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Protocol Title: The Effect of Treatment with the PathMaker MyoRegulator™ Neuromodulation System Incorporating Trans-spinal Direct Current Stimulation in Patients with Severe Hand Spasticity After Stroke

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Introduction

Spasticity is a disorder of motor function that results from central nervous system injury proximal to the anterior horn cell. It commonly occurs after stroke when it is specifically defined as a velocity-dependent increase in stretch reflex that causes decreased motor performance as well as pain and discomfort [1]. Put succinctly, spasticity is motor over-activity that interferes with functional recovery. Evidence from several sources strongly implicates enhanced excitability of spinal motor neurons, and in particular, inter-neurons, in the development and maintenance of spasticity [2-7]. Therefore, pharmacological intervention relies on drugs that are $GABA_A$ modulators (benzodiazepine) and $GABA_B$ agonists (baclofen) or α2 adrenergic agonists (tizanidine); the presumed mechanism of action of these classes of drugs is to increase inhibitory neurotransmission [8]. Other mainstays of pharmacological treatment are neuro-muscular blockade agents that block release of Ca^{2+} (dantrolene) or acetylcholine (botulinum toxin A). In addition there are more invasive treatments that are irreversible and depend on injection of alcohol or phenol. Successful therapy depends on the route of delivery and the dose. Non-pharmacological treatments include regular or supervised stretching, use of splints, orthoses or electrical stimulation or some combination of these interventions with a pharmacological strategy [9]. Most studies have a fixed period of observation, and clinical success is often defined by improvement in mobility, transfers, activities of daily living, or reduced co-contraction during voluntary movement. Improvements registered in studies are often temporary, and are related to the intensity and timing of the treatment. Permanent improvement with absence of spasticity happens only when more normal patterns of motor performance emerge. Thus spasticity is a common and permanent consequence for most survivors of stroke. The challenge of current spasticity treatments is that they all have unwanted side effects that include altered alertness, pain, addiction potential, withdrawal seizures/hallucinations, and weakness, especially for the irreversible/surgical procedures.

We propose a pilot experiment to use an investigational device, the MyoRegulator™ Neuromodulation System (MyoRegulator™), which pairs trans-spinal direct current stimulation (tsDCS) with peripheral DC stimulation (pDCS), to alter the spasticity in the affected upper extremity of patients with stroke. PathMaker Neurosystems Inc., the manufacturer of the MyoRegulator™, refers to this unique paired double stimulation treatment as the DoubleStim™ treatment, which will be referred to throughout this study protocol as "DoubleStim".

The precedent for tsDCS as a new spinal treatment procedure is based in part on transcranial direct current stimulation, tDCS, which modulates the excitability of a targeted brain region non-invasively by altering neuronal membrane potentials [15, 16]. tDCS effects are polarity-specific: anodal stimulation generally increases the excitability, while cathodal stimulation decreases it [17-19]. Depending on the current density [20], the depolarization is expected to induce acute modifications to the membrane of the neurons, thus inducing alterations in neuronal activity [18, 21]. Hence this technique can be used to increase or decrease the excitability of

neurons in a brain area, in order to determine if that region plays an integral role in a specific motor/cognitive function. In humans, 13 minutes of tDCS resulted in an increase in excitability up to 150% and lasting 90 minutes [22]. Research with tDCS has revealed that anodal stimulation can induce transient (on the order of 30 minutes) improvements in performance on cognitive, motor and linguistic tasks [23, 24]. For example, Hummel et al. found that anodal tDCS delivered to the primary motor area in the lesion hemisphere elicited significant improvements in motor control of the paretic limb [25]. The effect lasted for more than 25 minutes after stimulation. In a recent study, Fregni et al. also verified that anodal tDCS to the affected hemisphere and cathodal tDCS to the contralesional hemisphere improved motor function [26]. Other examples highlighting the efficacy of anodal tDCS include: safety of frontal DC brain stimulation [27]; anodal tDCS to dorsolateral prefrontal cortex elicited an improvement in working memory [28];stimulation to primary motor cortex improved motor learning [26, 29]; tDCS delivered to primary motor area or to visual area V5 induced improvements in visuo-motor coordination [30]; anodal stimulation of fronto-polar regions improved probabilistic classification learning [31]}; and left prefrontal cortical stimulation lead to increased verbal fluency [32]. Cathodal stimulation decreases cortical excitability in humans - i.e., affected neurons will be less likely to fire [33]. The studies using tDCS attest to efficacy and safety of the treatment in stroke patients, as well as its potential for therapeutic applications in stroke recovery, and by extension supports the potential application of tsDCS for the treatment of spasticity.

