Effects of Combined Spinal Direct Current Stimulation on Upper Limb Recovery in Acquired Brain Injury

NCT03100370

Version Date: 12/21/2021

UNIVERSITY OF TEXAS – HOUSTON MEDICAL SCHOOL PROTOCOL

PROTOCOL TITLE: Effects of Combined Spinal Direct Current Stimulation on Upper Limb Recovery in Acquired Brain Injury (IRB Number: HSC-MS-16-0237)

2. BACKGROUND and SIGNIFICANCE

Acquired brain injury (ABI) is the leading cause of neurological disability in the United States (Wolf et al.1999) and accounts for the poor physical health and the social dysfunction evident in survivors (Hankey et al. 1989). Hemiparesis due to acquired brain injury is the primary cause of disability (Bonita et al. 1988). Arm paresis is perceived as the primary cause of disability by individuals who have suffered ABI because of the limitations it creates in performing activities of daily living (ADL) (Broeks et al. 1999). Rehabilitation of the impaired limb is essential for improving motor function after ABI (Liepert 1998 and 2008), yet only 31% of ABI survivors receive outpatient rehabilitation (CDC 2007). Therefore, effective therapy for upper-limb paresis must be addressed. Approximately 80% of all ABI survivors suffer from upper limb paresis and only 18% of these individuals gain full motor recovery with conventional treatments in the year following ABI (Wing et al. 2008).

Rationale for using non-invasive spine stimulation as an add-on therapy modality for rehabilitation of upper-limb motor functions in ABI: Currently there is no cure for people with ABI having persistent arm and hand weakness. Particularly therapeutic approaches aiming to increase hand-movement dexterity should include the corticospinal tract (CST) as damage to the CST causes severe deficit in hand movements (Isa et al., 2014; Anderson et al., 2004). In this context, non-invasive central nervous system stimulation is a powerful method to modulate human brain function. It has a potential to be used as an add-on intervention to standard rehabilitation protocols, and have shown promising results in improving arm and hand function following stroke (Hesse et al., 2007; Edwards et al., 2009; Bolognini et al., 2011). Stimulation of primary motor cortex with high frequency repetitive transcranial magnetic stimulation (rTMS), another form of non-invasive brain stimulation, produced improvement in arm and hand functions after 5 days of treatment (Kuppuswamy et al.,2011; Belci et al.,2000). Researchers have hypothesized that increasing excitability of the primary motor cortex would modify descending corticospinal influences and increase inhibitory input, thus leading to more coordinated and skilled movements (Duque et al., 2003) with reduced spasticity. Moreover consecutive facilitation of components of the motor system at spinal level (spinal tract axons and spinal reflex pathways above injury) may have a potential to further augment therapeutic effects when combined with peripheral repetitive training.

Rationale for exoskeleton-assisted training of arm and wrist movements: There is evidence that treatment intensity has a profound effect on motor recovery and the use of robotic exoskeleton devices has potential to automate labor-intensive therapy procedures (Backhus et al., 2010; Sanchez et al., 2006). In this context, rehabilitative robotic exoskeleton devices can deliver high-dosage, high-intensity repetitive training of single joint movements or functional tasks by coordinated multi joint movements and can provide immediate feedback about performance. Our research team at NeuroRecovery Research Center at TIRR /Memorial Hermann, demonstrated that robotic exoskeleton- assisted training can provide positive gains in arm and hand functions in neural recovery (Yozbatiran et al., 2011; Kadivar et al., 2011). These observations have been supported by others (Zarrifa et al., 2011; Cortes et al., 2013).

3. PURPOSE OF THE STUDY:

The purposes of this project are: a) to evaluate if adults with chronic acquired brain injury can improve their upper-limb voluntary movement by participating in a therapeutic program that combines non-invasive spine stimulation with exoskeleton-assisted training (E-A training) to investigate neuroanatomical and neurophysiological mechanisms of therapeutic improvement. Our preliminary data and the literature support the model that augmentation of activity in spared corticospinal tract (CST) axons is a critical mechanism of motor improvement, and furthermore that CST activity can be increased by repetitive motor training and by electrical stimulation of the cervical spinal cord. Therefore, our project will address the goals of providing a direct, beneficial impact to persons with acquired brain injury while, at the same time, investigating the mechanisms that result in improved function.

