

## CASE REPORT

# White matter changes in corticospinal tract associated with improvement in arm and hand functions in incomplete cervical spinal cord injury: pilot case series

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**INTRODUCTION:** This is a prospective clinical pilot case series. Improvement of arm and hand functions after spinal cord injury (SCI) is one of the major rehabilitation goals. Electrical stimulation of the primary motor cortex via transcranial direct current stimulation (tDCS) coupled with high-intensity repetitive motor training may have potential to facilitate improvement in motor function in chronic, incomplete cervical SCI. We investigated the relationship between motor recovery and changes in white matter integrity in response to treatment intervention. This study was conducted in The Institute for Rehabilitation and Research Memorial Hermann, Houston, USA.

**CASE PRESENTATION:** Four right-handed adults with chronic, incomplete cervical SCI (age, 36–63 years, American Spinal Injury Association Impairment Scale grade C–D) were enrolled in 10 sessions of anodal tDCS at 2 mA versus sham tDCS followed by 1 h of robotic-assisted arm training. Changes in arm and hand function were measured with Jebsen–Taylor Hand Function Test and Motor Activity Log-Amount of Use. Diffusion tensor imaging was used to measure changes in fractional anisotropy (FA) of corticospinal tracts (CSTs).

**DISCUSSION:** After 10 sessions of treatment, we found greater improvement in hand function and hand usage in patients who received active tDCS treatment versus sham treatment. There was an overall positive change in FA values across all patients. We show changes in arm and hand function associated with changes in CST tractographic mapping to quantify the motor system components in chronic incomplete cervical SCI.

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## INTRODUCTION

Spinal cord injury (SCI) can cause substantial motor deficits in arm and hand functions that can result in significant loss in performance of daily activities for many years. The extent of neurological impairment is the major contributing factor to recovery from injury.<sup>1</sup> Even small improvements in arm and hand function may lead to improvements in self-care, transfers and quality of life.<sup>2–4</sup>

There are a number of factors that explain recovery of sensorimotor functions after injury. For example, preservation of longitudinally oriented axonal tracts in white matter, as well as proper conductance through spared white matter axons, has been directly related to neurological recovery.<sup>5</sup> In the chronic stage of injury, a number of pathologic changes such as spinal cord atrophy,<sup>6</sup> reduced axonal integrity,<sup>7</sup> demyelination<sup>8</sup> and remyelination<sup>9</sup> have been documented. Although most of these changes occur at the spinal cord level, both animal and human studies have also demonstrated structural and functional reorganization at remote cortical and subcortical structure.<sup>10–13</sup> Some of the structural changes in the white matter can be detectable by diffusion tensor imaging (DTI). DTI is an advanced magnetic resonance imaging (MRI) technique used to quantify fiber orientation properties and integrity of white matter pathways

within neural networks. Fractional anisotropy (FA), an index of the diffusion characteristics of water molecules directed along the axis of axonal pathways, can detect microstructural changes. In chronic SCI, FA values of the cervical spinal cord have been shown to be correlated with motor scores in patients with chronic cervical injury<sup>14–16</sup> and suggested to be non-invasive imaging biomarkers for SCI.<sup>17</sup>

Rehabilitation protocols that have been in use to improve upper-limb sensorimotor functions are sparse and have provided modest functional benefits. Traditional muscle strengthening, range of motion, massed practice,<sup>18</sup> electrical stimulation<sup>19,20</sup> and more recently robotic-assisted exercises<sup>21–23</sup> are used alone or in combination. Despite the fact that restoration of arm and hand function is an important part of rehabilitation, there is still no consensus in management of the tetraplegic upper limb. Most aforementioned approaches focus on the extremity muscles, and only a few studies have attempted to combine motor cortex stimulation with peripheral training.<sup>24–26</sup> In a recent study, we demonstrated greater improvement in arm and hand functions in the active anodal stimulation group compared with the sham stimulation group in incomplete cervical SCI.<sup>27</sup> Although combination therapies have emerged as an alternative approach to facilitate neurorecovery and improve motor skill performance,

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the accompanying neural changes for improved functions still remain unknown in SCI. Moreover, understanding the mechanism of recovery will force clinical researchers to develop rehabilitation protocols that aim to facilitate recovery from paralysis with less focus on compensatory techniques.

