Official title: Development of sensory augmentation methods to improve post-stroke gait stability

NCT number: NCT03988400

Document date: 3/3/20

PROTOCOL TITLE:

Development of sensory augmentation methods to improve post-stroke gait stability

PRINCIPAL INVESTIGATOR:

Jesse Dean

1.0 Objectives / Specific Aims

The objective of this project is to develop and test a method of providing real-time augmentation of hip proprioceptive feedback during post-stroke walking. Our central hypothesis is that augmented proprioception will increase the mechanics-dependent modulation of step width, an important gait stabilization strategy. The first aim of this study is to identify the physiological mechanism underlying the beneficial effects of sensory augmentation on step-by-step gait stabilization. Here, we will differentiate between the potential mechanisms of altered perception and cutaneous cueing. The second aim is to determine whether personalizing sensory augmentation methods to individual participants produces greater beneficial effects on post-stroke gait stability. Here, we will identify the optimal combination of vibration pattern and location for each participant, and test whether this personalized stimulation is superior to standard methods. The third aim is to establish the safety, feasibility, and efficacy of a rehabilitation intervention centered on repeated exposure to sensory augmentation during gait. This will be accomplished through a small-scale clinical trial.

2.0 Background

Chronic stroke survivors often experience gait instability, which can reduce quality of life through an increased fall-risk and fear of falling [1-5]. Unfortunately, recent clinical trials focused on strengthening and balance [6], multifactorial fall prevention [7], and locomotor training [8] have all failed to substantially impact this important problem, likely because they were not targeted to the specific mechanisms underlying post-stroke instability. To overcome this obstacle, we must design interventions based on a mechanistic understanding of gait instability, which can ultimately be accessed by patients outside of cutting-edge research laboratories

As it is unlikely that a single intervention will “cure” post-stroke gait instability, our long-term goal is to develop a toolbox of interventions, from which clinicians can select the most appropriate option for individual patients. Toward this goal, this study will investigate the real-time augmentation of hip proprioceptive feedback during post-stroke walking. Essentially, sensory stimulation will augment perceived movement errors, a direct extension of methods promoting useful gait adaptation by mechanically augmenting movement errors [9-10].

This proposal is based on our prior work revealing a sensorimotor strategy of sensing the body’s mechanical state using hip proprioceptive feedback [11] and actively adjusting foot placement in response [12]. This strategy is often disrupted in chronic stroke survivors with poor balance [13]. Our ongoing work indicates that deficits in this stabilization strategy can be improved through mechanical error-augmentation. Here, we will test

whether sensory error-augmentation has similar beneficial effects, while investigating the underlying mechanism and determining whether sensory augmentation should be personalized to individual patients.

3.0 Intervention to be studied

In this study, Aims 1 and 2 do not involve an intervention, instead including cross-sectional mechanistic experiments. Aim 3 will test the safety, feasibility, and efficacy of a novel intervention involving low-intensity vibration applied over the bilateral hip abductor muscles of chronic stroke survivors during walking. This Aim will take the form of an early-stage, small-scale (n=44 participants) randomized controlled clinical trial.

The precise intervention to be studied is novel, as the vibration amplitude applied during walking will be directly controlled by the user's walking mechanics, allowing us to augment the sensory information available to users. However, the method and form of the vibration itself is not novel. Many prior studies have used vibrating motors (as in the present study) to deliver the same type of mechanical vibration to clinical populations during the performance of functional movement tasks (e.g. reaching, standing, walking) [14-17]. We ourselves have published work investigating the effects of mechanical vibration [11, 18-19], and have an IRB-approved project that involves these methods (Pro00046775).

No medication is involved in the intervention, and FDA approval will not be required for the use of our vibrating tactors, which deliver minimal mechanical energy to users – instead simply evoking a sensory response.

The rationale for the intervention is to use non-invasive methods (vibration) to improve the sensory accuracy of chronic stroke survivors. This low-risk method could have the potential to produce large improvements in patient functional mobility. While we have observed no adverse events in the use of these methods, and no such adverse events have been reported in the literature due to the use of these methods, one of the goals of this project will be to definitively establish the safety of this intervention.

For the intervention, the control group will receive vibration applied over the bilateral hip abductors, just as the experimental group. However, the vibration will not be linked to the user's mechanics, instead being randomly delivered – a method that has been used previously [11].

