1. **Protocol Title**

Rehabilitation of Complex TBI with Sensory Integration Balance Deficits; Can Early Initiation of Rehabilitation with Wearable Sensor Technology Improve Outcomes?

2. **Objectives**

In Aim I, we will 1) determine the role of timing in rehabilitation after mTBI and 2) determine meaningful change measures of novel head stability and gait metrics after rehabilitation. In Aim II, we will 1) validate 3D head and trunk motion inertial algorithms with Motion Analyses during the 3 specified exercises 2) develop reports with visual displays for the physical therapist to determine performance and compliance of home exercises done during each week and 3) compare the outcome of the subjects who used wearable sensors during the home exercise program versus those who did not. In Aim III, we will 1) develop and validate real-time algorithms for physical therapists to observe and measure head movement and trunk stability during exercises (head movement - range of motion of head movement and peak velocity; trunk – stability RMS); 2) determine feasibility of physical therapists using the feedback system in the clinic during rehabilitation, and 3) collect normative values on 50 healthy control subjects to enhance interpretation of feedback and report to the physical therapist.

Our long-term goal is to clarify best practices for the rehabilitation of balance deficits in people with mTBI by comparing early vs late (standard of care) initiation of physical therapy with and without wearable sensors on balance deficits after mTBI. There are three objectives of this proposal: 1) To determine the role of timing in rehabilitation of balance deficits in people with mTBI 2) To determine if home monitoring of balance and vestibular exercises using wearable sensors improves outcomes and 3) To develop a novel feedback system using wearable sensors to provide physical therapists information, in real-time during training, about quality of head and trunk movement during exercise. To achieve these objectives, we have the following **Specific Aims**: Aim I. Early Intervention: To determine the effects of early versus late rehabilitation for balance deficits in mTBI. We hypothesize that early rehabilitation initiated at the initial physician visit will improve outcomes more than standard of care (later initiation of physical therapy) in people with mTBI who have complaints of imbalance. We will also determine clinically meaningful change measures due to rehabilitation for objective measures of head stability during gait, based on Patient Global Impression of Change Scale (Hurst and Bolton 2004). We will randomize 160 people with mTBI, between the ages of 18 and 60, into early rehabilitation (within first 2 weeks after physician visit) or late rehabilitation (standard of care; ~60 days from first physician visit). People will be tested before and after a 6-week rehabilitation program and again 6 months later to determine long-term effects. Our primary outcome to measure efficacy of rehabilitation is the Dizziness Handicap Inventory (DHI). Secondary outcomes will be structured along the International Classification of Function and Disability (ICF) models framework. We will measure baseline peripheral vestibular and ocular motor function and other covariates in rehabilitation efficacy. In Aim I, we will 1) determine the role of timing in rehabilitation after mTBI and 2) determine meaningful change measures of novel head stability and gait metrics after rehabilitation.

Aim II. Home Monitoring: To compare traditional balance rehabilitation versus balance rehabilitation with sensor-based home monitoring of compliance and quality of prescribed exercises. We hypothesize that providing physical therapists with objective measures on compliance and the quality of prescribed exercises performed at home, using wearable sensors, will improve outcomes in rehabilitation. Subjects entering rehabilitation in Aim 1 (both early and late rehabilitation) will be further randomized into either: 1) home exercise program or 2) the same home exercise program with wearable sensors worn on the forehead and trunk to monitor compliance and quality of performance during home exercises. The data from the sensors will be reviewed by the physical therapist at the subsequent weekly visit. All people will be seen 1x/week by a physical therapist and expected to do a home exercise program. People will be tested before and after a 6-week rehabilitation period and again 6 months later to determine long-term retention. In Aim II, we will 1) validate 3D head and trunk motion inertial algorithms with Motion Analyses during the 3 specified exercises 2) develop reports with visual displays for the physical therapist to determine performance and compliance of home

exercises done during each week and 3) compare outcome of the subjects who used wearable sensors during the home exercise program versus those who did not.

