PROTOCOL TEMPLATE: INTERVENTIONAL STUDY (PILOT)

Complete Title: The sensorimotor locus of balance control in elderly gait

Short Title: Optical flow perturbation training

FDA IND/IDE (if applicable): Not Applicable.

Sponsor: National Institutes of Health (Investigator Initiated)

Protocol Date: September 1, 2017

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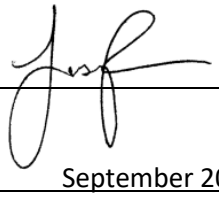
Version Date: September 1, 2017

I confirm that I have read this protocol and understand it.

Principal Investigator Name: Jason R. Franz

Principal Investigator Signature: 

Date: September 2017

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PROTOCOL SYNOPSIS

Study Title	The sensorimotor locus of balance control in elderly gait
Funder	National Institutes of Health
Clinical Phase	Pilot
Study Rationale	One third of adults age 65 and older fall annually with 20-30% of falls resulting in serious injuries. In 2009 alone, falls in older adults resulted in nearly 2.2 million emergency room visits. In 2000, direct medical cost of non-fatal falls in adults over age 65 was $19 billion, and in 2007 that cost was projected to increase to $54.9 billion/year by 2020. However, despite considerable efforts, falls rates over this time have been highly resistant to change. Thus, there is a critical need for more effective diagnostic efforts to identify older adults at risk of falls and rehabilitative efforts to successfully mitigate that risk once identified. Consistent with studies on the postural control of standing, our recent findings suggest that older adults prioritize visual feedback to control balance in walking. Accordingly, older adults are more susceptible than young adults to optical flow perturbations applied in the safety of virtual reality (VR). These perturbations elicit the visual perception of walking instability, and provide the opportunity to practice walking balance corrections in a controlled environment. The purpose of this proof of concept study is to investigate the propensity for time-dependent tuning of walking balance control and the presence of aftereffects in older adults following a single session of optical flow perturbation training.
Study Objective(s)	To investigate the propensity for time-dependent tuning of walking balance control and the presence of aftereffects in older adults following a single session of optical flow perturbation training.
Test Article(s) *(If Applicable)*	Mediolateral (ML; i.e., side-to-side) optical flow perturbations applied during treadmill walking using a projection-based virtual reality system.
Study Design	A randomized, crossover design that included a control session of normal unperturbed walking and an experimental session that incorporated mediolateral optical flow perturbations during walking.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria 1. Subjects Age 65+ years 2. Be able to walk without an assistive aid (i.e., walker, cane) 3. Have the full capacity to provide informed consent Exclusion Criteria 1. Current lower extremity injury or fracture 2. Taking medication that causes dizziness 3. Have a leg prosthesis 4. Prisoners 5. Individuals lacking the capacity to provide informed consent

Number of Subjects	Up to 20
Study Duration	Each subject will participate in two sessions, each lasting up to three (3) hours and separated by at least one week. The entire study is expected to last two years (approximately one year for data collection and another one year for data analysis)
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: We will use an initial telephone screening (attached) to evaluate basic study eligibility. Subjects that meet inclusion/exclusion criteria following phone screening will be invited to participate in the study. (2) Balance training: Subjects that provide written informed consent will participate in the cross-over design that includes one control session and one session of perturbation training, separated by at least one week.
Efficacy Evaluations	Primary outcome measures: (1) Change in Postural Sway (2) Change in kinematic (step width) variability (3) Change in foot placement targeting accuracy Secondary outcome measures: (1) Change in Cognitive-motor Interference Accuracy (2) Change in Cognitive-motor Interference Response Time After 10 Min of Walking (3) Change in Margin of Stability Variability After 10 Min of Walking
Statistical Analysis Plan	A one-way, repeated-measures analysis of variance will test for effects of time on dependent variables collected from each session. Significance will be defined using an alpha level of 0.05.
DATA AND SAFETY MONITORING PLAN	This study does not meet the criteria for an independent DSMP. The PI (Dr. Franz) will oversee all conduct to ensure the safety of all participants and the integrity of the data. At least one research staff member will be monitoring the subjects' movement patterns during the data collection. If the subject experiences any discomfort, the data collection will be stopped immediately. If any member of the research team encounters unanticipated problems (including by not limited to adverse events), we will make necessary adjustments to the protocol and, where appropriate, report these events to University administrative personnel.

1 BACKGROUND AND RATIONALE

1.1 Introduction

Older adults are at an exceptionally high risk of debilitating falls, contributing significantly to reduced independence and quality of life. Despite conventional diagnostic and rehabilitative efforts, one-third of people over age 65 fall annually and 20-30% of these falls lead to moderate to severe injury. When adjusted for inflation, annual direct medical costs from non-fatal falls in older adults are expected to reach $67.7 billion by 2020. Moreover, three decades of falls prevention research have led to present guidelines that include recommendations for targeted exercise interventions. However, most of the programs evaluated during this time only modestly influenced the sizeable portion of our aging population experiencing one or more falls annually. Unfortunately, our society now faces a growing dilemma – evidence suggests that the rate of injurious falls is accelerating, with 2.4 million emergency department visits in 2011, up 46% from 2001 despite only a 17% increase in the older adult population.