4.0 Study Endpoints

For the intervention in Aim 3, our outcome measure of <u>safety</u> will be the proportion of participants who experience an adverse event potentially related to the intervention (e.g. skin irritation; falls) or any serious adverse event (e.g. hospitalization; death). Our primary measures of <u>feasibility</u> will be participant adherence (percentage of training sessions attended) and drop-out (non-attendance of final assessment session). We will also track the total walking time across training sessions (of a maximum possible 312 minutes). Our primary measure of <u>efficacy</u> will be changes in ρ_{disp}, a metric that quantifies the extent to which participants effectively stabilize their gait by adjusting their step width to account for pelvis dynamics [20]. Our secondary measures of efficacy will be the common clinical measures of Functional Gait Assessment score, Activities-specific Balance Confidence score, overground gait speed, and fear of falling.

5.0 Inclusion and Exclusion Criteria/ Study Population

Participants will be recruited from an MUSC database containing the contact information of stroke survivors who have agreed to be contacted for research participation (Pro00037803). Initial screening will be performed by study staff through a phone call to confirm basic participant characteristics (e.g. timing of stroke) and interest in research participation. The ability of potential participants to meet the more detailed inclusion and exclusion criteria will subsequently be determined in person.

Inclusion Criteria

- Age ≥ 21 years
- Experience of a stroke ≥ 6 months prior to participation
- Gait speed of at least 0.2 m/s
- Ability to walk on a treadmill without a cane or walker
- Provision of informed consent

Exclusion Criteria

- Evidence of cerebellar damage
- Resting blood pressure higher than 220/110 mm Hg
- History of unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, angina or dyspnea at rest or during activities of daily living
- Preexisting neurological disorders or dementia
- Legal blindness or severe visual impairment
- History of DVT or pulmonary embolism within 6 months
- Uncontrolled diabetes with recent weight loss, diabetic coma, or frequent insulin reactions
- Orthopedic injuries or conditions (e.g. joint replacements) in the lower extremities with the potential to alter the gait pattern
- Recent (within last 6 months) Botox injections in the hip musculature

We plan to include a diverse participant population, paralleling the general demographic characteristics of the Charleston area. This will be accomplished using the database referenced above, which currently contains contact information for over 800 individuals. We will not exclude any sex/gender or racial/ethnic group. This study will not involve any special classes of subjects, including fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or other vulnerable populations. Children will not be included because this study focuses on individuals who have experienced a stroke. This is rare among children, and would be expected to involve a quite different mechanism or pattern of recovery.

6.0 Number of Subjects

A total of 120 chronic stroke survivors will be accrued, all locally.

7.0 Setting

All research will be performed in the MUSC College of Health Professions Research Building at 77 President St. Charleston, South Carolina.

8.0 Recruitment Methods

This study will recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803, IRB approved 9/6/14), which is a research tool sponsored by the National Institutes of Health (NIH) Center of Biomedical Research Excellence (COBRE) in Stroke Recovery with subjects consented for future contact to support stroke recovery research conducted at MUSC. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will contact subjects to further screen for potential enrollment.

Additionally, we have developed a study flyer that will be shared through the COBRE and distributed through stroke support groups attended by study personnel.

9.0 Consent Process

Informed consent will be obtained from participants prior to participation, using a VA Informed Consent form approved by the MUSC IRB. Participants will first be informed of the purpose of the experiments and possible risks. A member of the study staff will then review the Informed Consent form with the potential participant, ensuring they are given adequate time to review the document. The potential participant will be asked if they have any questions about the study, and asked if they agree to participate. The Informed Consent form will be signed by the participant. Copies of the signed forms will be given to the participant. The consent process will take place in a private room in the MUSC College of Health Professions Building. There will be no set period between informing the prospective participant and obtaining the consent. Participants will be reminded that they may end their participation in the study at any point.

10.0 Study Design / Methods

A total of 120 chronic stroke survivors will be recruited for an initial Screening session to determine eligibility for enrollment in the subsequent Aims. From this initial session, 40 stroke survivors will be recruited for Aim 1, and a separate 40 stroke survivors will be recruited for Aim 2. From these 80 participants in Aims 1 and 2, a total of 44 will be recruited for Aim 3. Aim 1 involves a single-session experiment, Aim 2 involves two experimental sessions, while Aim 3 involves an intervention with a total of 10-11 sessions. Participants will be enrolled in this study for a period of a year, allowing time to complete all potential sessions.

