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Multimodal cortical and subcortical exercise compared with treadmill training for spinal cord injury

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Abstract

Background and purpose

Spared fibers after spinal cord injury (SCI) tend to consist predominantly of subcortical circuits that are not under volitional (cortical) control. We aim to improve function after SCI by using targeted physical exercises designed to simultaneously stimulate cortical and spared subcortical neural circuits.

Methods

Participants with chronic motor-incomplete SCI enrolled in a single-center, prospective interventional crossover study. Participants underwent 48 sessions each of weight-supported robotic-assisted treadmill training and a novel combination of balance and fine hand exercises, in randomized order, with a 6-week washout period. Change post-intervention was measured for lower extremity motor score, soleus H-reflex facilitation; seated balance function; ambulation; spasticity; and pain.

Results

Only 9 of 21 enrolled participants completed both interventions. Thirteen participants completed at least one intervention. Although there were no statistically significant differences, multimodal training tended to increase short-interval H-reflex facilitation, whereas treadmill training tended to improve dynamic seated balance.

Discussion

The low number of participants who completed both phases of the crossover intervention limited the power of this study to detect significant effects. Other potential explanations for

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the lack of significant differences with multimodal training could include insufficient engagement of lower extremity motor cortex using skilled upper extremity exercises; and lack of skill transfer from upright postural stability during multimodal training to seated dynamic balance during testing. To our knowledge, this is the first published study to report seated posturography outcomes after rehabilitation interventions in individuals with SCI.

Conclusion

In participants with chronic incomplete SCI, a novel mix of multimodal exercises incorporating balance exercises with skilled upper extremity exercises showed no benefit compared to an active control program of body weight-supported treadmill training. To improve participant retention in long-term rehabilitation studies, subsequent trials would benefit from a parallel group rather than crossover study design.

Introduction

Most spinal cord injuries (SCI) spare a portion of axonal fibers at the injury level [1,2]. Fibers of subcortical pathways such as the reticulospinal and propriospinal tracts make up a significant portion of spared circuitry that can mediate substantial functional recovery [3,4]. Subcortical circuits connect to many of the same spinal motor neurons to which corticospinal circuits connect [5–8]. Corticospinal fibers also make collateral connections to reticulospinal and other descending subcortical circuits [7,9]. Experiments in animals have demonstrated the potential for alternate or detour connections between cortical, subcortical, and spinal circuits to mediate recovery after SCI [10–13].

Our group has previously applied targeted physical exercises that are designed to facilitate detour connectivity by repetitively and simultaneously stimulating cortical and spared subcortical circuits. This multimodal (MM) exercise strategy combines postural tasks (which activate subcortical circuits) with fine motor tasks (which activate cortical circuits). In animal models and non-disabled human volunteers, we found that compared with exercises stimulating cortical or spinal circuits alone, MM exercises promoted improved recovery from central nervous system injury and increased corticospinal neurotransmission [14–16].

Robotic-assisted weight-supported treadmill exercise (TM) is an established form of physical rehabilitation that is associated with positive clinical outcomes in participants with incomplete SCI [17–20]. Treadmill training largely targets spinal locomotor central pattern generator circuits [21,22]. However, it requires expensive equipment and space that is generally available only in institutional settings. Based on our earlier findings, we initiated a clinical trial in humans with chronic SCI designed to compare the effects of our novel multimodal exercise program to that of treadmill training (TM). We hypothesized that compared with TM, MM exercises would significantly increase volitional lower extremity motor scores and corticospinal neurotransmission.

Methods

Participants

Participants between the ages of 21 and 65 with motor incomplete SCI (as determined by the International Standards for Neurological Classification of SCI (ISNCSCI)), or volitional strength of at least 1/5 according to ISNCSCI in two or more key lower extremity muscles, with ≥1 year duration of injury were recruited. Enrollment occurred between February 2013 and May 2016. Initially, only participants with thoracic SCI were included; entry criteria were later expanded to include participants with injury level between C2-T12 who had at least antigravity strength in the deltoids, biceps, and triceps muscles. Exclusion criteria included significant neurological or coronary artery disease, severe osteoporosis, severe joint stiffness, or excessive risk of transcranial magnetic stimulation (epilepsy, prior intracranial hemorrhage, amphetamine usage, and other factors that increase seizure risk). A full list of inclusion and exclusion criteria is provided on ClinicalTrials.gov, where this study was registered (https://clinicaltrials.gov/ct2/show/NCT01740128). Subjects provided written informed consent. All procedures and data analysis occurred at the James J. Peters Veterans Affairs Medical Center, with approval by the Institutional Review Board of the Bronx VA Medical Center Research & Development Program (151) (Protocol #01407). All applicable institutional and governmental regulations concerning the ethical use of human volunteers according to the principles of the Declaration of Helsinki were followed during the course of this research.

Design

This study was a single-group, partially blinded crossover trial (Fig 1). Each phase consisted of 48 sessions of one intervention followed by a washout period of at least 6 weeks. TM or MM intervention order was randomly assigned using Research Randomizer (www.randomizer.org). An otherwise unaffiliated staff member revealed the intervention allocation after study personnel obtained informed consent from each newly enrolled participant. Three to five sessions per week were scheduled. For subject convenience, up to two sessions were performed during a single visit, with a rest period of at least 30 minutes between sessions. Outcome assessments were performed at baseline and within one week of completing an intervention. An expert evaluator blinded to intervention assessed the primary clinical outcome (lower extremity motor score). A follow-up evaluation was planned for 6 weeks after intervention completion. With expected dropout rate of 25% and effect size of 1 based on prior manuscripts reporting electrophysiological outcomes [23,24], enrollment of 24 participants was calculated to provide power ≥0.83 to reject the null hypothesis on a two-tailed independent-sample t-test with alpha of 0.05.

