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Transcutaneous spinal cord stimulation restores hand and arm function after spinal cord injury

Fatma Inanici, Lorie N. Brighton, Soshi Samejima, Christoph P. Hofstetter, Chet T. Moritz

***Abstract*— Paralysis of the upper extremity severely restricts independence and quality of life after spinal cord injury. Regaining control of hand and arm movements is the highest treatment priority for people with paralysis, 6-fold higher than restoring walking ability. Nevertheless, current approaches to improve upper extremity function typically do not restore independence. Spinal cord stimulation is an emerging neuromodulation strategy to restore motor function. Recent studies using surgically implanted electrodes demonstrate impressive improvements in voluntary control of standing and stepping. Here we show that transcutaneous electrical stimulation of the spinal cord leads to rapid and sustained recovery of hand and arm function, even after complete paralysis. Notably, the magnitude of these improvements matched or exceeded previously reported results from surgically implanted stimulation. Additionally, muscle spasticity was reduced and autonomic functions including heart rate, thermoregulation, and bladder function improved. Perhaps most striking is that all six participants maintained their gains for at least three to six months beyond stimulation, indicating functional recovery mediated by long-term neuroplasticity. Several participants resumed their hobbies that require fine motor control, such as playing the guitar and oil painting, for the first time in up to 12 years since their injuries. Our findings demonstrate that non-invasive transcutaneous electrical stimulation of the spinal networks restores movement and function of the hands and arm for people with both complete paralysis and long-term spinal cord injury.**

***Index Terms*— Neuroplasticity, spinal cord injury, transcutaneous electrical spinal cord stimulation, upper extremity function**

I. Introduction

DAMAGE to the spinal cord interrupts the communication between the brain and the body that leads varying level of permanent paralysis. At present, there is no cure for spinal cord injury (SCI) [1]. Regaining control of hand and arm movements is the highest treatment priority for people with paralysis, 6-fold higher than restoring walking ability [2]. Nevertheless, approaches to restore tetraplegic hand and arm function are scarce and outcomes inadequate in clinical practice.

Exercise therapy is the mainstay of the rehabilitation that aims to improve motor function [3], [4]. Studies have evaluated the augmentative effects of functional electrical stimulation [5], [6], somatosensory stimulation [7], and transcranial magnetic stimulation [8] on the outcomes of exercise therapy, but improvements were modest. There is recent evidence, however, that spinal cord circuits below an injury can be activated with electrical stimulation to enable conscious control of movement [9]–[11].

Ongoing electrical stimulation of the spinal cord surface via implanted epidural electrodes is typically required to enable movement of paralyzed limbs [9], [11]–[14]. The ultimate goal of rehabilitation, however, is to promote recovery of function such that stimulation is no longer required [15]. Intensive exercise training attempts to promote such adaptation and neuroplasticity [15], [16]. By combining therapy and stimulation, we aim to use electrical stimulation of the spinal cord to initially enable movement such that paralyzed individuals can participate in intensive training programs and achieve long-term recovery of function [17].

The use of electrical stimulation to enable rehabilitation has led to impressive restoration of leg movement and stepping using implanted epidural stimulation in individuals with both motor complete and incomplete SCI [11]–[14]. Despite the paramount importance after SCI, only a few studies focused on the effect of epidural spinal cord stimulation to restore upper extremity function [10], [18], [19], and none were combined with intensive rehabilitation training to facilitate activity-dependent plasticity.

While impressive functional gains have been reported with implanted epidural stimulation electrodes, a new method of non-invasive spinal stimulation has recently emerged. By adopting a 10 kHz overlapping-frequency [20], transcutaneous spinal cord stimulation allows application of high stimulation intensities through the skin that can reach the spinal cord without causing discomfort [21], [22]. Even without intensive exercise training, non-invasive cervical spinal cord stimulation modestly improves hand function in people with tetraplegia [23], [24].

II. Methods

A. Study Design

We conducted a prospective, open-label, two-arm, cross-over study. We began by repeating baseline measurements once per week for four weeks to evaluate each participant's functional variability over time and to control for learning the