In the initial Screening session, participants will walk on an instrumented treadmill for 2-minutes. We will calculate ρ_{disp} (a measure of the typical gait stabilization strategy) using LED markers and inertial measurement units placed over participants' legs and pelvis. If ρ_{disp} is less than 0.56 (well below control norms), participants will qualify to progress to the subsequent Aims. During the Screening session, we will also quantify the secondary

measures of: Functional Gait Assessment; Activities-specific Balance Confidence scale, Fugl-Meyer Lower Extremity Motor Function subscale; Fugl-Meyer Lower Extremity Sensation subscale; self-selected and fastest-comfortable overground gait speed; fear of falling; fall history. All of these secondary measures are commonly used in clinical practice.

In Aim 1, participants will complete a single-session experiment. We will quantify the cutaneous detection threshold for vibration delivered over the bilateral hip abductors. We will also calculate the lateral sway evoked by vibration of each leg, quantified as the shift in center of pressure while standing on a force plate. Participants will then perform a series of treadmill walking trials. In some of these trials, vibration will be applied to the hip abductors or lateral trunk, while we quantify ρ_{disp}.

In Aim 2, participants will complete two experimental sessions. In the first session, participants will perform a series of treadmill walking trials, across which we will vary the pattern and location of vibration applied over the bilateral hip abductors. We will identify the combination of pattern and location that produces the largest increase in ρ_{disp} for each participant. In the second session, participants will again perform a series of treadmill walking trials, across which we will compare the personalized stimulation (optimal pattern and location for this individual) with the standard pattern of stimulation used in prior work.

In Aim 3, participants will complete 10-11 experimental sessions. The first and last session will consist of pre and post assessments, in which we will quantify ρ_{disp}, Functional Gait Assessment score, Activities-specific Balance Confidence score, overground self-selected and fastest-comfortable walking speeds, and fear of falling. If Aim 2 reveals that personalized stimulation is superior to standard stimulation, the second session will be used to identify the optimal combination of stimulation pattern and location for each participant. Otherwise, this session will not be performed. The remaining sessions will be training sessions, in which participants will perform a series of walking trials at their self-selected speed. In some trials, hip abductor vibration will be applied on a step-by-step basis. In the Augmented group, this vibration will be scaled to augment sensory feedback providing information about the mechanical state of the pelvis. In the Control group, the magnitude of this vibration will be randomized, providing no additional information.

To reduce the risk of participants falling, participants will wear a harness attached to an overhead rail during all treadmill and overground walking trials. This harness will not support body weight, but would prevent participants from falling in the case of a loss of balance. The vibrating tactor and adhesive used to secure the tactor and LED markers to the skin may produce the risk of minor skin irritation. We will reduce this risk by asking participants if they have had any previous experience of skin irritation in reaction to specific gel or tape types, and by checking the participants' skin after each experiment.

11.0 Data Management

For Aim 1, our first analysis will be correlation-based, testing whether metrics of altered perception or cutaneous cueing are associated with the beneficial effects of sensory augmentation. For each participant, we will quantify four independent variables: cutaneous detection threshold (paretic and non-paretic legs); lateral sway distance evoked by hip abductor vibration (paretic and non-paretic legs). We will also quantify the effect of sensory augmentation during gait as the mean change in paretic ρ_{disp} between the Normal and Vibrated Abductors trials ($\Delta \rho_{disp}$). We will test whether each of the four independent

variables is significantly associated with $\Delta \rho_{disp}$, using an alpha value of 0.0125 to account for multiple comparisons. Our second analysis will involve a repeated measures experimental design – directly testing whether vibration designed solely to provide cutaneous cues (Vibrated Trunk condition) has a smaller beneficial effect than vibration designed to elicit both cutaneous cues and an altered perception of pelvis mechanics (Vibrated Abductors condition). For this analysis, we will use a repeated measures ANOVA to compare mean paretic ρ_{disp} values during the Normal, Vibrated Abductors, and Vibrated Trunk trials.

For Aim 2, our primary statistical analysis will compare the average increase in paretic ρ_{disp} values during Standard Augmentation and Personalized Augmentation conditions (relative to Normal). We will use a paired t-test to compare these $\Delta \rho_{disp}$ values. Secondarily, we will use a repeated measures ANOVA to test for group-wide effects of vibration pattern and location, based on data from the first session.

For Aim 3, our primary statistical analysis will use an independent t-test to determine whether the change in paretic ρ_{disp} differs significantly between the Augmented and Control groups.