Therefore, in the current study, we report findings of a case–control study to demonstrate structural white matter changes in the corticospinal tract (CST), the primary structure for motor control, especially for fine motor control of the hand.

## METHODS

### Participants

Four participants with chronic, incomplete cervical SCI were randomly assigned into active and control groups. Main enrollment criteria were as follows: (1) age between 18 and 65 years; (2) diagnosis of chronic, incomplete cervical SCI as defined by the American Spinal Injury Association Impairment scale classification at least 6 months before the study; (3) no neuropsychiatric comorbidities, including traumatic brain injury, evidenced by loss of consciousness because of brain trauma, post-traumatic amnesia or skull fracture, or objective neurological findings that can be reasonably attributed to traumatic brain injury; (4) no contraindications to transcranial direct current stimulation (tDCS) and MRI; (5) no prior history of seizure or family history of seizure disorder in a first degree relative; and (6) no use of medications containing a sodium-channel blocker such as carbamazepine.

This study was approved by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston. All participants gave written consent before participation.

### Intervention

All participants completed 10 sessions of treatment over a 2-week period. After randomization, they received either anodal tDCS or sham tDCS over M1 at 2 mA for 20 min, which was immediately followed by 1 h of robotic-assisted arm training (RAT). Participant #1 and Participant #2 received anodal tDCS+RAT. Participant #3 and Participant #4 received sham tDCS+RAT.

tDCS is a form of non-invasive cortical stimulation and has the potential to alter corticospinal excitability. Direct current is transferred by two saline-soaked surface sponge electrodes ( $7 \times 5 \text{ cm} = 35 \text{ cm}^2$  active areas) and delivered by a battery-driven stimulator device (medical tDCS for clinical trials device, Soterix Medical, New York, NY, USA). To stimulate the primary motor cortex (M1), the anode electrode (increasing cortical excitability) was placed over C3/C4 (according to the 10–20 international electroencephalogram electrode system) contralateral to the targeted arm. The cathode (reference) electrode was placed over the contralateral supraorbital area.

Immediately after cortical stimulation, repetitive movement training was provided using the MAHI Exo-II exoskeleton<sup>28</sup> operated in active-constrained mode. In this mode, the robotic device is commanded to display a force field proportional to the movement velocity at the intended joint that serves to oppose the subject's movement toward a fixed target displayed on the computer screen. Single degree of freedom movements for elbow, forearm and wrist were repeated at high intensity, with a visual display of the real-time cursor position and target position visible to the participant. Treatment was progressed gradually by increasing the number of repetitions and amount of resistance applied to each movement. On a computer screen, graphical feedback of the number of repetitions achieved was displayed after each attempt to maintain motivation. Standardized rest breaks were administered to avoid fatigue. The goal was to achieve ~1000 repetitions in a given session. During the study period, participants did not participate in any other occupational therapy program involving arm and hand training.

