Impact of Combining Transcutaneous Spinal Direct Current Stimulation (tsDCS) and Robotic Exoskeleton Gait Training on Spinal Excitability and Gait Function in Individuals with Spinal Cord Injury

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Protocol Title:	Impact of Combining Transcutaneous Spinal Direct Current Stimulation (tsDCS) and Robotic Exoskeleton Gait Training on Spinal Excitability and Gait Function in Individuals with Spinal Cord Injury
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Population:	Human subjects (male and female), age 18 years or older, who have a confirmed diagnosis of chronic (>6 months post injury) motor incomplete spinal cord injury.
Number of Sites:	1. TIRR Memorial Hermann
Study Duration:	2 years
Subject Duration:	5 weeks

GENERAL INFORMATION

Spinal cord injuries lead to a host of primary and secondary physical impairments that can interfere with an individual's health and participation in life activities. Even with intensive rehabilitation many persons affected by spinal cord injury (SCI) will lead sedentary lifestyles. Individuals with SCI face a multitude of challenges due to physical difficulties that impact their health, independence, and satisfaction with life. With the integration of modern technology into rehabilitation, multiple techniques have been developed that combine our knowledge of walking with robotic technology. Further, emerging research indicates that application of electrical stimulation directly to the spinal cord can result in active motor recruitment below the level of injury for individuals with complete SCI.[1-2] Non-invasive electrical stimulation, transcutaneous spinal direct current stimulation (tsDCS), has the ability to alter spinal reflexes and modulate spinal cord excitability in healthy subjects and individuals with SCI.[3-17] Therefore, tsDCS has the potential to modulate and induce spinal cord excitability and neuroplasticity that leads to recovery after SCI. The purpose of this study is to determine whether tsDCS is safe for individuals with SCI. In specific Aim 1, we will determine whether tsDCS is safe for patients with SCI. In specific aim 2, we will investigate the potential neurophysiological changes and functional improvements in gait for individuals with SCI after combined application of tsDCS and exoskeleton assisted gait training. We hypothesize that when subjects are receiving the tsDCS in combination with exoskeleton training they will demonstrate an increased magnitude in spinal reflex which will correlate with improvement in gait speed, as compared to when subjects are receiving exoskeleton training without tsDCS.

BACKGROUND INFORMATION

As of 2014, there were an estimated 276,000 persons in the United States living with a SCI, and an additional 12,500 new cases added each year. Of those injured, approximately 66%

presented with incomplete spinal lesions.[18] While individuals with motor incomplete lesions may regain some ability to ambulate over ground, ambulation in the community and household may be limited or impossible secondary to the physical demands encountered during gait. This contributes to an extremely limited number of steps taken per day, and often leads to a sedentary lifestyle.[19] It is well appreciated that a sedentary lifestyle from paralysis contributes to many secondary medical problems such as diabetes, obesity, osteoporosis/osteopenia, urinary, pulmonary and cardiovascular disease.[20-23] Walking, therefore, is not only an important activity of daily living but also helps to reduce secondary complications. Most importantly, recovery of walking ability is one of the single most predictors of quality of life after spinal cord injury.[24, 25]

Historically therapy was limited to teaching compensatory strategies, as little was known about neuroplasticity of the spinal cord. Evidence is now growing to support the ability of the spinal cord to adapt after injury.[26] Emerging research indicates that intentional massed practice of activity-based training may promote neural plasticity and cortical reorganization and subsequent recovery of walking ability after neurological injury, including SCI.[27-32] Moreover, studies have shown that placing the body in a load bearing position and moving the lower limbs in a repetitive stepping pattern leads to improved locomotor recovery.[33-35] *One example,* locomotor training, using body weight supported treadmill training (BWSTT), drives changes in spinal cord pathways by increasing the excitability of the spinal cord leading to recovery of movements controlled below the level of injury.[36, 37] In BWSTT, a body weight support system allows for unweighting of the body while using a treadmill to provide repetitive stepping. An alternative method for achieving load bearing, repetitive stepping in an overground environment with less cost and energy to clinicians is use of lower extremity robotic exoskeletons for gait training.

