Motor Recovery in Human SCI through Selective Activation of Muscle Synergies under Spinal Cord Stimulation

Richard Cheng, *Member, IEEE,* Yanan Sui, *Member, IEEE,* Dimitry Sayenko, and Joel W. Burdick, *Member, IEEE*

Abstract*—*Objective: **Spinal cord stimulation (SCS) has enabled recovery of motor control in paraplegics with complete spinal cord injury (SCI), but the physiological mechanisms underlying this recovery are poorly understood. This study analyzes muscle synergies in SCI patients under SCS and healthy subjects to elucidate the mechanisms enabling motor control through SCS.** ***Methods:*** **Muscle synergy extraction algorithms, such as NMF (non-negative matrix factorization), fail when applied to SCI patients under SCS. We develop a new algorithm – rShiftNMF – to extract muscle synergies in SCI cases. Then, we analyze muscle synergies from two complete SCI patients under SCS, and compare them with muscle synergies from five healthy subjects.** ***Results:*** **Muscle synergies extracted by rShiftNMF are significantly better at interpreting electromyography (EMG) from SCI patients under SCS, and resulting synergy features are more physiologically meaningful. Our analysis shows that (1) SCI patients rely more heavily on muscle synergy activation to generate motor activity than healthy subjects do, (2) optimal SCS selectively activates an additional muscle synergy which proves critical to SCI standing, and (3) motor activity resulting from optimal SCS is consistent with biomechanically efficient standing.** ***Conclusion:*** **Our algorithm successfully extracts muscle synergies in SCI patients. We provide evidence that muscle synergies are encoded in the human spinal cord, and that SCS selectively activates these synergies and thereby significantly influences motor function.** ***Significance:*** **Our results suggest that an important physiological mechanism enabling motor control under SCS is muscle synergy activation. Thus, properly targeting muscle synergies through SCS may improve efficacy of spinal stimulation therapies.**

I. Introduction

Motor activity requires a complex mapping from the brain to the spinal cord and then to individual muscles. In 1994, Mussa-Ivaldi et al. observed that in frogs, total muscle activity was encoded as a linear superposition of a few motor primitives, suggesting a low-dimensional, linear representation of motor output [1]. *Muscle synergies* capture these motor primitives and represent the low-dimensional, linear motor behavior; they are defined as the coordinated recruitment of a group of muscles with a specific activation signal. The idea is that each muscle synergy represents a network of interneurons activated by a single neural command. Each interneuronal network excites a specific pattern of motoneurons, resulting in fixed patterns of muscle activity following a similar activation signal. A current theory is that the spinal cord controls functional motor activity, in large part, by modulating activity of muscle synergies – as opposed to controlling individual muscles. Note that these muscle synergies constitute a closed-loop control mechanism, as the pattern of muscle activity generated by the interneuronal network depends on peripheral sensory input. Fig. 1 shows the concept of how muscle synergies contribute to electromyography (EMG) activity.

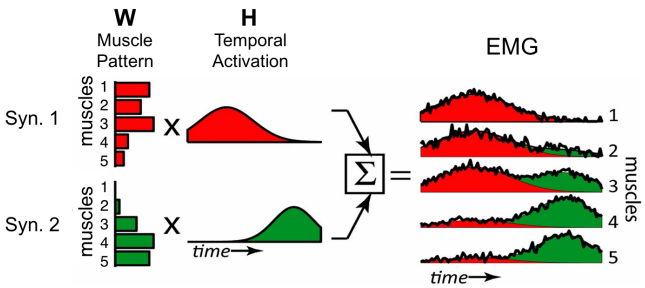


Fig. 1: Illustration of two muscle synergies composed to reconstruct EMG activity. W represents the activation pattern of muscles, and H represents the activating neural signal for two different muscle synergies. This figure was adapted from [2].

Animal studies have provided substantial evidence for muscle synergies. When stimulating different parts of the spinal cord together or separately (electrically or chemically), researchers have observed that resulting motor activity from joint stimulation is approximately a linear combination of the motor activity induced by separate stimulation [3]–[5]. By measuring activity from neurons in the spinal cord concurrently with muscle activity (in monkeys, cats, and frogs), studies show that muscle synergies may be encoded in the spinal cord through sets of dedicated interneurons [6], [7].

Although such experiments have not been done in humans, it has been shown that human muscle activity can be accurately described by the linear superposition of a few muscle synergies [2], [3], [8]–[12]. Synergies are extracted from human EMG measurements during specific tasks (e.g. reaching, stepping, etc...), and represent low-rank approximations of the muscle activity – i.e. a small number of muscle synergies linearly combine to compose overall muscle activity. Studies have indicated that many muscle synergies are associated with specific movement kinematics (such as the different parts of a walking gait) and may be shared across tasks [8]–[11].

Non-negative matrix factorization (NMF) is a widely used method for searching for this low rank approximation of muscle activity. This method extracts muscle *activation patterns* W (representing the coordinated recruitment of a group of muscles) and *neural activation signals* H (representing

the activation waveform that excites the specific group of muscles), which best fit the EMG data. The result is a set of muscle synergies that represent the EMG activity, and we can easily measure how good this representation is by the resulting error between the reconstructed EMG and measured EMG.

Tresch et al. showed that the set of muscle synergies extracted is reasonably robust to the choice of matrix factorization algorithm [13]. Different factorization algorithms were used in their study (PCA, FA, ICA, NMF, ICAPCA, and pICA) and it was found that NMF could identify the correct muscle synergies, even in the presence of noise. In addition to good performance and robustness to noise, NMF is a reasonable choice for muscle synergy extraction given that it ensures positive activation (a physiological assumption on muscle synergies) and does not assume independence of the different synergies (as methods such as PCA and ICA would do).

Several recent studies have suggested that after neurological injury (i.e. stroke, SCI, Parkinson's disease), patients exhibit fewer or merged muscle synergies [2], [12], [14]–[17]. Patients essentially lose muscle activity "complexity" since they activate fewer muscle synergies during given tasks, which results in decreased functional performance. Therefore, these studies suggest the desirability to retain an adequate number of muscle synergies to enable effective task behavior.

This paper explores the existence, extraction, and control of muscle synergies in paraplegics with motor complete spinal cord injury (SCI) under spinal cord stimulation (SCS). Until recently, it was believed that motor function could not be recovered after complete SCI, but studies have shown that motor complete SCI patients can recover motor function under spinal cord stimulation (SCS) [16], [18], [19].