Aim III. Real-time Monitoring for Training: To develop and evaluate a novel sensor system to provide real-time feedback to physical therapists on head and trunk movement during training. We hypothesize that real-time feedback on head and trunk movements during prescribed exercise will be feasible for a physical therapist to use during training sessions. Five physical therapists and 25 patients with mTBI will test and evaluate our new prototype head and trunk motion feedback system in preparation for future clinical efficacy trials. In Aim III, we will 1) develop and validate real-time algorithms for physical therapists to observe and measure head movement and trunk stability during exercises (head movement - range of motion of head movement and peak velocity; trunk – stability RMS); 2) determine feasibility of physical therapists using the feedback system in the clinic during rehabilitation, and 3) collect normative values on 50 healthy control subjects to enhance interpretation of feedback and report to the physical therapist. Input from researchers, physical therapists and mTBI patients on the perceived usability of the real-time feedback will be used for further tuning and optimizing the system.

3. Background

Every year 1.7 million people sustain a traumatic brain injury (TBI) in the United States and of these, 84% are considered mild TBI (mTBI) (Faul, Xu et al. 2010, Group 2016). According to data from the Defense and Veterans Brain Injury Center, 18,686 Service Members sustained a mTBI in 2015 (Defense 2015). The estimated annual cost to society from TBI, including lost productivity, was $60.4 billion (Corso, Finkelstein et al. 2006, Coronado, McGuire et al. 2012). Data suggest that during deployment as many as 20% of Service Members may have suffered a mTBI (Terrio, Brenner et al. 2009). Balance impairments are a common complaint after mTBI, with an estimated odds ratio of 3.14 in chronic mTBI compared to control subjects (Vanderploeg, Curtiss et al. 2007). Ongoing balance problems are significant contributors to anxiety, difficulty with return to work, and may even underlie the observation that people with a recent history of mTBI are at a threefold greater risk of sustaining a second mTBI (Guskiewicz, McCrea et al. 2003, McCrory 2011).

Although balance is one of the most common and debilitating complaints after mTBI, we currently lack clear guidelines on when to initiate balance rehabilitation and it is unclear if early physical therapy is beneficial. A recent systematic review that focused on early rehabilitation for mTBI was inconclusive stating that there was a paucity of well-designed trials that could address the question adequately (Gravel, D'Angelo et al. 2013). However, some evidence suggests that prolonged or strict rest, while it continues to be common practice, may be counterproductive (Silverberg and Iverson 2013, Thomas, Apps et al. 2015). Rest within the first week is well established as a guiding principle for treating physicians. A paper in 2016 surveyed 572 physicians and reported that 97% recommended rest within the first week of injury (Rose, Fischer et al. 2016). However, when symptoms do not resolve after a few weeks, the guidelines and practices are less clear and less consistent. Preliminary evidence suggests that beginning subthreshold activity as part of a rehabilitation program may be beneficial (Grabowski, Wilson et al. 2016) but this approach is not standard practice. A retrospective chart review reported that, of 266 patients, only 25% of people were referred to PT and/or vestibular rehabilitation during the management of their protracted recovery after mTBI (Kostyun and Hafeez 2015). Another recent study reported that the median time from injury to PT visit was 60 days (Alsalaheen, Mucha et al. 2010). There is evidence for peripheral vestibular dysfunction after mTBI (Hoffer, Gottshall et al. 2004, Akin and Murnane 2011) as well as central sensory integration deficits from mTBI (Walker, Cifu et al. 2012), both of which could cause imbalance. A systematic review identified impaired balance after injury as one of the most prevalent and consistent indicators of mTBI, along with disorientation or confusion, slowed reaction time and impaired verbal learning and memory (Carney, Ghajar et al. 2014).