In spite of the fact that the spinal cord has shown great potential for neuroplasticity, no one intervention has proven successful at inducing changes in the cord and return of full pre-injury function prior to SCI. It is important to make available in the clinic interventions that combine neuroplasticity principles and focus on restoring function after neurological injury. Electrical stimulation is currently readily available and utilized in the clinic for spasticity, pain, muscle strengthening and neurological recovery. Electrical stimulation can be applied at the muscle, nerve or spinal level. Exciting new research is demonstrating that application of electrical stimulation directly to the spinal cord can result in active motor recruitment below the level of injury for individuals with complete SCI.[1-2] However, this technology is only available in research phase and requires invasive surgery.

An alternative non-invasive method for stimulating the spinal cord is through the use of transcutaneous spinal direct current stimulation (tsDCS). tsDCS applies electrical current to the spinal cord via surface electrodes placed on the skin. It has been demonstrated in animal models and healthy human subjects that tsDCS has the ability to alter spinal reflexes and has an effect on spinal cord excitability.[3-16] The use of tsDCS has been evaluated in healthy individuals, however there is only one research study to date that investigates the use of tsDCS on individuals with SCI.[17] Hubli found that individuals with complete SCI demonstrated changes in spinal reflexes after application of tsDCS.[17] This means tsDCS has the potential to alter spinal cord excitability below the level of lesion.

Although this technology has been around for decades and tsDCS has been shown to modulate the excitability of the spinal cord, limited research has investigated its use in the SCI population. Before this technology could promote recovery after SCI, further research is needed to evaluate the safety and efficacy of this intervention. Therefore, the purpose of this pilot study is to determine whether tsDCS is safe for individuals with SCI. It is hypothesized that use of tsDCS will lead to measurable changes in spinal excitability (measured by H-reflex in soleus muscles) in individuals with SCI. We further hypothesize that this potential neurophysiological change could lead to gait improvements. To answer our questions, we will use exoskeleton assisted gait training as a standard gait training intervention in combination with tsDCS.

OBJECTIVES

The purpose of this study is to determine whether tsDCS is safe for individuals with SCI.

Specific Aim 1: To determine whether tsDCS is safe for patients with SCI. There is one study that has utilized tsDCS in 17 individuals SCI[17]. No adverse events were noted in this study, therefore we hypothesize that all subjects will tolerate the use of tsDCS without adverse reactions.

Specific Aim 2: To investigate the potential neurophysiological changes and functional improvements in gait for individuals with SCI after combined application of tsDCS and exoskeleton assisted gait training. It has been demonstrated that use of tsDCS has an impact on spinal excitability, however there has been no investigation on the potential impact changes in spinal excitability may have on functional mobility. We hypothesize that when subjects are receiving the tsDCS in combination with exoskeleton training they will demonstrate an increased magnitude in spinal reflex which will correlate with improvement in gait speed, as compared to when subjects are receiving exoskeleton training without tsDCS.

STUDY DESIGN

A single case series design (baseline, intervention, and combined intervention) is used in this pilot study. The study schematic diagram is presented in Figure 1.

STUDY POPULATION

We plan to enroll 4 human subjects (male and/or female), age 18 years or older, with a confirmed diagnosis of chronic motor incomplete SCI, classified by the American Spinal Injury Association Impairment Scale (AIS) grades C or D.

Potential subjects will be recruited from TIRR Memorial Hermann outpatient clinics and therapy services. Subjects will be excluded if they lack sufficient range of motion at lower extremity preventing achievement of normal stepping kinematics, are unable to physically fit within the exoskeleton, have evidence of an unstable spine, presence of lower extremity or pelvic fractures or other conditions limiting weight bearing into legs, history of severe neurological disorder other than SCI, known peripheral neuropathy or any pathology that could influence reflex excitability, difficulty completing forms written in English or following verbal instructions provided in English, use of mechanical ventilation for respiratory support. Final exclusion criteria include conditions in which use of electrical stimulation is contraindicated: presence of cardiac pacemaker, deep brain stimulator, or evidence of cancerous (malignant)

tissue, and presence of metal in thoracic spine and region of electrode placement. See chart for all inclusion and exclusion criteria.

