
Goutam Singh, PT, PhD1,2; Anastasia Keller, PhD3; Kathryn Lucas, PhD, PT2,4; Catherine Borders, OTD5; Danielle Stout, OTD5; Molly King, BA2,4; Parth Parikh, BS2,4; Nicole Stepp, MS2,4; Beatrice Ugiliweneza, PhD2,4; Jessica M. D’Amico, PhD6,7; Yury Gerasimenko, PhD2,4,8; Andrea L. Behrman, PhD, PT2,4

ABSTRACT

Objective: In adults with cervical spinal cord injury (SCI), transcutaneous spinal stimulation (scTS) has improved upper extremity strength and control. This novel noninvasive neurotherapeutic approach combined with training may modulate the inherent developmental plasticity of children with SCI, providing even greater improvements than training or stimulation alone. Because children with SCI represent a vulnerable population, we first must establish the safety and feasibility of any potential novel therapeutic approach. The objectives of this pilot study were to determine the safety, feasibility, and proof of principle of cervical and thoracic scTS for short-term effect on upper extremity strength in children with SCI.

Materials and Methods: In this nonrandomized, within-subject repeated measure design, seven participants with chronic cervical SCI performed upper extremity motor tasks without and with cervical (C3–C4 and C6–C7) and thoracic (T10–T11) scTS. Safety and feasibility of using cervical and thoracic sites scTS were determined by the frequency count of anticipated and unanticipated risks (eg, pain, numbness). Proof-of-principle concept was tested via change in force production during hand motor tasks.

Results: All seven participants tolerated cervical and thoracic scTS across the three days, with a wide range of stimulation intensities (cervical sites = 20–70 mA and thoracic site = 25–190 mA). Skin redness at the stimulation sites was observed in four of 21 assessments (19%) and dissipated in a few hours. No episode of autonomic dysreflexia was observed or reported. Hemodynamic parameters (systolic blood pressure and heart rate) remained within stable limits (p > 0.05) throughout the assessment time points at baseline, with scTS, and after the experiment. Hand-grip and wrist-extension strength increased (p < 0.05) with scTS.

Conclusions: We indicated that short-term application of scTS via two cervical and one thoracic site is safe and feasible in children with SCI and resulted in immediate improvements in hand-grip and wrist-extension strength in the presence of scTS.

Clinical Trial Registration: The Clinicaltrials.gov registration number for the study is NCT04032990.

Address correspondence to: Goutam Singh, PT, PhD, 900 S 3rd St, Louisville, KY 40203, USA. Email: goutam.singh@louisville.edu

1 Kosair Charities School of Physical Therapy, Spalding University, Louisville, KY, USA;
2 Kentucky Spinal Cord Injury Research Center, University of Louisville, Louisville, KY, USA;
3 University of California San Francisco, San Francisco, CA, USA;
4 Department of Neurological surgery, University of Louisville, KY, USA;
5 University of Louisville Health, Louisville, KY, USA;
6 Glenrose Rehabilitation Hospital, Alberta Health Services, Edmonton, Alberta, Canada;
7 Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; and
8 Pavlov Institute of Physiology, St Petersburg, Russia

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Keywords: Cervical spinal cord stimulation, hand grip, pediatric, safety and feasibility, spinal cord injury

Conflict of Interest: Yury Gerasimenko has a shareholder interest in Onward and Cosyma. He holds certain inventorship rights on intellectual property licensed by the regents of the University of California to NeuroRecovery Technologies and its subsidiaries. The remaining authors report no conflict of interest.

INTRODUCTION

In the United States, every year, there are approximately 54 new cases of spinal cord injury (SCI) per 1 million, with an estimated 302,000 people currently living with SCI. Children and adolescents aged <16 years account for 5% of all SCIs.22 Although children have a lower prevalence of SCI overall, they are at greater risk of cervical SCI owing to developmental cephalo-cervical proportions.22 Children with severe cervical SCI, that is, complete loss of motor and sensory function below injury level, experience the devastating consequences of limb and trunk muscle paralysis rendering them unable to sit upright, stand, walk, and use their hands and arms to reach and grasp. The inability to grasp a toy, stack blocks, or hold a cup profoundly limits a child’s typical development through play. According to the current standard of care, the aim of occupational and physical therapy is to teach children with SCI alternative movement strategies to compensate for paralysis. In the absence of voluntary finger flexion, for instance, children are taught to extend their wrist and to induce passive finger flexion to achieve grasping movement. These compensatory strategies are associated with long-term problems such as reduced range of motion, pain, and muscle contractures.2,7,8