4. DESCRIPTION OF STUDY:

Fifteen patients with weakness on one side of the body due to stroke ABI will receive ten sessions combined treatment of 20 minutes of 2.5 mA anodal, cathodal, and sham tsDCS over cervical spine combined with high intensity exoskeleton-assisted arm training, five days a week, for 2 consecutive weeks.

The study will use cross-over, randomized, sham controlled, double-blinded design in which 15 participants with subacute or chronic ABI will be assigned to receive either active anodal spinal stimulation, cathodal spinal stimulation, and sham spinal stimulation experiments for the same duration in a random order. In all the experiments participants will receive exoskeleton-assisted training for duration of 1.5 hours. The first 20 minutes of training will be coupled with spinal

stimulation. Treatment will be administered at an intensity of 5 sessions per week for 2 weeks (Please see study HSC-MS-15-0269 PI: Dr. Yozbatiran).

Pre-screening Procedures: During the pre-screening process, potential subjects with ABI will be contacted by phone from research personnel. The aim and details of the study will be explained in details (reading from a phone script) and information such as demographics, medical history, medications being used, etc. will be gathered. Also ABI subjects will be screened for tsDCS and transcranial magnetic stimulation (TMS) contraindications (attachment 1, attachment 2) and a subgroup of patients (n=5) will be screened for MRI contraindications (attachment 3). The pre-screening will last about 30 minutes and will be performed in a private area. Once this information is collected, the coordinator will consult with the Drs. Francisco (PI) and Dr. Yozbatiran and they will give final approval for the subject to come to The Institute for Rehabilitation and Research Memorial Hermann for the screening procedure.

Screening (Visit 1, duration: One hour): After subject arrives at TIRR a research personnel will meet him/her at the Motor Recovery Laboratory. The details of the study-specific procedures will be reviewed with the subject together. Subject will be screened for inclusion and exclusion criteria. Signed and dated informed consent will be obtained. Demographics, medical history, list of medications will be recorded. If the subject is female in child bearing ages, a urine pregnancy test will be requested. A medication diary will be given to the subject and asked to document all changes in type and dosage of the medication he/she has been using throughout the study. This will allow us to differentiate a potential effect of a change in dosage or type of medication on movement recovery. After subject meets all Inclusion an Exclusion Criteria he/she will be randomly assigned to active, cathodal or sham tsDCS group.

Baseline Assessment (Visit 2, duration: three to four hours): The baseline assessment can be on the same visit as screening and will be performed in the Motor Recovery Laboratory by an evaluator blinded to subject's group assignment. Subjects will be evaluated for upper extremity motor functions. Primary clinical outcome measure is Fugl-Meyer Assessment (FMA). Secondary clinical outcome measures will be Jebsen Taylor Hand Function Test (JTHFT), box and block test Modified Ashworth Scale (MAS by Bohannon &Smith 1987), Motor Activity Log (MAL), and neurophysiologic testing for spinal conductivity (SSEP), spinal reflexes and exoskeleton measurements for movement quality. Patients who are eligible also will undergo neurophysiological and neuroimaging testing with transcranial magnetic stimulation and one-hour MRI scan.

Neurophysiological testing: Transcranial Magnetic Stimulation (TMS) uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field. Single pulse

TMS causes neurons in the cortex under stimulation site to depolarize and discharge an action potential. In the current study we will use single pulse TMS for recording neurophysiological changes of corticospinal tract after treatment in comparison to baseline and at follow-up visits. Single pulse TMS will be applied over corresponding motor cortex and motor threshold (MT) will be determined. Single pulse TMS has been reported as safe. However subjects may experience; headache or neck pain which may occur due to extra muscle tension and from the straight posture of the head and neck during the application of TMS and ringing in the ear and due to loud clicking sound. In order to mitigate the aforementioned side effects, people will be asked to wear earplugs and will be offered acetaminophen or aspirin for pain. Recording motor evoked potentials: In order to record the muscle activity caused by the stimulation of movement related brain tissue, small surface electrodes will be placed on hand and forearm.