Inclusion Criteria	***Exclusion Criteria***
• Male or non-pregnant female • ≥18 years of age • Able to achieve adequate fit within exoskeleton • Diagnosis of spinal cord injury, T10 level and above (T11 and 12 may participate if no clinical signs of lower motor neuron lesion present) • Minimum of 6 months post injury • Sufficient range of motion to attain normal, reciprocal gait pattern, and transition from normal sit to stand or stand to sit • Weight <220 pounds • Intact skin on all surfaces in contact with device and load bearing surfaces • Ability to perform informed consent	• Pregnancy • Spinal instability • Unhealed limb or pelvic fractures or any condition restricting weight bearing in limbs • Presence of peripheral neuropathy or any pathology that could influence reflex excitability • Diagnosis of other neurological injury other than SCI such as CVA, MS, ABI, CP • Uncontrolled spasticity (≥3 on Modified Ashworth Scale) • Colostomy • Decreased range of motion or contractures in legs (>10° at hips, knees or ankles) • Uncontrolled autonomic dysreflexia • Unresolved deep vein thrombosis • Inability to tolerate standing due to cardiovascular issues or orthostatic hypotension • Severe comorbidities: active infections, heart, lung, or circulatory conditions • Pressure sores, impaired skin integrity • Use of mechanical ventilation for respiratory support • Presence of any of the following contraindications to electrical stimulation: cardiac pacemaker, deep brain stimulator, or evidence of cancerous (malignant) tissue • Presence of metal in thoracic spine or region of electrode placement

Procedures

The proposed investigation is a single case series design (baseline, intervention, combined intervention). The study schematic diagram is presented in Figure 1.

Subjects will be asked to attend a screening visit, 2 baseline visits and 15 training sessions. The screening visit will take 30 – 45 minutes and assessment of range of motion, flexibility, spasticity, mobility, and measurements will be performed to ensure individual will fit inside the robotic exoskeleton. Baseline visits will be scheduled for 1 hour and will include spinal reflex testing using the Soleus Hoffman Reflex (H-Reflex) and a 10 Meter Walk Test

(10MWT). Subjects will participate in two types of training visits; exoskeleton training and exoskeleton training plus tsDCS. Training visits will be scheduled for 0.5-1.5 hours depending on the intervention condition (exoskeleton training or exoskeleton training and tsDCS intervention). There will be a 1 week wash out period between intervention conditions. See Table 1 and 2 for timeline.

Table 1: Timeline for subjects 1 and 3: A-BC-C-BC design

Sub 1 (cathode) and Sub 3 (anode) A-BC-C-BC A = Baseline, B = tsDCS, C = Ekso 5 weeks, 17 visits, 17.5 hours																		
Visit	1/A	2/A	3/ BC	4/ BC	5/ BC	6/ BC	7/ BC	Wash out	8/C	9/C	10/C	11/C	12/C	Wash out	13/ BC	14/ BC	15/ BC	16/ BC	17/ BC
Day	1	5	8	9	10	11	12		22	23	24	25	26		36	37	38	39	40
Time	1 hr	1 hr	1.5 hr	1 hr	1 hr	1 hr	1.5 hr		1 hr	.5 hr	.5 hr	.5 hr	1 hr		1.5 hr	1 hr	1 hr	1 hr	1.5 hr
H-Reflex	X	X	X				X		X				X		X				X
10MWT	X	X	X				X		X				X		X				X
Ekso									X	X	X	X	X						
Ekso + tsDCS			X	X	X	X	X								X	X	X	X	X

Table 2: Timeline for Subjects 2 and 4: A-C-BC-C design

Sub 2 (cathode) and Sub 4 (anode) A-C-BC-C A = Baseline, B = tsDCS, C = Ekso 5 weeks, 17 visits, 15 hours																			
Visit	1/A	2/A	3/ C	4/ C	5/ C	6/ C	7/ C	Wash out	8/ BC	9/ BC	10/ BC	11/ BC	12/ BC	Wash out	13/ C	14/ C	15/ C	16/ C	17/ C
Day	1	5	8	9	10	11	12		22	23	24	25	26		36	37	38	39	40
Time	1 hr	1 hr	1 hr	.5 hr	.5 hr	.5 hr	1 hr		1.5 hr	1 hr	1 hr	1 hr	1.5 hr		1 hr	.5 hr	.5 hr	.5 hr	1 hr
H-Reflex	X	X	X				X		X				X		X				X
10MWT	X	X	X				X		X				X		X				X
Ekso			X	X	X	X	X								X	X	X	X	X
Ekso + tsDCS									X	X	X	X	X						

Screening

After informed consent is provided, the subject will undergo a screening evaluation to assess skin integrity, hip, knee, and ankle range of motion, and spasticity. We will also perform assessments of functional mobility and measurements to ensure the individual will safely fit inside the robotic exoskeletons.