### MRI-DTI data acquisition

Data were acquired on a Philips (Houston, TX, USA) 3.0T Achieva scanner using a SENSE receive neurovascular coil. The MRI protocol included conventional MRI and three-dimensional T1-weighted magnetization prepared rapid acquisition of gradient echo. The T1-weighted sequence spatial resolution was  $1 \times 1 \times 1 \text{ mm}$  and field of view was  $256 \times 256 \text{ mm}$ . Diffusion-weighted image data were acquired axially with the balanced and alternating polarity *Icosa21* tensor encoding scheme.<sup>29,30</sup> The b-factor =  $1000 \text{ s mm}^{-2}$ , repetition time (TR)/echo time (TE) =  $11\,000/65 \mu\text{s}$ , field of view (FOV) =  $320 \times 320 \text{ mm}$  and slice thickness/gap/#slices =  $4 \text{ mm}/0 \text{ mm}/80$ . The echo planar imaging (EPI) phase encoding used a SENSE k-space undersampling factor of two, with an effective k-space matrix of  $160 \times 160$  and an image matrix after zero filling of  $320 \times 320$ . The constructed image spatial resolution for the diffusion-weighted image data was  $\sim 1 \times 1 \times 4 \text{ mm}$ . The values for FA range from 0 to 1, where higher values suggest highly oriented water diffusion (that is, anisotropic diffusion), and therefore highly organized white matter structure.<sup>31</sup>

### MRI data processing

The MRI data processing pipeline used in this work are described in more detail elsewhere.<sup>32</sup>

### Brain diffusion tensor fiber tractography analysis

We have used a brute force and multiple regions-of-interest (ROI) tracking method, and fiber assignment with continuous tractography algorithm<sup>33</sup> b (DTI Studio, Johns Hopkins University, Baltimore, MD, USA; <http://cmrm.med.jhmi.edu>) to reconstruct CST. Reproducibility of fiber construction in both hemispheres was tested on all participants by two experienced raters (ZK, KH). Once a fiber tract was reconstructed, its entire trajectory was verified on a slice-by-slice basis to compare with established anatomical landmarks described in the human brain neuro-anatomy atlases.<sup>34</sup> Regions of interests used for CST were subcortical white matter of motor cortex, posterior limb of internal capsule, cerebral peduncle, pons and medulla.<sup>35</sup> FA values of the tracts were obtained by averaging the FA values in these regions of interests where CST goes through. The researcher who performed the analysis was blinded to participants' group assignment.

### Arm and hand function measurements

*Testing for arm and hand function.* The Jebsen–Taylor Hand Function Test (JTHFT) was used as the primary outcome measure of arm and hand functions. The test<sup>36</sup> has shown to have good to excellent inter-rater and intrarater reliability,<sup>37</sup> and capacity for detecting performance change in activities that resemble daily life activities. Time to perform seven everyday activities (for example, writing, feeding) was tested. We excluded the writing task because of heavy dependence on the side with less impairment.<sup>38</sup> Administration of the JTHFT subtests was discontinued after 120 s if a subject could not complete the task in that time. Scores were recorded in number of items completed/total time (in s).<sup>39</sup> This modified method of recording had superiority compared with traditional recordings of total time only. Thus, changes in number of items completed within 120 s could be reflected as an increase or decrease of performance.

*Self-report of arm function with Motor Activity Log.* Participants were asked to report 'how much' and 'how well' they have used their arm during 30 daily activities such as brushing hair, drinking from a glass and picking up the phone. Two scores were generated from this self-report; however, for the purpose of this study, only the amount of use was used as we were interested in increased activity of the arm in daily life.<sup>40</sup> A score of 0.50 was

**Table 1.** Participant demographics and clinical assessment scores

| Subject | Age | Gender | Neurological level of injury | AIS grade | Time since injury (months) | ISNCSCI scores |                  | Handedness (R/L) |                    |
|---------|-----|--------|------------------------------|-----------|----------------------------|----------------|------------------|------------------|--------------------|
|         |     |        |                              |           |                            | UEMS           | UESS (LT and PP) | Before injury    | Side being trained |
| 1       | 48  | Male   | C6                           | D         | 38                         | 23             | 32               | R                | R                  |
| 2       | 36  | Male   | C5                           | D         | 8                          | 37             | 21               | R                | R                  |
| 3       | 52  | Female | C5                           | C         | 202                        | 22             | 23               | R                | L                  |
| 4       | 63  | Male   | C5                           | D         | 47                         | 25             | 23               | R                | R                  |

Abbreviations: AIS, American Spinal Injury Association (ASIA) Impairment Scale; ISNCSCI, International Standard Neurological Classification of Spinal Cord Injury; L, left; LT, light touch; PP, pin prick; R, right; UEMS, upper-extremity motor score; UESS, upper-extremity sensory score.

used to report as minimal clinically important difference in stroke population.<sup>41</sup>

Assessments were performed by the same senior therapist who was blinded to study assignment.

