Relationship between sensorimotor cortex reorganization and post-injury time in patients with spinal cord injury

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ABSTRACT: Traumatic spinal cord injury (TSCI) is a widely discussed in the literature due to its high incidence and substantial socioeconomic impacts. Cortical motor reorganization is a particularly discussed area due to its importance in the rehabilitation of patients. Knowing the reorganization process is highly complex and is affected by several factors, such as the cortical level involvement, when the rehabilitation began, and the time after the injury itself. Thus, the aim of this study was to evaluate the changes in the spatial patterns of cortical motor activation associated with functional recovery after an TSCI. Our main objective was to explore the relationship between cerebral cortical reorganization and post-injury time. Ten patients with TSCI and paraplegia grade A or B according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS) were evaluated, along with ten control subjects, through functional magnetic resonance imaging (fMRI) related to the same task, using the BOLD technique, comparing the sensory-motor ratios (SMRs), which are estimated by the activation ratio of the post-central and pre-central gyrus. The tasks performed for the upper limbs were the execution of hand flexion/extension for all participants. The tasks performed for the lower limbs were the execution of dorsiflexion of the ankles for the control group and attempted dorsiflexion movement for individuals

with spinal cord injury. Subjects with TSCI showed reduced sensorimotor ratios (SMRs) in the left ankle compared to controls, while there were no differences observed in right ankle SMRs. In contrast, the SMRs related to motor execution of the right-hand increased compared to the controls, but no differences were found in the left-hand SMRs. The increase in SMRs for the right hand and the reduction in the left ankle SMRs may be associated with recruitment of the corresponding limbs; the increase in SMRs may be directly related to limb dominance, a factor that could have influenced this reorganization. A relationship between the right ankle SMRs and injury time was evidenced, indicating an increase in reorganization of the dominant limb over time. Thus, comparing the SMRs with respect to the time since the injury may help characterize the cortical patterns post-injury, which are currently not well understood, and be used to guide neurorehabilitation training protocols and the use of brain-machine interfaces.

INTRODUCTION

Spinal cord injury (SCI) has wide-ranging physical, social, and psychological impacts. According to the World Health Organization (WHO), there are between 250,000 and 500,000 new cases of Spinal cord injury (SCI) worldwide each year. The United States has an annual incidence of 54 cases per million inhabitants, with approximately 17900 new cases each year. About 78% of these cases occur in males. In addition, 30% are readmitted after the initial injury, with an average stay of 18 days (Jessica Lo J et al., 2021; NSCISC- National Center for Spinal Cord Injury Statistics, 2021). Many studies have sought to develop strategies to understand and mitigate the effects of SCI sequelae and improve the quality of life of individuals with SCI, either through new methods of physical or psychological rehabilitation, or through the development of new assistive devices and mobility aids (Capogrosso M et al., 2018; Semprini et al., 2018; Shah M et al., 2020).

A better understanding of cortical changes post-injury can aid in the development of more durable and robust tools that provide better treatment and rehabilitation strategies and, therefore, a better quality of life for individuals with SCI. In patients with traumatic spinal cord injury (TSCI), studies investigating the activation and preservation of the cerebral motor system have reported cortical motor reorganization (Kokotilo KJ, Eng JJ, Curt A, 2009; Capogrosso M, et al, 2018; Hou J, et al2016; Jessica Lo J, et al, 2021). These changes in cortical activation have been identified using functional magnetic resonance imaging (fMRI), which shows neural activity based on the blood-oxygen-level-dependent (BOLD) signal, an indirect non-invasive measure that indicates which parts of the cortex are active during a task.

Until the late 1990s, it was believed that cortical reorganization was limited to the developing nervous system; however, over the last two decades, it has been established that adaptive changes and substantial cortical reorganization can occur in the central nervous system (CNS) in adult humans. These changes may help recover some functions, but this may vary depending on the time since the injury, its extent, location, and the application of rehabilitation training, either alone or combined with pharmacological interventions and brain stimulation. (Merzenich M, 1996; Butefisch CM, 2004; Shih JJ and Cohen LG, 2004; Vértes PE and Bullmore ET, 2014).