Power analyses were performed for each Aim. For Aim 1, the proposed sample size (n=40) was selected to be able to detect a moderate correlation (r=0.5) between our input variables and $\Delta \rho_{disp}$. Aim 2 was powered to detect a moderate effect size (Cohen's d = 0.5) between Standard and Personalized sensory augmentation methods. For our Aim 3 intervention, we estimate an effect size of 1.0 based on our prior results. It should be noted that we expect this effect to increase with the repeated exposure to sensory augmentation proposed here. With an effect size of 1.0 and an alpha value of 0.05, we will need 17 participants per group for 0.80 power. We propose 22 participants per group to account for 20% dropout.

Steps will be taken to minimize the risk of loss of confidentiality. All data will be stored on a password-protected computer and password-protected secure server that is backed-up nightly.

The RESTORE registry (Pro#00037803), from which this study will recruit subjects, also serves as a data analysis tool by which interdisciplinary teams may share data across projects and provide MUSC's stroke recovery research community with a more complete registry with key stroke elements. Some subjects may have participated or will participate in other stroke related research studies at MUSC. Sharing data from this and other stroke research studies with RESTORE will allow for more targeted recruitment efforts in the future and could reduce the burden placed on subjects by reducing the duplicative efforts of collecting common data and physical function assessments requested by multiple studies and storing them in one centralized and secure location.

Subjects are informed in the consent process if they enroll into the RESTORE registry, their data from this study will be shared. Subjects will be asked to sign a HIPAA authorization stating their health information may be disclosed to MUSC investigators requiring their data for their research projects upon approval by an Institutional Review Board.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

A Data Safety Monitoring Board (DSMB) will oversee the experiments in Aim 3 (a small-scale randomized controlled trial). This board will consist of a neurologist, a statistician,

and an experienced rehabilitation researcher (all with no direct ties to this study). On a quarterly basis, the DSMB will review the status of the study. The role of the DSMB will be to:

- Protect the safety of study participants
- Review the research protocol, informed consent documents, amendments, and plans for data safety and monitoring
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual, and retention, participant risk vs. benefit, and other factors that may potentially affect study outcome
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator
- Report to the IRB on the safety and progress of the trial
- Ensure the confidentiality of the study data and the results of the monitoring
- Advise the IRB and the study investigators as to whether the protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process

Any adverse events will be recorded, monitored, and promptly reported to the IRB, following policy HRPP 4.7. Our exclusion criteria will minimize the risk of enrolling participants with severe cardiovascular risk. Scheduled rest breaks will be provided between trials during experimental testing, as well as whenever requested. Minimization of risk of adverse events will be accomplished by monitoring vital signs during trials in which subjects are performing potentially demanding exercise. Collected data and any events potentially affecting participant safety will be reviewed by the principal investigator after each data collection session.

13.0 Withdrawal of Subjects

Participants will be withdrawn from the study without their consent if study staff determine that the participants are at risk of negative health events (e.g. large increase in blood pressure from the initial screening assessment; consistent inability to maintain balance while walking on the treadmill). If a participant voluntarily withdraws from the study, their results will not be included in our data analysis, as our intervention sample size accounts for 20% dropout.

14.0 Risks to Subjects

Potential risks for participation in this study are low.

Participants will perform standing and walking trials, in which there is the risk of a loss of balance. To mitigate this risk, in these trials participants will wear a safety harness attached to an overhead rail. The harness is designed to eliminate the consequences of falling as the device “catches” the subject should they trip or stumble. Additionally, in all walking trials, an investigator will be near the participant to provide assistance in the event of a loss of balance. There is also the risk of minor muscle soreness due to the exercise of walking.

This risk will be mitigated by walking only at speeds that are comfortable for each participant, and allowing rest breaks if participants ever indicate they are fatigued.

General post-stroke function will be assessed using several commonly-used clinical tests. There is a risk of a loss of balance during the Functional Gait Assessment, in which individuals perform various functional gait tasks. We will mitigate this risk by having a physical therapist always next to participants, as is common in a clinical context. The other clinical tests either involve verbal questions or are of minimal physical risk.

In some treadmill walking trials, vibrating tactor motors will apply sensory stimuli to participants' hip muscles. This stimulation will deliver minimal mechanical energy to participants, as the vibration amplitude will be less than 2 mm. Extensive prior experiments have used these devices, without reports of adverse events. However, there is the risk of the vibration producing skin redness and minor irritation. After every session, we will check the skin for irritation, which should resolve within 24 hours.

All research studies have the risk of loss of participant confidentiality. Our Data Management Plan (see above) will minimize this risk.

