further compared our synergy extraction and analysis methods with the study by Lencioni and colleagues [17]. They compared muscle synergies in persons with MS and healthy subjects, walking at reduced speeds, and found consistency between walking patterns. They found a similar number of muscle synergies in persons with MS and healthy controls with an alteration in modular control evidenced by the modifications of activation timing profiles [17]. We found a number of key differences between the two studies in terms of synergy extraction methods and participants' characteristics. First and foremost, there is a difference in the muscle synergy extraction method. In our study, the synergies are extracted from 10 strides of walking that result in an EMG matrix of size $m \times 1010$. Lencioni *et al.* averaged the trials and the resulting EMG matrix was $m \times 101$. Here, m represents the total number of muscles used to extract the muscle synergies. We extracted synergies from a larger dimension matrix. Second, the criteria for VAF used in our study is also different from those used by Lencioni and colleagues. We selected synergies based on the following condition, i.e., if the average VAF of all muscles is >90% and at least 75% in each muscle [27, 28]. Lencioni *et al.* chose a more stringent criterion, i.e., they used a 90% average VAF with 90% in each muscle. Third, Lencioni *et al.* included subjects with EDSS 7 or lower. To have a more uniform sample, we included patients with EDSS 6.0-7.5, inclusive. This difference in the EDSS scores of the subjects between the two studies is underlined by the lower gait speed during the No-EXO condition in our study. The average walking speed during the No-EXO condition in our study was 0.35(0.18) m/s compared to 0.5(0.22) m/s for persons with MS in Lencioni *et al.* study. Despite the differences in synergy extracting methods and subjects' characteristics, the composition of the first four synergy modules is consistent between the two studies. The key difference in results occurs in the consistent presence of a 5th synergy module in our study during the EXO condition and in 4 subjects during the No-EXO condition. .

Boudarham and colleagues found increased co-activation in the ankle dorsi- and plantar-flexor muscles during the double support phase in persons with MS [7]. We did not observe any co-activation of these muscle groups as they appeared in separate synergies. Also, there was a significant difference between the average activation profiles during the stance phase of the synergy module 2 and 3. The contrasting results could be attributed to the distinct patients' characteristics, particularly their EDSS scores. In our study, the mean EDSS was 6.6 whereas in Boudarham *et al.* study, the enrolled subjects had an average EDSS of 3.8 [7]. Lower EDSS indicates the subjects in Boudarham *et al.* study were better functioning. Our findings of representation of muscle synergies with respect to neuromuscular deficits during the No-EXO condition are similar to the findings of Lencioni *et al.*, who observed no alteration in muscle synergies regardless of neuromuscular deficits when compared to intact subjects, despite differences

in subjects' characteristics and different synergy extracting methods [17]. Lencioni *et al.* investigated muscle activation profiles and muscle synergies during overground walking and compared them with muscle synergies of neurologically intact individuals. Their results showed a similar number of muscle synergies in persons with MS and healthy controls with an alteration in modular control evidenced by the modifications of activation timing profiles [17].

E. Study Limitation

There are some limitations of this study. The subjects were selected to have a similar walking deficiency by limiting the EDSS criterion, and the sample size was small. Despite having less variability in EDSS scores, the subjects' walking ability varies in gait speed during the No-EXO condition. In designing studies with subjects with MS, other parameters such as gait speed should also be considered in addition to the EDSS score. We collected the data from a single leg to compare synergies. An alternative approach would be to perform synergy analysis on EMG data collected from both legs and inclusion of gait analysis to identify different gait phases. Another limitation of the study is the limited neurophysiological relevance of the existing muscle synergy extracting algorithms. Whether there is a neural basis of muscle synergies or they are only a manifestation of the correlations induced by simultaneous muscle acrtivity is a matter of debate [20]. Since current decomposition methods do not employ enough prior knowledge from neurophysiology, Cheung and Seki have suggested to develop algorithms based on neurophysiollogically contrained models of muscle synergies [36]. Future studies could be undertaken to employ these models to evaluate muscle synergies in MS population.

V. Conclusion

This study examined the muscle synergies during walking with and without an exoskeleton. The key findings of the studies showed a decrese in the neural activation during EXO condition compared to No-EXO condition and the presence of a 5th synergy module predominantly during EXO condition. Our results highlight the utility of muscle synergy analysis in extracting meaningful clinical information about functional motor deficits in persons with MS. The analysis of muscle synergies and the activation patterns provides useful information regarding the timing of different muscles and any co-contractions. This information can also be used to evaluate the effect of exoskeleton assistance during walking, particularly informing about any co-activations of the muscles, alterations in the neural drive, walking complexity, etc. Furthermore, the analysis could be used by exoskeleton designers to improve/modify their designs for specific patient populations. Regarding hardware, a more realistic gait pattern would require actuation of the ankle joint. The current design allows for adjustment of hip width to fit the participant, however it limits hip abduction/adduction during walking as the hip actuators primarily operate in the sagittal plane. The current features in the software allow the therapist to modify the parameters such as step height, step length, and knee and hip flexion angles. The assistance from each leg adapts based on the effort of the participant. Realtime monitoring of EMG signals during walking would provide additional form of feedback to the therapist, assisting in gauging the performance of the patient and make the necessary changes in terms of exoskeleton assistance.

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