Ample scientific evidence for activity-dependent plasticity of spinal neural networks below the lesion has spurred a paradigm shift in rehabilitation to now target recovery after SCI.13,14 Neurotherapeutics, for example, activity-based locomotor training15 and neuromuscular electrical stimulation,15,16 uses sensory-driven stimulation of neural networks to generate motor output below the lesion, thereby improving the long-term capacity for movement below the SCI even after cessation of therapy.16,17 Incorporation of neuromodulatory techniques, such as epidural and transcutaneous spinal cord stimulation (scTS), further challenges the limits for recovery previously thought possible after SCI, with recent reports of adults with chronic complete SCI regaining the capacity to stand and walk18,19 and manipulate/grasp.20–22 scTS provides a noninvasive neuromodulatory tool that may increase the central state of excitability below the lesion, thereby enabling greater capacity for integration of sensory input and augmentation of motor output to potentiate motor recovery.23,24 Children with SCI may not only benefit from novel neurotherapeutic interventions but also may show even greater neurological recovery owing to inherent plasticity present during development.25–29 Although scTS has improved sitting posture30 and upper extremity (UE) function30 in the short term in adults with SCI, we propose to extend this work in children with SCI. Given children with SCI represent a vulnerable population, we first must establish the safety and feasibility of any potential novel therapeutic approach. In our recent work in children with trunk motor deficit after SCI, we revealed that the application of scTS at T10–T11 and L1 stimulation sites to enable upright sitting was a safe and feasible approach.31 However, these thoracolumbar stimulation sites were optimized to facilitate upright sitting. To our knowledge, there is no study that has reported safety and feasibility of cervical scTS applied to improve UE motor function in children with SCI. It is crucial to prioritize the safety of electrical stimulation administered over the cervical spinal cord because it may unintentionally stimulate nearby vital structures like the trachea, laryngeal muscles, diaphragm, and vagus nerve. Therefore, the objectives of this pilot study were to determine the safety, feasibility, and proof of principle of cervical combined with thoracic scTS for short-term (immediate) effect on UE strength in children with SCI.

MATERIALS AND METHODS

Demographics and Clinical Characteristics

This study is a registered clinical trial (NCT04032990). The institutional review board (IRB) ethics committee at the University of Louisville approved this study (IRB protocol no. 19.0810). Informed consent and assent were signed by legal guardians of children and children aged more than seven years, respectively. The Human Locomotion Research Center Database (University of Louisville Study no. 06.0647), Louisville, KY was used to identify and recruit potential research volunteers on the basis of eligibility criteria. Seven participants (one girl and six boys, aged 12 ± 5 years, range: six to 17 years) who met the following inclusion criteria participated in the study: chronic (>year after injury), acquired upper motor neuron cervical and/or high thoracic (T1) SCI (according to their medical records evaluated by medical doctor); discharge from in-patient rehabilitation; moderate to severe UE deficit as assessed by the Pediatric Neuromuscular Recovery UE Scale32 (Peds NRS) (scores <4A, including inability to reach overhead, grasp, or pinch); and completion of ≥40 sessions of neuromuscular electrical stimulation and a plateau in neuromuscular recovery (established by comparing scores from the assessment after last therapy session with the baseline assessment for this study). Exclusion criteria included the use of Botulinum within the past three months, current oral buprenorphine use, unhealed UE fracture, congenital SCI, total ventilator dependence, and any medical complication limiting participation in the assessment. Demographics related to etiology, age at the onset of SCI, and time since injury were collected and reported (Table 1) according to the National Institute of Neurologic Disorders and Stroke–Common Data Elements guidelines33 for pediatric SCI.
Experimental Design

This is an experimental pilot study using a within-subject, repeated measures design. For proof of principle, participants performed three attempts of each of the following tasks: maximal hand-grip, wrist-flexion, wrist-extension, and elbow-extension strength tasks under two conditions: no stimulation and with scTS. A precalibrated strain gauge-based isometric dynamometer with a linear response in the 0 to 800 Newton (N) range (MLT004/ST Grip Force Transducer, ADInstruments, Dunedin, New Zealand) and accuracy of ±5% of reading was used to measure hand-grip force generated during maximum voluntary contractions (isometric). The device measures hand-grip force by displaying a tracker on a monitor, representing force exerted upon the dynamometer.