## RESULTS

Participant demographics and clinical scores at baseline

Four participants with impairment in upper-limb motor functions caused by incomplete, cervical SCI were randomized into active versus sham stimulation groups. The characteristics of the participants are presented in Table 1. All four participants successfully completed the 2-week treatment intervention.

Motor function changes after active tDCS and repetitive training

After 10 sessions of active treatment, both participants demonstrated improvement in trained arms and, to a certain extent, in the non-trained arm as measured with JTHFT. Individual improvements were observed in subtests of JTHFT. For example, subject 1 completed the 'simulated feeding' subtest in 20 s, after scoring '0' at baseline. The task consists of scooping five beans with a spoon from the top of a table and dropping them one by one into a can. This task requires a firm grip of the spoon and proximal arm movements. Subtests of subject 2 showed significant improvement in page turning with the non-trained arm, in which he turned all five pages in 27 s, compared with being able to turn just one page in 120 s before treatment. He also showed improvements in picking up small objects with his non-trained side by picking up four items in 120 s versus '0' items in 120 s before treatment.

Amount of use (Motor Activity Log-Amount of Use) of the trained arm increased significantly by exceeding minimal clinical significant difference of 0.5.

Motor function changes after sham tDCS and repetitive training

Ten sessions of sham stimulation with repetitive robotic training resulted in minimal improvement of arm and hand functions. For example, subject 3 was able to initiate the page-turning task and turned two pages in 120 s with her trained arm, compared with zero pages before treatment. In addition, she was able to pick up and move six small items with the non-trained arm within 97 s, compared with '0' items before treatment, and was able to initiate simulated feeding by scooping and moving one bean with the non-trained arm within 120 s, compared with '0' before treatment. Subject 4 showed slightly higher improvements in the non-trained arm compared with his trained side.

Amount of use (Motor Activity Log-Amount of Use) of the trained arm did not show significant change (Table 2).

Brain diffusion tensor fiber tractography analysis

We found an overall positive trend in FA values in participants regardless of group assignments and arm being trained. FA was

**Table 2.** Changes in Jebsen–Taylor hand function score

|                     | Active group |      |           |      | Control group |      |           |      |
|---------------------|--------------|------|-----------|------|---------------|------|-----------|------|
|                     | Subject 1    |      | Subject 2 |      | Subject 3     |      | Subject 4 |      |
|                     | Pre          | Post | Pre       | Post | Pre           | Post | Pre       | Post |
| JTHFT TA (items/s)  | 0.12         | 0.25 | 0.42      | 0.48 | 0.01          | 0.02 | 0.08      | 0.09 |
| JTHFT NTA (items/s) | 0.12         | 0.1  | 0.02      | 0.04 | 0.02          | 0.04 | 0.24      | 0.28 |
| MAL-AOU (0–5)       | 0.4          | 3.5  | 3.2       | 5    | 0.2           | 0.4  | 0.1       | 0.1  |

Abbreviations: JTHFT, Jebsen–Taylor hand function test; MAL-AOU, motor activity log-amount of use; NTA, non-trained arm; TA, trained arm.

not found to be sensitive for the effects of tDCS in our small cohort. The mean FA change in active versus sham stimulation groups are shown in Table 3 and demonstrated in Figure 1.