The first section of this paper introduces a novel algorithm to extract muscle synergies from SCI patients under SCS, as standard algorithms fail due to the presence of consistent time delays between the activation of different muscle groups – these delays are prevalent in SCI patients under SCS (see Fig. 2). The second part of this study analyzes the muscle synergy activation patterns and the number of muscle synergies induced by SCS, and finds that proper stimulation can selectively activate an additional muscle synergy and produce markedly improved functional behavior. The last part of this study compares muscle synergies extracted from SCI patients attempting to stand under SCS, with those extracted from healthy human subjects standing. We find that the muscle activity resulting from SCS is significantly different from healthy muscle activity (see Fig. 11) and highly dependent on the spinal stimulation given.

The contributions of this paper are:

- Introduction and application of the rShiftNMF algorithm to enable extraction of muscle synergies in SCI patients under SCS,
- Evidence of muscle synergies retained in the human spinal cord after SCI, and activated through SCS,
- Comparison of SCI patient muscle synergies with healthy subject muscle synergies,
- Identification of SCS that improves SCI patient standing performance via selective activation of an additional muscle synergy.

A preliminary version of part of this work appeared in [20], which only focused on discussion the rShiftNMF algorithm for muscle synergy extraction.

II. Methods

A. Experiments

1) Spinal Cord Injury Patients: Data was collected from two complete, paraplegic SCI patients implanted with a Medtronic 5-6-5 epidural electrode array for SCS with a Medtronic RestoreAdvanced Neurostimulator. The patients (referred to as patients A and B) gave their written informed consent to participate in the study, whose experimental procedures were approved by the local Institutional Review Board. For patient A, experiments were performed over two non-consecutive weeks, six month apart, and a total of 109 trials of stimulation/EMG data were gathered (we'll refer to the earlier week as session 1 and the later week as session 2). For patient B, experiments were performed over one week, and a total of 15 trials of stimulation/EMG data were gathered. For each trial, the patient attempted to stand with minimal support for 1 to 5 minutes under spinal stimulation.

The choice of stimulating electrodes recruited on the array and their polarities (i.e. the stimulation patterns) were modified between trials. This choice was determined by a machine learning algorithm which continually proposed different "safe" stimuli (high probability of eliciting non-painful response), and continually tested good ones against each other to search for the optimal stimulation patterns (resulting in independent, natural standing) [21], [22]. Stimulation frequency and pulse width were kept constant between trials at 25 Hz and 200 μs, respectively. For a fixed stimulation pattern, frequency, and pulse width, SCS amplitude was ramped upward until reaching a well-performing value.

The patient achieved full weight-bearing standing with minimal assistance when empirically-optimal stimulating configurations were used.

We utilized measurements from 10 muscles (left and right muscles of 5 muscle groups) taken using sEMG (surface electromyography) at a sampling frequency of 2000 Hz. The 5 muscle groups were: VL (vastus lateralis), MH (medial hamstring), MG (medial gastrocnemius), TA (tibialis anterior), and SOL (soleus). The EMG was high-pass filtered at 1 Hz, rectified, and low-pass filtered at 60 Hz using a 3rd order butterworth filter.

It is important to note that the filtering applied here is significantly less aggressive (retains a much larger signal bandwidth) than the pre-process filtering typically applied to EMG in other muscle synergy studies. For example, the low-pass and high-pass filter cutoff frequencies are set at 35/40 respectively in [8], or 35/35 in [9], whereas our filter cutoff frequencies are set at 1/60. Our higher-bandwidth filter is necessary to retain important parts of our EMG spectrum induced by spinal stimulation, as seen by visual inspection of the frequency spectrum.

Table I describes how the clinicians quantified standing quality. We utilized a discrete scoring system that ranges from

1 to 10, with 1 being the worst and 10 being the best. From scores 1 to 5, the standing is not independent but requires less and less assistance by bungees across the knees or manual assistance from trainers as the score increases. From scores 6 to 10, standing is overall independent and full-weight bearing. As the score increases, standing is more natural, stable, and durable. After every trial, a score on the overall standing quality was assigned.

TABLE I: The Scoring Criterions

Score	Descriptions
1-2	Assisted by bungees or trainers (max)
3-4	Assisted by bungees or trainers (mod)
5	Assisted by bungees or trainers (min)
6-7	Hip: Not assisted, back arched Knee: Not assisted, loss of extension during shifting
8-10	Hip: Not assisted, back straight Knee: Not assisted, extended during shifting

For four of the experimental trials with patient A and one of the trials with patient B, rather than using a single fixed stimulation pattern, 4 different stimulating patterns were interleaved together with a frequency of 10 Hz. Therefore, the stimulation pattern was time-varying (changing every $\approx 25ms$), and the 4 chosen stimulation patterns would repeat every $100ms$. We will refer to these time-varying stimuli as *interleaving stimulation*. Empirically well-performing stimulation was used for each of the 4 patterns. The hypothesis was that each stimulation pattern might compensate for a different part of the patient's standing (e.g. one stimulation pattern would be optimal for right leg stability, another would be optimal for trunk stabilization, etc...).

2) Healthy Control: Data was collected from five healthy participants (age: 27.2 ± 4.5 years; height: 168 ± 9 cm; weight: 62.3 ± 10.9 kg). They had no medical history of neurological disorders. All subjects gave their written informed consent to participate in the study, whose experimental procedures were approved by the local ethics committee.

Each participant stood quietly with bare feet, eyes open, and arms hanging along the sides of the body for the duration of 60 s. The participant was instructed to stand quietly and to refrain from any voluntary movements.

EMG activity was recorded from 4 muscle groups measured bilaterally (VL, MH, MG, SOL), using a PowerLab 16/35 series DAQ system (ADInstruments, Australia) and amplifier Octal Bio Amp (ADInstruments, Australia). EMG signals were differentially amplified with a band-pass filter with a bandwidth between 10 and 2,000 Hz (-3 dB), and digitized at a sampling frequency of 4000 Hz. To compare results with the SCI patients, we downsampled the signal to emulate a sampling frequency of 2000 Hz. The EMG was then lowpass filtered at 50 Hz and then high-pass filtered at 4 Hz using a 5th order butterworth filter.