Participants reported to the laboratory on three separate days. Days 1 and 2 were used to familiarize participants with the task. In addition, optimization of cervical scTS parameters to improve hand-grip strength was performed on both day 1 and 2 (Fig. 1). On day 3, hand-grip, wrist-flexion, wrist-extension, and elbow-extension strength data at baseline (no scTS) and with optimized cervical and/or thoracic (T10–T11) scTS were collected and used for analysis, except for participant P14, for whom day 1 data were reported owing to the greatest improvement in hand-grip force that day. On the basis of our previous study showing facilitation of upright sitting posture via application of thoracic scTS in children with SCI, the T10–T11 scTS site was added to facilitate active upright sitting during upper extremity motor tasks. Monitoring for any adverse events was performed during all three days (cervical and thoracic scTS optimization and UE assessment). Safety and feasibility were determined by the frequency count of anticipated (eg, skin redness, muscle spasm) and unanticipated risks (eg, pain, numbness) with cervical and thoracic site scTS. All events were documented and followed over the next 24 hours with the caregiver. Blood pressure (BP), heart rate (HR) (using Welch Allyn Connex Spot Monitor, or manually) and pain (using FACES scale for children aged less than eight years and Visual Analogue Scale (VAS) scale for children aged eight years or more) were assessed at three standardized time points within the experiment: baseline (no scTS), with stimulation on at C3–C4 and C6–C7 sites and at the end of the experiment (no scTS). Compliance in attendance at all experiments was documented and reported. In addition, for exploratory assessment, to investigate presence or absence of voluntary muscle activation and effects of scTS on hand, wrist, and elbow flexor and extensor muscles during strength tasks, surface electromyography (sEMG) (Cometa, Italy) signals were recorded from proximal (bicep brachii and triceps brachii) and distal (extensor digitorum, flexor carpi radialis [FCR] and ulnaris) muscles from the dominant hand side. The sEMG signals were sampled at 2000 Hz, with a bandpass filter of 10 to 500 Hz before visualization of muscle activity with and without stimulation.

Participant Preparation

On the day of experiment, before placing the electrodes, each participant’s skin was examined for any redness or irritation, particularly in the areas of electrode placement. For cervical scTS, two 2.5-cm round electrodes (Syrtenty®, China) were placed midline between C3–C4 and C6–C7 spinous process, as cathodes, and two 5.0 × 8 cm rectangular plates (Syrtenty®) were placed symmetrically on the skin over the iliac crests, as anodes, by a designated team member (Fig. 2). The skin over the muscle belly was cleaned by alcohol swabs, and the multimuscle wireless surface

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**Table 1. Participant Demographics and Stimulation Parameters.**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>AIS Grade</th>
<th>Injury level</th>
<th>Time since injury (y)</th>
<th>Stimulation Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>P23</td>
<td>6</td>
<td>109</td>
<td>131</td>
<td>B</td>
<td>C4–C7</td>
<td>3 y, 9 mo</td>
<td>C3–C4 = 20 mA, 30 Hz, C6–C7 = 25 mA, 30 Hz, C10–T11 = 110 mA, 30 Hz</td>
</tr>
<tr>
<td>P22</td>
<td>7</td>
<td>131</td>
<td>122</td>
<td>C</td>
<td>C6–T4</td>
<td>3 y, 11 mo</td>
<td>C6–C6 = 25 mA, 30 Hz, T10–T11 = 100 mA, 30 Hz</td>
</tr>
<tr>
<td>P14</td>
<td>9</td>
<td>122</td>
<td>138</td>
<td>D</td>
<td>C7</td>
<td>5 y, 11 mo</td>
<td>C3–C4 = 44 mA, 30 Hz, C6–C7 = 45 mA, 30 Hz</td>
</tr>
<tr>
<td>P32</td>
<td>M</td>
<td>9</td>
<td>148</td>
<td>A</td>
<td>C7</td>
<td>2 y, 9 mo</td>
<td>C6–C7 = 70 mA, 30 Hz, T10–T11 = 190 mA, 30 Hz</td>
</tr>
<tr>
<td>D47</td>
<td>F</td>
<td>17</td>
<td>177</td>
<td>B</td>
<td>C5–C1</td>
<td>2 y, 2 mo</td>
<td>C6–C7 = 25 mA, 30 Hz, C10–T11 = 50 mA, 30 Hz</td>
</tr>
<tr>
<td>P50</td>
<td>M</td>
<td>17</td>
<td>187</td>
<td>A</td>
<td>C2–T1</td>
<td>13 y, 7 mo</td>
<td>C3–C4 = 70 mA, 30 Hz, C6–C7 = 60 mA, 30 Hz</td>
</tr>
<tr>
<td>P56</td>
<td>M</td>
<td>17</td>
<td>177</td>
<td>C</td>
<td>C6–C7</td>
<td>15 y, 10 mo</td>
<td>C3–C4 = 50 mA, 30 Hz, C6–C7 = 50 mA, 30 Hz</td>
</tr>
</tbody>
</table>