More recently, trans-spinal direct current stimulation of the spinal cord (tsDCS) has been proposed as a mechanism to modulate muscle tone and improve motor function. Trans-spinal direct current stimulation (tsDCS) has demonstrated in animal models [10-13], and in computer modeling [14] that the electric fields induce differential polarization of the various spinal motor neurons so that the dendritic Ca^{2+} persistent inward current modulates motor neuron excitability. More specifically, in an animal model, tsDCS plus pDCS as part of a DoubleStim regime, the anode placed over the spinal column (cathode over a peripheral nerve) decreased the tone, the opposite placement increased the tone [13]. In healthy humans, Winkler et al (2010) demonstrated that 2.5 mA of tsDCS can mediate the H-reflex response such that 20 minutes of anodal tsDCS significantly reduced H-reflex post-activation depression (e.g. facilitated H-reflex) and cathodal tsDCS increased post-activation depression (e.g. decreased H-reflex)[43]. Also in healthy controls, Bocci et al (2014) reported that cathodal tsDCS to the cervical or lower thoracic spinal cord significantly improved motor recruitment recorded at the ulnar and medial nerves with incremental multipoint stimulation of the abductor digiti minimi (ADM) and the abductor pollicis brevis (APB)[44]. In individuals with spinal cord injury, 20 minutes of 2.5mA anodal tsDCS to the thoracic spinal cord significantly increased spinal reflexes (SRs), while having no effect on the SRs of healthy controls [45]. Taken together, these data suggest that tsDCS can mediate spinal motor response in healthy controls and individuals with neurological injury. Whether this treatment alleviates multi-joint spasticity, post-stroke, needs clinical testing.

The PathMaker DoubleStim treatment- trans-spinal direct current stimulation of the spinal cord (tsDCS) paired with peripheralDC stimulation (pDCS) as delivered using the MyoRegulator system, has been proposed as a mechanism to modulate muscle tone and improve motor function. In this pilot study we will test whether the application of Double-Stim to 30 patients with extreme spasticity of the distal muscles of the upper extremity will alter standard clinical and objective measurements. We will test the effect after treatment and the cumulative effect over several treatments.

Specific Aims

SPECIFIC AIM 1: To evaluate whether a single session of anodal vs. sham DoubleStim will transiently alter the clinically and objectively measured spasticity in 12 patients with upper extremity spasticity after stroke and 6 healthy controls.

In patients with chronic post-stroke upper limb spasticity and healthy controls, we will use a within-subjects sham-controlled design to determine if a single session of anodal -DoubleStim significantly alters upper extremity spasticity as compared to the sham DoubleStim condition. We will also examine whether the two conditions (anodal/sham) differentially affect the two subject groups (stroke patients vs. healthy controls).

SPECIFIC AIM 2: To determine whether five consecutive sessions of anodal - DoubleStim will longitudinally alter clinically and objectively measured spasticity in 30 patients with upper extremity spasticity after stroke.

In patients with chronic post-stroke upper extremity spasticity, we will use a within-subjects repeated measures design to determine whether 5 repetitive sessions of DoubleStim (5 consecutive sessions of 4mA anodal DoubleStim across 1 week) significantly reduces upper extremity spasticity longitudinally.

Preliminary Data

We recently demonstrated that the combination of transcranial direct current stimulation (tDCS—cortical stimulation) and upper-arm robotic therapy improves motor performance after stroke, but only when tDCS is used to prime the therapy; that is, prior to robotic training [34]. When tDCS is applied during or after robotic therapy it confers no additional advantage.

The interpretation is that tDCS increases cortical excitability and neural plasticity for a time period, and that robotic therapy is more effective when applied at that time.

Having established that tDCS cortical excitability after-effects could be sustained during robotic upper-limb training, we further tested if this combination of tDCS and robotic training applied over multiple practice sessions might translate to improved motor function. Six right-handed patients with chronic stroke (>6 mo since ictus), received 2 weeks (6 sessions) of combined tDCS and robotic wrist training. Four patients received real tDCS and training, while 2 patients received sham stimulation and training (randomly assigned). The results demonstrated that in the group that received tDCS and robot training, but not the sham (no tDCS and robot training), a clinically meaningful improvement occurred over this short training period. Motor power at the wrist improved to 112±6% pre-training in the real-treatment group (pre-training = 19.5, to post training 22 points (out of 30) and no change in the sham group (pre training=19.5, post training=19.5). The wrist-hand Fugl-Meyer improved by 3 points (mean pre=16.83, post=19.83 out of 30) and improved 1 point in the sham condition (mean pre=18, post=19). Preliminary analysis of the kinematic data also revealed that the group that received tDCS had smoother movements (fewer jerks) than controls receiving sham tDCS. While this preliminary study was in a small number of patients, the results attest to the safety and potential clinical benefit of non-invasive direct current stimulation in individuals with chronic stroke.