Somatosensory evoked potentials (SSEP): to assess the conduction in the somatosensory pathway electrical stimulation will be applied over arm median nerve. Procedure will follow per clinical protocol.

Spinal reflexes: *Spinal reflexes (H-reflex, M-wave and F-wave)*: the responses are initiated by passing an electrical current through a mixed nerve that includes both muscle spindle afferents and motor efferents of the test muscle. To elicit this response in an arm muscle, the electrical stimulus will be passed through the median nerve (or radial, ulnar nerve). For this procedure surface electrodes will be used, and stimulating and recording electrodes will be placed over the forearm.

Electrophysiological testing: Electroencephalography (EEG) will be recorded to measure the electrical activity in the brain and to examine changes in cortical dynamics during tDCS combined with exoskeleton-assisted arm training. It allows for better understanding of the effects of electrical activity generated in different areas of the brain associated with tDCS and combined motor training. EEG only measures brain activity and does not induce electrical current in the brain. It is non-invasive and has been used extensively in clinical practice for diagnosis or neurological conditions such as epilepsy. There are no risks associated with EEG other than a mild discomfort caused by the tightness of the cap. The investigator will adjust the cap to allow for the comfort of the subject.

Neuroimaging: For persons who qualify for undergoing neuroimaging, structural and functional MRI is performed to understand the reorganization of cortical areas associated with motor recovery. Morphological changes (structural plasticity) will be measured with structural MRI by using diffusion tendon imaging techniques. MRI is noninvasive and has been used extensively in clinical studies. In order to eliminate the risks associated with magnetic field, subjects will be scanned for MRI safety.

Functional near-infrared spectroscopy (fNIRS) device will be used to measure and record to

relative changes in oxygenated and deoxygenated hemoglobin from the motor cortex of the brain. This in turn will help examine and understand the effects of a combined tsDCS/exoskeleton- assisted arm training treatment upon motor-related brain activity. FNIRS emits near-infrared light (740nm/850nm) into the head and acquires the amount of light returning using a detector positioned 3cm from the light source. It is a portable, non-invasive device similar to EEG and has been used in multiple research studies investigating brain function under various task-oriented settings. One major risk the fNIRS device poses is potential eye damage if the infrared light-emitting diodes (IR LEDs) are shined into an individual's eyes for an extended amount of time. This will be mitigated however by ensuring that the investigator leaves the device powered off before placing it on the user's head. An additional minor risk includes a mild discomfort caused by the tightness of the headband and straps. The investigator will adjust the device to provide optimal comfort to the subject.

Intervention Period (Visit 3-12, duration: one and a half hours per visit): Within one-week following the baseline visit, subjects will receive; 1) active, 2) cathodal or 3) sham tsDCS along with exoskeleton arm training daily (Monday-Friday) for weekdays for over two-weeks. Stimulation will last a total of 20 minutes along with exoskeleton-training will continue for another 75 minutes.

For spinal stimulation direct current will be delivered by a battery-driven direct current stimulator (Soterix Medical, Model 0707-A) connected to a pair of saline-soaked sponge electrodes (7x5cm, 35cm^2).

tsDCS: tsDCS active electrode will be placed on the midline of the posterior part of the cervico-thoracal vertebraes, and the neutral electrode will be placed over the shoulder. The stimulus intensity will be set at 2.5 mA and applied over a 20 min period (Cogiamanian et al., 2008; Winkler et al., 2010; Lamy et al., 2012) resulting in a current density of 0.071 mA/cm2 and a delivered total charge of 64 mC/ cm2. The current will be ramped up to 2.5 mA over a -30 s period and similarly ramped down at the end of stimulation.

Exoskeleton-assisted training: The side being trained (right vs left arm) will be weaker side of the body. Treatment will be provided by Dr.Yozbatiran, in a dedicated therapy area in the UTHealth Motor Recovery Lab at TIRR-Memorial Hermann. Subjects will individually perform upper-extremity therapy exercises that are supported by the exoskeleton device. Activities that the subjects will be asked to perform will be selected based on the subject's upper-extremity motor function, including elbow flexion-extension, forearm pronation-supination, wrist flexion-extension, and radial-ulnar deviation. The tasks will be repeated multiple times per session for improved performance. Graphic feedback about performance will be given after each attempt in order to maintain motivation. Rest breaks will be given in order to avoid fatigue.

fNIRS: to measure brain activity over the treatment duration at the beginning of each session fNIRS system will be placed over the head of the subject. Brain activity will be recorded during rest (no active movement with the hand) and during movement (performing a motor task with hand).