Note: AIS, American Spinal Cord Injury Association Impairment Scale; F, female; M, male.
Electromyography (EMG) electrodes (Cometa) were placed over the muscles of arm and forearm FCR. During data collection, participants were seated on a bench, with hip and knee flexed to 90° and feet on the ground and with manual support provided (as needed) at the trunk by a research technician. Trunk support was provided to prevent compensatory strategies during assessment. In addition to manual support, scTS at the thoracic site (T10–T11) (same anode as cervical sites) was used to facilitate upright sitting during assessments. A custom-made device was used to place and hold the testing arm/wrist/hand in a neutral position, with a slot for stabilization of the hand-grip dynamometer to reduce compensatory movements and standardize the task across participants at wrist, forearm, elbow, and shoulder during hand and arm tasks (Fig. 3a). During maximal hand-grip testing, participants were asked to squeeze the dynamometer with a maximal force by the dominant hand, with shoulder and wrist joint in neutral position and elbow joint flexed to 90° (Fig. 3b). During wrist flexion and extension strength tasks, in the same custom-made device, participants were asked to produce maximal force while pushing against the hand dynamometer (Fig. 3c,d). For elbow extension strength, participants placed their wrist (styloid process) on the hand dynamometer and pressed against it to produce maximal elbow extension force without lifting their elbow, arm, and/or shoulder (Fig. 3e). At the beginning of each assessment, participants were instructed and familiarized with the technique of producing force using isolated joint movement, specific to each task, and were allowed to practice two to three attempts before the assessment trials to reduce utilization of compensatory strategies. A trained pediatric occupational therapist closely monitored each trial and noted any attempts that engaged compensatory movement, which were then excluded from the analysis. Force measured in N during maximal strength tasks was displayed on a screen in front of the participant. Three trials of each task without stimulation and three trials with scTS were recorded, with each trial lasting for a minimum of 3 seconds and a minimum of a 10-second rest between each trial. The maximum value of each of the three trials was recorded, and average values were compared between the two conditions. If a participant was unable to grip the hand dynamometer or generate force without or with scTS, a value of zero was assigned.

Transcutaneous Spinal Stimulation Optimization

A proprietary five-channel transcutaneous stimulator, BioStim-5 (Cosyma, Denver Inc, Denver, CO), was used to deliver continuous biphasic rectangular waveform current with 1-millisecond pulse...
width and 30-Hz frequency with 10-kHz modulated carrier frequency.\textsuperscript{21} Stimulation frequency of 30 Hz at both C3–C4 and C6–C7 sites was chosen on the basis of previous studies in adults with SCI to target the dorsal roots of the cervical spinal cord.\textsuperscript{20,21,35,37} Optimization of stimulation intensity was performed for two cervical spinal sites (C3–C4 and C6–C7) separately, starting with C3–C4 and followed by the C6–C7 site. Stimulation intensity at both sites was increased gradually in 5-to-10 mA increments and adjusted to enable maximal hand-grip force at subthreshold intensity, that is, with no direct activation of hand muscles in the absence of a voluntary attempt, confirmed by visual inspection of live EMG recording and without producing discomfort at the neck region. Optimization of stimulation intensity at the T10–T11 site to facilitate upright sitting was performed, as reported in a previous study in pediatric patients with SCI with trunk control deficits.\textsuperscript{31} On average, total stimulation time was approximately 24 minutes. During optimization, participants were instructed to sit upright and report any discomfort at the site of stimulation, in arms or hand. Owing to increased sensitivity in the neck region, some participants reported discomfort, pain, or abnormal sensation, and in those cases, the stimulation was reduced to below the painful threshold or discontinued. Throughout the study, the comfort and status of the participants were carefully monitored.

Data/Statistical Analysis

The safety and feasibility outcomes were determined by the frequency count of anticipated and unanticipated risks with associated percentage and likelihood (Table 2). The likelihood of occurrence was classified as very unlikely to occur (0%–10%), unlikely to occur (11%–40%), may occur approximately half of the time (41%–60%), likely to occur (61%–90%), and very likely to occur (91%–100%).\textsuperscript{38} To determine effects of scTS on hemodynamic parameters, BP and HR values were averaged and compared at the three time points: baseline (no stimulation), with optimized cervical and thoracic scTS, and at the end of the experiment (no stimulation), across the three days. Each hemodynamics outcome was analyzed with linear mixed models including a random intercept per participant, random slope for time point (Baseline, scTS, End), and trial (three trials) nested within time point. To obtain the difference between time points, linear contrasts were formulated on the time-point factor with a Bonferroni p-value adjustment. The estimates of these differences were presented with least square mean from model and SD calculated as model derived standard error \( \times \sqrt{\text{sample size}} \).