B. Extraction of Muscle Synergies

For extracting muscle synergies from healthy subjects' EMG measurements, we utilized the NMF algorithm developed in [23]. The algorithm efficiently solves the optimization problem in Equation (1) using alternating least squares with multiplicative updates to find a local optimum.

$$\underset{W,H}{\text{minimize}} \quad ||EMG - \sum_{d} W_{n,d} H_{d,t}||_2^2 \tag{1}$$

In Equation (1), EMG refers to the rectified and filtered EMG signal – an N-by-T matrix composed of N signals (1 for each muscle) with length T. $W_{n,d}$ represents the activation pattern of each muscle synergy where n indexes each of the N muscles, and d indexes each of the D muscle synergies (i.e. each column represents the muscle activation pattern for synergy d). $H_{d,t}$ represents the time-varying activating signal for each muscle synergy where t indexes each time step of the activating signal, and d indexes each of the D muscle synergies (i.e. each row represents the activating signal for synergy d). This is illustrated in Fig. 1.

However, analyzing muscle synergies in SCI patients under SCS introduces a unique challenge, which causes NMF to work poorly in these cases. It is known that neural signals take differing times to reach different muscles, based on the distance these signals must travel and the finite speed of neural signals along axons (e.g. a neural signal sent from the spinal cord will reach the proximal muscles before distal muscles). In healthy subjects, it is assumed that the CNS accounts for these signal delays when processing and sending the appropriate motor signals to different muscles. However, in patients with SCI under spinal stimulation, an activating signal is externally induced at a specific area of the spinal cord at a fixed frequency. This activating signal must propagate through the interneuronal and motorneuron pathways down the lower limbs, resulting in measurable and diverse delays in the EMG response at distal muscles. Therefore, extracted muscle synergies must account for these delays, which NMF cannot do. The implicit assumption when using NMF for muscle synergy extraction is that each neural signal generated by the spinal cord must reach every muscle simultaneously.

Therefore, we utilize a variant of NMF that can account for delays, referred to as ***rShiftNMF*** (for regularized ShiftNMF). First, the optimization problem is reformulated to include delays, τ, as follows in Equation (2). An algorithm for efficiently solving this problem is derived in [24].

$$\underset{W,H,\tau}{\text{minimize}} \quad ||EMG - \sum_{d} W_{n,d} H_{d,t-\tau_{n,d}}||_2^2 \tag{2}$$

By adding a delay parameter, τ, to the original optimization problem, we can allow for delays, $\tau_{n,d}$, in arrival time (of neural signal, d) at each individual muscle, n. The index (n, d) would refer to the delay for muscle n (of N) in the d^{th} muscle synergy. These delays allow us to eliminate the assumption that all muscles are activated simultaneously by a given muscle synergy. The optimization problem in Equation (2) is solved by first doing a Fourier transform on the parameters W, H, τ to conveniently express the delay as multiplication by a complex exponential. Then we use alternating least squares with multiplicative updates to iteratively converge on parameter estimates. Details can be found in [24].

However, we also must ensure that the calculated delays are consistent with neurophysiology. Since Equation 2 defines

a non-convex problem, there are many local optima we may converge to that utilize non-physiological delays. Consider that a generic 10Hz periodic signal would be equally likely to have a 10ms delay and a 110ms delay. Hence, the optimization problem above may lead to non-physiological estimates of the delay τ, given that (1) many local optima exist and (2) many delays τ can lead to similarly good factorizations. However, based on the physiology of the CNS, we can estimate the order of magnitude of expected delays. For example, neural signals travel down motor nerves at speeds on the order of $100\frac{meter}{sec}$, and the length of a lower limb is approximately between 0.5 to 1 meters, so a signal sent from the spinal cord should take order of magnitude 10 milliseconds longer to reach a thigh muscle than shank muscle with variations from patient to patient.

Given order of magnitude estimates of expected delays, we can modify the algorithm to incorporate a prior, $T^{prior}_{n,d}$, on the delays to ensure that the delays remain consistent with physiology. If we assume the synergy reconstruction error is gaussian (i.e. $\mathbb{P}(EMG|W,H,\tau) = \mathcal{N}(\sum_d W_{n,d}H_{d,t-\tau_{n,d}},\Gamma)$), then adding a gaussian prior with mean T^{prior} on the delay, τ, in a Bayesian formulation of the problem is equivalent to adding L_2 regularization to the underlying optimization problem, as shown in Equation (3) below:

$$\underset{W,H,\tau}{\text{minimize}} \quad ||EMG - \sum_d W_{n,d}H_{d,t-\tau_{n,d}}||_2^2 + \lambda||\tau - T^{prior}||_2^2. \tag{3}$$

The new optimization problem can be solved by alternating least squares as in [24], and only the update law for the delays $\tau_{n,d}$ must be modified by linearly adding in the gradient/Hessian corresponding to the regularization term. This defines the rShiftNMF algorithm.

Note that since the rShiftNMF algorithm uses 10 more free parameters per synergy (for 10 muscles) compared with NMF, it is expected to better fit to the data. To address this, we run the algorithm on training data to obtain proper delays τ for the synergies, and then cross-validate by running the algorithm with the same fixed delay parameters, τ, on test data. Then we can directly compare the ShiftNMF fit results with NMF, since they utilize the same free parameters (after fixing τ).

To avoid overfitting and further cross-validate our results, we run the rShiftNMF algorithm on training data, then fix *both* the activation pattern W and delays τ, and then run the same algorithm on test data. We do the same for the NMF algorithm, but fix just the activation pattern W. This helps avoid overfitting to the data – see Fig. 3. Since the underlying EMG data is not stationary due to natural fluctuations in the muscle activity and patient's stance, we do not fix the activating signal, H.

C. Estimating the Number of Muscle Synergies

Note that in the muscle synergy extraction formulation (Equation 3), the number of muscle synergies D must be predefined. Most work on muscle synergies utilizes the *variance accounted for* (VAF) metric defined below to estimate the proper number of muscle synergies:

$$VAF = 1 - \frac{||EMG - \sum_{d=1}^{D} W_{:,d}H_{d,t-\tau_{n,d}}||_2}{||EMG||_2}.$$

This is a measure of how well the muscle synergies reconstruct the underlying EMG activity. In the NMF formulation, we have $\tau = 0$ (no delays).

Typically the number of synergies is defined as the minimum D such that VAF rises above some threshold. However, the number of synergies will be dependent on the threshold values used and the pre-process filtering of the EMG. Other work has attempted to improve on these methods by cross-validating over several trials [25], or utilizing different likelihood measures and information criteria [13].

In this work, we utilize the following 2-step method to determine the number of muscles synergies similar to the procedure in [25]:

- Determine the number of synergies by thresholding the slope of the VAF curve. For the threshold, we preliminarily set the number of synergies once the VAF increases by less than 0.2. This cutoff was chosen by visual inspection of the trends in the VAF curve.
- We then validate the result by looking at the muscle activation patterns of the synergies across different intervals of the patient's EMG, and see if they are consistent (i.e. the dot product between them is greater than 0.98). If they are consistent, we accept the number of muscle synergies to be correct. Otherwise, we lower the synergy number.