There is a clear gap in our clinical care guidelines after mTBI and it is unclear if initiating rehabilitation early would improve outcomes related to imbalance. The timing of physical therapy has been studied most extensively for orthopedic, stroke and vestibular impairments and there is a general consensus that earlier intervention is better

for conditions such as acute low back pain (Wand, Bird et al. 2004), dizziness (Whitney, Alghadir et al. 2016), post-surgery (Schaller, Anstey et al. 2016), and stroke rehabilitation (Musicco, Emberti et al. 2003). However, the message is less clear after mTBI since early activity may exacerbate symptoms and there is concern over Second Impact Syndrome (Rose, Fischer et al. 2016). Although rest is a well accepted recommendation acutely after injury, the rest period is not specified. Further, strict rest acutely after concussion may be less beneficial than a stepwise return to activity within days of injury (Thomas, Apps et al. 2015). It is thought that the brain can undergo plastic change throughout one's life and that there are critical periods during development and after injury in which neuroplasticity capabilities are highest (Nudo 2003). Experience–dependent plasticity during these phases may result in the largest behavioral changes (Wolf, Winstein et al. 2006, Kleim and Jones 2008, Holtmaat and Svoboda 2009). Conversely, maladaptive compensatory mechanisms may also develop after injury whereby avoidance of movements that provoke discomfort (i.e. dizziness or imbalance) may be inappropriate (Taub 1980, Shepard and Telian 1995). This notion of early intervention contradicts the 'prolonged rest' that many physicians adhere to in treating people with mTBI.

Measures of imbalance are subjective and are easily overlooked as a treatable deficit. The most frequently administered clinical balance test after mTBI is the Balance Error Scoring Scale (BESS) in which people are asked to stand in varying conditions (i.e. eyes closed on firm surface or foam surface) to challenge their postural stability. Errors, such as loss of balance, are counted subjectively by the clinician (Riemann and Guskiewicz 2000). Recent studies have reported that the BESS has a high degree of subjectivity and provides only limited, low-resolution information about the balance control system and does not provide a sensitive scale on which to judge progress or deficits (Finnoff, Peterson et al. 2009, Giza, Kutcher et al. 2013). Sub-optimal psychometric properties (sensitivity 34%–64% to detect mTBI) have also been reported for the BESS and are likely due to the subjectivity of the measurement (Finnoff, Peterson et al. 2009, Giza, Kutcher et al. 2013). We believe that such poor clinometric properties of this clinical test do not lend itself to timely referrals to physical therapy. Clinical balance tests with limited properties may lead to lower detection rates and make it difficult to detect those who might benefit from physical therapy. A more objective measure of balance may help identify people with impaired balance due to sensory deficits (i.e. vestibular) and/or central sensory motor integration deficits in which an early physical therapy may help recovery. Our work has provided evidence that instrumenting common balance tests with inertial sensors can better differentiate people after mTBI compared to standard subjective measures of balance (King, Horak et al. 2014) (See Preliminary Data).

Even with rehabilitation, recovery of balance in people with mTBI is challenging, particularly in people with central vestibular and sensory integration deficits (Pfaltz and Kamath 1970). In addition to addressing the timing of physical therapy intervention, this proposal addresses 2 other potential obstacles for successful rehabilitation after mTBI; 1) poor compliance and quality of performance of home exercise program (standard of care after mTBI for balance rehabilitation) and 2) lack of important feedback during training of balance and vestibular exercises on head and trunk movement during movement. In this proposal, we aim to improve home exercise program and improve training in the clinic; both using novel wearable sensor technology.

Home monitoring: Vestibular and balance rehabilitation after mTBI relies heavily on a home exercise program and repetition is essential for recovery (Shepard and Telian 1995). We recently published a paper showing that home exercise program is the least effective way to address balance deficits in people with Parkinson's disease compared to a group class or individualized physical therapy (King, Wilhelm et al. 2015). This finding was particularly true is if a person had common comorbidities such as depression or mild cognitive impairment, also commonly seen after mTBI. Despite this, a home exercise program remains an important part of care after mTBI and, in fact, all patients with mTBI in our rehabilitation clinic are prescribed a home exercise component to address imbalance and dizziness. The average time they are seen by physical therapy is only 1x/week. However, we believe that home exercise can be improved using wearable sensors to monitor compliance and performance at home.