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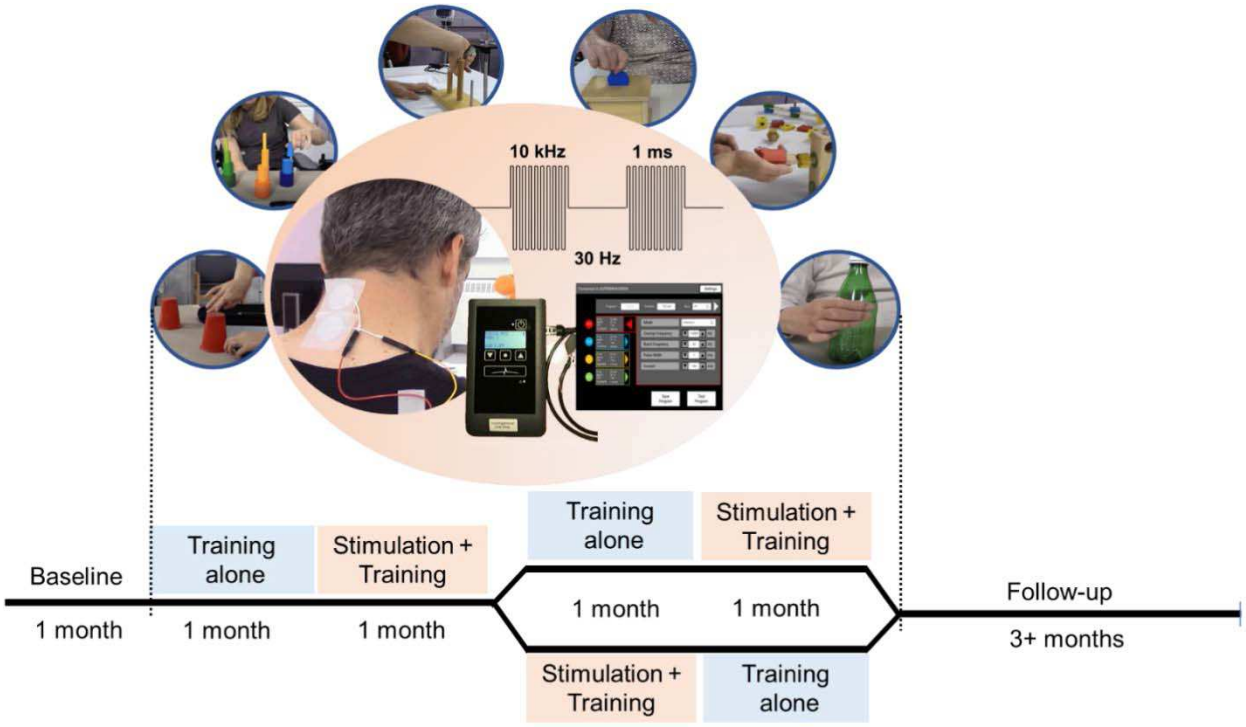


Fig. 1. **Study design and timetable.** A prospective, open-label, cross-over study. Outcome measurements were repeated weekly during baseline, every 2 weeks throughout the treatment period, and once a month during follow-up. We delivered training alone during the first month of treatment, and stimulation paired with training during the second month for all participants. We continued delivering stimulation to two participants with motor complete injuries (AIS B) and one participant with AIS D central cord syndrome, and interleaved a second month of training alone for other three participant with incomplete injuries (AIS C-D). Training: Intensive functional task training; Stimulation (inset): 1 ms bursts of 10 kHz transcutaneous cervical spinal cord stimulation delivered at 30 Hz.

outcome measures. The intervention began with four weeks of intensive functional task training following a specified protocol. Next, we delivered four weeks of transcutaneous electrical cervical spinal cord stimulation paired with the same training (Fig. 1). The order of the subsequent treatment arms was determined for each participant. We continued delivering stimulation to two participants with motor complete injuries (American Spinal Injury Impairment Scale (AIS) B), and one participant with AIS D central cord syndrome, and interleaved blocks of training alone for other three participants with incomplete injuries (AIS C-D). We interleaved blocks of treatment for participants with incomplete injuries to definitively test whether stimulation contributed to further improvements, as opposed to improvements accumulating regardless of the intervention. Additionally, repeated two arm cross-over design enabled each participant to serve as their own control. This is illustrated in Supplementary Fig. S1 and Supplementary Fig. S2, which clearly shows that improvements occur during the stimulation phases of the study.

The study was designed to follow participants for three months after the last treatment to document the persistence of functional gains without further intervention. All participants returned for monthly follow-up visits for at least three months, with one exception. Participant 1 was unavailable during the third month of follow-up, and instead returned 6 months after treatment for his final visit. Participant 3 also returned for an additional visit six months after treatment. The remaining participants were not eligible to return for this extra 6-months' follow-up visit due to enrolling in other studies or receiving Botulinum Toxin injections at the conclusion of our study. All procedures were approved by the University of Washington Institutional Review Board (STUDY00002985). The study was registered with ClinicalTrials.gov (NCT03184792).

B. Participants

Six volunteers with chronic cervical SCI participated in the study. The mean age of the participants was 42 years (SD±14, range 28 - 62), and the mean time since their injury was 4.6 years (SD±3.8, range 1.5-12). Demographics and clinical characteristics of the participants are listed in Table I. All participants gave written informed consent for all study procedures, including usage of video recordings/images. Participants 3 and 4 further consented to share their identifiable images and video clip in scientific publications. Inclusion and exclusion criteria are itemized in Table II.

C. Intensive Functional Task Training

Upper extremity motor training occurred three times per week and two hours per session. We used activity-based rehabilitation comprised of intensive, progressive, functional task training following a protocol. The protocol consisted of repetitive unimanual and bimanual activities of gross upper limb movement, isolated finger movements, bimanual task performance, simple and complex pinch, and grip performance

TABLE I

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS

	Age	Gender	Time since injury (yrs)	NLI	AIS category	INSCSCI UEMS
1	28	M	1.5	C5	B	24
2	33	M	4	C5	B	19
3	44	M	12	C5	C	38
4	32	F	5	C5	D*	43
5	62	F	2.5	C5	C	36
6	57	M	2.5	C3	D*	28

NLI: Neurologic Level of Injury; AIS: American Spinal Cord Injury Impairment Scale; ISNCSCI: International Standards for Classification of Spinal Cord Injury; UEMS: Upper Extremity Motor Score; M: male; F: female; * Central cord syndrome: paralysis in the arms and hands is more severe than the lower limbs

TABLE II

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:
- age between 21 and 70 years
- a traumatic SCI in the neck (C7 or higher level)
- at least one-year post-injury
- stable medical condition without cardiopulmonary disease or frequent autonomic dysreflexia that would contraindicate participation in upper extremity rehabilitation or testing activities
- difficulty independently performing hand and arm function in routine activities of daily living
- capability of performing simple cued motor tasks

