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Functional electrical stimulation therapy for upper extremity rehabilitation following spinal cord injury: a pilot study

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STUDY DESIGN: Pilot study.
OBJECTIVES: To examine if functional electrical stimulation therapy (FEST) improves neuromuscular factors underlying upper limb function in individuals with SCI.
SETTING: A tertiary spinal cord rehabilitation center specialized in spinal cord injury care in Canada.
METHODS: We examined 29 muscles from 4 individuals living with chronic, cervical, and incomplete SCI. The analysis was focused on the changes in muscle activation, as well as on how the treatment could change the ability to control a given muscle or on how multiple muscles would be coordinated during volitional efforts.
RESULTS: There was evidence of gains in muscle strength, activation, and median frequency after the FEST. Gains in muscle activation indicated the activation of a greater number of motor units and gains in muscle median frequency the involvement of higher threshold, faster motor units. In some individuals, these changes were smaller but accompanied by increased control over muscle contraction, evident in a greater ability to sustain a volitional contraction, reduce the co-contraction of antagonist muscles, and provide cortical drive.
CONCLUSIONS: FEST increases muscle strength and activation. Enhanced control of muscle contraction, reduced co-contraction of antagonist muscles, and a greater presence of cortical drive were some of the findings supporting the effects of FEST at the sensory-motor integration level.

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INTRODUCTION

Any damage causing transient or permanent functional change to the spinal cord can cause a spinal cord injury (SCI). A cervical SCI impairs upper limb function and reduces independence and quality of life. Therefore, upper limb function is the top priority of recovery for individuals with tetraplegia [1]. SCI interrupts the signal transmission between the central and peripheral nervous systems at the level of the spinal cord, but the functional state of the spinal networks can be changed through neuromodulation [2]. Functional electrical stimulation is a method of neuromodulation that focuses on producing functionally useful contractions through peripheral stimulation [3]. Since the 1960 s, functional electrical stimulation has been used to improve the function of the upper extremities for individuals with neurological disorders including cervical SCI in the context of both neuroprostheses and electrotherapy [4]. Functional electrical stimulation therapy (FEST) refers to the application of electrical stimulation as a therapeutic modality rather than a neuroprosthetic assistive device [5].

The majority of clinical trials on FEST to retrain hand reaching and grasping after SCI uses FEST sessions of 45–60 min delivered 3–5 days a week, for 8–16 weeks, for a total of ~40 sessions [6]. During these sessions, the patient attempts voluntary movements, such as forward-reaching, lateral pinch, and palmer grasping for performing activities of daily living such as object manipulation and self-feeding. Pulsed electrical stimulation is applied through electrodes placed close to the motor points of the target muscle groups in order to produce functional patterns of muscle contraction [6, 7]. A therapist activates the stimulation when the patient is not able to complete the movement on their own. The positive immediate effect of FEST has been shown to improve hand function of individuals with cervical SCI [8]. When applied over a period of several weeks, FEST has demonstrated promising improvements in clinical assessments of upper extremity function compared with conventional therapies for individuals with subacute or chronic cervical SCI, even in cases with motor complete SCI (American Spinal Injury Association [ASIA] Impairment Scale [AIS] A or B) [7, 9–12]. The efficacy of FEST in improving voluntary reaching and grasping after stroke has also been demonstrated in series of pilot studies and clinical trials, further confirming its potential for upper limb neurorehabilitation [13–17]. Despite these positive results, the mechanisms underlying FEST at the neuromuscular level remain incompletely understood [18].

The assessment of independence and function after SCI is commonly performed using well-established assessments of

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function and strength [8, 11], including the Spinal Cord Independence Measure version III [19], the Functional Independence Measure [20], the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) [21], the Toronto Rehabilitation Institute—Hand Function Test [22], and the Capabilities of Upper Extremity Test [23]. It is known that weakness of upper limb muscles is related to performance in functional tasks [24, 25], and the strength of a combination of defined, specific upper limb muscles is able to predict upper limb function [26]. In this line of thought, understanding the chronic changes in muscle strength with FEST may provide insights into the mechanisms of action of FEST at the muscle level, which are likely accounting for the functional gains seen after FEST. When it comes to evaluating muscle strength, Manual Muscle Testing (MMT) is the standard test used in both the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and GRASSP [27–30]. Nonetheless, neurophysiological assessments would afford a more detailed description of the effects of FEST on muscle activation and motor control [31]. Surface electromyography (sEMG) is a widely used technique to measure muscle activation noninvasively, providing complimentary information to the aforementioned clinical assessments of muscle strength. In individuals with SCI, even without visible contractions of impaired muscles during voluntary movement attempts, sEMG signals can in some cases be detected [32, 33]. Under the International Classification of Functioning, Disability, and Health framework (ICF) [34], sEMG can provide valuable information measured at the level of body functions and structure, which is complimentary to clinical assessments of upper extremity function that are predominantly associated with the activity domain of the ICF. Thereby, sEMG may be useful for evaluating therapeutic outcomes of FEST for individuals with SCI, beyond the functional gains, and provide insights on the mechanisms of action of FEST at the neuromuscular level - which are currently lacking in the literature [18].

In this pilot study, we seek to describe the outcomes of FEST using sEMG amplitude ($sEMG_{amp}$) and frequency ($sEMG_{freq}$) during voluntary movement attempts. We also quantify the efficacy of FEST on segmental strength recovery for individuals with an SCI using a standard clinical assessment of muscle strength, the well-established MMT. While prior research studies have focused on the intrinsic muscle changes after FEST [18], here we also explore different elements of the neuromuscular system, namely the control of muscle contraction and the coordination between multiple muscle groups. We expect that the well-established gain in upper limb function with FEST [6, 7, 10, 35] will be supported by changes in strength, activation, control, and coordination, at the single- or multi-muscle level.

METHODS

Participants and assessments

Individuals with SCI who participated in this study were receiving FEST for upper extremity rehabilitation either through a clinical program at our institution (SCI cases 1 and 4) or through an ongoing clinical trial (SCI cases 2 and 3) [36] (Institutional REB approval number: 17-6029, Research Ethics Board of the University Health Network, Toronto, Canada). Written consent was obtained from all individuals with SCI to undergo EMG assessments and MMT tracking (REB approval number: 19-5395.6), and from non-disabled individuals (ND) for sEMG assessments (REB approval number: 19-6175). Nine participants were enrolled in this study: 5 ND participants (reference group) and four individuals with SCI. There were two assessments for individuals with SCI, the first assessment was conducted before the FEST initiation, and the second assessment was after the last FEST session. All the assessments were conducted on days of the week when there were no FEST sessions scheduled or immediately before FEST administration. Only one assessment was performed for the ND group to obtain reference values. All the assessments were performed by the same investigator.