15.0 Potential Benefits to Subjects or Others

The research conducted in the Aim 3 intervention has the potential to improve the gait stability of chronic stroke participants, which may have beneficial effects on functional mobility and quality of life. Promising effects would justify larger-scale studies able to benefit a larger number of individuals. As the risks to participants are minimal (no more than a moderate period of exercise), we believe the risks are reasonable in relation to the anticipated benefits.

16.0 Sharing of Results with Subjects

Results will be in the form of research data, and will not be shared with participants or others.

17.0 Devices

This study will involve the use of tactors (Engineering Acoustics, Inc.), which are small vibrating motors designed to cause the sensation of pressure or movement. These tactors are non-invasive and will not be distributed to participants, but will only be used during research procedures in the laboratory setting over the course of this study.

References

1. Jones F, Riazi A. Self-efficacy and self-management after stroke: a systematic review. Disabil Rehabil. 2011; 33:797-810.
2. Jorgensen L, Engstad, Jacobsen BK. Higher incidence of falls in long-term stroke survivors than in population controls. Depressive symptoms predict falls after stroke. Stroke. 2002; 33:542-547.
3. Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke. A multicenter study. Stroke. 2000; 31:1223-1229.
4. Hyndman D, Ashburn A, Stack E. Fall events among people with stroke living in the community: circumstances of falls and characteristics of fallers. Arch Phys Med Rehabil. 2002; 83:165-170.
5. Ng SSM. Contribution of subjective balance confidence on functional mobility in subjects with chronic stroke. Disabil Rehab. 2011; 33:2291-2298.
6. Dean CM, Rissel C, Sherrington C, et al. Exercise to enhance mobility and prevent falls after stroke: the community stroke club randomized trial. Neurorehab Neural Repair. 2012; 26:1046-1057.
7. Batchelor FA, Hill KD, Mackintosh SF, et al. Effects of a multifactorial falls prevention program for people with stroke returning home after rehabilitation: a randomized controlled trial. Arch Phys Med Rehabil. 2012; 93:1648-1655.
8. Tilson JK, Wu SS, Cen SY, et al. Characterizing and identifying risk for falls in the LEAPS study. A randomized clinical trial of interventions to improve walking poststroke. Stroke. 2012; 43:446-452.
9. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurological injury. J NeuroEng Rehabil. 2009; 6:20.
10. Roemmich RT, Bastian AJ. Closing the loop: from motor neuroscience to neurorehabilitation. Ann Rev Neurosci. 2018; 41:415-429.
11. Roden-Reynolds DC, Walker MH, Wasserman CR, Dean JC. Hip proprioceptive feedback influences the control of mediolateral stability during human walking. J Neurophys. 2015; 114:2220-2229.
12. Rankin BL, Buffo SK, Dean JC. A neuromechanical strategy for mediolateral foot placement in walking humans. J Neurophys. 2014; 112:374-383.
13. Dean JC, Kautz SA. Foot placement control and gait instability among people with stroke. J Rehabil Res Dev. 2015; 52:577-590.
14. Paoloni M, Mangone M, Scretti P, Procaccianti R, Cometa A, Santilli V. Segmental muscle vibration improves walking in chronic stroke patients with foot drop: a randomized controlled trial. Neurorehab Neural Rep. 2010; 24:254-262.
15. Ma CZ, Zheng YP, Lee WC. Changes in gait and plantar foot loading upon using vibrotactile wearable biofeedback system in patients with stroke. Top Stroke Rehabil. 2018; 25:20-27.
16. Bonan I, Butet S, Jamal K, Yelnik A, Tasseel Ponche S, Leplaideur S. Difference between individuals with left and right hemiparesis in the effect of gluteus medius vibration on body weight shifting. Neurophysiol Clin. 2017; 47:419-426.
17. Maupas E, Dyer JO, Melo SA, Forget R. Patellar tendon vibration reduces the increased facilitation from quadriceps to soleus in post-stroke hemiparetic individuals. Ann Phys Rehabil Med. 2017; 60:319-328.
18. Floyd LM, Holmes TC, Dean JC. Reduced effects of tendon vibration with increased task demand during active, cyclical ankle movements. Exp Brain Res. 2014; 232:283-292.
19. Hubbuch JE, Bennett BW, Dean JC. Proprioceptive feedback contributes to the adaptation toward an economical gait pattern. J Biomech. 2015; 48:2925-2931.
20. Stimpson KH, Heitkamp LN, Horne JS, Dean JC. Effects of walking speed on the step-by-step control of step width. J Biomech. 2018; 68:78-83.