Exercises

General. Sessions lasted 30 minutes not including setup, with 1–2 minute rest periods at least every 10 minutes. Vital signs (brachial cuff blood pressure, heart rate recorded by Dinamap V100) and rating of perceived exertion (RPE) via the Borg Scale [25] were recorded at least twice per session. Exercise task difficulty was adjusted as detailed below to achieve a desired range of RPE between 11 to 15 (out of 20). Study personnel continuously monitored and frequently questioned participants for any adverse symptoms. Body weight support (BWS) for both interventions was provided by the overhead harness of the Lokomat system (Hocoma). BWS was set to 60% of body weight initially, and then gradually reduced as tolerated. Note that even subjects with complete paraplegia can passively support 40% or more of their own body weight in the upright position [26–28]. Several participants who reached independent weight support still wore the harness for safety.

Treadmill exercise (TM). Participants walked on a robotic-assisted treadmill (Lokomat, Hocoma) at initial speeds of 1–1.5 km/h. Speed was gradually increased as tolerated to a maximum of 3.2 km/h. The Lokomat's built-in guidance force (amount of assistance to reach a predefined gait kinematic pattern) was also gradually reduced as tolerated. Participants were reminded to swing their arms while walking.

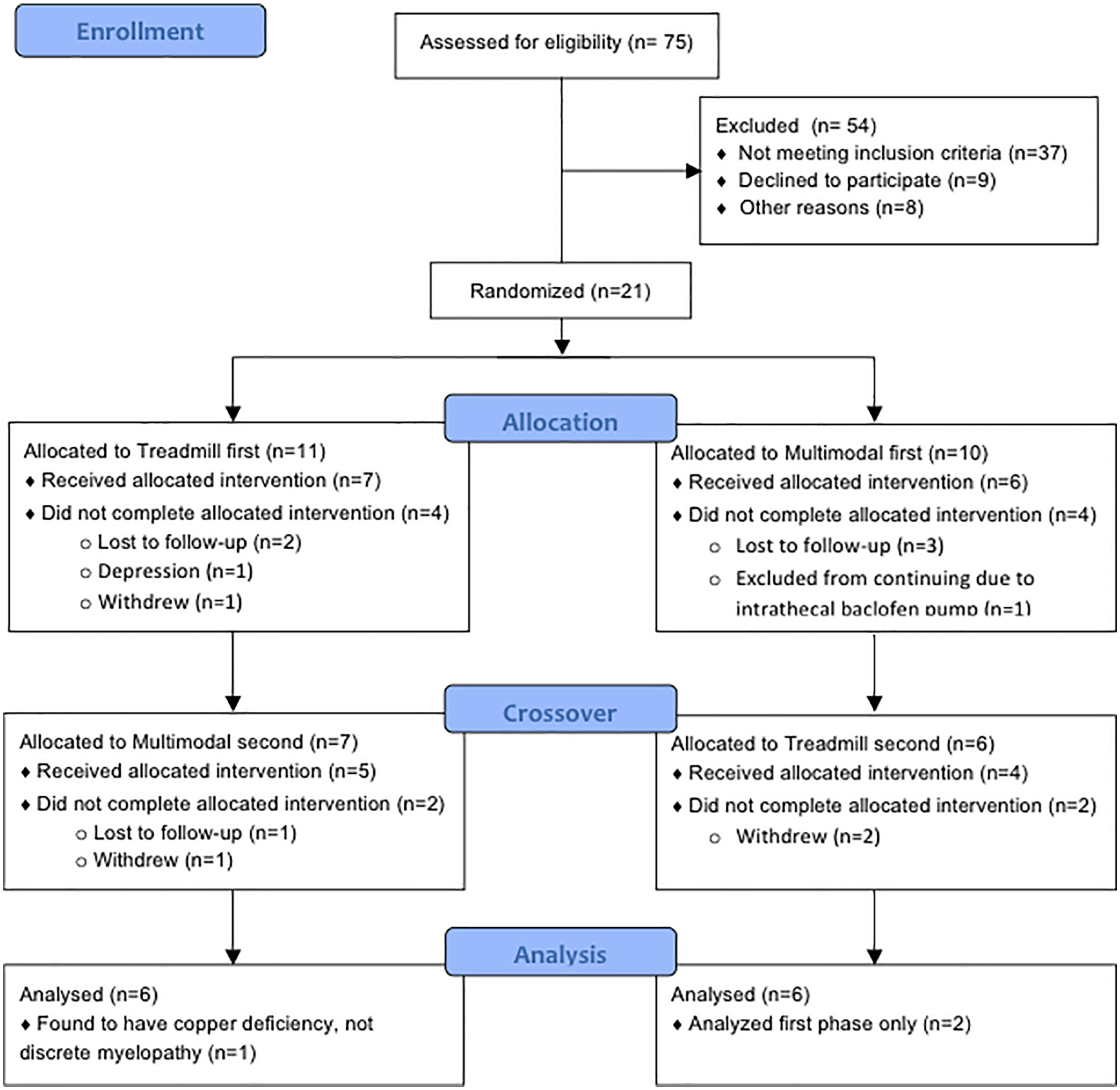

Fig 1. CONSORT flow diagram.