FEST delivery

FEST was delivered using the MyndMove® stimulation device (MyndTec, ON, Canada). The device offers a variety of stimulation protocols for the upper extremity, including protocols specifically designed for individuals with SCI [6, 7]. The pre-programmed stimulation sequences facilitate functional movements of the arm and/or hand(s), employing a wide variety of reaching and grasping movements. The therapy was tailored to each participant based on the therapists' assessment of the individual's needs and therapy goals. Supplementary Table 1 provides a detailed breakdown of the FEST protocols used with each participant.

Outcome assessment: MMT

We used the MMT, which is the muscle strength test used in both the ISNCSCI and GRASSP [21, 27, 28, 37] If a muscle did not have a defined MMT protocol in the ISNCSCI nor the GRASSP, the physiotherapist would develop custom protocols to assess muscle strength in these muscles. The MMT was scored using a standard 0–5 grading system [38] by a trained physical or occupational therapist before each FEST session. All the ND participants were considered as grade 5, and the MMT consisted of providing full resistance in a functional muscle position.

Outcome assessment: sEMG

To acquire sEMG signal from upper limb muscles, we used the eight-channel Bagnoli® system (Delsys, MA, USA) with a 4 kHz sampling frequency and ×1000 amplification (hardware filter at 20–450 Hz). The electrodes were positioned over the muscle belly using double-sided adhesive tape after trimming the hair and cleansing with alcohol. The positioning and orientation of the electrodes were based on the SENIAM guidelines [39] (i.e., *biceps brachii, triceps brachii, anterior deltoid, abductor pollicis brevis, opponens pollicis, flexor pollicis brevis*) or elsewhere in the literature if not included in the SENIAM guidelines (i.e., extensor carpi radialis, flexor carpi radialis, extensor digitorum communis, flexor digitorum superficialis, flexor pollicis longus, extensor carpi ulnaris, 1st dorsal intersossei) [40]. sEMG signals were acquired from upper extremity muscles during isometric voluntary attempts using the standard MMT assessment protocol for each muscle, both in SCI and ND participants. Three maximum voluntary contraction trials were obtained, followed by three trials at 50% MVC. The detailed protocol for sEMG acquisition is provided in the Supplementary Material.

Analysis of data on MMT

To understand the change in muscle strength after treatment, MMT change (ΔMMT) was calculated by subtracting baseline strength (the average of the first two MMT scores) from endpoint strength (the average of the last two MMT scores). Considering that most clinical studies show long-term effects of electrical stimulation (13 days to 6 weeks) on muscle strength [41], this averaging procedure was conducted to account for variability in the initial and final assessments.

Analysis of data on sEMG

All of the sEMG metrics described below were extracted from each trial and averaged over the 3 100% MVC trials and over the 3 50% MVC trials. Off-line sEMG signal processing involved the visual inspection of each contraction to ensure the absence of artifacts in the signal. sEMG was filtered using a 2nd order Butterworth filter, band-pass between 10 and 450 Hz, and a band-stop filter between 59–61 Hz (to remove the power line interference). The protocol for quality checking and extraction of analysis windows is provided in the Supplementary material. The amplitude of the sEMG ($sEMG_{amp}$) was quantified using the root mean square of the filtered sEMG signal for the entire analysis window during maximal voluntary contractions. To quantify the variability of the sEMG during the 50% maximal contractions, the root mean square of 0.1-second bins were calculated throughout the contraction, and the coefficient of variation of the root mean square bins was calculated [COV = (SD/Mean) × 100%]. Co-contraction was calculated for pairs of muscles using Eq. 1 [42].

$$Muscle\ co-activation = \frac{2 \times sEMG_{Antagonist}}{sEMG_{Agonist} + sEMG_{Antagonist}} \times 100\% \quad (1)$$

The frequency-domain representation of the sEMG signal was assessed by the median frequency of the sEMG spectrum between 0 and 250 Hz ($sEMG_{freq}$), also for the entire analysis window during maximal voluntary contractions. The median frequency was calculated using a procedure

Table 1. Demographics.

Subjects	Age	Sex	Level of injury	Time post-SCI	AIS	Treatment	Frequency
SCI 1	43	M	C5	8 months	B	20 sessions of Physiotherapy + FEST (60 mins) + 14 sessions of Physiotherapy only (60 mins),	1–2× Week
SCI 2	63	M	C4	3 years, 6 months	B	40 sessions of FEST + 30 min of home exercise daily	2× Week
SCI 3	64	M	C6	2 years, 8 months	D	40 FEST + 60 min Recreational Therapy 3x per week	3× Week
SCI 4	56	M	C3	10 months, 20 days	D	11 sessions of Physiotherapy + FEST(60 mins) + 5 sessions of Physiotherapy only (60 mins)	1–2× Week
ND 1	36	F	____	____	____	____	____
ND 2	26	F	____	____	____	____	____
ND 3	35	M	____	____	____	____	____
ND 4	40	M	____	____	____	____	____
ND 5	24	M	____	____	____	____	____

SCI spinal cord injury, *FEST* functional electrical stimulation therapy, *PT* physiotherapy.

previously described [43]. Briefly, for the calculation of the median frequency, the spectral profile of each window was divided into 100 bins (2.5 Hz resolution), and the numerical integral was calculated. The integrated sEMG was then split into two halves of equal areas, this value (split point) constituting the median frequency in Hz. To understand the change in muscle activation after treatment, the $sEMG_{freq}$ at the baseline was subtracted from the $sEMG_{freq}$ at endpoint ($\Delta sEMG_{freq}$). To visualize the frequency component of the sEMG throughout the volitional contraction, we computed the short-time Fourier transform-based spectrogram of sEMG signal (parameters are provided in the Supplementary material).