Exclusion criteria:
- etiology of SCI other than trauma
- dependency on ventilation support
- concomitant neurologic disease, such as traumatic brain injury, multiple sclerosis, stroke, or peripheral neuropathy
- significant medical disease; including uncontrolled systemic hypertension with values above 170/100 mmHg; cardiac or pulmonary disease; chronic contagious disease, uncorrected coagulation abnormalities or need for therapeutic anticoagulation
- unhealed fracture, contracture, pressure sore, urinary tract infection, or other illnesses that might interfere with upper extremity rehabilitation or testing activities
- botulinum toxin injection in upper extremity muscles in the prior six months
- tendon or nerve transfer surgery in the upper extremity
- any implanted stimulator in the body, e.g., vagus nerve stimulator, cardiac pacemaker, cochlear implant, etc.
- depression, anxiety or cognitive impairment based on Patient Health Questionnaire-9 [25] (score >9/27), General Anxiety Disorder-7 item Questionnaire [26] (score >9/21), and Short Portable Mental Status Questionnaire [27] (score >2/10)
- pregnancy
- active cancer
- alcohol and/or drug abuse
- inability to read and/or comprehend the consent form

[16], [28]. For each category, 8-10 activities with various difficulty levels were designated, and the participant performed 1-2 activities within each category in each training session. Activities were chosen according to the participant's ability and were changed or modified as function progressed over time. For instance, the size of the coins was reduced for a pinch grip task, or resistance level was increased for TheraPutty exercises. Typical movement patterns were encouraged by guidance and giving feedback. When the subject had little to no voluntary movement, active assistance was provided. We encouraged 3-5-minute rest periods between activities and when needed.

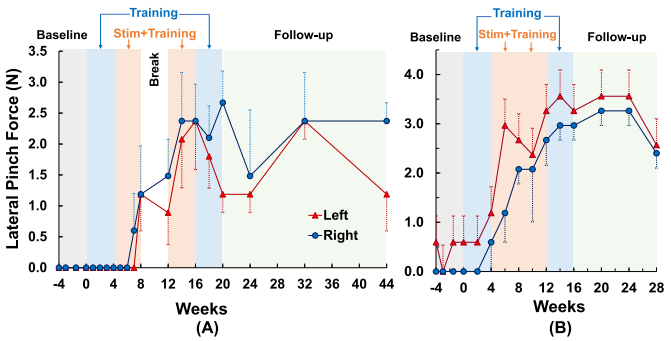


Fig. 2. **Restored movement after complete paralysis.** Transcutaneous spinal cord stimulation paired with intensive training enabled two paralyzed participants to regain digit movement and pinch force. Data points show the average of three maximal force measurements and the standard deviation bars per test session. **A**. Participant 1 (C5 AIS B) had no active movement distal to both wrists at baseline and throughout the first four weeks of training alone. Only with stimulation (stim) paired with training did this participant regain volitional movement of his fingers and thumbs that enabled him to produce measurable pinch force. Most notably, these gains in movement and pinch force were maintained for six months of follow-up without further treatment. **B**. Participant 2 (C5 AIS B) began the study with no function in either hand. Pinch force in both hands improved rapidly during stimulation paired with training, and was largely sustained for three months of follow-up without further treatment.

D. Transcutaneous Electrical Spinal Cord Stimulation

We delivered transcutaneous electrical stimulation to the cervical spinal cord utilizing the experimental device developed by NeuroRecovery Technologies Inc. (San Juan Capistrano, CA, USA). The device was approved for use in research by the University of Washington IRB. The stimulator delivers programmable electrical current waveforms that are comprised of two modulated frequencies: (1) base frequency and (2) overlapping frequency, on up to four independent channels (Fig. 1 inset). This current waveform is adapted from kilohertz-frequency muscle stimulation, and permits high amplitude stimulation without discomfort [29], [30]. Thus, stimulation over the skin can reach the spinal cord dorsal roots to activate spinal networks [31]. The rationale for the high overlapping frequency is that unmyelinated C-fibers in the skin can be selectively blocked by using high-frequency waveforms [20], [32], and stimulation may penetrate more deeply due to the lowering of the tissue impedance [20], [33].

We used an electrical current waveform for transcutaneous spinal cord stimulation that was either biphasic or monophasic, 1 millisecond pulse width, 30 Hz base frequency, with a 10 kHz overlapping frequency (Fig. 1 inset). Stimulation intensity was adjusted between 0 and 120 milliamperes (mA) using a tablet computer as a programmer. In this study, two independent channels were used to stimulate the cervical spinal cord at two locations on the skin over the vertebral processes. We used two 2.5 cm round self-adhesive hydrogel surface electrodes as cathodes and two 5 x 10 cm rectangular self-adhesive hydrogel electrodes as anodes (Axelgaard Manufacturing Co., Ltd., USA). Cathode electrodes were placed midline on the skin of the neck, one above and one below the injury level with the guidance of the occipital inion and spinous processes as landmarks. Anode electrodes were placed symmetrically over the anterior iliac crests of pelvis.