More recently, application of trans-spinal direct current stimulation of the spinal cord (tsDCS) has been proposed as a mechanism to modulate muscle tone and improve motor function. Ahmed (2014) demonstrated in a mouse model that tsDCS paired with pDCS, i.e., DoubleStim, significantly altered muscle tone, with anodal stimulation (spinal-sciatic nerve) inhibiting motor neurons and reducing muscle tone, and cathodal stimulation (sciatic nerve-spinal) exciting motor neurons and increasing muscle tone [13]. These findings attest to the potential clinical benefit of DoubleStim to alleviate the painful and constricting upper-limb muscle spasticity (hypertonia) commonly seen post-stroke. In humans, several recent studies have demonstrated the potential benefit of tsDCS to modulate reflex activity, improve motor recruitment at the nerve terminal, and increase pain tolerance. Winkler et al (2010) demonstrated that 2.5 mA of tsDCS can mediate the H-reflex response in healthy humans such that 20 minutes of anodal tsDCS significantly reduced H-reflex post-activation depression (e.g. facilitated H-reflex) and cathodal tsDCS increased post-activation depression (e.g. decreased H-reflex)[43]. Also in healthy controls, Bocci et al (2014) reported that cathodal tsDCS to the cervical or lower thoracic spinal cord significantly improved motor recruitment recorded at the ulnar and medial nerves with incremental multipoint stimulation of the abductor digiti minimi (ADM) and the abductor pollicis brevis (APB)[44]. In individuals with spinal cord injury, 20 minutes of 2.5mA anodal tsDCS to the thoracic spinal cord significantly increased spinal reflexes (SRs), while having no effect on the SRs of healthy controls [45]. Additionally, in a recently published conference abstract, Cortes et al. (2015) safely administered 4mA of anodal tsDCS stimulation to the C7 level of the spinal cord in 10 healthy human control subjects, and noted significant transient

changes in MEP amplitude at the FDI muscle as measured with TMS. [50]. Taken together, these data suggest that tsDCS can mediate spinal motor response in healthy controls and individuals with neurological injury. Whether this treatment alleviates multi-joint spasticity, post-stroke, needs clinical testing.

These studies support investigations aiming to understand the mechanisms and clinical benefit of non-invasive direct current stimulation after stroke, and also demonstrate the safety of tsDCS.

Research Design and Methods

This is a single-blind, sham-controlled pilot study with two consecutive phases. The first phase of the study will examine if a single session of anodal DoubleStim vs. sham DoubleStim will transiently, but significantly alter muscle tone in individuals with chronic, post-stroke wrist spasticity and in healthy control subjects. The second phase of the study will measure whether repeated treatments with anodal DoubleStim over five consecutive days will significantly reduce wrist spasticity in patients with post-stroke hypertonicity of the wrist flexor muscles, as compared to a sham stimulation condition. All patients will be recruited through our referral sources in the department of Neurology and Physical Medicine. Age-matched healthy control subjects will be recruited from health system employees and family members of participants with stroke via direct contact. All visits will be conducted in the clinical robotics and non-invasive brain stimulation suite at the Feinstein.

Inclusion/Exclusion Criteria for Individuals with Stroke:

Inclusion Criteria:

1. $\geq$ 18 years of age
2. First single focal unilateral hemisphere lesion with diagnosis verified by brain imaging (MRI or CT scans) that occurred at least 6 months prior
3. Cognitive function sufficient to understand the experiments and follow instructions (per interview with Speech Pathologist)
4. A Modified Ashworth score between 1-3 points for wrist flexors and extensor muscles
5. A minimum of 15 degrees wrist passive ROM for wrist flexion and extension from wrist neutral position.
6. Body fat range of 15-25mm for females/10-20mm for males of adipose tissue at the cervical neck level and a body fat range of 10-40mm for females/5-35mm for males of adipose tissue at the suprailiac crest, as determined by a body fat caliper.

Exclusion Criteria:

1. Focal brainstem or thalamic infarcts
2. Prior surgical treatments for spasticity of the upper limb

3. Ongoing use of CNS-active medications
4. Ongoing use of psychoactive medications, such as stimulants, antidepressants, and anti-psychotic medications
5. Botox or phenal alcohol treatment within 12 weeks of enrollment
6. Pregnancy in women, as determined by self-report
7. History of spinal cord injury or weakness
8. Chronic pain, defined by a report of a "5" or greater on the Wong-Baker Pain Scale [51,52].
9. Peripheral neuropathy including insulin dependent diabetes as determined by case history
10. Presence of additional potential tsDCS risk factors:
    - Damaged skin at the site of stimulation (i.e., skin with ingrown hairs, acne, razor nicks, wounds that have not healed recent scar tissue, broken skin, etc.)
    - Presence of an electrically, magnetically or mechanically activated implant (including cardiac pacemaker), an intracerebral vascular clip, or any other electrically sensitive support system; Loop recorders will be reviewed on a case by case basis by PI and the treating Cardiologist to make a determination
    - Highly conductive metal in any part of the body, including metal injury to the eye (jewelry must be removed during stimulation); this will be reviewed on a case by case basis for PI to make a determination
    - Past history of seizures or unexplained spells of loss of consciousness during the previous 36 months

Inclusion/Exclusion Criteria for Healthy Controls

Inclusion Criteria:

1. $\geq$ 18 years of age
2. Body fat range of 15-25mm for females/10-20mm for males of adipose tissue at the cervical neck level and a body fat range of 10-40mm for females/5-35mm for males of adipose tissue at the suprailiac crest, as determined by a body fat caliper

Exclusion Criteria

1. Ongoing use of psychoactive medications, such as stimulants, antidepressants, and anti-psychotic medications
2. Presence of additional potential tsDCS risk factors:
    a. Damaged skin at the site of stimulation (i.e., skin with ingrown hairs, acne, razor nicks, wounds that have not healed recent scar tissue, broken skin, etc.)
    b. Presence of an electrically, magnetically or mechanically activated implant (including cardiac pacemaker), an intracerebral vascular clip, or any other electrically sensitive support system

c. Metal in any part of the body, including metal injury to the eye (jewelry must be removed during stimulation)
d. Past history of seizures or unexplained spells of loss of consciousness during the previous 36 months