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Multimodal exercise (MM). Participants performed simultaneous balance and skilled upper extremity exercises. In addition to partial body weight support using the Lokomat harness, study personnel provided manual stabilization and perturbation as necessary. *Balance (subcortical) component*: Participants' feet were placed on a semi-spherical balance platform (Bosu™, 63.5 cm diameter, 23 cm height). Either the flat or convex sides of the balance ball were utilized as the standing surface, but generally, the flat side was in contact with the feet,

Fig 2. Multimodal (MM) exercise paradigm. MM involved balance exercises plus simultaneous fractionated hand exercises targeted at the corticospinal tract. Participants' feet were placed on either the flat or convex side of a semi-spherical balance platform (Bosu™). To increase challenge, participants were intermittently asked to perform tandem stance (A), or study personnel applied external perturbations. During balance exercise, participants performed a variety arm or hand manipulations that involve precision or power movements, such as placing pegs into a grooved pegboard, maintaining a ping-pong ball on a small handheld plastic dish (A); and other tasks. Tasks were varied every one to three minutes to maintain participant interest. Overhead partial body weight support was provided at all times.

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and the convex side was in contact with the ground (Fig 2). Participants were instructed to keep the balance surface as stable as possible. To increase level of difficulty in either orientation, study personnel manually applied external perturbations to either the balance ball or the participants' trunks. *Fine upper extremity (corticospinal) component*: During balance exercise, participants performed a variety of skilled arm or hand manipulations, either unimanually or bimanually. All tasks were designed to require movements that engage corticospinal circuits [29,30]. Tasks were varied every few minutes to maintain participant interest. Tasks included inserting different-sized coins into slots oriented at different angles; tightening or loosening screws from a board; picking up playing cards or paper clips off a flat surface; performing a skilled pegboard task (Lafayette Instruments); guiding a loop over an alarmed irregularly curved coil; typing numbers on a keypad; threading beads on a string; inserting long-handled keys into custom slots that required forearm supination; maintaining a ping-pong ball on a small handheld plastic dish; and others (Fig 2; S5 File).

Lower extremity motor score (LEMS)

Manual assessment of muscle strength in both legs was performed at 5 key myotomes (L2 = hip flexion; L3 = knee extension; L4 = ankle dorsiflexion; L5 = toe dorsiflexion; S1 = ankle plantarflexion) according to the ISNCSCI [31]. Muscles were scored on a scale of 0 to 5, resulting in possible LEMS ranging from 0 to 50.

Berg Balance Scale (BBS)

Most participants were unable to attempt the standing portions of the Berg Scale [32]. Therefore, the 'Sitting with back unsupported' subsection was compared. Participants sat on a cushioned adjustable chair without back support, with hip, knee, and ankle angles at approximately 90 degrees, and arms folded across the chest for up to two minutes.

Computerized posturography

A wooden block (46 cm W x 43 cm L x 31 cm H) was centered on a Smart Equitest (Natus) force plate, with an overlying foam pad (13 cm thick) for subject comfort and skin protection [33]. Participants were seated without back support, with hip, knee, and ankle angles at approximately 90 degrees, and arms folded across the chest. In the Limits of Stability test, participants were instructed to shift their center of gravity (represented as an avatar in real time) toward eight surrounding targets on a computer monitor. Key measures were endpoint and maximal excursion of the center of gravity (EPE and MXE), and directional control (DCL) of intended movements. In the Clinical Test of Sensory Integration on Balance, participants were asked to maintain static upright posture for 10 seconds each under four conditions: 1) arms crossed over the chest with eyes open; 2) arms over the chest with eyes closed; 3) arms outstretched forward with eyes open; 4) arms outstretched forward with eyes closed. Each condition was tested three times. COP angular displacement in the mediolateral and anteroposterior planes was averaged over 10 seconds per trial. The primary static outcome measure of sway velocity represents the difference in average sway (degrees per second) in the eyes-closed versus the eyes-open arms crossed condition.

Modified Ashworth Scale (mAS)

The mAS was assessed at the knee extensors on both sides using six scoring levels (0,1,1+, 2,3,4), where 0 is defined as no increase in muscle tone and 4 is defined as the affected part rigid in flexion or extension [34]. For analysis, mAS scores were transformed into a 0–5 scale and averaged between the left and right legs.

Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET)

This survey was used to evaluate how spasticity impacted a person's activities of daily living over the course of the previous 7 days [35].

McGill Pain Questionnaire (short form)

This survey was used to track whether any neural plastic changes resulted in adverse effects on neuropathic pain [36].

Gait speed and seated step test

The 10-meter walk test was administered using standard measures (walk at maximal safe speed, with or without assistive devices; 2-meter lead-in; average of three repetitions). For the

10-second seated step test [37], participants were seated with their hips and knees flexed to 90 degrees, then asked to lift one foot entirely off the ground and place it back down again. The average number of steps taken during three 10-second trials with each foot was recorded.

Surface EMG

Adhesive snap dual surface electrodes (Natus) were applied to the bellies of the tibialis anterior and soleus muscles. Recordings were collected using a Viking Select system (Natus) or a Motion Lab Systems system with wired electrodes. Samples were acquired at a rate of 5,000 Hz. Adverse events during electrophysiological testing were collected with a questionnaire developed by an international expert consensus panel on TMS safety [38].