Safety Assessment:

Questionnaire: At the end of each therapy session, tsDCS side effects questionnaire will be used to monitor any adverse events and study adherence (attachment 3). At the end of each session, the subject will describe any sensations they felt during stimulation and if they feel anything unexpected happened during the study visit. In addition the subject will be asked to rate his/her level of fatigue, pain, and satisfaction with the activities during the session.

Tolerability Assessment: Participants will be asked to rate the cervical spine unpleasantness and discomfort with a subject scale defining the level from “no discomfort at all” to “unbearable discomfort”.

Post-treatment and Follow-Up Assessment (Visit 13-15, duration: one and a half hours): During this period subjects will be asked to come within a-week after they have completed the study, at week-1 and month-1. Month-1 assessment will serve as the baseline assessment of the next treatment arm. Motor functions tests, exoskeleton measures and neurophysiological measurements with SSEP, TMS and fNIRS will be repeated after the treatment, at 1-week and at 3- months follow-up visits. MRI scan will be performed before and after treatment only. Portion of assessment sessions will be videotaped and/or photographed. Subjects will be asked to move or manipulate some objects with the arm while a project staff member will record or photograph. Subjects’ consent will be required to perform and photography or videotaping. Screening, assessment and treatment sessions will be held at the UTHealth Motor Recovery Laboratory at The Institute for Rehabilitation and Research and at UTHealth Medical School, MRI Facility. A total of up to 42 visits are required. Each visit will take about one-and-a-half hour. Schedule of assessments is shown in Table 1.

Table 1. Schedule of assessments for adults with ABI for the first arm of the design. The subjects will undergo same study schedule in second and third treatment arms (See figure 1).

Assessment	Screening	Baseline Assessment	Intervention period									Post-treatment Assessment	Follow-Up Assessment at 1- week	Follow-Up Assessment at 1- Months
	Day7- to Day1	Day 1	Day 4(±3) to Day 15(±3)									Day 19(±3)	Day 26 (±4)	Day 45 (±5)
	Visit 1	Visit 2	Visit 3-12									Visit 13	Visit 14	Visit 15
ICF	X													
I/E Criteria	X	X												
Randomization	X													
Demographics	X	X												
Medical History	X	X												
ASIA (motor and sensory score)		X										X	X	X
Modified Ashworth Scale		X										X	X	X
NHPT		X	X	X	X	X	X	X	X	X	X	X	X	X
Motor Activity Log		X	X	X	X	X	X	X	X	X	X	X	X	X
Grip Strength		X										X	X	X
Pinch Strength		X										X	X	X
JTHFT		X										X	X	X
FMA		X										X	X	X
Exoskeleton Measurement		X										X	X	X
tsDCS			X	X	X	X	X	X	X	X	X	X			
tsDCS related side effects			X	X	X	X	X	X	X	X	X	X			
MRI Scan		X										X		
TMS		X										X	X	X
SSEP		X										X	X	X
EEG		X										X	X	X
Spinal reflex		X										X	X	X
fNRIS		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X										X	X	X