To detect functional coupling in the frequency-domain, intermuscular coherence was calculated. sEMG recordings of submaximal contractions were rectified, low-pass filtered, and down-sampled to 100 Hz sampling rate. The recordings were divided into 1-second nonoverlapping windows. Denoting the Fourier transform of the ith window of the sEMG from two different muscles as $X_i(f)$ and $Y_i(f)$, respectively, the coherence is given by (Eq. 2) [44]:

$$Coh(f) = \frac{\left|\sum_{i-1}^{L} X_i^*(f) Y_i(f)\right|^2}{\sum_{i-1}^{L} X_i(f) X_i^*(f) \sum_{i-1}^{L} Y_i(f) Y_i^*(f)} \tag{2}$$

where L is the number of data windows available and * denotes the complex conjugate.

The analysis of variability (COV), co-contraction, and intermuscular coherence was conducted using the 50% maximal contraction trials. Where coherence was evaluated in the beta band (13–30 Hz), data from 20–30 Hz only was used due to hardware filtering below this range.

FEST intensity and duration

Each FEST protocol described in Supplementary Table 1 involved a different set of muscles. The muscles stimulated during each protocol were obtained from the manufacturer's manual. Detailed information about the current delivered to each muscle and the time of treatment in each protocol was extracted from the reports generated after each FEST session. For each muscle in each session, the current delivered was multiplied by the number of cycles the protocol was administered. This yielded the FEST dose delivered to each muscle per session in mA, which was summed across all FEST sessions for each muscle [$FEST_{dose(mA)}$]. Similarly, the time (in minutes) of FEST to each muscle was calculated [$FEST_{dose(min)}$].

Statistical analysis

LabVIEW and GraphPad Prism were used to conduct the statistical analysis. Descriptive statistics were expressed using mean ± SD followed by a qualitative analysis of graphs and results in comparison to the reference group (ND group). For the correlational analysis, the unit of measure was the individual muscle ($N = 29$). Data normality was assessed using the Shapiro–Wilk test, which indicated 7/12 variables used in the correlational analysis failed the normality test. Spearman correlation was used to test the relation between the clinical assessments, electrophysiological assessments, and the FEST dose. Significance was set at $\alpha = 0.05$.

RESULTS

Baseline data and treatment modalities applied for rehabilitation after SCI are summarized in Table 1.

Case 1

The first case is a 43-year-old male with a C5 motor complete (AIS B), chronic (8 months from injury onset), traumatic SCI. Prior to treatment, several upper limb muscles were assessed using MMT and considered weak (*triceps brachii* = 2; *extensor carpi radialis* = 1.5; *extensor digitorum communis* = 2.5; *flexor digitorum superficialis* = 2.5; *flexor pollicis longus* = 1; *flexor pollicis brevis* = 0; *extensor carpi ulnaris* = 1). These muscles were the focus of the FEST. The participant was enrolled in usual physiotherapy sessions (14 sessions) and FEST sessions (20 sessions). The treatment was focused on the muscles presenting with weakness, and also muscles involved in integrated functional movements.

After the FEST, an increase in muscle activation ($sEMG_{amp}$ and $sEMG_{freq}$) and strength (ΔMMT) was evident (Fig. S1). Pre-FEST, the participant had limited voluntary activation and difficulty in deactivating motor units (MUs) upon command to relax (Fig. 1A, C). Post-FEST, voluntary activation, and deactivation was improved, with an MDF shift towards higher frequencies, suggesting the involvement of faster MUs (Fig. 1B, D).

Case 2

The second case is a 63-year-old male with a C4 motor complete (AIS B), chronic (3 years and 6 months from injury onset), traumatic SCI. Persistent and chronic muscle weakness were evident at the baseline MMT assessment, especially for hand muscles (*anterior deltoid* = 2.5; *triceps brachii* = 1; *extensor carpi radialis* = 2.25; *flexor carpi radialis* = 1; *extensor digitorum communis* = 0.5; *opponens pollicis* = 1; *flexor digitorum superficialis* = 0.5; *first dorsal interosseous* = 0). These muscles were the focus of the FEST. The participant was prescribed daily home exercise (30 min) and 40 FEST sessions at the clinic. The FEST sessions consisted of active-assisted functional movements of the shoulder, elbow, and wrist coupled with the stimulation. Movements like reaching forward, grasping an object, reaching to the mouth were performed by the participant with the help of the therapist.

Prior to FEST, many muscles displayed absent sEMG with amplitude similar to noise levels—especially the hand muscles [noise levels (mV): *opponens pollicis* = 0.0079; *flexor digitorum*