A critical review (Melo, M.C. et al., 2020) reported contradictory findings regarding cortical reorganization after spinal cord injury in fMRI research and proposed possible reasons for this. First, several different potential factors are associated with changes in cortical volume, such as aging and spontaneous reorganization of the nervous system. The latter change may be due to the acquisition of simple or complex motor skills by altering the sensory-motor maps in the primary sensory cortices and in the connectivity pathways of intracortical networks. (Monfils MH, Plautz EJ, Kleim JA, 2005; Capaday C, Ethier C, Vreeswijk CV, 2013).

The influence of time can be assessed by examining changes in the activation volume in the motor cortex and whether there is partial or complete preservation of the functional musculature after the injury; however, there are few studies evaluating the associations between time after initial injury and the volume activation, mainly due to the large variability of injury time among patients (Turner JA et al., 2001; Curt A et al., 2002; Jurkiewicz MT et al., 2007; Jurkiewicz MT et al., 2010; Freund P et al. 2011; Lundell H et al. 2011; Saber L et al., 2016; Sharp KG, 2017). The preservation of afferent and efferent pathways depends on the extent and severity of the injury, with some studies reporting that brain networks related to motor tasks are generally preserved after injury (Cramer SC et al., 2005; Hotz-Boendermaker S et al., 2008); Sharp KG et al., 2017). The influence of laterality is an important factor that needs to be explored, and studies that consider dominance have so far evaluated only the upper limbs (Kapreli E et al., 2006; Hotz-Boendermaker S et al., 2011; Sabre L et al., 2013). Sample size is also an issue, as studies on spinal cord injuries are limited by the number of available individuals with injuries corresponding to the time since injury, the age at which the injury occurred, and the types of rehabilitation and pharmacological approaches adopted, making reliable comparisons difficult (Button KS et al., 2013; Turner BO et al., 2018).

Our work focused on exploring the activation ratio of the post-central and pre-central gyrus for two reasons. The first is that the pre-central gyrus is the main area of the brain's motor cortex, responsible for controlling voluntary body movements, and the post-central gyrus is the main area of the brain's somatosensory cortex, responsible for processing sensory information received from the body, such as touch, temperature, pain, and proprioception. The other reason is the possibility of better understanding the behavior of neuroplasticity in volunteers who suffered spinal cord injury in the thoracic region considering the time post-injury.

To establish a reference pattern, we opted to analyze the changes by parity, as this allows us to understand what behavior patterns occur due of the loss of motor functions and sensitivity. Finding if there is any variation and how it behaves will significantly aid in research and development of electroencephalic or electrocorticographic devices used for BMI controls for different devices, resulting in increased accuracy in data collection and understanding of the behavior of cortical signals post-spinal cord injury, thereby enhanced the performance of these devices. (Alam, et al 2016; Grau, et al 2020; Karamian, B.A., Siegel, N., Nourie, B. et al, 2022)

Thus, we believe that there is an increase in activation in the sensory areas associated with the upper limbs due to the high daily demand placed on them by daily routines, and that this activation would be positively correlated with the dominant limb associated with the time post-injury. Therefore, to better understand the impact of SCI on the sensorimotor region, we used fMRI and BOLD to investigate the activation patterns in these regions in patients with TSCI with a paradigm that encompasses motor execution or attempts at movements to the upper and lower limbs. We used a sensory-motor index to eavluate how these areas were affected by the injury and how this related to the time since the injury.

Next, we investigated changes in cortical activity in the patients with TSCI compared to uninjured controls during the motor tasks, how these changes occurred, and the influence of time since injury and laterality on reorganization. Our central hypothesis is that there is an increase in activation in the sensory areas associated with the upper limbs due to the high daily demand placed on them by daily routines, and that this activation would be positively correlated with the dominant limb.