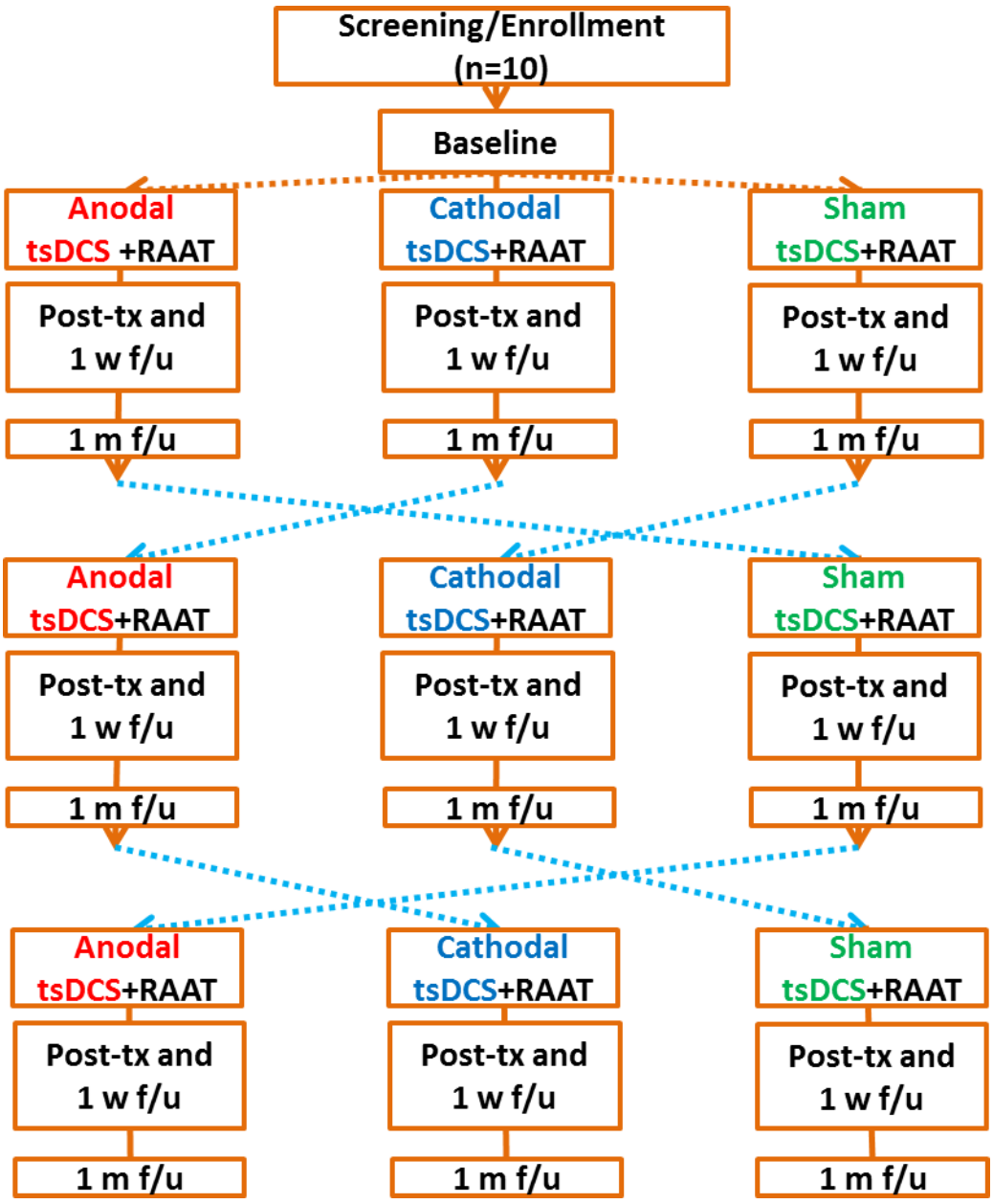

Figure 1. The cross-over design of the study is illustrated. Abbreviations: Post-tx=Post-treatment assessment, EAAT= Exoskeleton -assisted arm training, tsDCS=transcutaneous spinal direct current stimulation, 1 w f/u= 1 week follow-up after the study intervention, 1 m f/u=1 month follow-up assessment after the study intervention.

Specimens to be collected, including frequency and size/amount: None.

5. SUBJECT POPULATION:

Fifteen adults with acquired brain injury (ABI) will be recruited from TIRR Memorial Hermann,

TIRR Outpatient Rehabilitation at Kirby Glen and from the Houston area.