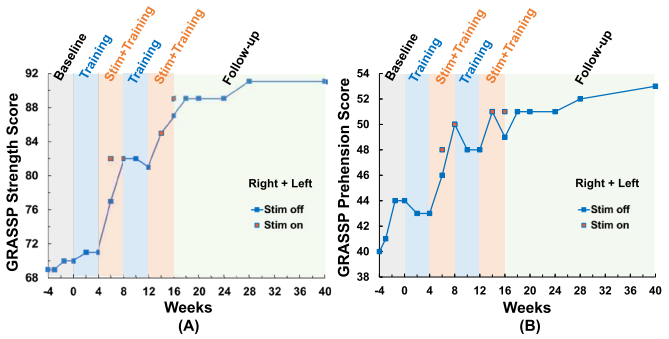


Fig. 3. **Hand function improved 12 years after injury.** Typical progression in strength and quantitative prehension measured by the Graded Redefined Assessment of Strength Sensation and Prehension (GRASSP). Participant 3 (C5 AIS C) began the study 12 years after injury. **A**. Strength in both hands and arms improved by only 2 points during each phase of baseline testing and training alone, compared to 11 points stronger during the first four weeks of stimulation paired with training. **B**. GRASSP prehension score did not increase during training alone, but improved by 7 points during the first month of stimulation and training and 3 points further during the second month of stimulation and training. All improvements were sustained throughout 6-months follow-up.

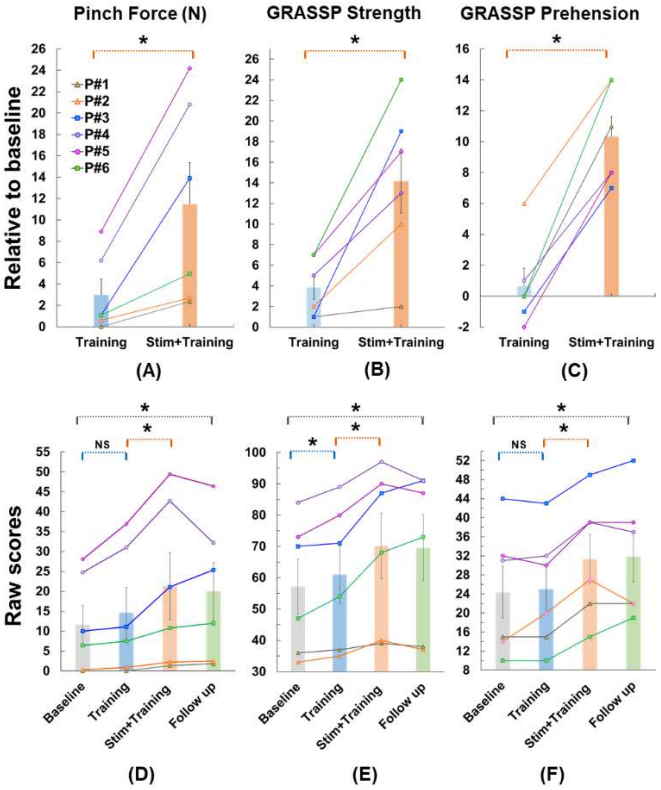


Fig. 4. **Stimulation improved hand function that was sustained for months.** All six participants improved hand function during transcutaneous stimulation paired with training, and maintained those gains throughout three to six months of follow-up. Stimulation combined with training led to greater improvements than training alone in bilateral **(A)** pinch force ($t\,(5) = 3.2$, $p = 0.024$), **(B)** GRASSP strength ($t\,(5) = 4.0$, $p = 0.010$), and **(C)** prehension ($t\,(5) = 8.5$, $p < 0.001$; paired sample T-test). Improvements that occurred during stimulation paired with training were maintained for at least 3 to 6 months of follow-up (**D**-**F**); all measures were significantly greater at final follow-up visit than baseline ($p \leq 0.045$; one-way repeated measures ANOVA and Tukey LSD post-hoc). All outcome measures were significantly greater at the end of stimulation than training alone ($p \leq 0.022$), and only the GRASSP strength measure improved due to training alone (Table IV). Pinch force shows the average of the right and left hands, GRASSP strength and prehension show bilateral (right+left) scores $*$: $p < 0.05$; NS: $p > 0.05$.

For therapeutic stimulation, we increased the stimulation intensity in increments of 5 mA to a subthreshold level. Subthreshold stimulation intensity for each activity was adjusted based on feedback from the participant about which intensity made the task easiest. We typically observed enhanced volitional control over weak or paralyzed muscles between 40-90 mA stimulation intensities. We confirmed that stimulation parameters for each participant were not evoking direct muscle contractions using surface EMG (Delsys Trigno wireless system, Boston, MA, USA). Electrodes were placed on eight upper extremity muscles (deltoid, triceps, biceps, extensor digitorum, flexor digitorum, first dorsal interosseous, abductor pollicis brevis, and abductor digiti minimi) on each arm and hand.

Monophasic and biphasic stimulation waveforms activate neural circuits differently [34], and both waveforms were tested for their ability to enable functional movements. In each session, participants received either monophasic or biphasic stimulation waveforms determined according to the best response obtained for each task training (Supplementary Table S1). In general, monophasic stimulation facilitated activities that require strength, whereas biphasic stimulation promoted fine motor skills.

Stimulation was delivered for up to 120 minutes during each session of stimulation paired with training. For safety precautions, we closely monitored heart rate and blood pressure throughout each session. Stimulation intensity was re-adjusted as needed throughout the intervention phase of the study (Supplementary Table S1). For example, dexterity training required less stimulation current than strengthening exercises for some participants.

E. Outcome Measures

The primary outcome measure was the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) version 1.0 [35] (Neural Outcomes Consulting Inc. Toronto, ON, Canada). Secondary outcomes included the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) exam [36], lateral pinch force measurement, and clinical assessment of spasticity.