There is a growing appreciation that interventions designed to challenge balance are those most likely to have positive impact on balance integrity. Unfortunately, conventional interventions based on this premise elicit only modest improvements unlikely to impact the high prevalence of falls. Our research group is at the forefront of using optical flow perturbations applied during walking in the safety of virtual reality (VR) to elicit the visual perception of instability during walking. The purpose of this proof-of-concept study is to evaluate change in walking balance in older adults responding to a single session of optical flow perturbation training compared to a control session of normal walking.

1.2 Name and Description of Investigational Product or Intervention

Optical flow perturbation system and paradigm: Subjects walk on a treadmill surrounded by a semicircular curved screen on which a speed-matched virtual hallway is projected. To this motion, the system adds pseudo-random mediolateral (ML, side-to-side) oscillations of the virtual hallway, designed to elicit the visual perception of lateral instability.

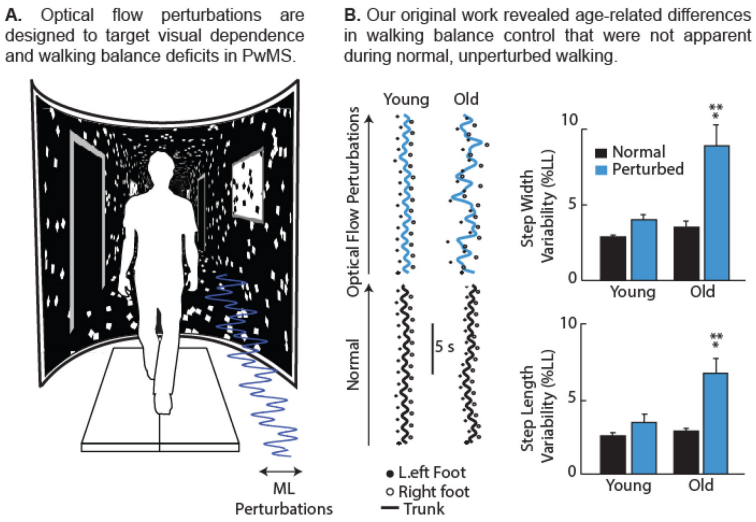

Figure 1. System and disproportionate effects in older versus young adults.

1.3 Relevant Literature and Data

The investigators have a significant history of testing the effects of optical flow perturbations on walking balance in young and older adults and in patients with multiple sclerosis. Our cumulative evidence from these studies (listed below) demonstrate that older adults are significantly more susceptible to these perturbations than young

adults (Fig. 1). Accordingly, we now know that this environment uniquely disrupts walking balance in older adults, thereby providing an opportunity to "practice" corrective motor adjustments relevant to preserving balance.

2 STUDY OBJECTIVE

The purpose of this proof-of-concept study is to evaluate change in walking balance in older adults responding to a single session of optical flow perturbation training compared to a control session of normal walking.

2.1 Primary Objective

Quantify the time-dependent changes in metrics of walking balance in older adults after walking with optical flow perturbations.

2.2 Secondary Objective

Contrast effects of walking with optical flow perturbations to those of normal treadmill walking.

3 INVESTIGATIONAL PLAN (brief overview)

3.1 Study Design

(Session A: Normal walking, Session B: Continuous optical flow perturbations). In a randomized cross-over designed (assigned at enrollment using a random number generator), subjects will walk normally (session A) and be exposed to continuous side-to-side motions of the virtual hallway (Session B). These walking trials will last up to 20 min and will be separated by at least one week.

3.2 Study Duration, Enrollment and Number of Subjects

This study will last up to 36 months. Subject recruitment and data collection will take up to 24 months. The remaining 12 months will focus on data analysis, data interpretation, and manuscript preparation. We will recruit up to 20 older adults to participate.

3.3 Study Population

Inclusion Criteria:

1. Subjects Age 65+ years
2. Be able to walk without an assistive aid (i.e., walker, cane)
3. Have the full capacity to provide informed consent

Exclusion Criteria:

1. Current lower extremity injury or fracture
2. Taking medication that causes dizziness
3. Have a leg prosthesis
4. Prisoners
5. Individuals lacking the capacity to provide informed consent

4 STUDY PROCEDURES (what will be done)

Subjects will be comfortably fit with a safety harness and instructed on all safety procedures. Subjects will then walk at their preferred speed on a force-sensing treadmill for 5 min to acclimate to the equipment and allow their movement patterns to stabilize.

Subjects will then complete a block protocol design with pre and post measurements separated by up to 20 min of normal treadmill walking (Session A) or in the presence of optical flow perturbations (Session B). Pre and post measurements will include baseline measurements during normal walking and:

1) Foot placement targeting task. Subjects will be exposed to a series of footprint targets intermittently projected onto the treadmill belt. Subjects will be asked to direct their feet to the target with their next step as accurately as possible.

2) Auditory 'Stroop' task. While wearing headphones with a microphone, subjects will hear the words high and low in pitches that are either high or low and asked to verbally identify the pitch of those words as quickly as possible.