This procedure allows us to robustly identify the number of synergies present using thresholding methods and cross-validation.

III. Results

A. Analysis of SCI Patient EMG Activity

1) Improvement in Synergy Extraction with rShiftNMF: We extracted muscle synergies from the EMG activity of the SCI patients using rShiftNMF as well as NMF. As discussed in Section II-B, delays in muscle activation between muscle groups are present in paraplegics undergoing SCS-induced standing. These delays are illustrated in Fig. 2, where we see that muscles further from the spinal cord follow a similar waveform pattern as muscles closer to the spinal cord, but with a slight ($\approx 10ms$) delay.

These delays are only accounted for in the rShiftNMF algorithm, so we expect it to better capture low-dimensional muscle synergy structure in the EMG activity. We confirm this by examining the VAF of the EMG using synergies extracted by each algorithm. This is shown in Fig. 3, and we see that rShiftNMF is effective at capturing the EMG activity with few muscle synergies. In fact, when cross-validating with respect to both the activation pattern W and delay τ, a single synergy extracted by rShiftNMF is able to account for $\approx 60\%$ of the variance in the EMG signals, whereas NMF achieves that reconstruction accuracy only with 2-3 synergies. The fact that the performance of rShiftNMF remains high (and significantly better than NMF) with cross-validation, suggests that we are

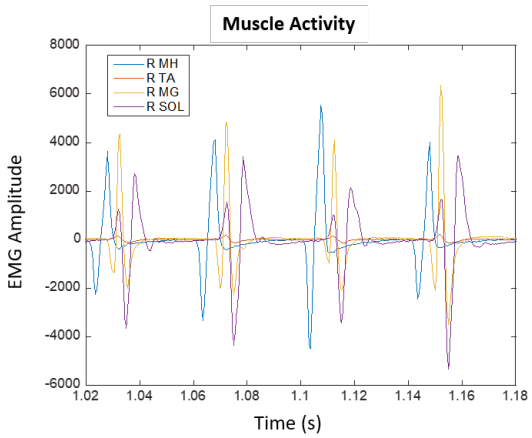


Fig. 2: Example of delays in EMG activity between different muscles. Note that MH and MG muscles have a similar waveform, with MG activated slightly after MH.

able to capture meaningful structure in the EMG activity with few muscle synergies.

One may note that the VAF observed here is lower than values typically recorded in the literature, which is due to the fact that we retain a much larger frequency spectrum of the EMG signals in pre-processing (as discussed in the Section II-A1). Thus, the important features to note are (1) improved performance compared to NMF, and (2) consistency of VAF after cross-validation.

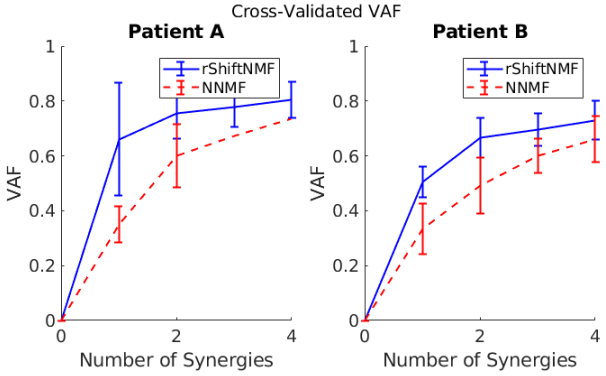


Fig. 3: The variance accounted for (VAF) plotted against the number of synergies extracted. For each plot, the VAF with the rShiftNMF algorithm was compared to the VAF with the NMF algorithm. In all cases, the synergies were cross-validated with fixed delay, τ, and activation pattern, W. (Left) Results for patient A; (Right) Results for patient B.

To validate the results of the rShiftNMF algorithm, we note that the algorithm's calculated delays, τ, are consistent with expected values based on the speed of neural signals and the relative distance between muscles, as discussed in II-B. If the delays, τ, were inconsistent with neurophysiology, this would be an indicator that the rShiftNMF algorithm might be fitting to noise in the EMG activity rather than meaningful structure in the CNS. The delays when considering one synergy are shown in Fig. 4.

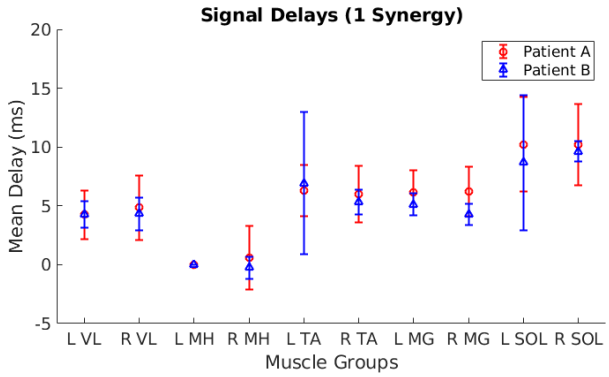
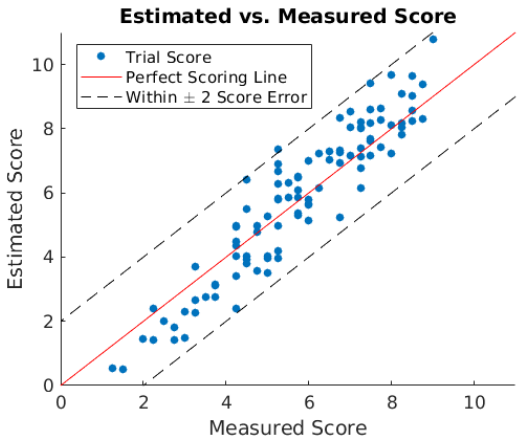


Fig. 4: Muscle activation delay for each muscle in the muscle synergy (normalized to the left MH muscle).

Note that left/right muscles within each muscle group have similar delays, and that delays increase as we go from MH to VL to TA/MG to SOL muscles, which reflects an ordering based on distance from the spinal cord. We also note that the observed delays are in line with the order of magnitude delay expected ($\approx 10ms$) as discussed in Section II-B. The consistency of the delays with physiological models is further evidence that rShiftNMF muscle synergies are capturing physiological phenomena that would be missed with muscle synergies extracted by NMF. NMF muscle synergies would necessarily treat distant muscle groups (e.g. MH and SOL) as part of different synergies because their relative delays make them seem to arise from different neural signals. Muscle synergies extracted by rShiftNMF can better identify co-activated groups of muscles that may be physically distant.