Hand-grip, wrist-flexion, wrist-extension, and elbow-extension strength outcomes were summarized with mean and SD. Normality was tested using the Kolmogorov-Smirnov test. Imme-

<table>
<thead>
<tr>
<th>Risk</th>
<th>Number of instances (%)</th>
<th>Likelihood of event based on probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin redness under stimulation site</td>
<td>4 (19%)</td>
<td>Unlikely to occur</td>
</tr>
<tr>
<td>Mild changes in blood pressure</td>
<td>6 (28%)</td>
<td>Unlikely to occur</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (14%)</td>
<td>Unlikely to occur</td>
</tr>
<tr>
<td>Tingling</td>
<td>2 (10%)</td>
<td>Very unlikely to occur</td>
</tr>
<tr>
<td>Spasticity (upper extremity)</td>
<td>0 (0%)</td>
<td>Very unlikely to occur</td>
</tr>
<tr>
<td>Autonomic dysreflexia</td>
<td>0 (0%)</td>
<td>Very unlikely to occur</td>
</tr>
<tr>
<td>Bowel accident</td>
<td>0 (0%)</td>
<td>Very unlikely to occur</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (10%)</td>
<td>Very unlikely to occur</td>
</tr>
<tr>
<td>Head/neckache</td>
<td>1 (5%)</td>
<td>Very unlikely to occur</td>
</tr>
<tr>
<td>Undesirable changes in stimulation</td>
<td>0 (0%)</td>
<td>Very unlikely to occur</td>
</tr>
</tbody>
</table>

Total of 21 assessments in seven children, %, instances/21 total assessments in seven children.
Immediate effects of scTS (ie, stimulation on vs off) were evaluated with two-tailed paired t-tests. Because of the small sample size, change also was evaluated using the effect size, \(^{39,40} \text{ES} \), which looks at the meaningfulness in terms of SDs and is independent of the sample size. It provides a quantification of the changes. \(^{41} \text{The effect size can be qualified as irrelevant (<0.01), very small (0.01–0.2), small (0.2–0.5), medium (0.5–0.8), large (0.8–1.2), very large (1.2–2), and huge (>2).}^{39,40} \) The tests were two sided, with a 0.05 significance level. Analyses were performed in SAS (version 9.4, SAS Inc, Cary, NC).

## RESULTS

### Safety and Feasibility of Short-term scTS in Children With SCI

The study compliance and attendance rate was 100%, with a total of 21 experiments attended by all seven participants. Participants underwent 21 experiment sessions of cervical scTS without stimulation-related adverse events. All seven participants tolerated cervical (C3–C4 and C6–C7) and thoracic (T10–T11) scTS across the three days, with a wide range of stimulation intensities (cervical sites = 20–70 mA and thoracic site = 25–190 mA) (Table 1). For two participants (participants P22 and P56), only one cervical site (C6–C7) was used to apply stimulation during the assessments. In one participant, one stimulation electrode was chosen owing to increased sensitivity at the neck region, and they requested that an electrode not be placed at the C3–C4 location (participant P22). In the second participant (participant P56), stimulation was not provided at the C3–C4 level owing to a metal implant spanning the C3–C4 spinous level. There were three instances with three participants (participants P14, P23, and P22) reporting pain at cervical stimulation sites during scTS optimization sessions on day 1 or day 2. Participant P14 reported a sudden episode of pain sensation of 3 of 10 on the VAS at cervical scTS sites (on day 2), triggered by turning his head to the right side/neck movement. Participant P23 described stimulation at the C6–C7 site at 30 mA (on day 2) as painful and rated it 2 of 10 on VAS scale. Participant P22 reported pain of 2 of 10 at C6–C7 site (on day 2). In all three of these instances, once pain was reported, stimulation intensity was decreased below the painful threshold, and hand and arm functional tasks were performed at that intensity.

Skin redness at the stimulation sites was observed in four of 21 assessments (19%) and dissipated in a few hours or by the next day, as reported in a follow-up inquiry. BP changes (28%), incidence of pain (2%), and fatigue (2%) were reported, and likelihood occurrence analysis deemed these events “less likely” to occur during stimulation (Table 2). No episode of AD was observed or reported. Hemodynamic parameters (systolic BP and HR) remained within stable limits (systolic BP \( p = 0.14 \), HR \( p = 1.0 \)) throughout the designated assessment timepoints at baseline, with scTS, and after the experiment (Fig. 4, Table 3). We did observe a significant increase in diastolic BP by 6 mm Hg (\( p = 0.01 \)) and mean arterial pressure (MAP) by 7 mm Hg (\( p = 0.01 \)) from baseline to scTS condition; however, these values decreased to the baseline range at the end of the experiment with stimulation turned off.