MATERIALS AND METHODS

Subjects

The volunteers with TSCI were recruited from two institutions: the University Hospital of the Federal University of Uberlândia (UFU) and an organization supporting people with paraplegia, also located in the city of Uberlândia, called *the Association of Paraplegics of Uberlândia (APARU).* For the group with TSCI, the inclusion criteria were a diagnosis of paraplegia due to LTME, an age between 18 and 60 years and classification as ASIA A or B. The exclusion criteria were if the volunteers with TSCI had a non-thoracic level of injury, an implant composed of metallic materials (dental implant, pacemaker, orthopedic materials) within six months prior to the start of data collection and if they were claustrophobic. Thus, a total of ten individuals with paraplegia (two women and eight men; mean age of 30.9 years, SD 11.9) were included in this study (Table 1). The right hand and right ankle were dominant in all individuals. Eight patients were classified as ASIA A, while two were classified as ASIA B, according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS). (National Center for Spinal Cord Injuries, Available at: https://www.nscisc.uab.edu/)

Patient	Gender	Age (years)	Post-injury time (years)	ASIA	Level of Injury
1	M	30	5.5	A	T1
2	F	21	< 1	B	T5-T6-T7
3	M	54	2.5	A	T3-T4
4	M	46	14	A	T12
5	F	19	4	A	T7-T8
6	M	18	1	A	T6
7	M	26	< 1	A	T12
8	M	24	4	B	T8
9	M	35	3.5	A	T2-T3
10	M	36	5.5	A	T4-T5

TABLE I. Demographic and clinical characteristics of the patients in the TSCI group

Due to the age-matched study, the inclusion criterion was individuals of the same age and without spinal cord injury. The exclusion criterion were if they had suffered a brain injury or to hada history of neurological or psychiatric diseases. Ten healthy right-handed volunteers (four women and six men) matched by age (31.1 ± 10.0 years) served as controls. All participants provided informed consent, and the Research Ethics Committee of the Federal University of Uberlândia approved the experimental protocol CAAE:64580116.0.0000.5152.

Experimental design

Participants were informed about the procedure, tasks, and duration of the experiment at the beginning of the experimental session. Motor execution or movement attempts during the fMRI experiment consisted of six individual tasks:

1. Opening and closing the right hand (RH) at an individualized pace of approximately 2.0Hz
2. Open and close the left hand (LH) at an individualized pace of approximately 2.0Hz
3. Perform right ankle dorsiflexion (RA) at an individualized pace of approximately 2.0Hz
4. Perform left ankle dorsiflexion (LA) at an individualized pace of approximately 2.0Hz
5. Attempt to perform right ankle dorsiflexion (RA) at an individualized pace of approximately 2.0Hz
6. Attempt to perform left ankle dorsiflexion (LA) at an individualized pace of approximately 2.0Hz

These tasks were selected to activate the following cortical areas: postcentral and precentral gyri. All participants were instructed and pre-trained on attention and concentration throughout the experiment and on individual tasks before entering the collection room and when they were already properly positioned in the MRI machine, before starting to capture the images. The order of the tasks was alternated among the subjects, that is, if an individual starts with one of the lower limbs, the next one would start with one of the lower limbs and so on.

In the scanner, the tasks of motor execution (ME) or attempted movements were requested by a visual command (rest or movement) presented on a screen. For each limb, a sequence was visualized consisting of a 30-s block of rest commands, followed by a 30-s block of activity commands. Five repetitions of this sequence were performed for 5 minutes for each motor task associated with each limb (Figure 1).

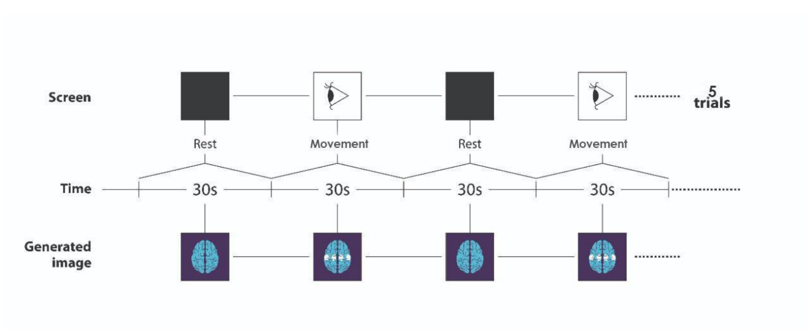

Figure 1 - Timeline of each motor task using a visual command (rest or limb movement) presented on a screen. Each command was shown for 30 seconds, during which time the volunteer had to perform the movement or remain at rest. Five trials were executed for a total time of 5 minutes for each individual motor task.