As further validation, we note that for patient A, muscle synergy features extracted by rShiftNMF are more strongly correlated with functional performance (standing ability) than muscle synergy features extracted by NMF. Note that we did not repeat the analysis with patient B due to the smaller number of trials and lower variance in standing scores. Fig. 5(a) shows prediction accuracy based on linear regression with EMG power and rShiftNMF muscle synergy features. Using these features to estimate patient standing scores, we found that 74% of the estimates were within ± 1 of the true score, and 97% were within ± 2 of the true score. In comparison, if we did not include the muscle synergy features, only 59% of the estimates were within ± 1 of the true score, and 91% were within ± 2 of the true score. Thus adding rShiftNMF muscle synergy features leads to significant improvements in prediction accuracy, suggesting that these synergies capture some meaningful structure that correlate with motor activity. Fig. 5 (b) compares score classification accuracy – independent standing (score $\geq$ 6) vs. non-independent standing – using synergy features from either NMF or rShiftNMF and 3-fold cross-validation. The results indicate stronger correlation with rShiftNMF muscle synergy features. This result, combined with the accurate modeling of physiological delays and significantly improved EMG reconstruction, suggests that rShiftNMF provides a more useful and physiological description of muscle synergies for SCI patients.



(a)

	Score Error using All Synergy Features	Score Error using VAF	Linear Regression with VAF (% trials predicted within ±2)
NNMF	1.21	1.49	69.20%
Regularized ShiftNMF	1.12	1.26	76.90%
Prediction Method	Random Forest	Linear Regression	Linear Regression

(b)

Fig. 5: (a) Accuracy in standing score prediction using linear regression with ShiftNMF muscle synergy features and raw EMG power. (b) Standing score prediction performance based on muscle synergy features only, using scoring scale between 1-10. First and second columns show mean absolute error in score prediction, whereas the third column shows percentage of trials correctly predicted within ± 2 of true score.

2) Number of Muscle Synergies: Utilizing the methodology described in section II-C, we calculated the number of synergies present in each stimulation trial. For 96% of the trials, we found that only one muscle synergy was activated during patient standing under SCS.

However, for 4 of the 109 trials for patient A and 1 of the 15 trials for patient B, we found two distinct and consistent muscle synergies were active during patient standing under SCS. We found that these trials where 2 synergies were active also corresponded to the highest performance trials *and* occurred when (and only when) the patient was stimulated with multiple interleaving stimulation patterns (as described in section II-A1) rather than a single fixed stimulation pattern. We will argue that the interleaving stimulation achieves *selective spinal circuit activation* (SSCA) of a second spinal circuit (i.e. muscle synergy), and in this paper, we will refer to the trials with 2 synergies as SSCA trials.

B. Activation of Additional Synergy with SCS

In this section, we confirm that there is indeed a second distinct muscle synergy that is activated in the SSCA trials due to spinal stimulation, and we explore its characteristics and importance to functional SCS-based standing.

First, we show that for the SSCA trials, the activation pattern, W, is distinct for the two muscle synergies – the first is the same muscle synergy common to all the non-SSCA trials, and the second muscle synergy is distinct from the first in activation pattern. Fig. 6 compares the mean activation pattern for the muscle synergy from non-SSCA trials, to the activation pattern of the two muscle synergies from the SSCA trials. We find that the first muscle synergy from the SSCA trials aligns with the muscle synergy extracted from the non-SSCA trials (with respect to the activation pattern W) – mainly activating the lower leg muscles (MG and SOL). The second synergy primarily activates the VL muscle group, showing a distinct pattern from synergy 1. We can think of this second synergy as activating a second neural circuit responsible for a complementary set of muscles. Therefore, the first synergy primarily activates the lower leg muscles, while the second muscle synergy primarily activates the upper leg/thigh muscles.

We tested the statistical significance of this hypothesis using a permutation test based on minimum statistical energy developed in [26]. We calculated the p-value corresponding to the hypothesis that the first synergy activation pattern from the SSCA trials matches the synergy activation pattern from the non-SSCA trials, and found that $p > 0.2$ ($p = 0.21$ for patient A session 1, $p = 0.20$ for patient A session 2, and $p = 0.47$ for patient B). We *cannot* reject the hypothesis that the activation patterns come from the same distribution, even at the 20% confidence level. However, if we consider the second muscle synergy from the SSCA trials, we *can* reject the hypothesis that it comes from the same distribution as the muscle synergy of the non-SSCA trials at the 5% confidence level ($p = 0.003$ for patient A session 1, $p = 0.001$ for patient A session 2, and $p = 0.05$ for patient B). These results suggest that the interleaving stimulation introduces a distinct second muscle synergy during patient standing, while also activating the original muscle synergy.

Surprisingly, the activation pattern for both synergies is quite similar for both patients as seen in Fig. 6. While the small sample size prevents us from making strong claims, one hypothesis is that these muscle synergy activation patterns reflect efficient activation patterns that arose from the patients' stand training after SCI. This hypothesis is discussed further in Section III-C3.

Note that we have omitted the MH muscles in Fig. 6 and the permutation test, because it is activated significantly by both synergy 1 and synergy 2 in the SSCA trials; this overlap means that MH activity can often equivalently be attributed to either synergy 1 or synergy 2, and often changes across runs of the algorithm. Therefore, it is difficult for the algorithm to confidently attribute it to one synergy or the other.

The introduction of the second muscle synergy (activating the VL muscles) increases the complexity of the muscle activity, requiring the composition of 2 neural commands instead of 1. Fig. 7 illustrates this increased complexity through an additional muscle synergy. In the SSCA trials, the 2^{nd} synergy introduces a significant (in amplitude) and different "basis signal", which allows the spinal cord to generate richer muscle activity. In contrast, for the non-SSCA trials, if we attempt to extract two synergies by the rShiftNMF algorithm, the 2^{nd} synergy barely contributes to the muscle activity as seen in the bottom plots of Fig. 7 and its waveform significantly mirrors the 1^{st} synergy, essentially becoming a redundant synergy.