### Short-term Effects of scTS on Hand-grip and Arm-strength Outcomes

Short-term application of cervical scTS significantly increased (\( p = 0.03 \)) hand-grip force in six of seven participants. Six participants showed minimal detectable hand-grip force (>0N) without stimulation during baseline assessment. A combination of stimulation at C3–C4 and C6–C7 sites, in the presence of T10–T11 for upright trunk sitting, increased the hand-grip force on average by 5.7N ± 5N (mean ± SD) (Fig. 5, Table 4). Three of six participants showed increases in hand-grip force by >20%. One participant, owing to severe cervical SCI (AIS grade A), was unable to grasp the hand dynamometer without and with stimulation and was therefore excluded from hand-grip force analysis. Mean wrist-extension force value significantly increased (\( p = 0.04 \)) by 8.7N ± 9N during short-term application of optimized cervical scTS. Optimal cervical scTS similarly increased wrist flexion force by 0.5N ± 6N; however, the change in the mean value was not significant (\( p = 0.83 \)) (Table 4). Elbow-extension force production decreased by 0.99N ± 9N; however, this reduction was insignificant (\( p = 0.80 \)). This increase in hand-grip force was accompanied by an increase in the EMG activity in several muscles (Fig. 6).

### DISCUSSION

This pilot study examined the safety and feasibility of using cervical and thoracic scTS to modulate spinal cord excitability in the short term and augment UE motor capacity (ie, strength) in children aged five to 17 years with chronic SCI and impaired UE function. Using repeated measure design, we indicated that cervical and thoracic scTS are safe and feasible in children within this age range. All seven participants tolerated cervical scTS over a total of 21 experiment sessions (three per participant) without any serious adverse events. Three of seven participants perceived mild pain, with intensity ramp-up during optimization, ranging from 2 to 3 of 10 on VAS scale. One participant self-reported increased sensitivity at the higher neck region and requested not to have the C3–C4 electrode placed. Another participant had a metal fixation spanning the C3–C4 region. Experimental studies on the utilization of direct electrical current with metal used in implants have indicated its safety at the recommended therapeutic dosage. Currently, there are no recommended guidelines for scTS intensity (dosage). Furthermore, there is a lack of safety evidence regarding using electrical stimulation on patients with metal implants. Therefore, we limited our study population to children with no metal implants under the stimulation area. The remaining participants described stimulation at cervical sites as a tingling sensation or vibration. The compliance rate of 100% showed an overall positive response to cervical stimulation. Consistently with our previous study, \(^{31} \text{addition of stimulation at the T10–T11 site facilitated active upright posture during hand and arm functional tasks. However, to avoid losing balance and allow maximum effort during the assessment, each participant also was manually supported to maintain upright posture.}^{31} \) Hemodynamic parameters (BP and HR) were monitored throughout the study for any signs of AD and otherwise abnormally high or low BP with stimulation. AD is one of the common complications in children with high thoracic or cervical SCI, with signs and symptoms similar to those seen in adults with SCI. Urologic complications and bowel impact are two common causes of AD in children with SCI; however, any noxious sensory stimuli below the injury may cause onset of AD. \(^{45} \text{No incidence or episode of AD was observed or reported in participants throughout this study.}^{45} \) BP increases observed in participants during cervical and thoracic scTS were asymptomatic and not significantly different from baseline.
recordings, except diastolic BP. The elevation in diastolic BP and MAP was <10 mm Hg and therefore considered clinically insignificant. Studies in adults with SCI have confirmed that application of cervical or thoracic scTS may result in asymptomatic increases in BP. Placement of scTS electrodes at the cervical sites may create an electric field that unintentionally projects to nearby vital structures, such as laryngeal muscles and the vagus nerve. Therefore, as a safety precaution, we closely monitored HR and BP throughout each assessment session. Overall, the tolerability of cervical scTS in children was high, without any clinically significant adverse effects related to stimulation.

As a proof of principle, these data suggest that application of cervical and thoracic scTS with intensity ranging between 20 and 70 mA for cervical site and 25 and 190 mA at thoracic site increased hand-grip strength in all six participants who could perform this task without stimulation (Table 4). These findings indicated that short-term application of scTS can immediately increase hand-grip strength in children with SCI aged between six and 17 years.

**Table 3. Main Effects Results.**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>SBP</td>
<td>97 ± 11</td>
<td>104 ± 11</td>
<td>104 ± 11</td>
<td>0.1404</td>
</tr>
<tr>
<td>DBP</td>
<td>56 ± 13</td>
<td>62 ± 13</td>
<td>61 ± 13</td>
<td>0.015*</td>
</tr>
<tr>
<td>MAP</td>
<td>69 ± 11</td>
<td>76 ± 11</td>
<td>75 ± 11</td>
<td>0.0186*</td>
</tr>
<tr>
<td>HR</td>
<td>82 ± 13</td>
<td>83 ± 13</td>
<td>79 ± 13</td>
<td>1</td>
</tr>
</tbody>
</table>

*Denotes significant difference between DBP and MAP between baseline and scTS condition.