Peripheral responses

Responses to external stimulation were recorded in the resting supine position, with the knees resting on a foam roll and the ankles in neutral position. Electrical stimuli were delivered using a Grass S88 dual-output stimulator (Natus) or a DS7A stimulator (Digitimer). The peroneal nerve was stimulated at the fibular head with 0.2 ms pulses at supramaximal intensity to define the tibialis anterior (TA) maximal compound motor action potential (Mmax) as well as to elicit F-waves in the antidromic orientation. The tibial nerve was stimulated in the popliteal fossa with 1.0 ms pulses at a range of intensities to determine the threshold and slope of the H-reflex recruitment curve, and the maximal soleus M-wave amplitude (Mmax). A minimum of 5 seconds elapsed between each tibial nerve pulse.

Transcranial magnetic stimulation

A MagPro system (Magventure) with 80mm winged coil (D-B80) was centered over the leg motor cortex hotspot for maximal tibialis anterior response (usually 2 cm lateral to the vertex). The coil was maintained in position with a multijointed mechanical arm (MagVenture). Subjects wore a white cloth TMS cap. The 'hotspot' was marked in permanent ink on the cap, which was carefully repositioned and reused for each subject across testing sessions. Assessors vigilantly checked coil, cap, and head positioning during testing. Resting motor threshold (RMT) was determined as the percent of maximal stimulator output required to elicit a potential of at least 25μV in 5 out of 10 repetitions. The 25μV rather than 50μV threshold was used due to the inherently lower capability to evoke responses in the leg muscles in comparison to hand muscles. Motor evoked potential (MEP) amplitudes were averaged across 5 repetitions per intensity. To account for changes in electrode placement and conductance over different testing sessions, MEPs were normalized to that session's peripherally evoked Mmax [39].

Soleus H-reflex facilitation by transcranial magnetic stimulation

H-reflex stimuli were delivered via surface electrodes in the popliteal fossa with intensity set to elicit an H-reflex of 10–20% of Mmax [40]. TMS pulses were delivered at 80–90% of tibialis anterior resting motor threshold (or 80–90% of maximum stimulator output if TA RMT was unobtainable), at interstimulus intervals (ISI) of 0–120 ms prior to the H-reflex stimulus. Sets of ISI combinations were delivered in pseudorandom order. A minimum of 10 seconds elapsed between each pulse. Participants were instructed to mentally focus on plantarflexing the targeted ankle during H-reflex facilitation assessment. TMS-conditioned soleus H-reflex amplitude (average over 5 repetitions) was compared to unconditioned H-reflex amplitude to determine the percent facilitation at each ISI. Results at ISI between 0 and 20 ms were grouped into 'short-interval facilitation', whereas results at ISI between 60–120 ms were grouped into 'long-interval facilitation' [41]. H-reflex amplitudes were averaged between both legs within each subject, except for two participants who had elicitable H-reflexes on only one side.

Statistics

The a priori primary clinical outcome was post-intervention change in lower extremity motor score. The intended a priori primary neurophysiological outcome was post-intervention change in the amplitude of the tibialis anterior motor evoked potential (TA MEP). However, only two participants demonstrated consistent TA MEPs at baseline. Therefore, soleus H-reflex facilitation was employed as the primary neurophysiological outcome measure. Due to the small sample size, median and interquartile range are reported for all outcomes. The data were analyzed using linear mixed modeling with intervention (TM vs MM; a repeated measure factor) and order (TM-first or MM-first; a between-subjects factor) modeled as fixed effects. The dependent variable was the change score (post—pre) for the respective measurements. The underlying covariance structure was compound symmetry.

Missing values for specific outcome tests (highlighted in S4 File) were not imputed. Carry-over effect among participants who completed both intervention phases was tested by subtracting changes during the second intervention from changes during the first intervention for each subject, then performing an unpaired t-test between subjects who performed TM first and subjects who performed MM first. Significance (including Bonferroni correction) was set at $p<0.025$ for primary outcomes and $p<0.005$ for secondary outcomes. Post hoc power calculations for the outcomes of short-interval H-reflex facilitation and lower extremity motor score were calculated from the fixed effects of Intervention using G*Power version 3.1.9.3. Microsoft Excel, IBM SPSS, and the lme4 package in R statistical software were used for all other analyses.

Results

21 of a planned 24 participants were enrolled between February 2013 and May 2016. Enrollment completed when funding expired. Only 13 participants completed at least one intervention phase of the study, and 9 completed both phases of the study (Fig 1). We report data from participants who completed at least one intervention (demographics detailed in Table 1). One subject was found after study entry to have copper-deficient myeloneuropathy rather than a discrete spinal injury, so his data was not included. One subject who had been classified as motor incomplete SCI in another research study within our center was reclassified as motor-complete SCI after enrolling in our study. However, due to the presence of three other subjects with baseline LEMS of three or less in the small subject sample, he was retained in our study. There were no serious adverse events during the study. Several participants reported mild adverse events such as lightheadedness or skin abrasions.

All outcomes are summarized in Table 2. No statistically significant differences between or within interventions were found for any outcome. Raw data and statistical tabulations are detailed in S4 File.

Lower extremity motor score

Participants had a wide range of LEMS at baseline (0–44). After TM, three participants demonstrated improvement in LEMS, three showed no change, and four deteriorated. After MM, three participants demonstrated improvement in LEMS, three showed no change, and three deteriorated (Fig 3). One post-MM participant completed all post-testing except for the INSCSCI examination. There was no significant difference in the rates or degree of LEMS improvement between the two interventions. The post-hoc observed power was 0.051.