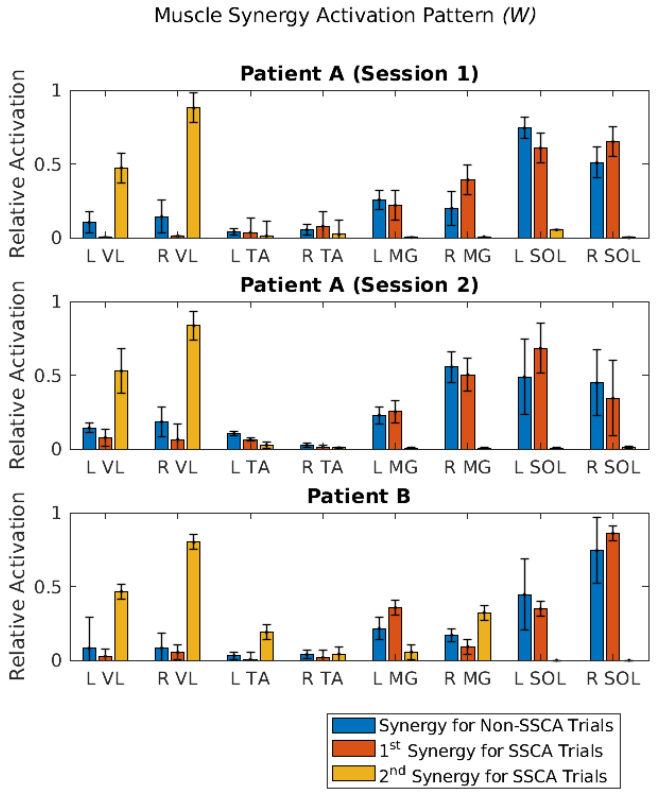


Fig. 6: Comparison of mean activation pattern for non-SSCA trials (single synergy - blue bar) with activation patterns for synergy 1 (red bar) and synergy 2 (yellow bar) of SSCA trials. Note that the confidence intervals for the synergy 1 activation pattern in the SSCA trials overlaps with the activation pattern of the non-SSCA trials. *(Top)* Patient A (Session 1); *(Middle)* Patient A (Session 2); *(Bottom)* Patient B

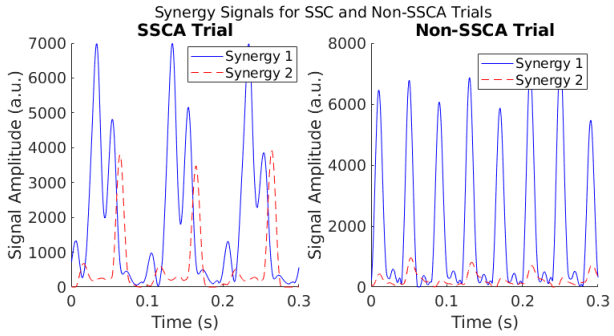


Fig. 7: Representative illustration of synergy activation waveform, H, for SSCA trials vs. non-SSCA trials. Note that in SSCA trials (left plot), the synergy 2 activation waveform plays a significant role in composing EMG activity. In non-SSCA trials (right plot), adding a second synergy results in an activation waveform that is similar to the synergy 1 activation waveform with much smaller amplitude – thus not playing an important role in composing EMG activity.

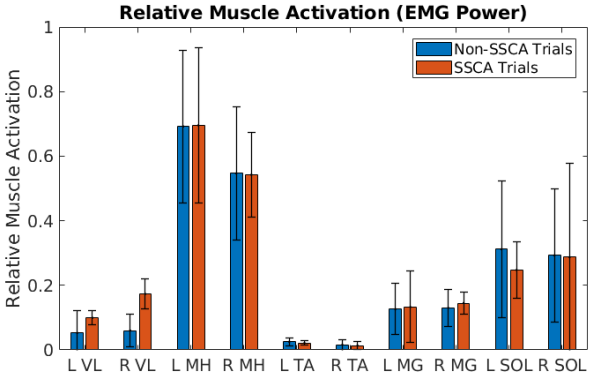


Fig. 8: Relative EMG power of different muscles during patient standing under SCS for SSCA vs. non-SSCA trials. Data from patients A and B were combined.

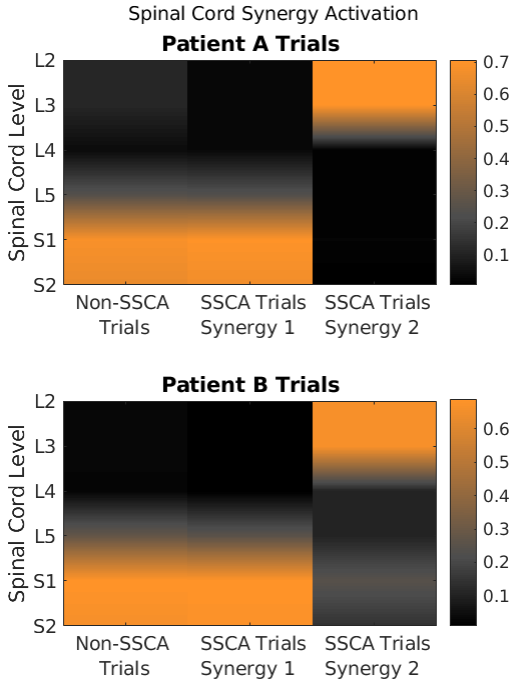
This is also reflected by the smaller increase in VAF seen in the non-SSCA trials from adding a second synergy.

If we compare the relative EMG power from each muscle for the SSCA vs. non-SSCA trials, as shown in Fig. 8, we see that the only significant difference between the two is in the activation of the VL muscle. This provides further verification that the difference in muscle activity in the SSCA trials is due to the excitation of a second muscle synergy that is responsible for significant VL muscle activation.

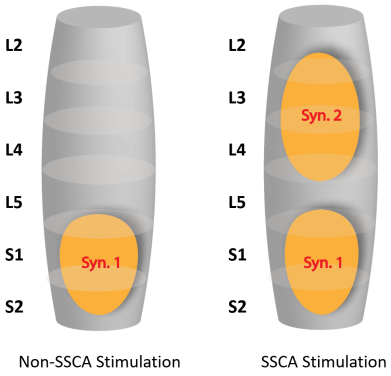
It is important to note that the therapist-rated standing scores *were highest for the SSCA trials* (the score was ≥ 8.75 for all SSCA trials). Therefore, proper spinal stimulation can activate a 2^{nd} muscle synergy (corresponding to a separate neural circuit), which *is critical to independent standing* in stimulated SCI patients and results in more complex muscle activity.

1) Spinal Activation Mapping: Next, we mapped the EMG activity for each muscle synergy to regions of the spinal cord for both patients. We obtained a mapping of muscles to spinal cord segments based on charts collected in Kandel [27], and calculated the resulting activation of each spinal segment from each muscle synergy. As we did above, we exclude the MH muscle in the visualization due to the ambiguity in attributing it to synergy 1 or 2. Fig. 9a shows the approximate mapping of the muscle synergies to the spinal cord for the non-SSCA trials and SSCA trials for both patients. We see that the first synergy for the SSCA trials and only synergy for the non-SSCA trials maps to the lower lumbo-sacral spinal cord region ($\approx$ L5-S2), whereas the second synergy for the SSCA trials maps to the upper lumbo-sacral spinal cord ($\approx$ L2-L4).