The slow progress in balance rehabilitation may be partially due to an inability of people with mTBI to correctly perform the prescribed rehabilitation exercises on their own. There is evidence that people with vestibular pathology have impaired perception of body position such as head in relationship to trunk and may limit head velocity and head in relation to trunk to minimize symptoms (Borel, Harlay et al. 2002). After mTBI, participating in a home exercise program that emphasizes head movement may be particularly difficult to comply with and may explain slow or delayed recovery. Vestibular and balance rehabilitation relies on progressively increasing head movement amplitude and velocity during static and dynamic balance tasks while maintaining a stable trunk (Konrad, Tomlinson et al. 1992, Kang and Tusa 2013). Further, other comorbidities such as depression could limit compliance and determination to perform the home portion of rehabilitation.

Training in the physical therapy clinic: One of the most important components of motor learning is feedback of performance, yet this important feature is hard to implement objectively in balance rehabilitation. For example, orthopedic physical therapy focuses on objective measures of joint angles, peak torques and gait speed during task acquisition. Rehabilitation of balance deficits is more difficult to quantify and to provide feedback around a training task. Subtle movements, such as postural sway and head and trunk synchronicity are often not detected visually. Furthermore, people with mTBI show more deficits during complex mobility tasks, yet we do not objectively evaluate and provide feedback on complex tasks in the clinic. For example, an average individual turns over 800X/ day (Mancini, El-Gohary et al. 2015) and 35-45% of all steps during daily locomotion are not straight (Glaister, Bernatz et al. 2007). A stereotyped multi-segmental sequence of reorientation occurs during turning, whereby vision is realigned with the new direction of travel and closely followed by the head then trunk and pelvis (Authié, Hilt et al. 2015). The anticipatory lead of the head and “top-down” reorientation is necessary to maintain gaze stabilization in the new direction of movement (Akram, Frank et al. 2010). Yet, individuals with recent mTBI show more variable reorientation sequencing (Powers, Kalmar et al. 2014). Independent eye movement, head rotation, and trunk rotation, is important for everyday mobility to integrate visual, vestibular, and somatosensory information and may be impaired after mTBI. Even during straight ahead gait, the role of head stability is critical to maintain a stable visual field. Less independent oculomotor control has been associated with poorer balance performance in athletes with mTBI (Murray, Ambati et al. 2014). A recent study using Motion Analysis showed a lack of head and trunk synchronicity during gait on a treadmill in people with vestibular deficits and TBI (Sessoms, Gottshall et al. 2015) and such asynchronicity may lead to avoidance behavior and decreased quality of life, and delayed return to previous levels of function (Shepard and Telian 1995). We believe it is critical to evaluate and treat complex balance skills and to incorporate performance information objectively into training and rehabilitation.

Biofeedback is a clinical technique that provides physiologic information that would otherwise be unknown to patients and may improve outcomes after mTBI. Biofeedback complements the patients’ internal feedback (visual, auditory, and proprioceptive) and reinforces patients’ weaker or absent sensory signals. Different forms of biofeedback have successfully been used in laboratories for the treatment of gait abnormalities in patients with Parkinson's disease (McIntosh, Brown et al. 1997, Nieuwboer, Kwakkel et al. 2007, Horak, Wrisley et al. 2009), Multiple Sclerosis (Baram and Miller 2006, Baram and Miller 2007), Stroke (Glanz, Klawansky et al. 1997, Thikey, Grealy et al. 2012), Amputation (Lee, LIN et al. 2006), and Spinal Cord Injuries (Jensen, Barber et al. 2009). We have also shown significant benefits of practicing tandem gait with vibrotactile biofeedback in people with unilateral vestibular loss (Horak, Dozza et al. 2009) and auditory biofeedback to improve postural sway during standing in subjects with bilateral vestibular (Dozza, Chiari et al. 2006, Dozza, Wall Iii et al. 2007). Biofeedback has also been successfully used in the laboratory to reduce leg loading after total hip arthroplasty (Pataky, Rodriguez et al. 2009), increase knee motion symmetry after total knee arthroplasty (McClelland, Zeni Jr et al. 2012), and to modify gait and reduce knee joint loads (Dowling, Fisher et al. 2010). While electroencephalography biofeedback has been explored to rehabilitate cognition (Thornton and Carmody 2009) and others have described the potential of biofeedback to improve balance and gait in the mTBI population (Lawson and Rupert 2010, Collins, Markham et al. 2015, Mortimer, McGrath et al. 2015, Sessoms, Gottshall et al. 2015), we are unaware of any