Table 1. Subject demographic characteristics.

MF	Age	Trauma/NT	DOI	Level	AIS	Interventions
F	36	NT	18	T2	C	MM
M	45	T	5.5	T8	A	TM, MM
M	50	NT	1	T9	C	TM, MM
M	23	T	4	T10	D	TM, MM
M	46	T	23	T4	C	MM, TM
M	41	T	1	T8	C	MM
M	42	T	4	T1	B	TM, MM
F	37	T	11	T11	C	TM
M	40	T	4	C6	D	TM
M	51	T	16	C8	D	MM, TM
M	29	T	2.5	C8	C	MM, TM
F	44	T	5	T10	C	MM, TM

M = male. F = female. T = traumatic. NT = non-traumatic. DOI = duration of injury (years). AIS = ASIA Impairment Scale. TM = treadmill intervention. MM = multimodal intervention. Subjects completed 48 sessions of the listed intervention(s). Interventions are listed in order of completion.

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Soleus H-reflex facilitation

After TM, three participants demonstrated an increase in short—interval facilitation (interstimulus interval 0–20 ms), and five showed a decrease. After MM, five participants

Table 2. Intervention effects on study endpoints.

			LEMS	Short Facil	Long Facil	Berg S3	Sway	EPE	MXE	DCL	mAsh	10 MWT	Seated Steps	SCI-SET	SD	AD
Post	**TM**	n	10	8	8	8	9	9	9	9	9	3	4	6	7	7
		Median	**0.0**	**-5.9**	**-2.1**	**0.0**	**0.0**	**8.9**	**5.1**	**9.0**	**0.0**	**0.1**	**-1.3**	**-0.5**	**0.0**	**0.0**
		IQR	-2.0, 0.8	-13.8,2.4	-11.2,5.0	0.0, 0.0	-0.1, 0.2	-5.1, 17.1	1.8, 23.8	-1.4, 18.5	-0.5, 0.0	0.1,0.2	-2.4, -1.1	-1.0, 0.0	-2.0, 0.0	-0.0, 0.0
	MM	n	9	7	7	10	10	10	10	10	5	1	4	7	9	9
		Median	**0.0**	**2.4**	**-6.7**	**0.0**	**-0.2**	**2.3**	**1.6**	**-0.4**	**0.0**	**0.0**	**3.3**	**0.0**	**0.0**	**0.0**
		IQR	-2.0, 2.0	-0.6, 12.1	-27.8, 2.0	0.0, 0.0	-0.3, 0.0	-1.2, 12.3	-3.2, 8.5	-2.4, 1.8	0.0, 0.1	0.0, 0.0	2.0, 4.6	-4.0, 9.0	0.0, 4.0	0.0, 1.0
6 Wk	**TM**	n	7			6	8	8	8	8	6	3	3	5	6	6
		Median	**0.0**			**0.0**	**0.1**	**0.7**	**-3.1**	**1.5**	**0.0**	**0.1**	**1.3**	**5.0**	**0.0**	**0.0**
		IQR	-1.0, 1.5			0.0, 0.0	-0.2, 0.3	-4.9, 9.3	-5.0, 8.3	0.2, 5.2	-0.4, 0.0	0.0, 0.2	0.8, 2.7	3.0, 7.0	-0.8, 1.5	-0.8, 0.0
	MM	n	6			6	6	6	6	6	4	1	2	4	5	5
		Median	**0.0**			**0.0**	**-0.3**	**11.3**	**3.6**	**4.9**	**-0.3**	**0.0**	**1.7**	**3.0**	**-2.0**	**0.0**
		IQR	-1.5, 0.0			0.0, 0.8	-0.5, -0.1	3.4, 13.8	1.4, 7.5	1.5, 8.3	-0.8, 0.0	0.0, 0.0	1.3, 2.1	-3.3, 9.0	-3.0, 0.0	0.0, 0.0

No statistically significant differences between or within interventions were found for any outcome. Post = immediately post-intervention. 6 Wk = 6-week follow-up. TM = treadmill intervention. MM = multimodal intervention. n = number of subjects completing assessment. IQR = interquartile range. LEMS = lower extremity motor score. Short Facil = soleus H-reflex facilitation by subthreshold TMS between 0–20 ms interstimulus interval. Long Facil = soleus H-reflex facilitation by subthreshold TMS at 60 ms or more interstimulus interval. Berg S3 = score on the "Sitting with back unsupported subsection of Berg Balance Scale". Sway = postural sway during upright sitting in eyes-closed relative to eyes-open condition. EPE = endpoint excursion. MXE = maximal excursion. DCL = directional control. mAsh = modified Ashworth. 10MWT = 10-meter walk test (m/s). SCI-SET = Spinal Cord Injury Spasticity Evaluation Tool. SD = sensory domain of McGill Pain Questionnaire. AD = affective domain of McGill Pain Questionnaire.