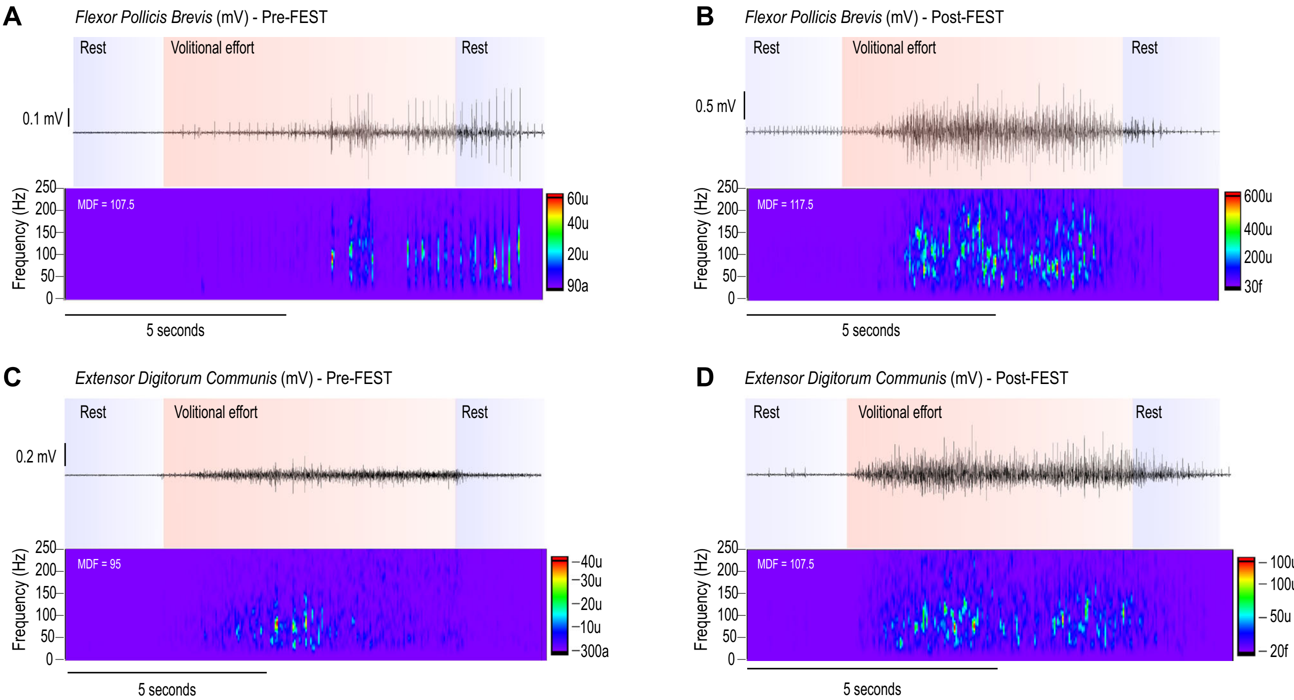

Fig. 1 Case 1: FEST promoted abundant increases in muscle activation and muscle strength. A, B An example of a muscle with pronounced gain in activation and strength, the *flexors pollicis brevis*. **A** Before the FEST, this muscle is weak (motor score = 0) with only sparse firing upon motor command (volitional effort; red), also note the deficit in deactivating these MUs (blue). **B** After the FEST, the muscle regained strength (motor score = 2) and displays stronger activation; the $sEMG_{freq}$ increase from 107.5 to 117.5 suggests an ability to volitionally activate faster, higher threshold MUs. **C, D** Similar effects of FEST were evident for other muscles. ND non-disabled, FEST functional electrical stimulation therapy, MDF median frequency, MMT manual muscle testing, MU motor unit.

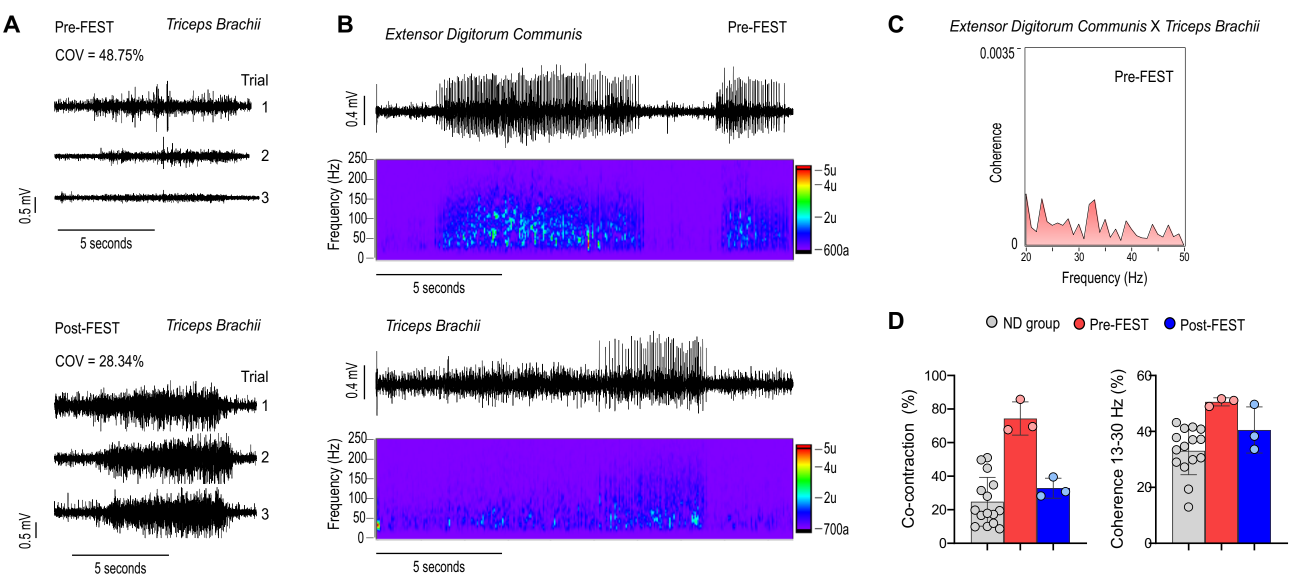

Fig. 2 Case 2: FEST promoted increases in muscle activation in proximal arm and forearm muscles and greater coordination of the activation between muscle groups. A Activation of the *triceps brachii* muscle during the 3 maximum voluntary contraction attempts pre- (upper panel) and post-FEST (lower panel). **B** While attempting a volitional contraction of the *extensor digitorum communis* muscle, the subject shifted the activation to functionally unrelated muscles of the arm (*triceps brachii*) in an effort to extend the digits. **C** This effort demands cortical drive evident in the 13–30 Hz coherence between the pair of muscles involved, reflecting the difficulty in locating and isolating the activation of the *extensor digitorum communis*. **D** After the FEST, the abnormal co-contraction between this pair of muscles is reduced and the cortical drive, reflected in the β-band coherence, is similar to control levels. **D** Data is all trials for ND participants (three trials per participant, gray) and the case participant pre-FEST (3 trials; red) and post-FEST (blue). ND non-disabled, COV coefficient of variation, FEST functional electrical stimulation therapy, MMT manual muscle testing, MU motor unit.