3. Pregnancy in women, determined by self-report
4. History of stroke, brain injury, or neurodegenerative disease
5. History of spinal cord injury or weakness
6. Chronic pain, defined by a report of a "5" or greater on the Wong-Baker Pain Scale [51,52].
7. Peripheral neuropathy including insulin dependent diabetes as determined by case history

Visit Schedule:

Phase I: Single Session of DoubleStim

Twelve patients with chronic, post-stroke wrist spasticity and six healthy control subjects will be accepted into this study. There will be 3 baseline measurement periods prior to treatment. Following the lead-in period, all subjects will participate in a training period to compare muscles response during a single session of anodal DoubleStim treatment to a sham-controlled session. During the first treatment session, subjects will receive a single 20 minute session of sham stimulation, and undergo clinical and/or instrumental measurements before, during, immediately following, and 20 minutes after stimulation. The second treatment session will occur 5-8 days after the first. During the second treatment session, subjects will receive a single 20 minute session of anodal DoubleStim, and undergo clinical and/or instrumental measurements before, during, immediately following, and 20 minutes after stimulation. Subjects will undergo 3 additional follow-up clinical evaluations. Two of these evaluations will occur 4-7 days after each training condition, and the final evaluation will occur one month after study completion.

Lead-in Period

- Week 1, Visit 1 (approximately 90 minutes)
  - Baseline clinical outcome measures
  - Instrumental measures with EMG
  - Medical screening
  - Consent
- Week 1, Visits 2-3 (approximately 60 minutes each)
  - Baseline clinical outcome measures
  - Instrumental measures with EMG

Training Period Phase I

- Week 2, Visit 4 (approximately 90 minutes)
    - 20 min of sham stimulation
    - Instrumental measures with EMG before, during, immediately after, and 20 minutes following stimulation
    - Sham condition clinical discharge measures

Follow Up Testing Phase I

- Week 2, Visit 5 (approximately 60 minutes)
    - Sham condition clinical follow-up measures
    - Instrumental measures with EMG

Training Period Phase II

- Week 3, Visit 6 (approximately 90 minutes)
    - 20 min of anodal stimulation
    - Instrumental measures with EMG before, during, immediately after, and 20 minutes following stimulation
    - Anodal condition clinical discharge measures

Follow Up Testing Phase II

- Week 3, Visit 7 (approximately 60 minutes)
    - Anodal condition clinical follow-up measures
    - Instrumental measures with EMG
- Week 7, Visit 8 (approximately 60 minutes)
    - Anodal condition clinical follow-up measures
    - Instrumental measures with EMG

Phase I
Schedule

	Screen 1	Screen 2	Screen 3	Sham Tx	Sham FU	Anodal Tx	Anodal FU	Anodal FU 2
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Informed Consent	X							
Medical Hx	X							
Demographic Info	X							
Inclusion Criteria	X							

Neurological Exam	**X**							
Medication check	**X**							
Outcome Measures	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Instrumental Assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
tsDCS (anodal v. sham)				**X**		**X**		

Phase II: Consecutive Sessions of DoubleStim

Thirty patients with chronic, post-stroke wrist spasticity will be accepted into this study. There will be 2-3 baseline measurement periods prior to treatment. Following the lead-in period, subjects will participate in a sham-controlled training period to compare five, consecutive sessions of DoubleStim treatment under the two conditions (anodal vs. sham). The training portion of the study will occur over a total of 3 weeks. During that time, subjects will attend five consecutive, 20-minute sessions of sham stimulation, followed by a week rest interval, and then another five consecutive sessions of training under the anodal stimulation condition. During training sessions, subjects will undergo instrumental measurements before and 10 min post stimulation, and may undergo clinical assessments. Subjects will also undergo additional follow-up evaluations throughout the course of the study, the first of which will occur between treatment conditions (sham follow-up), and the remaining of which will occur 1x/week after completion of both training conditions (anodal follow-up) until the FCR (flexor carpi radialis) EMG response during the instrumental muscle tone assessment has returned to baseline, or up to 6 weeks. These repeated follow-up measures will be obtained in order to measure the potential longitudinal benefits of repetitive DoubleStim treatments.