Lateral pinch force was measured for both the right and left hands (Echo wireless and IRIS software; JTech Medical Industries, Inc. Midvale, UT, USA). To avoid tenodesis movement, tests were performed in a standardized way with participants seated upright against the back of their wheelchair, shoulder adducted and neutrally rotated, elbow flexed 90 degrees, and forearm in the neutral position as much as possible given muscle tone [37]. Verbal encouragement was provided to the subjects to exert maximum force. Visual feedback of force was not provided. The average of three maximal force measurements per test session was reported [37].

Spasticity was graded by the Modified Ashworth Scale (MAS) [38]. A total MAS score was calculated by adding five upper extremity scores from each arm and hand (shoulder

abduction; elbow extension and supination; and wrist extension; and finger extension) (range 0 – 40, 1+ grade was calculated as 1.5 points). Additionally, the Spinal Cord Independence Measure III (SCIM III) [39] self-care subdomain, and the WHO Quality of Life – BREF [40] questionnaire were administered to capture improvements in independence and quality of life.

GRASSP test and pinch force measurements were repeated once every week at baseline, every two weeks throughout the interventions and every month during the first three months of follow-up. Measurements were performed with and without stimulation in random order during all stimulation intervention periods. These measurements were done on consecutive days to avoid fatigue. All other measurements were repeated once at baseline, at the end of each month of treatment, and during monthly follow-up visits.

F. Data Analyses

For comparison of the functional changes occurring during each intervention phase, one-way repeated measures ANOVA was used with post-hoc pairwise analysis as per Tukey LSD test (IBM SPSS version 26). A Shapiro-Wilk Test showed that repeated measurements followed a normal distribution. Mauchly's test was used to analyze the assumption of sphericity, and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity when the assumption was violated.

We directly compared the benefits of training alone and stimulation combined with training by calculating the cumulative changes in each outcome measure across each intervention arm. These values were normalized to baseline to control for individual variation in function when beginning the study, and compared between training and stimulation + training interventions using a paired-samples T-test.

Additionally, score changes relative to the preceding treatment block were calculated to compare the improvement rates between intervention phases repeated monthly. These data failed the test for normality, and thus the Wilcoxon Signed-Rank test was used for comparisons.

To evaluate the possible predictors of outcome due to stimulation, we performed Pearson correlation analysis between residual motor function and spasticity at baseline and magnitude of the improvements. Percentage change was calculated as the improvement rate relative to baseline.

For all tests, $p < 0.05$ was considered significant. All participants' data were included in all analyses. Group data displays individual values as dot plots and mean ± standard error of the mean (SEM) as bar plots. Given the early stage of research and lack of prior data on transcutaneous spinal cord stimulation for restoring upper limb function, power analysis and sample size were not computed.

III. Results

Here we show that transcutaneous cervical spinal cord stimulation paired with intensive exercise training restored substantial and prolonged upper extremity function in six people with both motor complete and incomplete cervical SCI (Table 1). We directly compared improvements during the application of training alone to stimulation paired with training, as well as long-term benefits that persisted for many months beyond stimulation.

People with complete paralysis due to SCI typically do not recover significant function beyond the first year after injury [41]. Our first participant with such motor complete paralysis had no active movement of his fingers or thumbs when he joined the study. His hands remained paralyzed despite four weeks of intensive training (Fig. 2A). It was only during four subsequent weeks of transcutaneous stimulation paired with the same training that he began to move his fingers and thumbs for the first time since his injury. Restored hand movement allowed him to produce pinch force between his fingers and thumb in both hands (Fig. 2A). Four additional weeks of stimulation paired with training nearly doubled the force he could produce in both hands, whereas four additional weeks of training alone had no effect. Most notably, his gains in movement and pinch force were maintained for at least six months of follow-up without any further treatment (Fig. 2A).

We observed similar results for the second participant with a motor complete injury who had no functional finger and thumb movement when he began the study (Fig. 2B). His parallel improvements in pinch force in both hands reinforce that the pairing of transcutaneous stimulation and training leads to lasting benefits for people with motor complete cervical SCI.

Our remaining four participants joined the study with limited ability to move their fingers and thumbs. Some of these participants responded almost instantly to stimulation. For example, after 12 years of severe weakness following SCI, our third participant regained the ability to manipulate objects on the first day of stimulation (Supplementary movie 1). By the second day of stimulation, this participant could reliably grasp and release much smaller objects (Supplementary movie 2). Active stimulation was initially required for improved hand function in this third participant, as measured by the Graded, Redefined Assessment of Strength Sensation and Prehension (GRASSP). Within one month of stimulation and training, however, he could achieve a high level of function even without stimulation (Fig. 3). An additional month of stimulation further enhanced his hand function, which was retained for at least six months after the end of all treatment.

Similar benefits of improved strength and grasping ability were observed in all participants. Performance was significantly higher at the end of stimulation compared to training alone for pinch force, arm and hand strength, and dexterity (Fig. 4 A-C, $p < 0.025$, paired-samples T-test, Table III). For example, pinch force improved between 2.4- and 4.8-fold during stimulation combined with training compared to baseline levels. Stimulation treatment improved function in every subject, whereas training alone led to only slight improvements. (Supplementary Fig. S1). The magnitudes of the improvements during the first and second blocks of training alone vs. stimulation+training are shown in Supplementary Fig. S2 D-F.