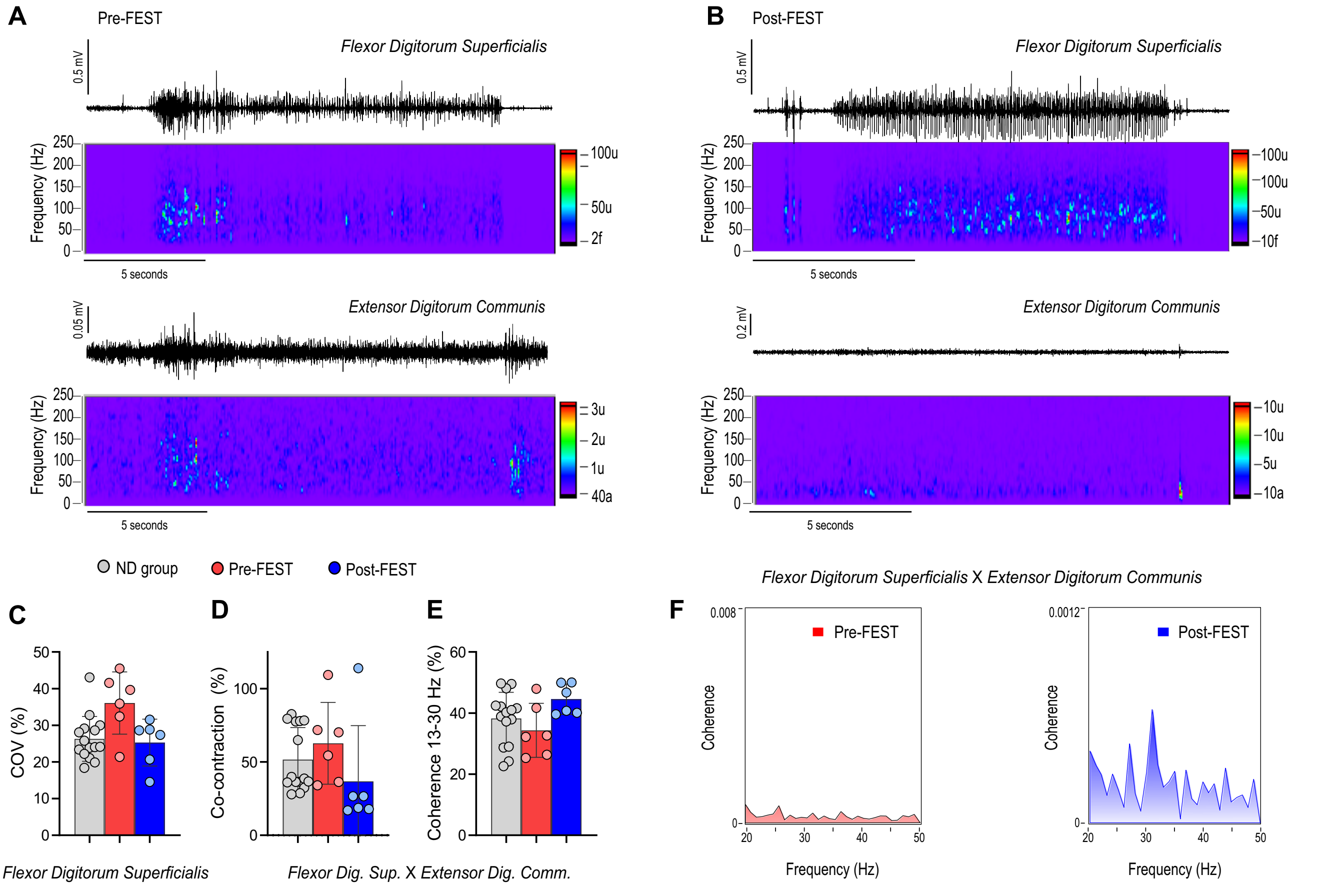

Fig. 3 Case 3: FEST promoted greater bilateral activation of extrinsic hand muscles in the forearm and greater coordination between agonist-antagonist muscles. **A**, **B** A steadier activation is evident post-FEST, with the *flexor digitorum superficialis* muscle varying less during the volitional effort. **C** Reduced MU activation variability for the *flexor digitorum superficialis* muscles post-FEST. **D** Reduced co-contraction between the *flexor digitorum superficialis* and *extensor digitorum communis* muscles. **E**, **F** The contribution of cortically generated rhythms (13–30 Hz) is increased post-FEST. **C**–**E** Data is all trials for ND participants (three trials per participant; gray) and the case participant pre-FEST (3 trials for each side of the body; red) and post-FEST (blue). ND non-disabled, COV coefficient of variation, FEST functional electrical stimulation therapy, MMT manual muscle testing, MU motor unit.

superficialis = 0.0042; *first dorsal interosseous* = 0.0028] (Fig. S2). FEST was able to increase muscle activation of *triceps brachii*—an increase not detectable by the MMT assessment (Fig. 2A), and *extensor digitorum communis*. The effect of FEST in multi-muscle activation is also notable. For example, before the FEST, the participant was not able to hold the muscle activation of some muscles, shifting between muscles of close innervation (e.g., C7, C8). In Fig. 2B this shift is depicted, where the activation of the *extensor digitorum communis* was not sustained and shifted to the *triceps brachii*. In this effort to activate the intended muscle, the intermuscular coherence between this pair of muscles was high in the 13–30 Hz frequency, indicating great cortical drive in executing the motor task (Fig. 2C). From before to after FEST, the co-contraction between these muscles was reduced and the coherence shifted to control levels, indicating greater ability to selectively activate and control the contraction of the *extensor digitorum communis* muscle (Fig. 2D).

Case 3

The third case is a 64-year-old male with C6 incomplete (AIS D), chronic (2 years and 8 months from the injury onset), traumatic SCI. Despite the close-to-normal strength and function of proximal upper extremity muscles, this participant displayed persistent hand muscle weakness on both sides based on MMT assessments [*flexor digitorum superficialis* = 0 (right), 0 (left); *abductor pollicis brevis* = 0 (right), 1 (left); *opponens pollicis* = 1 (right), 0 (left)]. The participant was enrolled in 60 minutes of recreational therapy (3x per week) and completed 40 FEST sessions at the clinic. Generally, the session started with unilateral simple functional tasks like pinching and grasping different objects with assistance when needed and progressed to bilateral more complex tasks like 3D puzzles and opening containers.

Prior to FEST, the $sEMG_{amp}$ of the intrinsic hand muscles was close to noise levels (*abductor pollicis brevis* and *opponens pollicis* ≈ 0.0028) with an absent change post-FEST (noise levels ≈ 0.0051). On the other hand, extrinsic hand muscles such as the *flexor digitorum superficialis* displayed residual muscle activity pre-FEST, and this activity increased post-FEST with respective gains in strength (ΔMMT) (Fig. S3). The muscle activation for the *flexor digitorum superficialis* muscle was less steady pre-FEST with respective co-activation of the antagonist, *extensor digitorum communis* (Fig. 3A). After FEST, the muscle activation of the *flexor digitorum superficialis* muscles was steadier and the reduced co-contraction with the agonist involves high-frequency coherence—which is indicative of greater volitional drive (Fig. 3B). These results are summarized in Fig. 3C–F, where the bilateral reduction in the COV of the sEMG amplitude for the *flexor digitorum superficialis* muscles is evident (Fig. 3C), indicating greater control. Also, the co-contraction with the antagonist, *extensor digitorum communis*, was reduced alongside the greater contribution of intermuscular coherence in the β-frequency range (indicative of greater cortical drive) (Fig. 3D–F).