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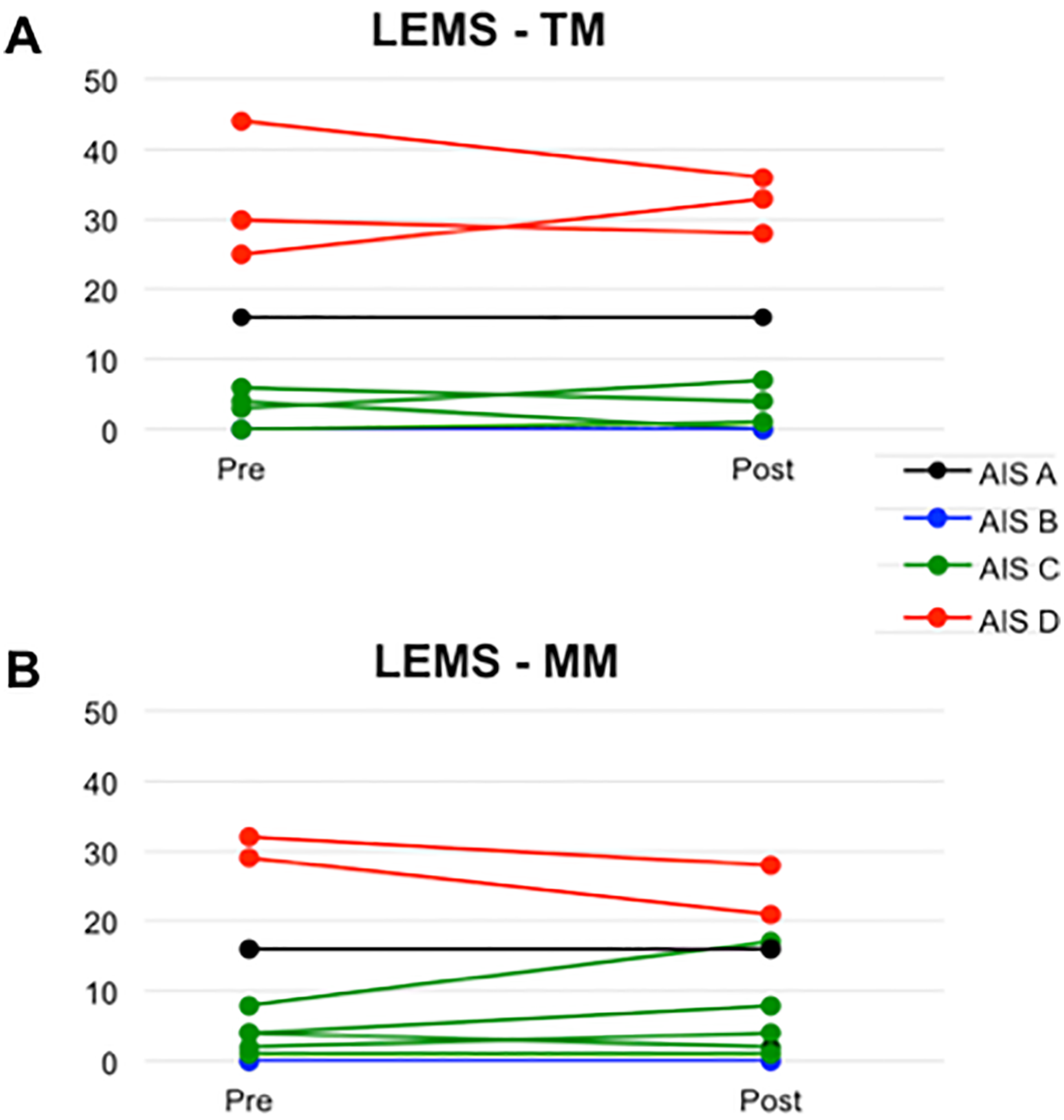

Fig 3. Change in Lower Extremity Motor Score (LEMS). Pre- and post-intervention data shown for each subject. **A**, Multimodal; **B**, Treadmill. Red lines indicate subjects with baseline ASIA Impairment Scale (AIS) Grade D. Green lines indicate subjects with baseline AIS Grade C. Blue line indicates subject with baseline AIS Grade B. Black line indicates subject with baseline AIS Grade A (and significant zone of partial preservation).

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demonstrated an increase in short-interval facilitation, and two showed a decrease (Fig 4). There was no statistically significant difference in the degree of H-reflex facilitation change between the two interventions, although MM tended to result in larger improvement than TM in short-interval facilitation (p = 0.053 before Bonferroni correction). The post-hoc observed power was 0.211.

Secondary outcomes

Seated balance. Most participants were able to sit independently at baseline, achieving the highest possible score on the Sitting unsupported portion of the Berg Scale, thereby establishing a ceiling effect. Computerized posturography assessments were more sensitive for