study that has examined the use of biofeedback to improve the compliance and performance of prescribed rehabilitation exercises for mTBI.

There are no commercially available systems to provide the physical therapist and/or patient objective information on the quality of head movements during training of rehabilitation tasks that involve balance and walking. Despite evidence that people with vestibular deficits and TBI may have impaired perception of head movement (Borel, Harlay et al. 2002), we currently have no easy way to quantify or provide feedback during therapy on these important aspects during functional mobility. Computerized dynamic visual acuity testing is available to measure 1) changes in visual acuity at head velocities associated with the Vestibulo-Ocular Reflex (VOR) and 2) the maximum head velocity the patient can achieve while maintaining accurate vision during a gaze stabilization test (Herdman, Tusa et al. 1998). While this system provides a quantitative assessment of gaze stabilization with head movement, it is limited to stationary, in-clinic use. Since home exercise programs are an integral part of rehabilitation care after mTBI, a portable system for monitoring head movements and one that can assess head movement in walking conditions is needed. The ideal system would be wearable and portable for both clinic and home use and would combine biofeedback with monitoring capabilities. Our intention is to design and build a wireless biofeedback system to allow therapists to select among a variety of exercises that target balance and vestibular function. This system will (1) enable physical therapists to teach their patients to perform the exercises correctly, (2) monitor quality and rate of improvement in home exercise performance, and (3) enable patients to monitor their own progress and increase their adherence to home exercise regimen.

Relationship to other funded studies: Our group has extensive experience running clinical trials and studies related to gait, balance and rehabilitation in people with mTBI. This proposal is a natural continuation of previous funding. In 2012 we were awarded a pilot grant (Center for Translation of Rehabilitation Engineering Advances and Technology; King PI) to develop a protocol for instrumented balance testing which was tested on people with chronic post-concussion syndrome (King, Horak et al. 2014). From there, we moved the instrumented balance testing to onsite assessment at 6 local Universities (NIH; Oregon Clinical Translational Research Center (OCTRI) KL2 Award and National Institute of Health KL2TR000152; R21 NIH R21HD080398; King PI) to explore the usefulness of wearable sensors in acutely injured athletes and to determine trajectory of balance recovery after concussion. We enrolled 50 people with mTBI and 75 controls (results are under review). Most recently, we received funding from the DOD (King PI-W81XWH-15-1-0620) to investigate central sensorimotor integration and vestibular deficits in people with chronic non-resolving balance deficits after mTBI. With that funding we have developed new methodology to assess central sensorimotor integration (CSMI test) using a commercially available Neurocom platform and are currently executing that study. We will use the CSMI test in the proposed study as an impairment level outcome measure.

PRELIMINARY STUDIES

Pilot data for Aim I

The primary goal of Aim I is to determine the role timing plays in rehabilitation efficacy after mTBI. To accomplish this goal, we will randomize people into early physical therapy (within first two weeks of physician visit) or late physical therapy (standard of care; 8 weeks from first physician visit). We will use both recommended Common Data Elements (CDE) outcome measures alongside innovative objective measures to quantify balance control and change after rehabilitation. In preparation for this proposal, we have investigated current rehabilitation practice at our University and summarized our ongoing and published research demonstrating the value of objective balance and gait measures for mTBI.