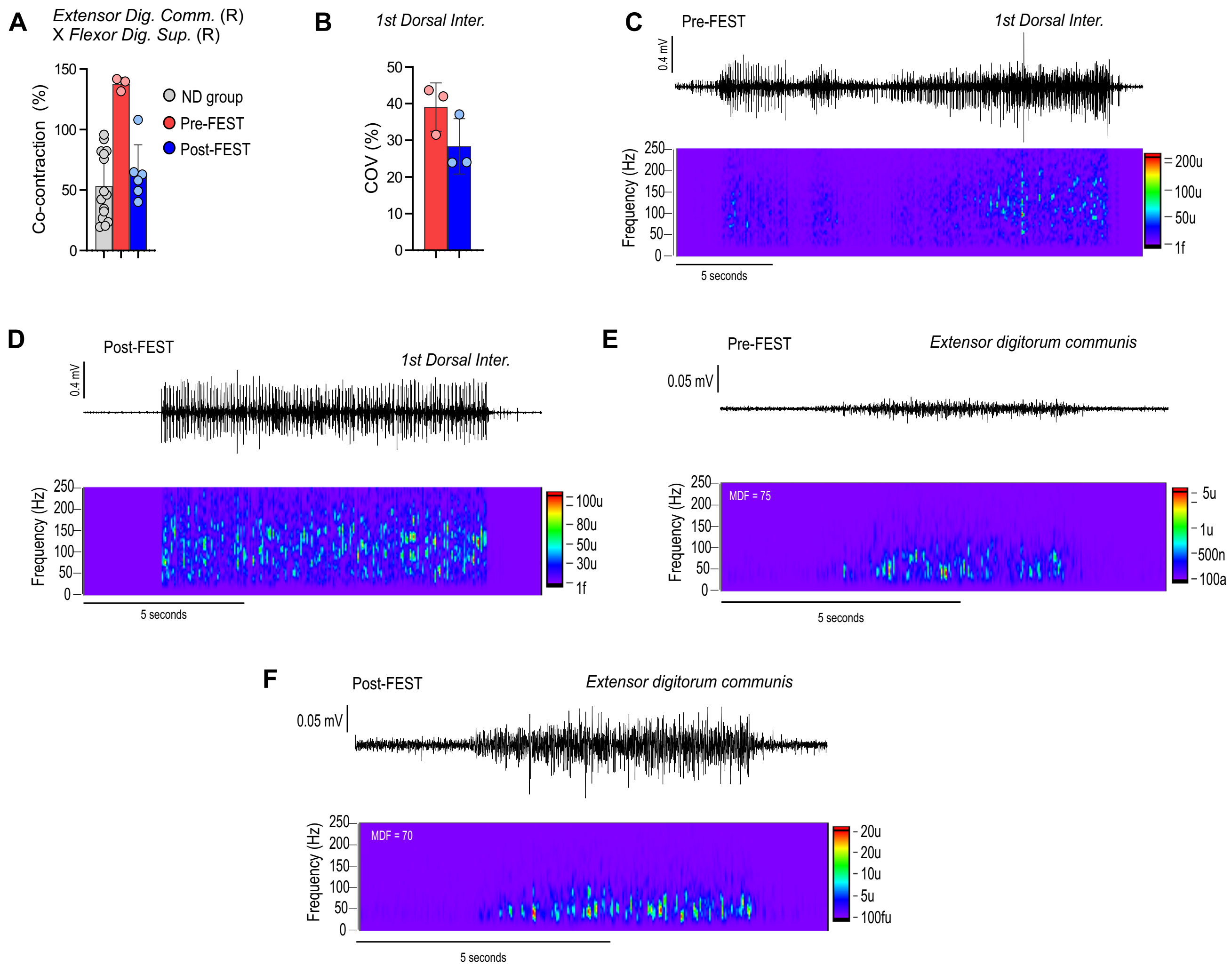

Fig. 4 Case 4: FEST promoted abundant increases in strength without pronounced changes in muscle activation. **A** Despite the limited change in $sEMG_{amp}$, the reduction of co-activation of antagonist muscles is evident, such as the *extensor digitorum communis* and the *flexor digitorum superficialis* post-FEST. **B–D** Hand muscles regained activation, strength, and control. **E**, **F** Greater $sEMG_{amp}$ was evident for the *extensor digitorum communis* muscle post-FEST. **A** Data is all trials for ND participants (3 trials per participant; gray) and the case participant pre-FEST (3 trials; red) and post-FEST (blue). ND non-disabled, COV coefficient of variation, FEST functional electrical stimulation therapy, MMT manual muscle testing, MU motor unit.

Case 4

The fourth case is a 56-year-old male with a C3 incomplete (AIS D), chronic (1 year from the injury onset), traumatic SCI. This participant displayed preserved against gravity strength in proximal upper limb muscles but weakness in extrinsic and intrinsic hand muscles [MMT score: *anterior deltoid* = 3.5 (L), 2 (R); *triceps brachii* = 3.5 (L), 2.5 (R); *biceps brachii* = 4 (R); *extensor digitorum communis* = 2.5 (R); *flexor digitorum superficialis* = 2 (R); *first dorsal interosseous* = 2 (R)]. The participant was enrolled in a shorter but intensive FEST program with 5 sessions of physiotherapy and 11 sessions of FEST at the clinic.

Despite the lack of more pronounced effects on sEMG amplitude, which was only evident for the *extensor digitorum communis* and the 1st *dorsal interossei* muscles, there was an overall gain in strength (Fig. S4). After FEST, the participant was able to exert against gravity strength in all arm and hand muscles [MMT score: *anterior deltoid* = 4 (L), 3.5 (R); *triceps brachii* = 5 (L), 4.5 (R); *biceps brachii* = 5 (R); *extensor digitorum communis* = 4 (R); *flexor digitorum superficialis* = 4 (R); 1st dorsal interosseous = 4 (R)]. This discrepancy between gains in strength and MU activation may indicate: (i) less co-contraction or (ii) compensatory use of other muscles not assessed using sEMG but involved as agonists in the movements measured by the physiotherapists. Indeed, for some pairs of antagonist muscles, the reduced co-activation is evident (Fig. 4A). We also observed the gain in fine control of the hand muscles during sustained 50% maximal voluntary contractions after FEST (Fig. 4B–F).