Lead-in Period

- Week 1, Visit 1 (approximately 90 minutes)
    - Baseline clinical outcome measures
    - Instrumental measures with EMG
    - Medical screening
    - Consent
- Week 1, Visits 2-3 (approximately 60 minutes each)
    - Baseline clinical outcome measures
    - Instrumental measures with EMG

Training Period Phase I

- Week 2, Visit 4-7 (approximately 60 minutes)
    - 20 min of sham stimulation
- Instrumental measures with EMG
- Clinical measurements during 1-2 visits
- Week 2, Visit 8 (approximately 90 minutes)
    - 20 min of sham stimulation
    - Instrumental measures with EMG before and 10 min post stimulation
    - Sham condition clinical discharge measures

Follow Up Testing Phase I

- Week 3, Visit 9 (approximately 60 minutes)
    - Sham condition clinical follow-up measures
    - Instrumental measures with EMG

Training Period Phase II

- Week 4, Visit 10-13 (approximately 60 minutes)
    - 20 min of anodal stimulation
- Instrumental measures with EMG before and 10 min post stimulation
- Clinical measurements during 1-2 visits
- Week 4, Visit 14 (approximately 90 minutes)
    - 20 min of anodal stimulation
    - Instrumental measures with EMG before and 10 min post stimulation Anodal condition clinical discharge measures

Follow Up Testing Phase II

- Week 5-10, Visit 15-20 (approximately 60 minutes)
    - Anodal condition clinical follow-up measures
    - Instrumental measures with EMG

PhaseII Schedule

	Screen 1	**Screen 2**	**Screen 3**	**Tx Cond 1 (Sham)**		**Cond 1 FU**	**Tx Cond 2 (anodal)**		**Cond 2 FU**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4-7**	**Visit 8**	**Visit 9**	**Visit 10-13**	**Visit 14**	**Visit 15-20**
Informed Consent	**X**								
Medical Hx	**X**								

Demographic Info	**X**								
Inclusion Criteria	**X**								
Neurological Exam	**X**								
Medication check	**X**								
Outcome Measures	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Instrumental Assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
tsDCS (anodal v. sham)				**X**	**X**		**X**	**X**	

Clinical Outcome Measures

Modified Ashworth Scale (Primary): The MAS is a valid and reliable assessment of spasticity in patients with chronic stroke [39-40].

Tardieu Scale (Primary): The Tardieu Scale is a valid and reliable measure of spasticity that accounts for resistance to passive movement at both slow and fast speeds [41-42].

Fugl-Meyer (Primary): The Fugl-Meyer scale is a valid and reliable evaluation instrument used for measuring performance-based impairment in stroke patients [54, 55].

Medical Research Council motor power score (MRC): The MCR is a valid and reliable score that measures strength in isolated muscle groups of the involved shoulder and elbow on an ordinal scale (scale range: 0, no muscle contraction; 5, normal strength) .

Wolf Motor Function: The Wolf Motor Function Test is a valid and reliable assessment of upper extremity function by asking the patient to complete 15 motor-based tasks and two strength-based tasks [56]. Photos and/or video recordings will be taken during this assessment for review and scoring by approved clinicians, and also potentially for use in clinical efficacy demonstrations of tsDCS.

Robotic Wrist Evaluation: Robotic wrist evaluations will be performed using Interactive Motion Technologies™ wrist robot device, which objectively assesses volitional movement (e.g. speed,

smoothness, power, and trajectory) across two types of wrist rotation (extension/flexion and pronation/supination), as well as one type of forearm rotation.

Instrumental Assessments of Muscle Tone

Passive muscle resistance will be measured using force transducer that is attached to participant's hand. The force transducer is attached to a stepper motor to move it. The slope of muscle resistance will be calculated and used for analysis. The slope of muscle resistance will be measured at four speeds.

DoubleStim Protocol

Procedure: In this study of cervical trans-spinal DC stimulation (tsDCS) paired with median nerve stimulation (pDCS) to treat spasticity of the wrist and hand, participants will be seated in a chair with the arm and hand supported comfortably. The stimulation will be delivered using two sets of rubber sponge electrodes(one 3x3 inch anode/cathode pair and one 2x2 inch anode/cathode pair). Each disposable electrode sponge will be soaked with saline (0.9% NaCl) prior to application. New electrode sponges will be used for each subject treatment.

The 3x3 inch electrode pair is used to deliver the tsDCS. The anodal electrode of this pair, which will be the active electrode, will be placed to cover the level of C6 to the upper edge of T1. These cervical segments contain the motor neuron pools for the wrist flexors muscles (the target for testing). The cathodal electrode of this pair, which will be the reference electrode, will be placed over the skin of the frontal aspect of the iliac crest.

The 2x2 inch pair of electrodes is used to deliver peripheral DC stimulation (pDCS) to the median nerve. These two electrodes will be placed over the skin on the front of the wrist joint such that the anode electrode is placed over the nerve relatively distal to the spine (toward the hand) and the cathode electrode will be placed over the nerve relatively proximal to the spine (toward the spine) .

Participants will receive stimulation for 20 minutes. The current passing through the two electrode sets will be biased using an adjustable electrical circuit. The current intensity passing through the spinal cord and iliac crest electrodes will be 4mA, or the maximally tolerated current intensity. The current intensity passing through the wrist electrodes will be ramped up slowly, to ensure that it is subthreshold (causing no electrical activity (EMG) from the innervated muscles), at a range from 1-3 mA. Sham DoubleStim will have a comparable set-up to active DoubleStim, with 30 seconds of real current ramping to the maximally tolerated current intensity at commencement, then after 5 seconds, a slow decrease to no current, sustained for 20 minutes.