Despite evidence of early intervention being a critical aspect of rehabilitation for many balance problems, people with mTBI are not being seen early by physical therapy. Our University has a comprehensive mTBI rehabilitation program that incorporates physical therapy recommendations from recent guidelines to include work on vestibular dysfunction, high-level balance dysfunction, attention and dual-task performance deficits (Weightman, Bolgla et al. 2010). However, even at our specialized mTBI clinic, the referral patterns for physical therapy are late and inconsistent. We randomly sampled 40 patients who were seen in OHSU Rehabilitation Center between October 2014 and September 2016. The average age of this population was 37.5 ±12 years. Figure 1 shows the average timeline for patients seeking care after mTBI. On average, people were seen by the primary care physician on average 10 days after injury. In this group, 80% had complaints of imbalance and/or dizziness at their first physician office visit and yet the average time to see physical therapy was on average 61 days later.

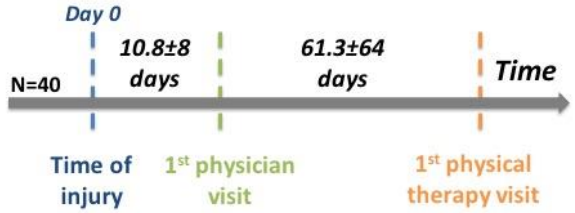
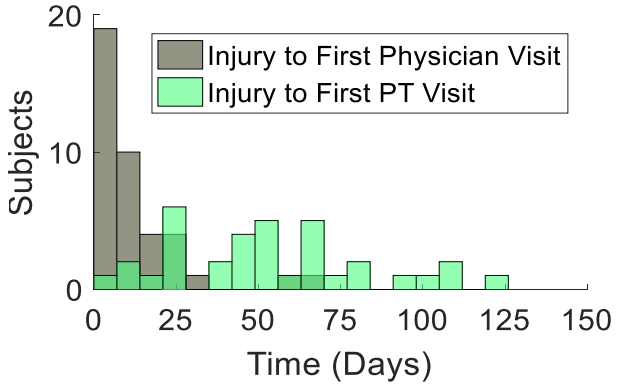


Figure 1. *Average time from injury to first visit with a physician and time from first physician visit to first visit with a physical therapist*

The lack of guidelines after the initial 'rest period' leads to inconsistent rehabilitation care. In the same 40 mTBI patients, we found that, unlike the initial physician visit, the timing for the initial physical therapy visit was extremely varied and unrelated to patients' symptoms (r = -0.049, p = 0.32). Figure 2 compares the right-skewed distribution of the time from injury to the first physician visit, with the delayed and variable distribution of the time from injury to the first physical therapy visit. The people who were seen early in physical therapy were the small percentage of people who had a direct referral from the OHSU Concussion Clinic. Similarly, we found that a random sampling of 20 Veterans with mTBI seen at our Portland VA in Sept 2016, 60% (12/20) had subjective complaints of imbalance and/or dizziness and the average length of time to be seen by physical therapy for the first visit for Veterans was approximately 48 days from that physician visit. However, this group represented a more chronic population and had likely been seen outside the VA prior to the first physician visit at the Portland VA.



igure 2. *Histograms showing distribution of time from injury until e first physician visit and until the first physical therapy visit.*