## DISCUSSION

In this pilot case series, individuals with chronic, incomplete cervical SCI underwent an intervention consisting of 10 sessions of combined anodal tDCS with RAT or RAT only. Neural correlates related to treatment-induced changes before and after treatment were measured with DTI. After treatment, our findings demonstrate (a) modest improvement in motor functions in patients treated with anodal tDCS and repetitive training and (b) a positive trend in DTI measures demonstrated as an overall increase in FA change.

In contrast to a large number of studies in stroke recovery, very few studies have examined the effects of primary motor cortex stimulation in improving arm and leg motor functions after SCI. Several researchers have reported improvement in International Neurological Classification motor and sensory scores, hand functions,<sup>24,26,42</sup> or gait functions<sup>43,44</sup> when stimulating M1 with high-frequency repetitive transcranial magnetic stimulation. On the basis of findings from our study, one can speculate that anodal tDCS, when applied at 2 mA for 20 min before a high-intensity repetitive arm training protocol, has the potential to facilitate movement recovery, but this must be interpreted with caution because of the very small sample size, differences in elapsed time since injury (longer in the control group), age (higher in control group) and differences in baseline motor function (lower in the control group).

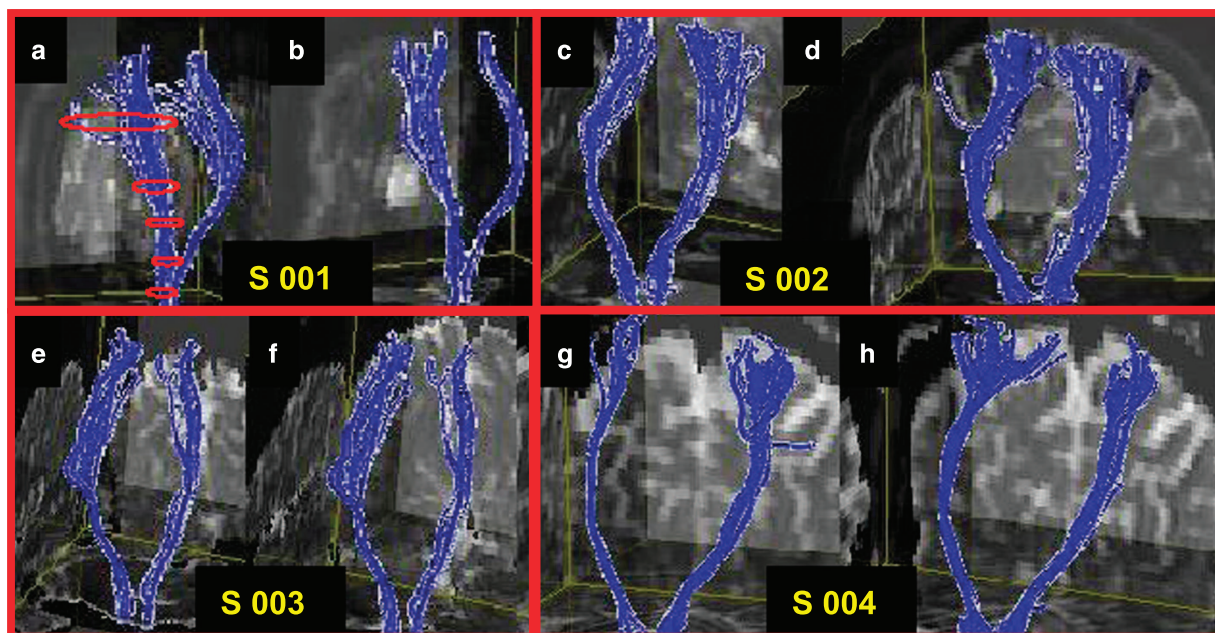
When comparing groups for amount of arm use in real-life environments, three out of four patients reported minimal use at the beginning of the study. As expected, high-functioning patients had the highest score on Motor Activity Log-Amount of Use. However, after treatment, patients in the active group started to use their arms during daily activities more than patients in the control group. The so-called 'learned non-use' was first proposed