To ensure participant tolerance of stimulation, current will be introduced on sliding scale of 2.5mA, 3mA, and 4mA. Beginning with 2.5mA, each patient will receive stimulation for 1 minute, and confirm that the stimulation is tolerable. If tolerated, the current will then be increased progressively to 4mA. 20 min of treatment stimulation will then be administered at the maximum tolerated threshold for each pt. This tolerability dose will be determined prior to every treatment schedule for all patients.

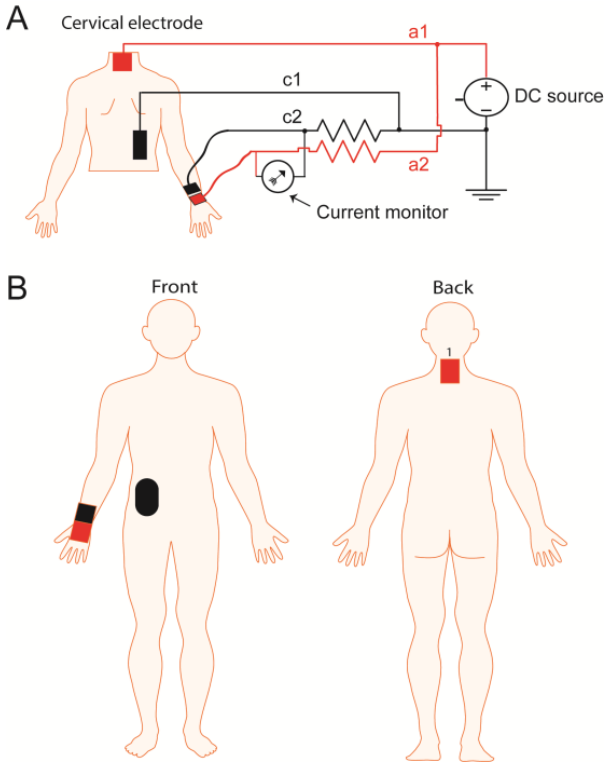

Figure 1. Electrode placement in human subjects to reduce muscle tone. Red: Anode; black: cathode. A, electrode placement and connection to the DC device. Note that the DC device includes a circuit that can bias the current passing through the wrist electrodes in one custom made box. B, the diagrams show the placement of the electrodes in a whole body diagram for clarity.

Electromyography: Electrical activity of the muscle will be differentially recorded during DoubleStim sessions using a bipolar electrode montage placed on the belly of the muscle. Recordings will be made from flexor carpi radialis and brevis, and from the extrinsic finger flexors (flexor digitorum superficialis, and/or flexor digitorum profundus), which are the muscles responsible for post-stroke wrist and finger flexor spasticity. The stimulator output will be adjusted to produce no activity from the muscle (subthreshold), which is approximately 3 to 4 mA at the spinal-abdominal circuit and about 1 to 3mA at the median nerve circuit (in front of the wrist).

Randomization

All subjects will undergo the sham stimulation condition first and the active stimulation condition second. The order of stimulation will not be randomized as this is a small, investigational pilot study, and the investigators wish to ensure that the results of the active stimulation condition do not carry over into the sham condition.

Blinding

This is a single-blind, pilot study. Subjects will be told that they will participate in both the active and sham conditions, but they will not be told the order of stimulation, as non-invasive brain stimulation has known placebo effects. Consequently, the MyoRegulator device will be covered such that the participants will remain unaware of condition. For the sham condition, the stimulation automatically ramps down after 30 seconds because the perceived sensation of tDCS on the skin has been reported to fade after this period [21]. Though investigators will be aware of the order of stimulation, the primary outcome measures are objective (EMG recordings and instrumental assessment of muscle resistance), and will serve as valid measurements of changes in muscle tone.

Statistical Considerations and Data Analysis

SPECIFIC AIM 1: To evaluate whether a single session of anodal vs. sham will transiently alter the clinically and objectively measured spasticity in 12 patients with upper extremity spasticity after stroke and 6 healthy controls.

Methods to address specific aim 1: We predict the changes in muscle tone will be greater following anodal DoubleStim compared with sham DoubleStim. This will be examined with a 2x2 repeated measures ANOVA for muscle resistance scores with stimulation type (A-DoubleStim, S-DoubleStim) and group (stroke patient, healthy control) as factors.

SPECIFIC AIM 2: To determine whether five consecutive sessions of anodal DoubleStim will longitudinally alter the clinically and objectively measured spasticity in 30 patients with upper extremity spasticity after stroke.

Methods to address specific aim 2: A 2X2 repeated measures ANOVA for muscle resistance scores will be used with stimulation type (A-DoubleStim, S-DoubleStim) and time (admission, discharge) as factors.

Protection of Human Subjects

RISKS TO SUBJECTS

Human Subject Involvement and Characteristics: We anticipate enrolling 42 patients and 6 healthy control subjects. Inclusion and exclusion criteria are stated above in the Research Design and Methods section.

Sources of Material: Sources of research material will be the hospital records providing demographic and medical information including CT or MRI imaging studies, and clinical examinations performed at outpatient facilities run by the Department of Physical Medicine and Rehabilitation of the North Shore University Hospital (NSUH) and LIJ Medical Center (LIJMC), or copies of medical records from outside hospitals provided by participants.