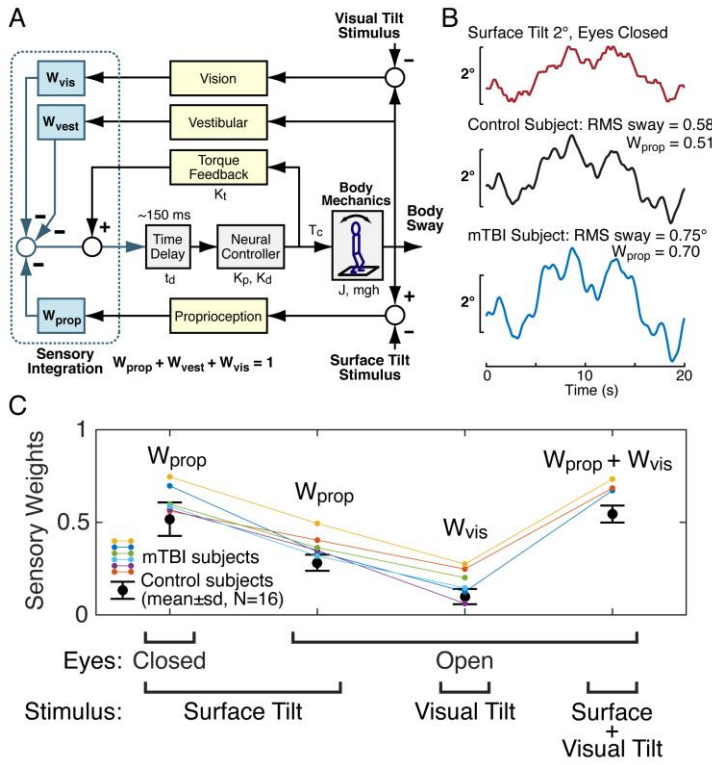


Figure 3*. Central Sensorimotor Integration (CSMI) test. A. Balance control model used to interpret experimental body sway evoked by surface and/or visual tilt stimuli. B. Example results showing mean CoM body sway across 11 stimulus cycles evoked in a control subject and an mTBI subject by a surface tilt stimulus during eyes closed stance. C. Sensory weighting factors from control subjects (mean±sd) and individual mTBI subjects from 4 test conditions.*

We have data indicating that mTBI subjects with chronic balance complaints demonstrate abnormal sensorimotor weighting strategies for balance control. We tested 6 subjects with

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chronic mTBI and 16 healthy control subjects using a novel Central Sensorimotor Integration (CSMI) test. This data was obtained from currently funded DOD project # W81XWH-15-1-0620. The CSMI test evokes body sway in response to continuously applied pseudorandom wide-bandwidth, low-amplitude rotations of the stance surface and/or the visual scene viewed by the subject (Fig. 3B). The Center of Mass sway responses are interpreted with reference to a mathematical model (Fig. 3A) of the balance control system by adjusting model parameters to optimally account for the experimentally observed body sway. The identified model parameters are physiologically meaningful and include 'sensory weights', which quantify the proportional contributions of sensory systems to balance control, neural controller parameters, which quantify the amount of corrective action (ankle torque) generated to control balance, and the time delay in initiating corrective actions (Peterka 2002). Four of 6 chronic mTBI subjects tested to date showed abnormalities in sensory weighting scores on at least 1 of 4 test conditions indicating increased abnormal reliance on proprioception and/or vision for balance control (Fig. 3C). Additionally, 4 of the 6 mTBI subjects also showed reduced corrective action in one or more test conditions (not shown). Abnormally high sensory weights in a given test condition correspond to a greater disruption of balance in response to balance disturbances and balance is further disrupted when corrective actions are weaker than normal.

Our preliminary results demonstrate that major sensorimotor integration deficits are present in many mTBI subjects with chronic balance complaints and that CSMI testing can characterize these deficits in individual subjects. The identified abnormal balance control (i.e. decreased weighting on vestibular information) strategies may be responsive to rehabilitation. Therefore, CSMI testing has the potential to track the effectiveness of rehabilitation in restoring normal balance control strategies. It is currently unknown if the abnormal strategies observed in chronic mTBI are due to maladaptive compensation that may be avoided with early intervention.
We have recently demonstrated that instrumented tests of balance and gait are more senstive to mTBI than the clinical BESS. Balance impairment is most commonly assessed with a subjective question on imbalance (Guskiewicz, Register-Mihalik et al. 2013) and, sometimes, a clinical assessment such as the BESS (Shumway-Cook and Horak 1986, Riemann and Guskiewicz 2000). The low sensitivity (< 64%) (Finnoff, Peterson et al. 2009) of the BESS may contribute to inconsistent referrals. We have shown that wearing an inertial sensor on the waist while performing the BESS significantly improves its sensitivity to mild impairments (Mancini, Salarian et al. 2012, King, Horak et al. 2014). Specifically, mediolateral (ML) root-mean-squared (RMS) acceleration during double stance with eyes closed was more sensitive to classifying mTBI than clinical error counts when comparing the areas under the receiver operator characteristic curves (ROC) (AUC = 0.74 vs, 0.61) from 128 college athletes; 50 with acute mTBI at approximately 2 days post-injury (Fig. 4). While wearable sensor data is not currently used for balance assessment in the clinic, we have found it feasible for a trained assistant to perform instrumented tests of static and dynamic balance in patients with mTBI presenting to our clinic. Wearable sensor technology is commercially available and could readily be adopted for use in rehabilitation of balance disorders in mTBI patients presenting with imbalance. In this proposal we will develop and refine test protocols that can be used specifically for mTBI. Increasing the sensitivity of clinical balance testing may improve the consistency of referrals for physical therapy