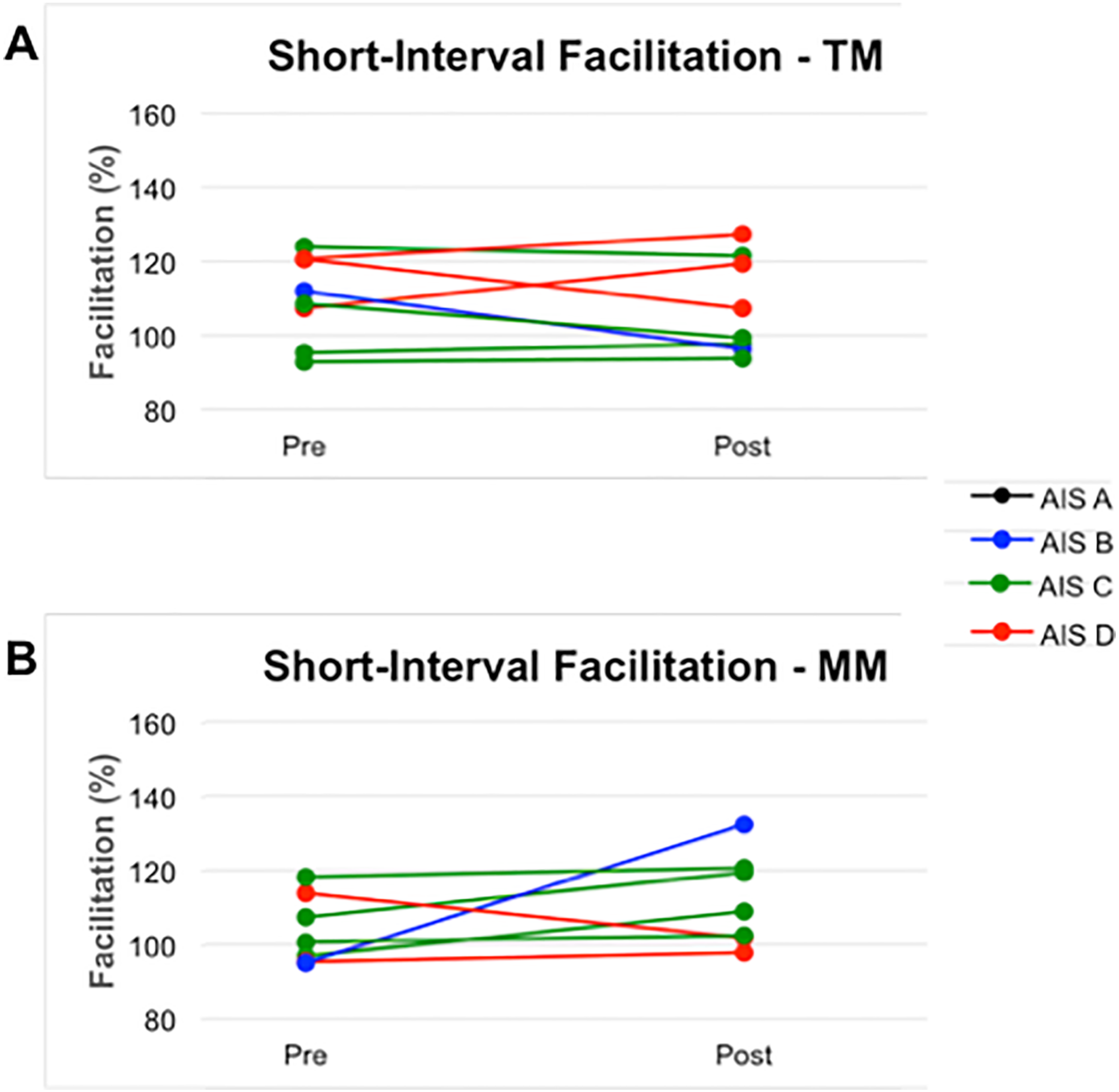

Fig 4. Change in short-interval (0–20 ms) soleus H-reflex facilitation by subthreshold transcranial magnetic stimulation. Pre- and post-intervention data shown for each subject. **A**, Multimodal; **B**, Treadmill. Red lines indicate subjects with baseline ASIA Impairment Scale (AIS) Grade D. Green lines indicate subjects with baseline AIS Grade C. Blue line indicates subject with baseline AIS Grade B. Black line indicates subject with baseline AIS Grade A (and significant zone of partial preservation).

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detecting change after intervention [33]. Contrary to our hypothesis, dynamic seated reaching tests, especially maximal excursion and directional control, showed a slight trend (p value 0.26 and 0.29, respectively, before Bonferroni correction) toward more improvement after TM than MM.

Spasticity. After TM, five participants demonstrated no change in knee extensor mAsh, and four showed a decrease. After MM, three participants demonstrated no change in mAsh, and 2 showed an increase. The SCI-SET survey was initiated partway through the study, so fewer subjects completed pre- and post-testing. SCI-SET score changes were minimal on the individual and group level.

McGill Pain Questionnaire (short form). Median sensory and affective domain scores did not change after either intervention.

Gait speed and seated step test. Data was successfully collected from only a few participants with ambulatory capability and is shown in Table 2. After TM, one of four subjects increased the number of seated steps. After MM, four of four subjects increased the number of seated steps. However, these results did not reach statistical significance (step test p = 0.076 before Bonferroni correction).

Effects of order and carryover. Of the eight included subjects who completed both phases of the study, four each performed TM first or MM first. Order, included as a between-subjects factor in the multilevel analysis of variance, did not significantly affect any primary or secondary outcome. Carryover effect (defined as change during the second intervention subtracted from change during the first intervention within each subject) for primary outcomes was compared using unpaired t-tests between subjects who performed TM first and subjects who performed MM first. There were no statistically significant carryover effects.

Discussion

Our novel targeted approach aims to improve the specificity and efficacy of exercise rehabilitation by simultaneously activating corticospinal and subcortical circuits. The corticospinal tract makes collateral connections with subcortical pathways as it passes through the brainstem. Subcortical circuits are often spared after SCI [3]. Based on our prior studies, we speculated that repetitive, synchronized activation of cortical and subcortical circuits through physical exercises could improve recovery by strengthening collateral corticobulbar synapses that could mediate functional detour connections between cortical and spared spinal circuits [6,13,42].