Image acquisition

The images were obtained in a Signa HDxt 1.5 T fMMR (General Electric) system at the Federal University of Uberlândia. Prior to the functional examinations, high-resolution T1-weighted anatomical images were obtained with 3D-SPGR (TR/TE=12/3.1 ms, inversion angle of 12°, isotropic resolution 1x1x1 mm^3). T2* weighted functional images were obtained using a 2D gradient-echo EPI sequence (TR=2.5 s, TE=60 ms, 90° inversion angle, 64× 64 acquisition matrix, voxel size 3 × 3 × 3mm^3, 25 axial slices with no gap). For processing, one hundred and twenty brain volumes were used for each volunteer during the execution of each requested task.

Image processing

Image processing was performed using the Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London, United Kingdom). In conjunction with guidance and observation , pre-processing was performed to remove unwanted variability from the data, improve the signal-to-noise ratio, reduce the total variance in the data, and prepare the data for statistical analysis. We applied all the stages of the SPM (STATISTICAL PARAMETRIC MAPPING), going through (initial image diagnosis, reorientation, realignment, cut-off time correction, distortion, co-registration). (Friston, K. et al 2006; Caredda, C., et al, 2023; Di X.; Biswal, BB, 2023)

The first step of spatial preprocessing was the realignment of the functional images. High-resolution anatomical images were co-recorded with functional images, maximizing mutual information. Pre-processing continued with the segmentation of high-resolution anatomical images.

White matter, gray matter, and cerebrospinal fluid probability maps from the Montreal Neurological Institute (MNI) 452 were used to produce a parametric description for normalization. During normalization, the images were also corrected for bias. Image pre-processing ended with smoothing using a 6 × 6 × 6 mm3 isotropic Gaussian kernel with half the maximum (FWHM).

The modeling was performed with convoluted functions with a canonical hemodynamic response function. We used SPM12 to estimate the model parameters. Low-frequency noise was eliminated using a 160s high-pass filter. Subsequently, task versus rest activation was assessed by applying a t-test to the estimates of first-order parameters, resulting in statistical parametric t-maps for each participant with $p=0.05$.

For the proposed tasks, the activation volume (VOA) analyzed was from the following regions: left postcentral gyrus (LPoG), left precentral gyrus (LPrG), right precentral gyrus (RPrG) and right postcentral gyrus (RPoG), areas related to sensory and motor functions affected by SCI. To measure the sensorimotor alterations resulting from SCI, the ratio between the cortical areas related to sensory (postcentral gyrus) and motor (precentral gyrus) functions on both sides of the upper and lower limbs was estimated. Thus, it was possible to infer an increase or decrease in VOM for these functions correlated with the time of injury.

Statistical analysis

To evaluate VOAs in the sensorimotor areas, the relationship between the postcentral gyrus and the precentral gyrus, which we call the sensorimotor ratio (SR), was estimated in the control and experimental groups. And the non-parametric Mann-Whitney test was used to compare the differences between the groups in relation to this proportion.

RESULTS

Here, we present the results of the comparison of the sensorimotor ratios between the groups and graphs that relate the time since the injury and the SRs. Both for the upper and lower limbs.

Upper limbs

Right Hand: There was a statistically significant difference in sensory-motor ratios (SRs) with p=0.021, indicating that the sensory-motor relationship tends to increase with the time since the injury (Figure 2a). =0.021, and the sensory-motor ratio tends to increase with the time of injury (Figure 2a).

Left Hand: No statistical differences were found in the SRs between the groups, as shown in Figure 2b.

Lower limbs

Right Ankle: There were no statistical differences in sensory-motor relationships between the groups, but the relationship tends to increase with the time since the injury (Figure 2c).

Left Ankle: A statistically significant difference was observed with p=0.002, showing that the SRs were significantly lower in the experimental group. For some individuals, the SR remained low even after a long time since the injury (Figure 2d).

In the Figure 3 illustrates the activation volumes obtained for the two tasks that differed significantly between the groups: opening and closing of the right hand and dorsiflexion of the left ankle.