Potential Risks:

tsDCS Risks: tsDCS is a relatively new nonsignificant risk stimulation approach that uses the same direct-current non-invasive stimulation technology as tDCS, though it directs the current towards the spinal column instead of the cortex. DoubleStim further incorporates simultaneous peripheral stimulation at the nerve of interest again using the same direct-current non-invasive stimulation technology. tDCS (transcranial direct current stimulation) has been used in more than 30 research studies involving hundreds of participants. No undesirable or long-lasting effects have been reported, nor have any participants reportedly abandoned a study due to discomfort. Researchers at the National Institute of Neurological Disorders and Stroke (NINDS) conducted a safety study on tDCS, investigating 20-minute sessions of 1 mA and 2 mA current stimulation with healthy controls (n=103) (20). No negative effects were identified. Nitsche and colleagues (2004) found no measurable structural changes in brain tissue due to tDCS (23). Similarly, trans-spinal direct current stimulation (tsDCS) has been used in several recent research studies without any serious adverse events reported [43-48, 49-50]. Additionally, our collaborator on this study, Dr. Zhagloul Ahmed has used tsDCS at the intensity proposed in this study in unpublished work with human subjects, without any serious adverse events.

Documented side-effects of noninvasive direct current stimulation include the potential for a tingling sensation at the time of stimulation and erythema – redness of the skin that is uniform or mottled around the area of stimulation. The tingling and reddening have been found to be transient [20-21]. Our present research indicates that in rare instances, subjects may experience more moderate-severe redness and soreness, similar to a sunburn, which may last 1-2 days after stimulation. Any subject with this reaction will be examined by PI, and may not be a candidate for Doublestim. Because the DoubleStim device will have two circuits (one at the level of the spinal cord and one at the level of the median nerve) there is a small additional risk

of overactivation at the nerve. However, activation at the median nerve will be continuously monitored with EMG to ensure that the current intensity passing through the wrist electrodes (median nerve) is subthreshold (causing no electrical activity (EMG) from the innervated muscles), and at ranges from 1-3 mA, while the stimulation at the level of the spinal cord remains at 4mA. EMG monitoring will ensure that activation of the median nerve remains subthreshold, and without risk of overactivation.

Confidentiality Risk: One additional risk concerns the risk to confidentiality incurred with any collection of medical data. **ADEQUACY OF PROTECTION AGAINST RISKS**

Recruitment and Informed Consent: Stroke subjects who meet inclusion criteria and do not meet exclusion criteria will be recruited by consenting professionals through the Department of Physical Medicine and Rehabilitation of NSUH and LIJMC. Healthy control subjects will be recruited healthcare professionals through Northwel Health and healthy family members of study participants with stroke. Recruitment will be done with direct contact and flyers.

Northwell Health physicians and clinicians who have appropriate patient populations will be made aware of the research study protocol and procedures, and given an overview of the study through contacts with the study personnel. These clinicians will identify potential study participants. If the patient expresses interest in participation, the clinician will either: 1.) provide the patient with the study coordinator's contact information or 2.) provide the patient's contact information to study personnel.

Investigators may contact (or be contacted by) a potential subject or subject's LAR/next-of-kin by telephone to discuss participation in this research protocol. The investigator will provide the subject/LAR/next-of-kin with all the information contained in the written consent form. The investigator will answer any questions regarding the research and give the subject/LAR/next-of-kin ample time to consider participation in the study which may require a follow-up phone conversation.

Partial Request for HIPAA Waiver: In addition to the above efforts to recruit patients, and because our experiments have prompted the possibility of a multi-center trial in which many more patients will be required than are currently being supplied by the consenting professionals in the departments mentioned above, and because we do not have a treating physician of record on this protocol, we request partial HIPAA waiver to recruit patients after access to the electronic medical records for the in-patient and out-patient population of the Northwell Health system. We understand completely that without this waiver we have no general access to medical records for the purpose of study subject accrual. We are requesting this access so that we can successfully recruit patients to this study as well as offer alternative treatments in our Bioelectronic division, should they not qualify for inclusion in this study or should they seek additional services.

If granted, we plan to supply the electronic medical record department with a list of identifying characteristics, name, address and zip code, telephone number, alternate telephone number, physician of record, inclusion / exclusion criteria (appropriate ICD 9 AND ICD 10 codes) to be used in generating a list of potential patients. Once we receive the list of potentially eligible patients, we will attempt to contact the physician of record for the patient in order to inform the physician about the goals and the risks of the study and to obtain permission to contact their patient. We will then contact the potential patient-subject (or LAR/next-of kin) by phone and/or by recruitment mailer to introduce the possibility of participation in the study described in this protocol. By phone, we plan to explain the goals and the risks of participating in this research study. We will describe the requirements of participation, review a pre-screening checklist, and schedule a meeting with the patient-subject. We will also inform the patient that it is possible if they come in for the meeting, s/he they may not be eligible for this study. If the subject is interested in participating in the study and has obtained a brain scan within the health system that is accessible through EMR, we can review that scan prior to the meeting if the subject provides verbal consent. Review of brain scans will occur in the interest of expediting determination of study candidacy, as many of our study participants have significant mobility impairments and prescreening brain scans may prevent excess hardship/travel to study site for ineligible subjects.