DBP, diastolic blood pressure (mm Hg); HR, heart rate (beats/min); MAP, mean arterial pressure (mm Hg); SBP, systolic blood pressure (mm Hg).
Short-term improvements in hand-grip strength using scTS may be attributed to the concept that scTS can modulate cervical spinal networks to generate excitatory potentials and thus decrease the threshold potential for the spinal motor network so as to enable greater motor output. \cite{20,21} Improvements in hand-grip force require increased activation in flexor and extensor muscles of the wrist. This was evident from EMG signals recorded from the wrist muscles, with and without stimulation, during hand-grip task (Fig. 6). In addition, increased activation in arm (bicep and triceps) muscles was observed with stimulation. This study examined a short-term application of spinal stimulation during the participant’s voluntary effort to generate hand (grip), wrist (flexion and extension), and elbow (extension) forces. Similar improvements in hand-grip strength have been reported after longitudinal application of cervical scTS in adults with SCI. \cite{21} However, these improvements in hand-grip strength were observed immediately during initial stimulation optimization session, in addition to after 40 to 60 days of task-specific training sessions in combination with scTS. Concomitantly with significant improvements in hand grip, six of seven participants generated greater force with stimulation during wrist extension. Although not directly assessed in this study, the increase in UE motor output in the presence of scTS may translate to the child’s increased ability to hold and grasp a feeding spoon, toy, water bottle, and so on, improving independence and thus quality of life.

**Table 4.** Hand and Arm Assessment Outcomes.

<table>
<thead>
<tr>
<th>Motor task</th>
<th>No Stim</th>
<th>scTS</th>
<th>Change</th>
<th>p Value</th>
<th>Effect size</th>
<th>Effect size classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>(force production in N)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand grip</td>
<td>42 ± 35</td>
<td>48 ± 36</td>
<td>5.76 ± 5.06</td>
<td>0.0386</td>
<td>1.14</td>
<td>Large</td>
</tr>
<tr>
<td>Wrist flexion</td>
<td>19 ± 15</td>
<td>19 ± 14</td>
<td>0.5 ± 6.29</td>
<td>0.839</td>
<td>0.08</td>
<td>Very small</td>
</tr>
<tr>
<td>Wrist extension</td>
<td>16 ± 9</td>
<td>24 ± 18</td>
<td>8.77 ± 9</td>
<td>0.0419</td>
<td>0.97</td>
<td>Large</td>
</tr>
<tr>
<td>Elbow extension</td>
<td>29 ± 15</td>
<td>28 ± 19</td>
<td>−0.99 ± 9.26</td>
<td>0.8048</td>
<td>0.11</td>
<td>Very small</td>
</tr>
</tbody>
</table>

N, Newton; scTS, transcutaneous spinal stimulation.
Stimulation paradigms such as location, intensity, and frequency play a significant role in enabling task-specific motor responses in segments below the injury level. To produce neuromodulatory effects, transcutaneous stimulation must penetrate through various layers of skin, fat, muscles, and bone to reach spinal structures.\textsuperscript{58–59} Thus, the intensity of stimulation must be great enough to overcome the resistance offered by these structures. However, some participants may have a low tolerance for stimulation intensity, particularly around the neck region, owing to hypersensitivity. Consequently, these participants may not have received enough stimulation intensity to produce the desired neuromodulatory effects.\textsuperscript{51,52} Further studies should aim to explore the optimal balance between the maximum tolerance for stimulation intensity and the functional improvements achieved. In adults, multisite scTS is consistently effective in neuromodulating spinal neuronal networks above, at, and below the lesion.\textsuperscript{20,35,53,54} Likely owing to stimulation of dorsal roots projecting to interneurons and motor neuron pools within the cervical spinal cord. For this reason, two cervical sites were used to apply stimulation in this study. Concurrently, the scTS frequency parameter of 30 Hz at both cervical sites was chosen on the basis of established safety and efficacy studies in adults with SCI.\textsuperscript{70,1,12,34} In the current study, the T10–T11 site was stimulated specifically to facilitate upright sitting during UE motor tasks assessment. Studies in neurologically intact adults have reported facilitation of UE spinal reflex and corticospinal excitability using combined stimulation at cervical and thoracic region.\textsuperscript{35,56} Therefore, the T10–T11 site stimulation, in addition to facilitating posture, may also potentiate UE function.