Stimulation allowed the participants to engage more fully in the training exercises by permitting activation of previously weak or paralyzed muscles. This led to functional improve-

TABLE III
RESULTS OF PAIRED SAMPLES T-TEST FOR CUMULATIVE IMPROVEMENTS

	Pinch Force (N)*	GRASSP Strength**	GRASSP Prehension**
Mean (SEM)			
Training alone	3.0 (1.5)	3.8 (1.2)	0.7 (1.1)
Stim + Training	11.5 (3.9)	14.2 (3.1)	10.2 (1.2)
95% CI for Mean Difference	1.7, 15. 3	3.7, 17.0	6.6, 12.4
Correlation coefficient (r)	0.9	0.61	0.54
Test statistics (t)	3.22	4	8.5
Degrees of freedom (df)	5	5	5
p-value	0.024	0.010	0.000
Effect size (Cohen's d)	1.34	1.63	3.75

SEM: standard error of the mean
*Average of the right and left hands; **Bilateral (right+left) score

TABLE IV
RESULTS OF ONE-WAY REPEATED MEASURES ANOVA

	Pinch Force†‡	GRASSP Strength*	GRASSP Prehension*
Mean (SEM)			
(1) Baseline	11.6 (5.0)	57.2 (8.7)	24.3 (5.4)
(2) Training alone	14.6 (6.4)	61.0 (9.2)	25.0 (5.0)
(3) Stim +Training	23.1 (8.8)	71.3 (10.4)	34.7 (4.3)
Test statistics	$F(1.1,5.3)=8.8$	$F(2,10)=18$	$F(2,10)=49.3$
p-value	0.029	0.000	0.000
Partial eta^2 (η_p^2)	0.638	0.783	0.908
Tukey LSD			
(1) vs. (2)	$p = 0.102$	$p = 0.022$	$p = 0.586$
(1) vs. (3)	$p = 0.032$	$p = 0.006$	$p = 0.000$
(2) vs. (3)	$p = 0.022$	$p = 0.010$	$p = 0.000$

SEM: standard error of the mean; F: test statistics, η2: partial eta squared. A Shapiro-Wilk Test showed that repeated GRASSP strength and prehension scores, and pinch force follow a normal distribution.
Mauchly's test indicated that the assumption of sphericity was met for GRASSP strength ($\chi2(2)= 2.46$, $p = 0.078$), quantitative prehension ($\chi2(2)= 0.22$, $p = 0.897$) scores.
†The assumption of sphericity for pinch force ($\chi2(2)= 9.1$, $p = 0.011$) has been violated; therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity for pinch force ($\varepsilon = 0.527$)
‡Average of the right and left hands; *Bilateral (right+left) score

TABLE V
ISNCSCI EXAMINATION SCORES

Participants	**1**	**2**	**3**	**4**	**5**	**6**
NLI, AIS, Motor Level Right | Left						
Baseline	C5, B, C6|C6	C5, B, C5|C5	C5, C, C6|T1	C5, D, C8|C8	C5, C, C7|C5	C3, D, C5|C3
Training	C5, B, C6|C6	C5, B, C5|C5	C5, C, C6|T1	C5, D, C8|C8	C5, C, C7|C5	C3, D, C5|C3
Stim+Training	C5, B, **C7**|C6	C5, B, C5|**C6**	C5, **D,** C6|T1	C5, D, C8|**T1**	C5, C, **C8|C7**	C3, D, **C6**|C3
Follow-up	C5, B, **C7**|C6	C5, B, C5|**C6**	C5, **D,** C6|T1	C5, D, C8|C8	C5, C, C7|**C6**	C3, D, **C6**|C3
UEMS Right | Left						
Baseline	12|12	9|10	14|24	19|23	19|17	16|12
Training	12|12	9|**11**	14|24	**21**|23	19|17	16|12
Stim+Training	**14**|12	**12|14**	**20|25**	**22|24**	**21|20**	**20|16**
Follow-up	**14**|12	**12|13**	**20|25**	**21|24**	**21|19**	**20|15**
LEMS Right | Left						
Baseline	0|0	0|0	6|11	21|22	5|13	20|19
Training	0|0	0|0	6|11	21|22	5|13	20|19
Stim+Training	0|0	0|0	**8|12**	21|**23**	5|12	**24**|19
Follow-up	0|0	0|0	**8|12**	22|**23**	5|12	**24**|19
Light touch | Pin prick						
Baseline	31|30	29|31	64|72	68|71	68|68	65|67
Training	31|30	30|31	64|72	67|71	68|68	65|67
Stim+Training	**39|39**	30|31	64|**76**	66|70	68|**69**	65|67
Follow-up	**35|35**	30|31	64|**74**	67|71	68|**70**	65|65

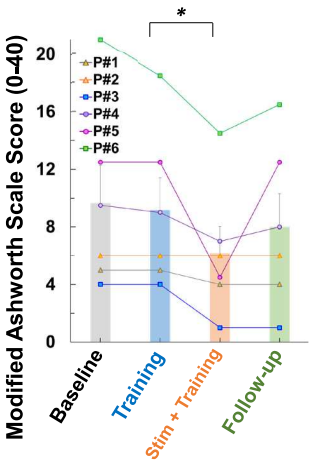
ISNCSCI: International Standards for Classification of Spinal Cord Injury; NLI: Neurologic Level of Injury; AIS: American Spinal Cord Injury Impairment Scale; UEMS: Upper Extremity Motor Score (0-50 points); LEMS: Lower Extremity Motor Score (0-50 points); Light touch and pin prick sensation (each 0-112 points)

ments that persisted for three to six months beyond the stimulation in all participants (Fig. 4 D-F, Table IV). One-way repeated measures ANOVA confirmed significant differences over the study in GRASSP measures for strength ($F(2,10) = 18.0$, $p < 0.001$), quantitative prehension ($F(2,10) = 49.3$, $p < 0.001$), and pinch force ($F(1.1,5.3) = 8.8$, $p = 0.029$). Post-hoc comparisons showed that all measures were significantly greater at the end of stimulation than training alone, whereas the differences between baseline and training alone were not significant except GRASSP strength (Supplementary Fig. S1).