During the meeting we will review the inclusion and exclusion criteria and explain the details of the study, also the goals and risks as is our usual custom in the process of obtaining informed consent. We will also inform the patient-subject about the alternative treatments available in our Bioelectronic Division.

Additionally, participating subjects will be asked to have photos and video recordings taken during clinical measures in order to document improvement, and to share potential improvements with PathMaker Neurosystems Inc. These photos videos may be used in promotional demonstrations to the public. Photo and video recording will be optional. Subjects who agree to be recorded will additionally sign the Health System AV authorization form, and the signature of this form will be noted on the consent. During the consenting process, a potential subject and/or a potential subject's legally authorized representative (LAR)/next of kin will be given a copy of the consent form and Health System AV Authorization by one of the study investigators. The investigator will review and explain the consent and AV authorization forms. All information about the study will be provided. Ample time will be given for individuals to ask questions regarding participation and to have questions answered prior to signing the consent and AV authorization forms. If so desired, those interested will be given a copy of the consent form so that they may have the opportunity to discuss participation further with family and/or advisors. Only those investigators listed in the study protocol will obtain informed consent. If an individual chooses to enroll, the consent form will be signed before

participation begins. Once an individual joins the study and informed consent is obtained, the subject will receive a signed copy of the consent form. The subject may withdraw from the study at any time without repercussions to subsequent care.

If the patient is awake, alert, and oriented to person, place, and time, and demonstrates appropriate cognitive and communicative abilities as determined by the study coordinator or PI, the patient will be deemed to have the appropriate capacity to consent; however, given that borderline cognitive dysfunction and/or aphasia may not be easily distinguishable, the patient's LAR/next of kin will be routinely included when consent to participate is being obtained for all subjects.

If it is determined that a patient is unable to consent for him/herself, due to a lack of capacity or lack of comprehension, consent will be sought from the patient's LAR/next of kin. Assent of the adult subject with LAR/next-of-kin will be obtained as appropriate. If such a subject regains his/her ability to make healthcare decisions, he/she will be given the opportunity to provide consent. This consent will be documented using the Addendum to Consent by Research Proxy for Continuing Participation in a Research Study form.

If the patient provides the consent delegate with assent to participate in the research but, due to a physical disability, is unable to sign the consent form, the patient will provide verbal consent and two witnesses and the patient's LAR/next of kin will sign the document affirming their presence during the consent process and the patient's physical disability as reason for an absent signature.

Healthy family members of participants with stroke and employees from the health system will be recruited as healthy controls through direct contact. Health System employees will not be consented by anyone with a supervisory role over them, and they will be explicitly told that if they decline to participate, it will have no effect on their employment status. Subject family members will not be recruited in the presence of the participant with stroke. They will be informed at the time of recruitment that they can decline to participate in the study, and that their decisions will not impact the affected subjects' participation in the study. In addition, their decision to decline or to participate in the study will not be communicated to the affected subject by the research staff, unless permitted by the recruited family member.

Protection Against Risk:

Protection against DoubleStim-related risks: If any redness is apparent where the electrodes were placed, a cold compress will be offered to the subject. Mild-moderate redness at any stimulation site immediately following stimulation is a known side effect of non-invasive stimulation. However, if a subject experiences any greater than mild redness and/or soreness at the stimulation site 24 hrs after stimulation, the subject will be deemed intolerant of the intervention and Doublestim will be ceased for the duration of the study. Stimulation at the median nerve will be continuously monitored with EMG to ensure that the current intensity passing through the wrist electrodes (median nerve) is subthreshold (causing no electrical

activity (EMG) from the innervated muscles), and ranges from 1-3 mA, while the stimulation at the level of the spinal cord remains at 4mA. EMG monitoring will ensure that activation of the median nerve remains subthreshold, and without risk of overactivation.

We will monitor subjects continually during the stimulation period, and will be in constant contact with the subjects. The study can be immediately stopped at the subject's request.

Protection of Confidentiality: To protect subjects' confidentiality, each subject will be assigned an ID number, and all data will be stored with the subject ID number only and not the subject's name. Data will be stored on a password-protected computer and on the cloud data server, REDcap, which is encrypted and password protected. Subject charts with medical history and assigned subject numbers will be kept in locked file cabinets stored at the Feinstein robot suite. Access to charts will be granted only to study investigators and company representatives from Pathmaker Neurosystems, Inc. Charts will be kept confidential and will not be shared with any third parties without permission from the subject. Any study data containing PHI that is transferred between investigators at Feinstein and collaborating institutes/company will be shared via encrypted email or encrypted storage drives.

Data and Safety Monitoring: To protect both the integrity of the data and the safety of all study participants, study data review in aggregate will occur every 4 months by the Principal Investigator. PathMaker Neurosystems Inc. will also have access to the data upon request.

POTENTIAL BENEFIT TO SUBJECTS AND OTHERS

The risk/benefit ratio is very low in the proposed study due to the established safety of the protocol and to the great potential for using the findings to improve rehabilitation methods.

SCIENTIFIC VALUE

The results of this study may help to improve rehabilitation of post-stroke upper extremity spasticity.

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