Although this study indicated improvements in hand-grip and wrist-extension strength using these parameters, no significant improvements in wrist-flexion and elbow-extension strength were observed with application of cervical scTS. Because hand-grip strength was the primary outcome measure of this study, optimization of stimulation parameters was targeted to this task. Therefore, depending on the individual goals of the intervention/rehabilitation program, location of the electrode placement and stimulation parameters should be optimized for each task to ultimately improve hand motor function in children with SCI. Limited studies in children with neuromotor impairments (cerebral palsy and spina bifida) have reported using scTS to improve balance and locomotion.\textsuperscript{57–58} However, differences in etiology, upper and lower motor neuron presentation, and outcomes specific to sensorimotor presentations may vary from children with SCI.\textsuperscript{60} In this study, four participants experienced SCI due to transverse myelitis, whereas three participants had SCI resulting from traumatic incidents. Participants with transverse myelitis exhibited greater baseline hand-grip force than did those with traumatic SCI. However, because of the limited sample size, we were unable to quantify these discrepancies. Therefore, injury etiology should be considered as a potential factor that could influence the responses to scTS. To reduce such variability in the future, long-term studies with more homogeneous sample sizes should be conducted. To conclude, the objective of this study was to first show the clinical safety and feasibility of short-term application of cervical and thoracic scTS in children with SCI, aged six to 17 years, who can cognitively respond to inquiries and report adverse conditions. There are fundamental anatomical, physiological, and biomechanical differences between adults and children. These factors are to be considered with the use of scTS to improve hand function in children with SCI. More studies will be important to investigate optimal stimulation sites (individual or combination), dosage, long-term safety and feasibility, and task-specific optimization through a standardized protocol and progression of stimulation parameters with training.

**Limitations**

In this pilot study, several limitations are identified. First, in this study, anode electrodes were placed over the iliac crests, bilaterally. However, recent studies in adults with SCI have placed the anodes over the clavicles, bilaterally. Owing to the proximity to critical physiological structures (eg, heart, trachea, and vagus nerve), this placement could increase the severity and/or likelihood of adverse effects related to stimulation. Therefore, the safety and feasibility outcomes reported here are stimulation-parameter specific and cannot be generalized. Second, stimulation intensity was only optimized for the hand-grip task and was kept at the same level for other motor tasks. This may have influenced the force production observed during other motor tasks for which the stimulation parameters were not optimized. During activity-based training in combination with spinal stimulation studies in adults with SCI, stimulation intensity is adjusted throughout the intervention, depending on the tasks (strengthening vs dexterity).\textsuperscript{52} therefore, in future studies, we recommend stimulation optimization to be task-specific.

**Figure 6.** Representative EMG (microvolts) and force in N during hand-grip strength task without and with cervical sites stimulation in two participants. Raw EMG traces of wrist and arm muscles during a single attempt of hand-grip strength task from participants C52, P56, and P22 without and with cervical and thoracic stimulation. Note the increase in hand-grip force production and EMG activation with stimulation. ED, extensor digitorum; FCU, flexor carpi ulnaris.
specific. Third, given four different motor tasks were attempted in sequence without randomization, it is possible that the testing itself influenced the outcome measured in last place.

CONCLUSIONS

The current study serves as a foundational step in providing necessary preliminary data to advance the study of scTS as a neurotherapeutic agent for SCI from adults to the pediatric population. The results of this study provide initial evidence of the safety and feasibility of using cervical and thoracic scTS to improve UE motor output (ie, hand-grip strength) in the short term in children with SCI. Future studies should aim to investigate optimal scTS sites, intensity, and safety and feasibility of cumulative application of scTS during UE training. In addition, future study objectives should include determining efficacy of cervical scTS and task-specific training for improving UE motor function and durability of the training effects in children with SCI.

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Authorship Statements

Goutam Singh conceptualized study design, executed experimental stimulation protocol, directed data analysis and interpretation, and prepared the article. Anastasia Keller conceptualized study design, data acquisition, contributed to data analysis interpretation, and revised the article. Kathryn Lucas executed upper extremity (UE) motor assessments, contributed to data analysis interpretation, and revised the article. Catherine Borders and Danielle Stout contributed to UE motor assessments and data analysis. Molly King facilitated safety-related outcomes data acquisition and analysis. Parth Parikh led data acquisition and analysis. Molly King facilitated safety-related outcomes data acquisition and analysis. Parth Parikh led data acquisition and analysis. Molly King facilitated safety-related outcomes data acquisition and analysis.

Beatrice Ugiliweneza contributed to study design and executed statistical data analysis. Jessica D’Amico contributed to study design conceptualization and revised the article. Yury Gerasimenko contributed to study design conceptualization and revised the article. Andrea L. Behrman, the pediatric research program director, conceptualized study design, secured grant funding, oversaw study execution, and revised the article. All authors approved the final version of the manuscript.

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