Inclusion Criteria:

1. Providing written informed consent prior to any study related procedures;
2. Age above 18;
3. Diagnosis of acquired brain injury at least for 6 month
4. No neuropsychiatric comorbidities
5. Not being involved in any specific exercise program (e.g., NMES, FES) within the previous 3 months;
6. No planned alteration in upper-extremity therapy or medication for muscle tone during the course of the study;
7. Eligibility for standard upper-extremity rehabilitation at the time of enrollment (i.e., absence medical comorbidities that would prevent standard rehabilitation);
8. No condition (e.g., severe arthritis, extreme shoulder pain) that would interfere with valid administration of the measures or with interpreting motor testing;
9. No contraindications to tsDCS:
    - metal in the head between stimulation area
    - metal in the spine between stimulation area
    - implanted brain medical devices
10. No pregnancy;
11. No contraindications for TMS and MRI based on TMS and MRI screening forms

Exclusion Criteria: Subjects will be excluded if they have:

1. Uncontrolled epilepsy;
2. Any joint contracture or severe spasticity in the affected upper extremity, as measured by a Modified Ashworth Score > than 3 out of 4;
3. History of substance abuse;
4. Subject who cannot provide self-transportation to the study location.

6. SUBJECT ENROLLMENT:

Potential subjects will be identified by the following sources:

1- Flyers will be posted in the TIRR Memorial Hermann outpatient clinic, TIRR Memorial

Herman Adult and Pediatric Outpatient Rehabilitation Kirby Glen, MHH Rehabilitation Centers. Attending physicians and therapists may refer their acquired brain injury outpatients to the study. In order to reach out to individuals with ABI; flyers will be distributed through an e-mail distribution, through social media such as Facebook and LinkedIn and twitter.

2- After subjects are identified by their treating physicians and therapists, they will be referred to the co-investigator. During this first contact, the researcher will briefly explain the study content and request their phone number and e-mail address to contact them later for a pre-screening. During a phone call, a brief pre-screening procedure will be applied. Demographics and medical information such as surgery implants, medications, psychiatric, drug and alcohol history as inclusion and exclusion criteria will be gathered. Drs. Francisco and Yozbatiran will review the information gathered during phone screening and may request more information about the surgery such as type of surgical implants, previous MRI notes, etc. In our experience with previous projects, we always needed to collect information from patients' medical record before the person could be enrolled into the study. For example if a surgery had been performed an approval from surgeon's office was requested to confirm the compatibility of surgical instruments with 3Tesla MRI. In some circumstances we further confirmed the surgical implants' compatibility with the manufacturing company. After all information are gathered Drs.Francisco and Yozbatiran will agree or decline subject's enrollment into the study. A copy of consent form will be e-mailed to subject.

3- Potential subjects will be invited to come for a screening visit to Motor Recovery Laboratory at TIRR Memorial Hermann. Any information gathered during phone screening will be stored in a locked file cabinet and password protected electronic file. During the screening visit, an investigator at TIRR will obtain informed consent. The test procedures will be described and the testing equipment will be shown to the subject. A co-investigator will clearly explain all the procedures and risks of the testing outlined in the consent form. The subject will be given sufficient time to consider their decision and will be encouraged to ask questions, both during the initial interview and throughout the study. The PI or a co-investigator will answer any questions regarding the study at the time consent is given. Once enrolled, the subject may pause or terminate his/her participation at any time during the study.

4- Alternatively any person with ABI who are living in the community and been informed through flyers can contact the researchers directly and request more information about the study.

7. DATA ANALYSIS:

Data analysis: Analyses will be performed with two-tailed significance tests at the 95% confidence level and are planned using parametric methods with continuous variables.

However, before performing parametric analyses we will examine the data for evidence of assumption violations and, if such violations are serious, we will perform data transformations or use non-parametric methods as appropriate. Four comparisons will be made. The primary efficacy variable will be the change in hand functions as measured with Jebsen-Taylor Hand Function test. Secondary outcome measures include change in strength of selective muscle groups, change in movement function and number of subjects who will reach minimally clinical significant change (ARAT), and muscle tonus (Modified Ashworth Scale) and change in movement smoothness (exoskeleton measurements), and change in the neurophysiological responses of central nervous system (TMS, SSEP). Adverse effects will be monitored with a Side Effects Questionnaire.

Within subject comparison of after treatment vs. baseline will be performed, separately for each group, using paired t-test. Second, a between groups will examine the effects of treatment by using a repeated measures of ANOVA to test for a time x group interaction. Third subjects' ratings of pain and fatigue after each therapy session will be compared the pain and fatigue ratings, to determine if there was unacceptable to subjects.