After the first month of stimulation, improvements in pinch force and GRASSP strength score required the stimulator to be active during testing to exceed gains made during the preceding month of training alone ($p \leq 0.041$; Wilcoxon Signed Rank test; Supplementary Fig. S2 D-E). After the second month of stimulation, however, strength gains were greater than the second month of training alone even when measured with the stimulator off ($p \leq 0.046$; Wilcoxon Signed Rank test; Supplementary Fig. S2 D-E). Although strength measures decreased a few points during the second month of training, they remained significantly higher than those measured at baseline and after the first month of training alone (Supplementary Fig. S1). Finally, functional improvements were mostly sustained for three to six months of follow-up; all measures were significantly greater ($p < 0.05$) at the final follow-up visit compared to baseline (Fig. 4 D-F, Table IV, Supplementary Fig. S1).

The upper extremity motor scores of all participants improved by up to eight points at the end of stimulation compared to two points or less following training alone (Table V). Our third participant also converted from AIS C to AIS D during stimulation treatment and retained this improvement throughout six months follow-up. An expanded summary of the ISNCSCI sensory and motor examination results of all participants is illustrated in Supplementary Fig. S3.

Spasticity severely interferes with residual motor function and complicates performing activities of daily living in about 80% of people with chronic SCI [42]. Previous studies demonstrated that ongoing epidural spinal cord stimulation had beneficial effect on spasticity [19], [43]. After several sessions of transcutaneous stimulation, there was a notable attenuation of high muscle tone both during and between stimulation sessions in the upper limbs of our participants



Modified Ashworth Scale						
Participants	**1**	**2**	**3**	**4**	**5**	**6**
Baseline	5	6	4	9.5	13	21
Training	5	6	4	9	13	19
Stim+Training	4	6	1	7	4.5	15
Follow-up	4	6	1	8	13	17

Fig. 5. **Spasticity reduced during stimulation treatment.** The average decrease in MAS score was 3.5 ± 3.0 points (range 0 – 8 points). Paired-samples T-test indicated that the reduction in spasticity was statistically significant ($t = 2.6$, $p = 0.048$).

with spasticity. This reduction of spasticity contributed to substantial improvements in function. For example, our fifth participant could not open her fingers and thumb to grasp a 2.5 cm block during training alone, but progressed to grasping 7.5 cm blocks during stimulation combined with training (Supplementary movie 3). Spasticity improved by eight points for this participant as measured by the Modified Ashworth Scale, and by an average of 3.5 ± 3.0 points for all participants ($p < 0.05$). Reduction in spasticity was progressive throughout stimulation sessions and maintained up to 10-15 days after stimulation treatment ended (Fig. 5).

The benefits of non-invasive stimulation extended beyond restoration of hand function to improvements in autonomic function. One participant's heart rate returned to normal after being bradycardic for 12 years. His heart rate was between 40 and 45 beats per minute (bpm) throughout the initial phases of the study. This made him feel dizzy and close to fainting early in the day. Beginning on the fourth day of stimulation, his resting heart rate gradually improved to a normal 60-65 bpm, which was maintained throughout the follow-up period. This participant also regained diaphoresis below his injury level, and thermoregulation was improved in three other participants. Two participants reported improvement in the quality of sleep due to the relief of nighttime spasms. Participants 2 and 3, who used intermittent catheterization for bladder management, reported improved control of volitional voiding and decreased residual urine volume (Table VI). Moreover, one of the participants with motor complete injury and another with central cord syndrome pointed out that their core stability, balance control, and lower extremity function improved during their routine exercise program, which was confirmed by their trainers.

Stimulation enabled functional recovery and allowed participants to resume their hobbies. Participant 3 resumed playing guitar for the first time in 12 years since his injury (Supplementary movie 4; Supplementary Fig. S4 A). Participant 4 was able to return to oil painting five years after her injury (Supplementary Fig. S4 B). In parallel with functional

TABLE VI
INDEPENDENCE AND QUALITY OF LIFE SCORES

Participants	**1**	**2**	**3**	**4**	**5**	**6**
SCIM III-Self Care						
Baseline	5	0	16	7	3	1
Training	5	0	16	7	3	1
Stim+Training	**8**	**2**	**18**	**8**	**4**	**5**
Follow-up	**6**	**2**	**18**	**10**	**4**	**5**
SCIM III-Respiration and Sphincter management						
Baseline	15	30	33	17	15	15
Training	**16**	30	33	17	15	15
Stim+Training	**17**	**35**	**34**	17	**16**	15
Follow-up	**17**	30	**34**	17	**16**	15
WHO-QoL-BREF, Physical Health						
Baseline	56	56	56	63	44	69
Training	75	63	56	63	44	69
Stim+Training	81	69	75	69	56	69
Follow-up	69	50	75	69	56	69
WHO-QoL-BREF, Psychological Well-Being						
Baseline	44	75	56	69	44	63
Training	56	81	63	75	44	63
Stim+Training	56	81	69	81	44	81
Follow-up	56	69	69	81	44	75