Baseline Visits

Subjects will participate in two baseline visits, 4 days apart. The visit will last 1 hour and will include assessment of soleus H-Reflex and 10 meter walk test on arrival and 40 minutes after initial assessment. Subjects will be asked to minimize their activity between assessments by either sitting in a chair or lying on a mat.

Training Visits

Each training visit will involve either an exoskeleton intervention or a combined exoskeleton and tsDCS intervention. Subjects will participate in a total of 15 training visits.

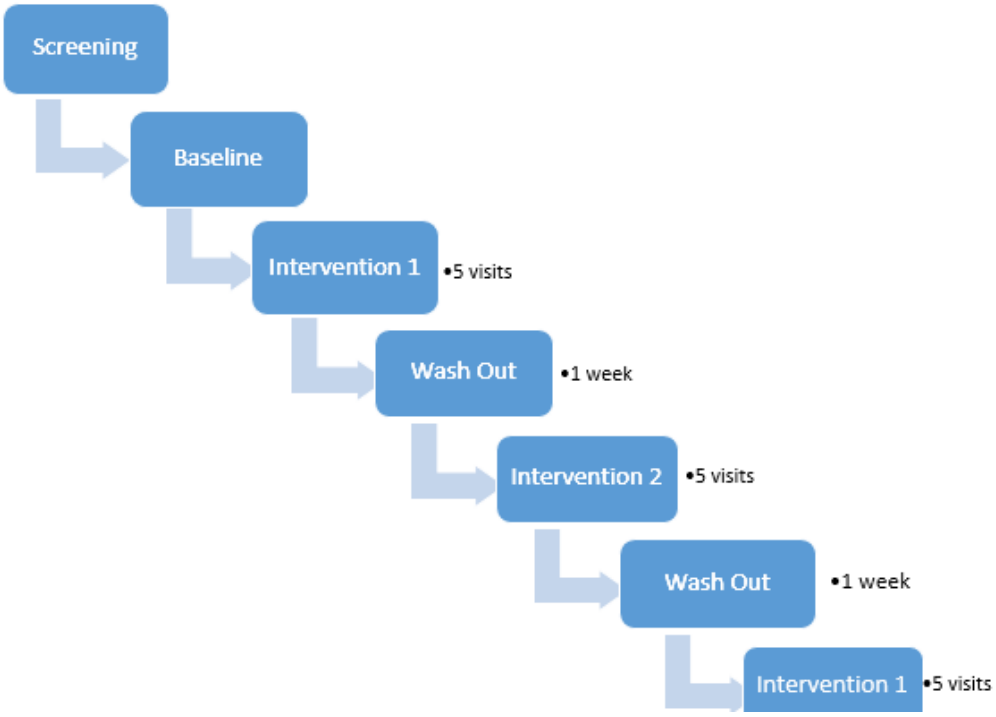
Exoskeleton Intervention: Each exoskeleton intervention will last 20 minutes. During the exoskeleton training session, subjects will wear Ekso®, a lower extremity exoskeleton robotic walking device. Initial training will focus on static and dynamic standing balance and weight shift training with the exoskeleton and progress to more difficult activities such as transitioning form sit-to-stand and stand-to-sit, walking, and turning. There will always be at least one trainer present during the training sessions to provide varying levels of assistance. As a subject's skill with the powered exoskeleton improves, the need for trainer assistance will be proportionately reduced. At the conclusion of 20 minutes of exoskeleton gait training, the subject will perform a 10 Meter Walk Test.