The level of significance used will be $p<0.05$.

Analysis for Neuroimaging scans: Biological correlates of the tsDCS and training will be obtained by computing white matter fiber integrity measures of the CST using diffusion tensor imaging an analysis in AFNI (Cox, 1996) and DTI Query (Sherbondy et al, 2005). Integrity measures will include fiber tract density, strength, and their interaction (Ellmore et al 2011), as well as a comparison of parallel and perpendicular diffusivities to investigate changes in axonal integrity and myelination, respectively. We specifically predict that tsDCS combined with repetitive training will result in increased white matter integrity, including increased fractional anisotropy, increased tract density, and changes in axial and radial diffusivities that are consistent with improved myelination and axonal coherence.

Cortical activity assessment with electroencephalogram (EEG): EEG activity will be assessed in all participants using standardized procedures during baseline, during each training session, and after training in the follow-up sessions. EEG will be sampled with up to 64 electrodes using an electrode cap, which places the electrodes in the standard 10-20 international placement system (Electro-Cap International, Inc). Ground electrode is built into the cap and will be at site AFZ. In this context, neuroplastic changes in oscillatory cortical dynamics were shown to outlast motor cortical tDCS for up to 25 minutes, particularly in a fronto-parietal network (Venkatakrishnan et al., 2011). Therefore, in order to characterize and track neuroplasticity associated with tDCS combined exoskeleton training, here changes in cortical network properties (E.g., functional connectivity estimated using granger causality etc.) will be

investigated using a data-driven approaches (e.g., graph theoretical approaches) and contrasted/compared with hypothesis-driven methods (Chen et al., 2011, Venkatakrishnan & Sandrini, 2012).

8. POTENTIAL RISKS/DISCOMFORTS:

tsDCS: Transcutaneous Spinal Direct Current Stimulation (tsDCS) is a noninvasive procedure in which a device sends a small Direct Current (DC) across the skin to modulate spinal function. The use of tDCS in therapeutic protocols to date has not resulted in severe adverse effects. In addition our protocol of 2.5mA has been used by other researchers with no signficant adverse events (Meyer-Friessem et al., 2015; Bocci et al., 2014).

Transcranial Magnetic Stimulation (TMS): According to published studies, single pulse and paired-pulse TMS is both safe and useful for investigating the neurophysiological aspects of human health and disease. Although rare with single pulse TMS compared to repetitive TMS, discomfort or pain from the stimulation of the scalp and associated nerves and muscles on the overlying skin may occur. In addition TMS coil produces a loud clicking sound that increases with the stimulation intensity. We will use earplugs to reduce the sound from the coil. If subject presents any contraindication to TMS application, he/she will not be exposed to TMS.

Magnetic Resonance Imaging (MRI): The structural MRI is performed to measure the structural connectivity of the corticospinal tract. MRI is noninvasive and has been used extensively in clinical studies. In order to eliminate the risks associated with magnetic field, only subjects from each group with no contraindication to MRI will be scanned, and only subjects who pass MRI screening will be invited to undergo MRI. All scanning sessions will be supervised by Dr.Yozbatiran.

Electromyography (EMG): The EMG, involves testing of the muscle activity through electrical signals. In the current project, it will allow to record motor evoked potentials. It is non-invasive and non-painful to the subject and has been used widely in clinical or research settings. The risks associated with surface EMG is some skin irritation.

SSEP: Somatosensory evoked potential is recording electrical signals of sensation going from body to brain. Recording electrodes are attached to the scalp and arm. The stimulus will last about 2 minutes at a time and may cause some twitching and tingling sensation in the target area. However it is painless and carries no significant risk.

Spinal reflexes measurement: Stimuli above the action threshold of peripheral nerves will be administered through skin. This might cause some discomfort that is anticipated to be mild and easily tolerated by the subjects. Also skin irritation might occur due to electrode attachment to the skin.