Subject Completion/ Withdrawal procedures

If subjects are unable to complete the protocol or suffer a musculoskeletal injury before or during the time period when they are involved in the study, they will be withdrawn from the study.

5 STUDY EVALUATIONS AND MEASUREMENTS (how measurements will be made)

3D motion capture and an instrumented treadmill will record the position and orientation of body segments and joints and ground reaction forces. Using custom software, we will compute the mean and standard deviation of step width variability, postural sway variability, and margin of stability variability. The outcome measure from the foot placement targeting task will be foot placement accuracy. The outcome measures from the auditory Stroop task will be cognitive-motor interference accuracy and response time. Efficacy measurements will be made using the change in each outcome measure after walking normally or with optical flow perturbations.

6 STATISTICAL CONSIDERATION

Sample size is based on our published estimates of age-related differences in balance outcome measures. n=14 subjects per group would have 90% power to detect ($p<0.05$) a difference in dynamic instability during visually perturbed walking between healthy older (1.38 ± 0.20, unitless) and healthy young (1.20 ± 0.10, unitless) adults (Franz et al., 2015). This number of subjects would also sufficiently power our detecting differences in step width variability (8.92 ± 1.00 vs. 4.02 ± 0.96) (Francis et al., 2015).

6.1 Statistical Methods

A two-way rmANOVA will test for significant main effects and interactions between time (Pre versus Post) and experimental session (perturbations versus normal walking). Significance will be defined for each main effect using an alpha level of 0.05.

6.2 Interim Analysis

Given the non-invasive nature of the experiment and the relative risk involved, there are no criteria that will be used to stop the entire study prematurely.

7 STUDY INTERVENTION (drug, device or other intervention details)

This study uses a custom virtual reality environment described in detail elsewhere (Franz et al., 2015), which consists of a virtual hallway that is speed-matched to a treadmill positioned inside the projection screen (Fig. 1). To the speed-matched virtual hallway, we add continuous mediolateral oscillations of optical flow which are prescribed as the sum of three sine waves (phase, $\phi = 0$), such that a full 0.35 m amplitude is applied at 0.250 Hz and half that amplitude is applied at 0.125 Hz and 0.442 Hz.

8 SAFETY MANAGEMENT

If a subject needs immediate medical assistance, we will call “911” for emergency services. Should a subject need non-urgent medical or psychological follow-up, research members will contact UNC Health Care to provide referrals.

At least one research staff member will be monitoring the subjects' movement patterns during the data collection. If the subject experiences any discomfort, the data collection will be stopped immediately.

If any member of the research team encounters unanticipated problems (including by not limited to adverse events), we will make necessary adjustments to the protocol and, where appropriate, report these events to IRB personnel. Our goal with protocol adjustments will be to further lessen the likelihood of unanticipated problems.

If subjects are unable to complete the protocol or suffer a musculoskeletal injury before or during the time period when they are involved in the study, they will be withdrawn from the study.

9 DATA COLLECTION AND MANAGMENT

We will minimize the breach of confidentiality as follows. All research will be conducted with only members of the research team present. The collection of information about subjects will be limited to the amount necessary to achieve the aims of the research. We are not utilizing computer-generated questionnaires. All data will be coded with unique subject identification numbers except consent forms (which are directly identifiable). Only members of the core research team will have access to the list that pairs subject names with numbers. This list will be kept separately from electronic data on password protected hard drives connected to a secure network and managed by Dr. Jason Franz. Subject data folders will be maintained in a secure filing cabinet where only the core research team has access. This

filing cabinet is located in the Applied Biomechanics Laboratory. Electronic data will be stored on computers managed via a secure School of Medicine network with password access.

10 RECRUITMENT STRATEGY

All subjects will be primarily identified in person by communicating with UNC students and using flyers posted around the UNC campus and Chapel Hill community, after receiving approval to do so. Older adults will be further identified in person or by using flyers posted at local retirement communities and senior centers after receiving approval to do so.

11 CONSENT PROCESS

Only persons with a prior knowledge of the research will be approached and identified in person. This may include, for example, an informational gathering at retirement community. This interaction will be limited to information contained in the email template and recruitment flyer, or to information needed to address any questions asked about the research by persons in attendance.

Subjects recruited using the flyer or email template will contact a member of the research team by phone or email if interested in being recruited to participate. Once preliminary communication has been established, subjects will be invited to complete the telephone screening to assess basic eligibility criteria. If the subjects email or leave a phone message with their contact information, the study team will return the message to implement the telephone script.

We will emphasize to prospective subjects that participation in this study is voluntary, and any discussions during the recruitment process will be strictly confidential. Our phone screening script further informs the subject that, if they do not qualify or choose not to complete the written informed consent, the phone screening data will be destroyed.

We will not exclude potential subjects based on race, sex, gender, or ethnicity and thus we will ensure equal access to participation including women and minorities.

12 PLANS FOR PUBLICATION

The publication policy will be based on the relative scientific contributions of each investigator and other key personnel.

13 REFERENCES