Safety: There will always be at least one trainer present during the training sessions to provide varying levels of assistance. A 2nd staff will stand and walk with the subject if needed to ensure safety and prevent falls. Subjects will wear a safety harness attached to an overhead body weight support system to prevent falls if necessary.

tsDCS Intervention: tsDCS interventions will last 20 minutes. Subjects will be assigned to receive anode or cathode stimulation. Direct current stimulation will be delivered using Soterix Medical 2x1s Transcutaneous Spinal Direct Current Stimulator. Stimulation will be provided following published tsDCS protocol[7, 17]. One electrode (50 cm^2) will be placed along center of spine centered over the spinous processes of T10. The reference electrode will be placed over the R shoulder. Direct current intensity will be applied at 2.5 mA (0.05 mA/cm^2) with a total charge of 60 mC/cm^2 for 20 minutes. These stimulation parameters are below the known threshold for possible tissue damage[38].

Subjects will participate in individualized training sessions at UT Health Motor Recovery Laboratory at the NeuroRecovery Research Center at TIRR Memorial Hermann.

Figure 1: Study Schematic Diagram



Outcome Measures

Subjects will participate in a screening, 2 baseline visits and 15 intervention visits. Outcome measures that will occur at baseline and during intervention visits and will include spinal reflex testing using the Hoffman Reflex (H-Reflex) and 10 Meter Walk Test (10MWT).

Assessments:

- Soleus H-reflexes: H-reflex will be elicited by placing the cathode of an electrical stimulator in the popliteal fossa and stimulating N. tibialis. Surface electromyography electrodes will be placed at the soleus muscle of the testing leg to record the electrical-induced muscle activity. At the beginning of the test, stimulus thresholds and maximal amplitudes of H-responses (Hmax) and M-responses (Mmax) will be assessed. The stimulus intensity applied to elicit H-reflexes will be chosen just below stimulus intensity required to elicit Hmax, i.e. 0.9 times. The size of each H-reflex will be measured as the peak-to-peak amplitude of the non-rectified EMG trace (Figure 2). H-reflex magnitude will be normalized by expressing it as a percentage of the amplitude of Mmax.

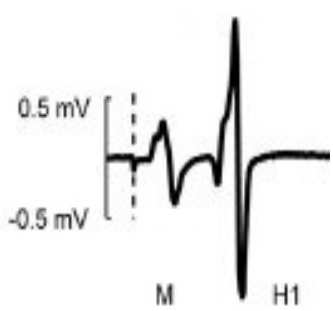


Figure 2. An illustration of H-reflex and proceeding M-wave elicited from a patient with SCI

- 10 Meter Walk Test (10MWT): The 10MWT will assess subject's gait speed. Four marks will be placed on the ground at 0, 2, 12 and 14 meters. Subjects will walk a total of 14 meters. The middle 10 meters (between marks at 2 and 12 meters) will be timed and recorded as their gait speed. Subjects will perform a 10MWT without use of exoskeleton.
- Exoskeleton user feedback: A questionnaire will be administered to allow participants to provide feedback regarding their experience after completion of treatment sessions.

Treatment sessions: We will track any signs of adverse reaction to the tsDCS intervention such as skin irritation, complaints of pain or discomfort continuously throughout subject's participation.

Tentative Timeline The proposed timeline to complete the study is 2 years.

PHOTOGRAPHY and VIDEOTAPING

We would like to obtain photographs and video during the tsDCS and exoskeleton treatment sessions. The goal of the photography and videotaping will be used for educational

purposes when presenting results of this study. The photographs will be used to demonstrate application of tsDCS and what exoskeleton training looks like. The identity of subjects will not be revealed in the photograph. If a photograph or video is used, a black box will be placed in front of subject's face to protect their identity. Any photographs and videos taken during the study will be saved on a locked computer in a file labeled with the subject's research number and no other identifying information. These files will be saved for five years after which they will be deleted.

DATA and SAFETY MONITORING

We will use following strategies to prevent some expected events for this study:

1) Loss of confidentiality or privacy

Information obtained for this study will be kept private to the extent allowed by law. However, research information may be shared with the University of Texas Health Science Center at Houston Institutional Review Board (IRB), the research physician investigator, the research staff and others who are responsible for ensuring compliance with laws and regulations related to research.

The study will be performed at UT Health Motor Recovery Laboratory at the TIRR NeuroRecovery Research Center.

Data will be collected on paper forms which will be kept in a locked room in a locked filing cabinet in the research office. To allow for data analysis, data will be de-identified and entered into an excel spreadsheet. All computers are password protected and therefore, only authorized persons have the access to the electronic files saved in computers and will adhere to TIRR Memorial Hermann standards.