We tested a multimodal exercise paradigm combining fine hand tasks with postural stabilization exercises. Hand tasks such as the ones used in this study require fractionated finger movements and forearm supination, which activate corticospinal circuits [9,43]. Postural instability activates multiple subcortical areas, including reticulospinal, vestibulospinal, propriospinal, basal ganglia, and cerebellar pathways [44,45]. The MM regimen does not require a treadmill, robotic exoskeleton, or extensive manual assistance–therefore, MM would be simpler and less expensive than body weight-supported treadmill training to implement as a treatment modality.

In a small population with chronic incomplete SCI, we did not observe a significant difference in any outcome between MM and TM training in a 48-session crossover study. Although TM training (with manual or robotic assistance) has repeatedly been shown to improve stepping and locomotor function in individuals with chronic SCI, it has not been proven superior to other forms of physical rehabilitation, and its effects on lower extremity motor score have been mixed [17,46–51]. Treadmill training targets spinal locomotor central pattern generator circuits more strongly than corticospinal circuits [21,22], although cortical circuits may also be modulated [52,53]. The skilled tasks incorporated into MM training, though focused on the upper extremities, likely activated lower extremity neural circuits as well [54]. Regardless, there was a higher degree of participant dropout and variability than expected in this study, leading to changes that did not reach significance for either intervention.

The originally intended primary neurophysiological outcome was tibialis anterior motor evoked potential amplitude (TA MEP). TA MEP depends largely on residual intact corticospinal circuits. However, only two participants had clear TA MEPs at baseline, far fewer than had been anticipated. Therefore, soleus H-reflex facilitation was analyzed as the primary neurophysiological outcome. H-reflex facilitation by subthreshold TMS depends on both direct and indirect connections between cortical and spinal motor neurons [40,41,55]. Facilitation mediated by subthreshold TMS pulses within 20 ms prior to tibial nerve H-reflex pulses ('short-interval') likely occurs through direct corticospinal circuits, whereas facilitation mediated by TMS pulses 60–120 ms prior to tibial nerve pulses ('long-interval') likely occurs through polysynaptic circuits involving brainstem and spinal pathways [41,44,56].

A trend toward greater H-reflex facilitation was observed in the short-interval window after MM versus TM training (median 2.4% vs -5.9%), consistent with corticospinal facilitation. These data are comparable to our previous results in non-disabled volunteers demonstrating that one session of MM exercise increased short-interval H-reflex facilitation by 6.2% ± 4.0%, whereas one session of TM exercise decreased short-interval facilitation by 1.4% ± 3.8% [16]. Although we did not observe similar changes in long-interval H-reflex facilitation in the current study, those results were much more variable, possibly due to differences in degree of sparing of subcortical pathways among our subjects [40,41].

We know of no other published studies that have reported seated posturography outcomes after rehabilitation interventions in individuals with SCI. MM training did not lead to significantly greater improvement in seated balance performance than TM training did, despite upright postural exercises being incorporated into the MM regimen. Weight-supported treadmill training itself has been shown to improve both gait and clinical balance outcomes [57–59]. We speculate that either upright postural instability during MM training does not transfer efficiently to seated dynamic balance skills, or that simultaneous performance of fine upper extremity tasks interferes with learning or retention of seated dynamic balance skills.

This study has multiple limitations. Participants were more severely impaired than anticipated, making it difficult or impossible to collect data on several of the outcomes. More significantly, fewer than the anticipated number of participants completed the study interventions, limiting the power of this study to detect a difference or to conclusively establish equivalence between the interventions. Including the 6-week washout period, full study participation required at least 30 weeks per subject, which proved burdensome for subjects to maintain, mostly due to transportation issues. In some cases, participants participated in inconsistent numbers of sessions per week, potentially diluting effects of intervention. In others, participants dropped out of the crossover study after completing only a single intervention. This incomplete crossover dataset necessitated a more complicated multilevel statistical analysis, and increased the risk of both Type 1 and Type 2 error. Furthermore, despite attempts to push participants toward the 'Hard' level of exertion on the Borg Rating of Perceived Exertion, subjects ranged across a broader range from fairly light (RPE 11) to hard (RPE 15) exertion.

Incorporating lessons from this study should lead to improved yield from future studies–given the prolonged course of each intervention, a parallel-group design, though requiring more subjects, would improve subject retention and simplify statistical analysis. Confirming presence and stability of baseline values across two rather than one screening visit would reduce variability. Finally, we speculate that synergy between cortical and brainstem signaling to the legs may be facilitated by combining balance exercises with concurrent skilled *lower* rather than *upper* extremity exercises. The participants in our study did not generally have the ability to perform skilled lower extremity movements, but perhaps motor imagery may be a mechanism to implement this type of approach [60].

Conclusion

In participants with chronic incomplete SCI, 48 sessions of a multimodal exercise rehabilitation program incorporating balance exercises with skilled upper extremity exercises showed no benefit compared to 48 sessions of body weight-supported treadmill training. The small number of participants that completed both phases of the crossover intervention limited the power of this study to detect significant effects. Whether a combination of exercises simultaneously stimulating cortical and subcortical circuits may improve rehabilitation in persons with SCI or other neurological conditions remains undetermined.

Supporting information

S1 File. IRB approval letter.
(PDF)

S2 File. IRB protocol.
(PDF)

S3 File. Consort checklist.
(DOC)

S4 File. Subject-level outcome data.
(XLSX)

S5 File. List of skilled upper extremity tasks.
(XLSX)

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