Relationship between muscle strength, muscle activity, and FEST intensity and duration

To explore the relationship between the clinical assessments, electrophysiological assessments, and the FEST dose, we used a correlational analysis (Fig. 5A). Hand muscles were overall weaker at baseline, with respective reduced activation (Fig. 5B–D). There was a correlation between muscle strength (MMT score) and muscle activation ($sEMG_{amp}$) both at the baseline and endpoint measurements (Fig. 5E, F). The amount of strength gain post-FEST was related to the level of muscle activation at baseline, indicating that residual MU activity at baseline is important for this type of treatment (Fig. 5G). The dose of the FEST delivered to each muscle was related to the strength of the muscles at baseline, likely reflecting the therapist's choice of delivering most of the treatment to weaker muscles (Fig. 5H, I).

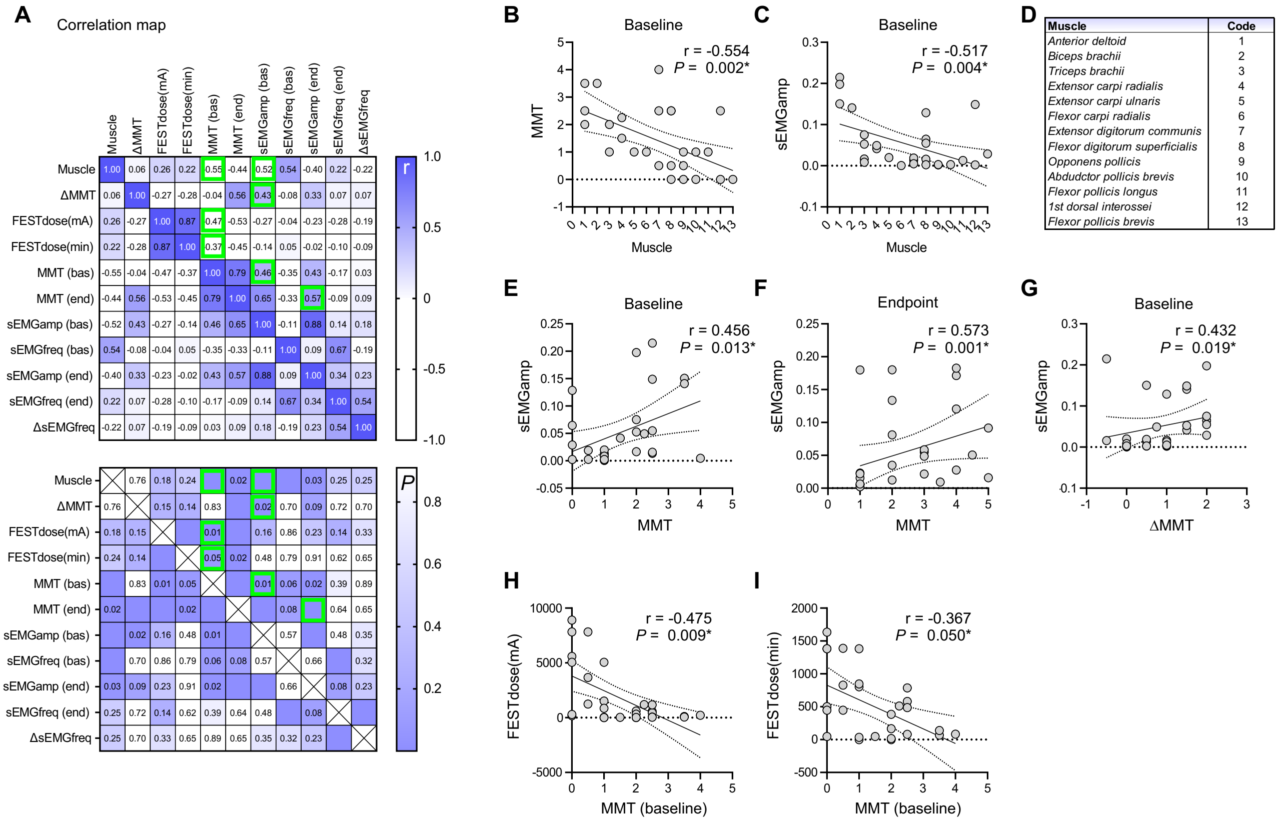

Fig. 5 Correlation map. **A** Spearman correlation between the clinical assessments, electrophysiological assessments, and the FEST dose. The green squares indicate the correlations depicted in **B**–**I**. **B**, **D** Proximal muscles display greater strength and activation at baseline, compared to distal upper limb muscles. **E**, **F** A moderate correlation is evident between the muscle strength (MMT score) and muscle activation ($sEMG_{amp}$) both in the baseline and the endpoint assessments. **G** Muscles that regained strength post-FEST display greater muscle activation at baseline. **H**, **I** The dose of FEST was related to the muscle strength at baseline, reflecting the focus of the therapy on weaker muscles. MMT manual muscle testing; bas baseline; end endpoint. Unit of measure muscle ($N = 29$). $^{*}P < 0.05$, Spearman correlation.

DISCUSSION

In this pilot study, we show evidence that FEST promotes gains in muscle strength, which are accompanied by several electrophysiological changes. Some individuals display a pronounced response to the treatment, with increases in both muscle strength and activation. This includes a greater amplitude of the muscle activation and frequency-domain changes that reflect altered MU recruitment patterns. Small gains in muscle activation are accompanied by greater control during sustained activation or greater coordination between muscle groups. This is evident in reductions in the variability in activation during controlled contractions, in reductions in muscle co-activation between pairs of antagonist muscles, and changes in intermuscular coherence between muscles. The dose of therapy is related to how weak the muscle was at baseline—the latter likely reflecting the therapist's choice of treating weaker muscles.