Thus we can interpret the effect of the interleaving spinal stimulation (for the SSCA trials), as activating a separate, previously untapped neural circuit which modulates motor pools in the upper lumbo-sacral spinal cord. Note that the muscle activity generated by these muscle synergies depend *both* on the spinal stimulation and the patient's peripheral sensory input. The muscle synergies are visualized in Fig. 9b, where we see the 2^{nd} synergy activates motor pools in a higher region of the spinal cord, which is critical to natural standing. This knowledge can enhance SCI therapies by localizing important muscle synergies like the ones in Fig. 9, and helping to activate and train them to improve functional performance and rehabilitation.



(a)



(b)

Fig. 9: (a) Visualization of activation of spinal cord regions resulting from each muscle synergy's activation. The left region represents spinal activation of the muscle synergy from non-SSCA trials. The middle region represents spinal activation of the first muscle synergy from the SSCA trials, whereas the right region represents spinal activation of the second muscle synergy from the SSCA trials. The top plot shows results for patient A, and bottom plot shows results for patient B.
(b) Visualization of approximate spinal cord regions activated by each muscle synergy for SSCA trials (on the right) and non-SSCA trials (on the left).

C. Analysis of Uninjured Human EMG Activity

1) Muscle Synergy Extraction: We now look at EMG activity from five healthy subjects during standing, and utilize NMF and rShiftNMF to look for muscle synergy structure. From Fig. 10 we see that a single cross-validated muscle synergy can reconstruct more than 50% of EMG activity. However, we note that rShiftNMF performs slightly worse than standard NMF under cross-validation, especially as we add more synergies. Therefore, it seems that rShiftNMF overfits to the delay parameters, and the incorporation of delays in the muscle synergies is not necessary or desirable when extracting muscle synergies from healthy subjects. We hypothesize that the absence of signal delays in healthy subjects' muscle synergies is due to the CNS's ability to account for muscle activation delays, as discussed in section II-B. We conclude that NMF provides a better, simpler-to-implement algorithm for extracting muscle synergies in healthy patients.

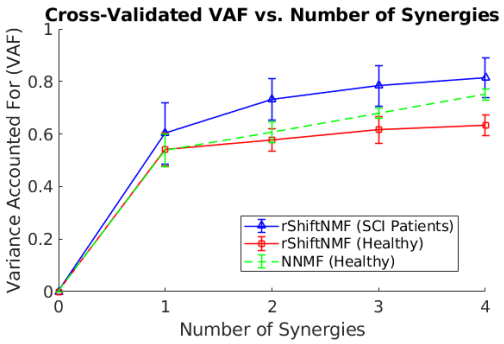


Fig. 10: The variance accounted for (VAF) plotted against the number of synergies extracted for healthy subjects and SCI patients. The mean VAF across all trials for a given synergy number was used for each data point. Synergies were cross-validated with fixed delay, τ, and activation pattern, W. Note that in order to directly compare SCI and healthy subjects, we ran the rShiftNMF algorithm on only the subset of 8 muscles measured from all subjects.

2) Comparison of Healthy EMG and SCI EMG activity: Based on our prior methodology, we calculate that a single muscle synergy is activated during quiet standing in all healthy subjects. *However*, we also note that the VAF captured by a single muscle synergy in healthy subjects is smaller than the VAF captured by a single muscle synergy in the SCI patient (see Fig. 10), even though we apply a more aggressive filter to the healthy subjects' EMG data. When we calculate the number of synergies, the VAF does not increase significantly after 1 synergy and the muscle activation patterns are not consistent if we add more than 1 synergy. This indicates that while healthy subjects exhibit the same or fewer number of muscle synergies during standing, there is a separate control mechanism that is not active in SCI patients, which contributes to the complexity in healthy EMG activity during standing.

This phenomenon suggests that healthy subjects' muscle activity is "richer" and more complex, and may arise due to supraspinal input enabling healthy subjects to generate nonlinear combinations of motor units that cannot be generated by muscle synergies (which represent muscle activity as *linear* combinations of motor units). Another hypothesis is that supraspinal input allows the healthy subjects to precisely control a wider variety of interneuronal networks that participate in the control of posture, or that important sensory feedback

circuits for standing rely on descending pathways not available to SCI patients.

Nevertheless, SCI patients' muscle activity has less complexity and can be more easily captured in low dimension, which can be seen from the EMG activity shown in Fig. 11. Qualitatively, the healthy subjects' EMG activity is more varied and exhibits a spectrum of frequencies in the signal waveform, whereas the SCI patients' EMG activity is very regular, periodic, and synchronized to the SCS stimulating frequency. Thus activation of the second muscle synergy for SCI patients may serve as a compensatory mechanism to increase motor complexity necessary for improving functional performance.

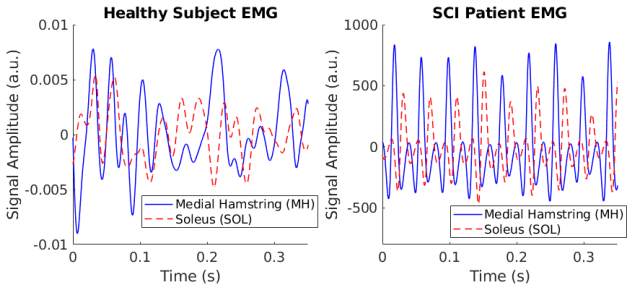


Fig. 11: (Left) Representative EMG activity for SOL and MH muscles for healthy subject; (Right) Representative EMG activity for SOL and MH muscles for SCI patient under SCS.

3) Biomechanics of Healthy Standing versus SCI Standing: Note that the muscle synergy activation pattern, W, is similar for both SCI patients (in both SSCA and non-SSCA trials), even though the activation pattern, W, for the healthy subjects is highly variable, as shown in Fig. 12. More interestingly though, the muscle synergy activation pattern for the SSCA trials for both patients is consistent with principles for maximally efficient (minimum required torque) stable standing. The authors in [28] found that maximally efficient stable standing should utilize 2 muscles for knee flexion/extension, 2 muscles for ankle dorsiflexion/plantarflexion, 1 muscle for hip abduction/adduction, and 1 muscle for hip flexion/extension. This is consistent with the SSCA trials, where VL/MH serve as two muscles for knee flexion/extension and MG/SOL serve as two muscles for ankle dorsiflexion/plantarflexion, and TA is not active (no EMG measurements for hip muscles). Furthermore, [29] found that TA muscle activity in healthy elderly individuals surprisingly *decreases* postural steadiness in standing, which is consistent with the SCI patients under SCS exhibiting no TA activation. On the other hand, the muscle synergy activation patterns for healthy subjects, seen in Fig. 12, are highly varied and are not consistent with the principles for maximally efficient stable standing.