MAS UE Score: Modified Ashworth Scale Upper Extremity score (range 0-40 points, lower is better, see Methods); WHO-QoL-BREF: World Health Organization-Quality of Life-BREF Questionnaire (range 0-100) SCIM: Spinal Cord Injury Independence Measurement Questionnaire, Self-care (range 0-20 points); Respiration and Sphincter management (range 0-40 points)

improvements, psychological well-being and physical health domains of World Health Organization-Quality of Life-BREF scores increased up to 19 points, and Spinal Cord Injury Independence Measure (SCIM) self-care domain improved by 1 to 4 points for each participant following treatment with stimulation (Table VI).

Stimulation was well tolerated by all participants. We did not observe any significant adverse events or maladaptive plasticity related to transcutaneous spinal cord stimulation. The only adverse event was a mild allergic skin rash on the hands and distal forearms of the third participant, who has a family history of urticaria. Considering that this participant returned to normal sweating below the injury level for the first time since injury and normalization of heart rate, this minor adverse event was attributed to partial restoration of his pre-injury autonomic nervous and immune system function.

IV. DISCUSSION

Our findings demonstrate that transcutaneous spinal cord stimulation leads to both rapid and sustained recovery of hand and arm function for people with both motor complete and incomplete cervical SCI. The magnitude of the functional improvements in our study is greater than all previous reports of interventions in individuals with even subacute or chronic SCI, such as activity-based physical therapy [44], functional electrical training [5], [6], somatosensory stimulation [28], and upper extremity robotic rehabilitation [45]. The discovery that all functional improvements were maintained for many months beyond stimulation treatment is strong evidence for the

induction of neuroplasticity within the injured central nervous system [46], [47].

Gad et al. [23] demonstrated in an open-label, uncontrolled study that transcutaneous cervical spinal cord stimulation improved grip force 2-fold without simultaneous stimulation active and 3-fold during stimulation. In this study, six participants were trained for maximum voluntary grip force and rhythmic grip and release activity in the presence of stimulation in 8 sessions over four weeks. In the present study, we controlled the effect of transcutaneous spinal cord stimulation by comparing training alone to the same training combined with stimulation using a cross-over design. This cross-over design allowed each participant to serve as their own control when comparing intervention arms over time. In addition, intensive upper extremity functional training combined with stimulation may improve the functional outcomes of stimulation as observed in our previous work [22].

Several participants began moving their fingers for the first time since injury following stimulation treatment and were able to produce measurable pinch force. Although these participants only produced 2-4 N of pinch force, functional tasks such as pressing control button on a remote control or opening a vertical zipper can be performed with this level of force [48].

Statistically significant reduction in spasticity contributed to functional improvement. Improvement in MAS score was maintained up to two weeks after stimulation treatment ended. This finding is consistent with other research, which found transcutaneous direct current spinal cord stimulation progressively improves muscle tone during active stimulation period and up to seven days following stimulation [49]. Hofstoetter et al. suggested that transcutaneous spinal cord stimulation can be used for spasticity management and may serve to determine responders to electrical spinal cord stimulation after SCI [49].

Several groups reported beneficial effects of thoracic and lumbosacral epidural stimulation on cardiovascular [50]–[52], bowel [52], bladder [9], [52], sexual function [9], [52], and thermoregulation [9]. Gad et al. [53] reported improvement in bladder and urethral sphincter function via transcutaneous spinal stimulation applied to the thoracic spinal cord. Normalization of bradycardic heart rate in one of our participants 12 years after SCI demonstrates the potential of non-invasive cervical spinal cord stimulation to markedly improve cardiovascular dysfunction.

The unique combination of transcutaneous spinal stimulation and intensive training most likely enabled both immediate and long-term recovery via the following mechanisms. Transcutaneous stimulation activates the spinal cord via sensory pathways in the dorsal roots to provide sub-threshold excitation to the interneurons and motor neurons within the spinal cord distal to the lesion [54], [55]. Motor neurons close to threshold are then more easily activated by the intact but dormant residual descending pathways from the brain, restoring volitional control of movement [17], [56]. The regained ability to move during stimulation enables people to participate actively in rehabilitation training, which in turn induces reorganization of the spinal networks, strengthen synaptic connections, and leads to long-term recovery of function via neuroplasticity [15], [46], [57].

Epidural stimulation likely activates similar sensory afferents pathway via the implanted stimulation electrodes [58], and a subset of studies are beginning to report that some functional gains persist beyond epidural stimulation [11], [59]. The non-invasive nature of transcutaneous spinal cord stimulation, however, can accelerate its translation to clinical practice and restore long-term function to people with hand and arm paralysis.

There are several limitations of this study. First, sham stimulation and blinding are difficult to achieve due to the sensation associated with stimulation. Second, we did not explicitly test the requirements for training combined with stimulation, although it is generally accepted that training during stimulation is needed to produce functional plasticity [60]–[61]. A final limitation of this and other studies is that diverse injury severity and baseline function among people with SCI results in variability when studying a small sample size. Future studies using larger sample size and evaluator-blinded assessments are needed to rigorously characterize the response to spinal stimulation. Nevertheless, the findings of the present study provide evidence that transcutaneous cervical spinal cord stimulation promotes immediate and prolonged improvement in hand function that outlasts the intervention by many months.

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