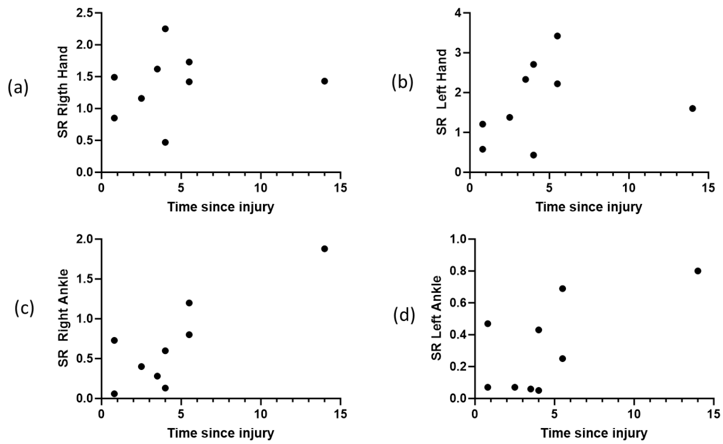

Figure 2 –Correlation plots between time since injury and the SRs in (a) right hand, (b) left hand, (c) right ankle, (d) left ankle.

Figure 3 presents the activation volumes obtained for the two tasks which differed significantly between groups, namely, opening and closing of the right hand, and left ankle dorsiflexion.

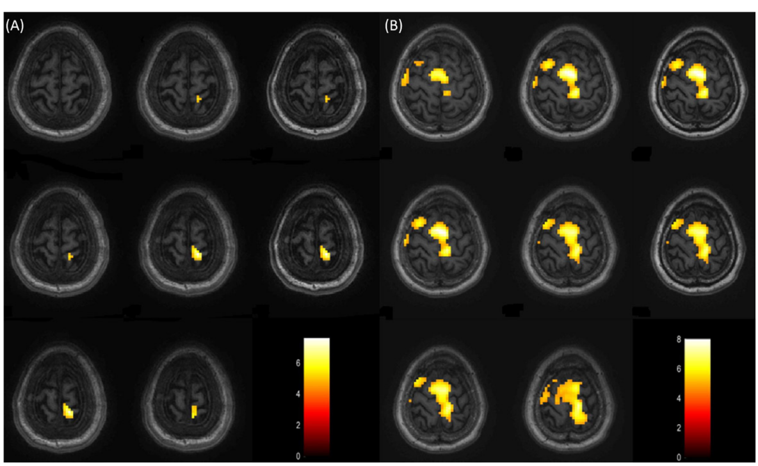

Figure 3 – BOLD representation of the tasks of opening and closing the right hand, and left ankle dorsiflexion. (A) Volume of activation of a 54-year-old participant in the experimental group during LA dorsiflexion.(B) Volume of activation of a 50-year-old participant in the control group during RA dorsiflexion. There is a noticeable increase in the volume of activation for the RH in the experimental group and a decrease for LA dorsiflexion.

DISCUSSION

This study aimed to investigate the reason for activation (RA) in the post-central and pre-central areas following spinal cord injury (SCI) to assess whether these regions are affected by the injury and, if so, how this relates to the time since the injury. An increase in RA in the right hand and a reduction in RA in the left ankle were observed in individuals with SCI compared to controls. Additionally, a trend of increased RA in the right ankle in relation to the time since the injury was evidenced.

Regarding the upper limbs, when comparing the SCI group and the control group in the task of moving the right hand, the RA was significantly greater in the SCI group. This phenomenon may be attributed to motor learning induced by the injuries through changes in plasticity, representing a compensatory mechanism for lost functions (Muir GD, Steeves JD, 1997; Nakanishi et al., 2021). Cortical motor maps are plastic and reorganize in response to learning, altered sensory experiences, amputations, and injuries to peripheral nerves and the spinal cord (Mohammed H., Hollis F.D., 2018).

Similar results were found by Sabre et al. (2016), who investigated brain activation in the chronic phase of SCI. During hand movements, activation in the contralateral primary motor cortex was significantly greater among patients with chronic SCI than among controls. Other studies have also indicated functional reorganization in the representations of upper limbs, which expand in people with SCI. For example, individuals with SCI showed a medial shift in the representation of the S1 finger during tactile sensory stimulation (Henderson LA et al., 2011; Hou J. et al., 2016). Our results reinforce the evidence that the somatosensory cortex is dynamic and mutable.