These results, combined with our findings, allow us to hypothesize that stimulated SCI patients attempt to achieve maximally efficient stable standing, whereas healthy subjects utilize a different strategy for standing. In the SSCA trials, SCI standing activates muscle patterns that are maximally efficient for stable standing, and activation of the second muscle synergy is crucial to activate the two necessary muscles for knee flexion/extension. However, in the non-SSCA trials,

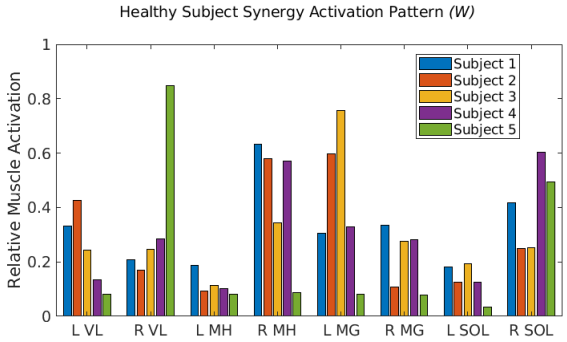


Fig. 12: Muscle synergy activation pattern, W, for healthy subjects (single synergy).

stable standing is not as well achieved because the absence of the second synergy leads to only one of the two necessary muscles for knee flexion/extension being active.

Due to the limited number of muscles we measured from (e.g. no hip muscles) and limited sample size, we cannot make a strong general statement about the biomechanics arising from muscle synergy activation. However, the consistency of our results (for both patients examined) with prior literature on efficient stable standing suggests our hypothesis is worth further exploration.

IV. Discussion

A. Commentary on additional synergy

We have seen that spinal stimulation with specific characteristics during SCI patient standing can lead to activation of an additional neural circuit (i.e. a second muscle synergy), which significantly improves patient standing ability. The effect of the two muscle synergies then linearly combine to generate the patient's muscle activity. This is reminiscent of the frog experiments described in Section I, where stimulation at different sites of the frog's spinal cord led to activation of muscle synergies, and co-activation of those sites often led to a linear combination of those muscle synergies in the resulting muscle activity. While other studies have relied on post-processing EMG activity to look for muscle synergies in human EMG data, the fact that we are able to mirror the synergy phenomenon in [1], [3]–[5] with humans (selectively activate and linearly combine multiple muscle synergies through spinal stimulation) provides substantial direct evidence of the existence of muscle synergies in the human spinal cord and their survival after SCI.

Furthermore, studies have hypothesized that neurological injury/disease leads to a decrease in the number of muscle synergies activated when composing overall muscle activity [2], [12], [14], [15]. These prior efforts suggested that muscle synergies may have been "destroyed" or "merged" after injury. *However*, the fact that proper stimulation was able to activate an additional muscle synergy suggests that muscle synergies are still encoded in the spinal cord and remain intact after neurological injury. Moreover, these muscle synergies were consistent across both observed patients. Hence, we hypothesize that spinal injury impairs the ability of the CNS to

properly activate muscle synergies, even though those neural circuits remain intact in the spinal cord and can be activated by SCS. This is consistent with the conclusions in [2] that after stroke, the brain loses its ability to accurately and distinctly activate separate muscle synergies, making synergies seem "merged".

The ability to accurately and distinctly activate important muscle synergies is critical to proper functional performance, as was seen in this study. It seems that healthy subjects only partially rely on muscle synergies to compose their muscle activity, with supraspinal input contributing significantly to the complexity of their EMG, whereas SCI patients rely more heavily on muscle synergies which compose the majority of their motor activity. The activation of additional muscle synergies may then serve as a compensatory mechanism for SCI patients to add motor complexity and more effectively achieve stable postural control.

1) Note on Interleaving Stimulation: We saw that interleaving spinal stimulation patterns (i.e. time-varying stimuli) activated a second muscle synergy, whereas a single fixed pattern of spinal stimulation did not achieve this (even in the best case). Originally, the hypothesis for using interleaving stimulation was that each interleaved stimulation pattern would compensate for a different part of the patient's performance (i.e. one stimulation pattern would be optimal for right leg stability, another would be optimal for trunk stabilization, etc...). However, we saw that interleaving stimulation actually allowed us to activate an additional muscle synergy, leading to the significant improvements in functional performance. Interleaving stimulation thus can enable activation of multiple synergies, but *how* it does this is an open question. Learning the mechanism by which this occurs will be important in enabling us to selectively search for and activate other synergies. It is clear though that optimal SCS will require time-varying stimuli to enable optimal functional performance.

B. Commentary on extraction of muscle synergies.

It is clear from the delays present that NMF cannot effectively be used to identify muscle synergies in SCI patients under spinal stimulation. Thus rShiftNMF should be used in these cases, where we can identify, and compensate for, the delays in muscle activation due to spinal stimulation. Regularization can be used to ensure that we obtain physiological delays, consistent with our knowledge of the CNS. In cases not involving spinal stimulation (i.e. in healthy subjects), NMF remains an effective matrix factorization algorithm for extracting muscle synergies from EMG data.

V. Conclusion

This is the first human study analyzing muscle synergies in SCI patients under SCS, and comparing them with healthy subjects, and our results shed light on muscle synergies as a key physiological mechanism by which SCS generates motor function. We described a new algorithm to extract muscle synergies from SCI patients under multi-electrode spinal stimulation, and we provided evidence that different muscle synergies are not only encoded in the human spinal cord, but can be selectively activated through SCS. Patient motor function is heavily influenced through activation of these muscle synergies, and SCI standing ability can be greatly improved through activation of an additional muscle synergy. Furthermore, we have compared the role of muscle synergies in SCI patients to their role in healthy subjects, and shown that SCI patients rely more heavily on muscle synergies for generating motor activity.

We believe these results will have significant implications for rehabilitation as we better learn how to activate and train critical muscle synergies through spinal stimulation and motor training. A recent animal study suggested that targeted neuromodulation of muscle synergies in SCI rats could provide significant improvements in motor control [30]. Our work provides a next step towards extending this idea to humans, and could open up new possibilities for SCI therapies.

Acknowledgment

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