EEG: An electroencephalogram (EEG) is a test that detects electrical activity in the brain using small, flat metal discs (electrodes) attached to your scalp. This activity shows up as wavy lines on an EEG recording. Like in EMG, the main risk associated with it is skin irritation.

fNIRS: Prototypes analogous to the Axem Home prototype to be used in the present study have been utilized in four previous REB-approved studies (Dalhousie REB# 2017-4267, National Research Council REB# 2018-107, Dalhousie REB# 2019-4762, Veritas IRB# 16439-11:51:2730-09-2019), with no reported adverse events. fNIRS is generally regarded as a non-invasive method of brain activity measurement given that the risks associated with it are minor. fNIRS involves the emission of non-ionizing radiation (light at 740 and 850nm respectively) into the skull. The amount of radiation being emitted from the Axem Home prototype is within the exempt risk category for skin exposure according to IEC 62471 (Photobiological safety of lamps and lamp systems) section 4.3.8, and thus does not impose any risk. However, the participant will be told that they should report any discomfort on their head, whether it is from feelings of warmth, or discomfort with the fit of the prototype on their head. However, given that the light output from the Axem Home prototype is not in the exempt risk category for retinal exposure (IEC 62471 section 4.3.7), in the present study the device will only be powered on once it is secured on the head, with the chin strap in place; and moreover, the device will be powered off prior to its removal by the experimenter.
Moreover, the electrical architecture of the device is such that firmware on the device's microcontroller directly controls the current (and thereby the power output) supplied to the LEDs. Further safeguards are in place on the circuit board itself, as resistors on the board physically limit the potential maximum current (and thereby power output) supplied to the LEDs. And finally, the system overall is equipped with a resettable fuse that stops it from drawing more current than it is intended to and utilizes a certified battery pack as well as protection circuitry prevent any damage from occurring to the battery.
All materials used in this experiment will comply with biocompatibility standards (ISO 10993), and both the surface model and the Axem Home prototype will be wiped with alcohol pads following each use.

Exoskeleton-training: Patients with acquired brain injury sometimes develop pain or discomfort in the shoulders and arm. In an ongoing study in our laboratory with subjects who are undergoing robotic-exoskeleton exoskeleton training for three- hours per session and three-sessions per week for four weeks, didn't show any significant fatigue, discomfort or pain lasting longer than 24 hours after training (Yozbatiran et al, 2012). If there is evidence that pain or

fatigue is worsened by the therapy, the sessions will be reduced or discontinued. All therapy sessions will be supervised by a project staff member. **Assessment/Questionnaires:** All assessments will be performed in a designated room inside Motor Recovery Laboratory. None of these tests are either painful or uncomfortable to perform. In order to prevent potential embarrassment during the testing the test will be done individually and in private. If subjects feel uncomfortable in answering any of the questions they may stop the study at any time.

9. POTENTIAL BENEFITS:

As with any study focusing on basic research, the subjects will derive no direct benefit. The results of these studies may benefit subsequent future subjects if combined spinal stimulation with repetitive training via a exoskeleton device proves to be effective when compared to cortical stimulation with repetitive training. We envision that in the near future the information obtained from the proposed research will provide a better understanding for treatment options of upper extremity motor function in acquired brain injury.

The benefits of participating in this study may be improved arm and hand movement. However, there may be no benefit from participating in this study.

10. RISK-BENEFIT RATIO:

The potential improvement of arm and hand movement outweighs the risk of non-invasive spine stimulation, fatigue, pain and discomfort.

11. CONSENT PROCEDURES:

Informed consent will be obtained from the subject at Motor Recovery Laboratory at The Institute for Rehabilitation and Research. After the patient is identified by the PI and her research team study criteria and he/she is interested in participating, informed, written consent will be obtained by a member of the research team.
In addition a photography/videotaping consent will be obtained from the subject, if he/she agrees to be photographed / videotaped during the assessments or treatment sessions.

12. CONFIDENTIALITY PROCEDURE:

All data will be coded with identification number, database will be in a password –protected computer and kept in a locked file cabinet.

13. COSTS

The subject will not be expected to pay any costs.

14. PAYMENTS:

Subjects who travel to the study appointments will be reimbursed $20 for per screening, assessment and treatment visit in order to pay for parking and travel. Subjects who will undergo MRI scan will receive additional $50 for reimbursement upon completion of all scans.

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