2) Loss of saved electronic data after a computer crash

All original data will be maintained on paper data collection forms. De-identified data may be entered into computer for data analysis. A standard procedure of electronic file backup is established and enforced by the PI. All file backups are routinely performed in the local hard drive.

However, if there are other unanticipated problems which occur during and after data collection: the original paper version of the data will be maintained in the locked file cabinet.

3) Loss of balance or fall from testing

One research team member will remain next to the subject as long as the subject is donned in the exoskeleton robot to prevent loss of balance or fall whether sitting or standing. If a fall or significant loss of balance occurs, one staff physician will be notified immediately. All adverse events will be reported per CPHS protocol.

4) Possible skin irritation

Local skin irritation, bruising, swelling, or temporary discomfort following wearing of the exoskeleton and/or post tsDCS intervention may occur. Prior to tsDCS application and donning the exoskeleton subject's skin will be inspected by a licensed Physical Therapist for baseline, and compared after tsDCS intervention and doffing exoskeleton. Any differences will be recorded and followed up with the study physician accordingly. All adverse events will be reported per CPHS protocol.

5) Bone Fracture

The risk of fracture to the subject is no greater with the use of exoskeleton than conventional weight bearing and walking therapy.

STATISTICS

Descriptive statistical analysis will be performed to examine the trend of the outcome measures at baseline, intervention and combined intervention for each case study series.

ETHICS

The study will be performed under the prevue and in accordance with the rules set by the Committee for the Protection of Human Subjects (UT IRB). Potential subjects will be identified by physiatrists working in the outpatient clinic and/or on the inpatient wards at The Institute for Rehabilitation and Research (TIRR) Memorial Hermann. Once identified, the potential subjects will be approached and asked if they wish to discuss a study utilizing electrical stimulation and exoskeletons (Robotic suits worn on the outside of the body) for individuals with spinal cord injury. It will also be explained that choosing not to inquire further about the study will in no way jeopardize the relationship with anyone at TIRR or in the Memorial Hermann system. Once the potential subject agrees he/she will be introduced to either the Principal Investigator or the Co-Investigator. Once the potential subject agrees to discuss the study, the individual and anyone that the potential subject wishes to accompany him/her will go into a private room to discuss the contents of the consent form with either the Principal Investigator or the Co-Investigator. After the consent is reviewed in its entirety, and after allowing ample time for questions, either the Principal Investigator or the Co-Investigator will give the potential subject time to discuss the study with whomever the potential subject cares to discuss the study with. If the subject agrees to enroll in the study, the Principal Investigator or Co-Investigator will review the informed consent form with the subject in its entirety.

DATA HANDLING and RECORD KEEPING

The subject's name and demographic information will be collected prior to testing. Each subject will be assigned an identification number which will be used from this point forward. All measurements will be stored according to the identification number. All research materials will be kept in a locked file cabinet in the research office. All computers are password protected and only authorized persons have the access to the electronic files saved in computers. Paper data will be stored in the UT Health Motor Recovery Laboratory research office in a locked file cabinet. Access to the file cabinet will be given to the Primary Investigator and authorized team members. All electronic data stored on the hard drive of the desktop machine will be password protected and available only to the authorized research team members. Identifiable data will be stored for 5 years after the study is completed. Stored files will be deleted from the portable hard drive after 5 years as well. Identifiable data will be shredded at the end of 5 years after the completion of the study.

QUALITY CONTROL and ASSURANCE

To ensure research integrity, standard written procedures for all tests will be established by the Principle Investigator and the Study Coordinator who will then assess each team member's competence for research conduction on a regular basis. Therefore, the testing protocol will be consistent throughout the entire data collection for this study.

COSTS, REIMBURSEMENTS and COMPENSATION

Subjects will receive $150 stipend for participation in this study upon completion of 15th treatment visit. Subject's parking fees for each visit will also be covered. Therefore, subjects will incur no costs for participating in the study.

FUTURE STUDIES

Subject will be asked to answer a question regarding their interest in being contacted in the future to participate in other studies. Subjects will be given the choice to say yes or no if they agree to be contacted in the future regarding other projects.

PUBLICATION PLAN

The results of this study will be used for presentation at national conferences and publications in peer-reviewed journals. The publications will be provided without cost to the study participants.

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