**Table 3.** Diffusion tensor imaging attributes of corticospinal tract at two time points before and after therapy

| CST      | Participant 1 |             | Participant 2 |             | Participant 3 |             | Participant 4 |             |
|----------|---------------|-------------|---------------|-------------|---------------|-------------|---------------|-------------|
| FA       | Pre           | Post        | Pre           | Post        | Pre           | Post        | Pre           | Post        |
| CST (TA) | 0.62 ± 0.11   | 0.67 ± 0.10 | 0.63 ± 0.12   | 0.66 ± 0.13 | 0.69 ± 0.08   | 0.71 ± 0.10 | 0.59 ± 0.11   | 0.57 ± 0.10 |
| CST(NTA) | 0.63 ± 0.15   | 0.69 ± 0.16 | 0.72 ± 0.13   | 0.75 ± 0.11 | 0.67 ± 0.11   | 0.72 ± 0.14 | 0.61 ± 0.13   | 0.65 ± 0.15 |

Abbreviations: CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy (no units); NTA, non-trained arm; TA, trained arm. Data are presented as mean ± s.d.



**Figure 1.** Illustration of the corticospinal tracts of each subject from two time points: before (a, c, e, g) and after (b, d, f, h). Regions of interest used to construct the pathways were subcortical white matter of the motor cortex, posterior limb of the internal capsule, cerebral peduncle, pons and medulla (ROIs are illustrated in the descending order in a, respectively). As background, b0 map from diffusion tensor imaging maps is used.

by Taub *et al.*<sup>45</sup> Regardless of the etiology (that is, stroke or SCI), learned non-use usually develops in response to excess motor disability after central nervous system injury.<sup>45</sup> Unfortunately, most patients with long-term paralysis tend to use their paretic hand less in daily life, despite residual motor function. This acquired non-use can further lead to reversible loss of neural and behavioral function. Therefore, overcoming learned non-use and decreasing compensatory movements should be carefully integrated into successful therapeutic strategies that aim to improve motor functions after SCI. In the present study, we were able to demonstrate positive changes in the amount of use in participants who received M1 stimulation in addition to intense exercise. However, further studies are needed to explore short- and long-term effects of learned non-use in patients with SCI and its negative effect on poor recovery.

To the best of our knowledge, no previous studies in adults have investigated changes in DTI values in response to relatively short intensive repetitive treatments of upper limbs. In previous studies, recovery of motor functions after SCI has been highly correlated to preservation of longitudinally oriented axonal tracts in the white matter<sup>46</sup> and myelination of intact axons. Tract quality has been roughly defined to correlate positively with FA. In our study, we observed a positive FA change in both right and left corticospinal tracts and across all participants. Interestingly, JTHFT

performance not only improved in the trained arm, but also in the non-trained side. Despite unilateral training, this finding is particularly interesting and needs to be further explored. One can speculate that increased FA values might be a reflection of training-induced modification in white matter microstructure and may indicate increased coherence of CST fibers, increased myelination or increased axon density with resulting improvement in fine motor control, but results should be interpreted with caution.

The results from this study demonstrated that *in vivo* quantification of the CST, the main motor pathway, is feasible in adults with chronic cervical incomplete SCI using 2 mm slices at 3.0 T. Furthermore, this study has shown that this pathway is sensitive to the extent of functional recovery induced by a combination therapy protocol.

The main limitation of this study is the small sample size ( $n = 4$ ). A larger sample size with groups homogeneous in, that is, baseline motor function and time since injury is warranted to draw a stronger conclusion. In addition, interpretation of the changes in diffusion in white matter is not straightforward. In the future, we expect to see the use of DTI in mainstream clinical practice to both prognosticate and to monitor recovery in patients with spinal cord disease. In the long term, we believe our work will shed light onto controlled clinical trials with larger sample sizes.

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## COMPETING INTERESTS

The authors declare no conflict of interest.

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