A recent scoping review documented the effects of FEST on the muscles, encompassing the changes in muscle composition, peripheral nerves, and central nervous system [18]. Evidence from animal models of SCI indicated that FEST can improve neurovascular activation [45] and reduce the inflammatory response in the spinal cord (microglia activation) [46], suppress muscle fatigue [47], and prevent muscle hypotrophy [48, 49]. Clinical studies indicate the maintenance or increase of muscle size, changes in muscle structure, increase in muscle fatigue resistance, increase in muscle blood flow, increase in H-reflex excitability, and increase in the excitability of corticospinal pathways (for references see [18]). Because of the positive relationship between muscle cross-sectional area and strength [50, 51], we indirectly corroborate the changes in muscle size by reporting strength gains after FEST in individuals with SCI, similar to other treatments [52]. We further report changes in MU activation, evident in the greater amplitude and frequency components of the sEMG, indicating that a greater number of MUs are activated post-FEST. In addition, the observed shifts in $sEMG_{freq}$ toward higher frequencies likely indicate that higher threshold, faster MUs are active or that the muscles are overall less fatigued after FEST. Nonetheless, these effects were not common to all muscles among the cases included in this study. Weaker muscles did not display a pronounced gain in strength or activation, but yet there was evidence of enhanced control and coordination—likely explaining the striking ability of the FEST in improving upper limb function [6, 7, 10, 35]. sEMG analysis adds subclinical details to the clinical picture of lesion severity and progression during hand rehabilitation, including the amount of muscle activation and the ability to activate prime movers without involuntary activity in the other muscles [53]. This enabled us to study the effects of FEST in great detail and to unveil subtle neuromuscular changes with therapy.

In the nerve fibers innervating the human arm, it is known that the axonal components are mostly composed of sensory axons, which outnumber motor axons by a ratio of at least 9:1 [54]. Therefore, when the electrical stimuli are delivered to the mixed peripheral nerve both efferent and afferent fibers are recruited, but ~90% of the triggered activity will ascend to the central nervous system by the afferent pathways. This contrasts with the Rushton hypothesis of therapy-related synaptic modifications at the anterior horn cell level—by antidromic stimulation of motor fibers [55], which are known now to represent a much lower percentage of the fibers contained in the mixed peripheral nerve [54]. Ascending afferent volleys are also generated by (secondary) reafference arising from the invoked muscle contraction (reviewed in [56]). In this line of thought, the sensory-mediated consequences of the stimulation significantly alter the state of sensory networks and induce sustained neuroplastic modifications within central motor networks [56]. Indeed, changes in corticospinal excitability are evident after electrical stimulation both in ND [57, 58], and individuals with SCI [18, 59]. Here we provide insights on the ability of FEST in increasing sensory-motor integration, which was evident in the greater control of muscle contraction and between muscles coordination post-FEST. Before the treatment, some individuals activated multiple and often functionally unrelated muscles upon command to contract a single and specific muscle. This effort also demanded more cortical drive, evident in the predominance of coherence in the β-band [51], compared to ND individuals—reflecting the difficulty in selecting the activation of the correct muscle. In other individuals, the co-contraction of antagonists muscles was reduced post-FEST while accomplishing this coordinated multi-muscle action, with a respective increase in the cortical drive [51, 60–63] evident in increases in β-band intermuscular coherence. Finally, it was also evident that some individuals improved the control of MU activation, reflected in a lower variability of the amplitude during sustained and controlled submaximal, visually guided contractions. The bulk of these findings provide the first evidence on what neuromuscular factors may be responsible for the improvement in motor function seen after FEST [6, 7, 10, 35]. Further studies are necessary to confirm these findings in a large sample of individuals, under similar or enhanced sEMG instrumentation and analysis such as high-density EMG or the decomposition of the sEMG [32, 64].

Finally, we demonstrated the correlation between $sEMG_{amp}$ and the well-established MMT assessment, which agrees with previous findings [65]. Another important insight indicates that the $sEMG_{amp}$ at baseline was related to the change in MMT with the FEST treatment. This indicates that the level of residual muscle activity is important for the efficacy of FEST on muscle strength, similar to previous reports [66]. Therefore, the results of this study indicate that sEMG has the potential to complement the clinical assessment on the efficacy of FEST with valuable information, including the opportunity to predict the efficacy of FEST - as discussed below in the “Clinical perspectives” section.

Clinical perspectives

In addition to supporting the use of FEST in rehabilitation programs following an SCI, the results of this pilot study suggest that longer FEST duration could increase meaningful and functional gains. The stimulation was delivered to very weak muscles without active movement against gravity (i.e., MMT score <3) and promoted increased activation and strength in most of them. Future studies should investigate the effects of longer FEST regimens.

This study also demonstrated the potential use of sEMG to assess the efficacy of FEST for very weak muscles for which MMT might not be sensitive enough. The sEMG could also be helpful to assess which muscle might benefit from FEST and if they are responding to the treatment in order to offer customized and efficient FEST programs to each individual. Finally, sEMG can be a valuable biomarker, and has been used to identify discomplete patients [67]. However, the question remains whether treating a muscle with a grade 0 or 1 with good sEMG signal can show motor function recovery.

Limitations

This pilot study shows potential, clinically relevant benefits of FEST in individuals with chronic SCI, which can be electrophysiologically evaluated using sEMG. However, there are limitations to this case series that must be taken into consideration in future studies. For example, our data analysis did not control for the presence of spasticity and the important differences between spastic in contrast to flaccid paralysis because of the small sample size. Future full-scale studies should account for the presence of spasticity given its importance for recovery after SCI.

CONCLUSION

In this pilot study, we explored the ability of FEST to increase muscle strength and activation and provided insights on how the therapy might change sensory-motor integration. Enhanced control of the muscle contraction during visually guided half-maximal contractions, reduced co-contraction of antagonist muscles, and a greater presence of cortical drive were some of the findings supporting the effects of FEST at the sensory-motor integration level. FEST has the striking ability to generate ascending afferent volleys, with the sensory-mediated consequences of the stimulation being able to alter the state of sensory networks and induce sustained neuroplastic modifications within central motor networks. Here we support the use of FEST to increase muscle strength and activation in individuals with an SCI and provide preliminary evidence on how FEST can change sensory-motor integration to enhance upper limb function.

DATA AVAILABILITY

Data generated during the study is available upon reasonable request to the corresponding author.

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AUTHOR CONTRIBUTIONS

G.B. collected data, carried out analysis, interpreted and wrote the results and figures, and wrote the first draft of the manuscript. G.L. contributed to manuscript drafting and analysis. C.G. contributed to data collection. J.Z., S.K.R., and K.E.M. supervised the study and contributed to the analysis and drafting of the manuscript. All authors edited and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no competing interests.

ADDITIONAL INFORMATION

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