In individuals with SCI, there is greater stimulation of the upper limbs, primarily the dominant limb (which in this study was the right limb for all participants), in most activities, such as entering and exiting a wheelchair or a bed, among many other daily activities. Sensory-motor activation may be caused by increased use of the upper limbs in patients with SCI who have paralysis of the lower limbs (Mohammed et al., 2018). Our findings emphasize the importance of training for recovery and rehabilitation. Nakanishi et al. (2021) investigated the neural basis of the recent finding that individuals with complete spinal cord injury have a greater ability to control grip strength in their intact upper limbs than healthy individuals. The authors suggested that adaptive mechanisms in the brain in response to the complete loss of afferent signals from the lower limbs and efferent signals from the brain may have applications in neurorehabilitation, such as brain-targeted interventions to improve the functions of intact limbs after SCI. Nicolelis et al. (2022) showed that training with a non-invasive brain-machine interface, tactile feedback, and rehabilitation focused on limb movement potentially enhances neurological recovery in individuals with complete paraplegia.

Regarding the lower limbs, the reason for activation of the left ankle was significantly lower in the experimental group compared to the control group. Unlike the upper limbs, this result may be due to the lack of training and use of this limb during daily activities. Several studies have described the relationship between brain reorganization in the sensorimotor cortex and paralyzed body parts following SCI (Matsubayashi et al., 2018; Jutzeler et al., 2015; Kokotilo et al., 2009; Nardone et al., 2018), although findings related to ankle dorsiflexion and activation volume remain divergent, as shown by Melo et al. (2020).

Interestingly, our results showed a possible relationship between the reasons for activation and the time since the injury in the right ankle, which was not found for the other limbs. Few studies have evaluated the correlation between ankle dorsiflexion, reasons for activation, voluntary activation, and time since the injury. Our results suggest that the longer the time since the injury, the more brain activation is needed to generate voluntary movement in individuals with incomplete SCI. Similarly to our findings, Sharp et al. (2017) discovered that increased time following incomplete SCI was associated with increased activation in specific brain regions, including the post-central gyrus and the supplementary motor area, during right ankle dorsiflexion. Curt et al. (2002) reported that increased voluntary activation in patients with SCI did not necessarily correlate with the duration of SCI concerning the upper limbs, as observed in our findings. In contrast, Sabre et al. (2016) found a strong correlation between the time since the injury and voluntary activation during hand movements. Jurkiewicz et al. (2007) identified a negative correlation between the extent of sensory-motor activation during the attempt to dorsiflex the right ankle and the time post-SCI, indicating that activation decreases over the duration of the injury.

It is important to note that when comparing the experimental and control groups, the reasons for activation related to the left hand and right ankle did not show statistical differences. These results imply that the reason for activation was not affected in these limbs due to SCI, indicating evidence of sensory-motor preservation for the respective limbs, or that there was no increase or decrease in training levels for these limbs to induce any reorganization. Some authors have found preservation of functional networks for the upper limbs (Mikulis et al., 2002) and lower limbs (Sabre et al., 2016).

Several limitations should be considered when interpreting the results. Due to the small sample size, the results should be interpreted as preliminary guidance to be considered in future studies. Future research may focus on groups with divergent times since the injury and ASIA grades to explore in more detail the impact of these factors on voluntary activation. Additionally, future studies should include consideration of connectivity parameters to understand how activation relates to functional networks.

The study provides evidence supporting the hypothesis that cortical changes could potentially be related to the amount of recruitment and training of the upper and lower limbs. A simple activation reason index was used, which could be useful in assessing these changes. This may lead to the development and validation of neurorehabilitation methods to promote neurological recovery in the sensory-motor areas affected by SCI.

CONCLUSION

Understanding cortical reorganization, how it occurs, and its consequences is a challenge due to the heterogeneity of variables in individuals with spinal cord injury, which can lead to significant divergences in findings across studies in this area. We assessed four limbs through motor execution tasks or attempts to move to investigate the influence of time since the injury and laterality on the somatosensory areas of individuals with spinal cord injury during motor activities.

Our results suggest possible alterations in the sensory-motor relationship of the left ankle and right hand of individuals classified as ASIA A and ASIA B, possibly influenced by how different limbs are utilized in performing daily activities. More studies should be conducted to understand how the time since the injury alters activation levels. Furthermore, the idea that increased use of a limb could induce reorganization of the sensorimotor cortex could lead to the development and validation of neurorehabilitation methods to induce some level of neurological recovery in individuals with spinal cord injury.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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