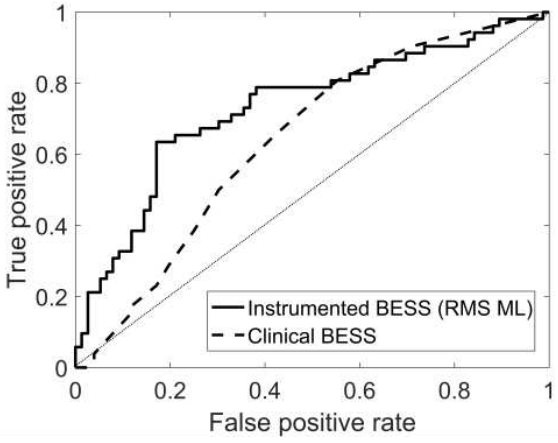


Figure 4. *ROC curves for Instrumented and non-instrumented BESS*

Pilot data for Aim II

The primary goal of Aim II is to improve the compliance and quality of the rehabilitation exercises after mTBI by monitoring and reporting the performance of a home exercise program while using wearable sensors during self-directed exercise at home. Here, we summarize preliminary data showing that head control is abnormal after mTBI which presents a challenge to consistently high quality exercises that target impairment.

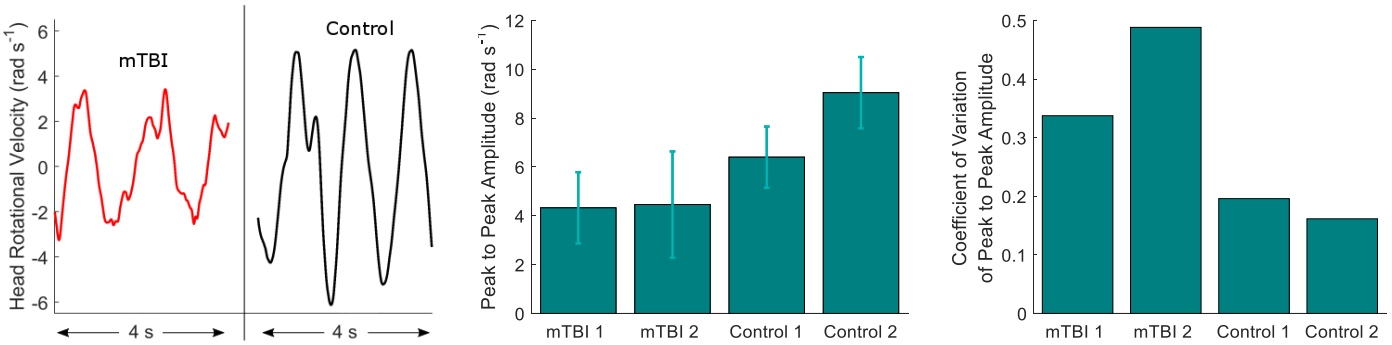


Figure 5. *Head rotational velocity of participants with complex mTBI and controls when instructed to rotate their head left and right while standing on a foam surface with eyes closed. Left shows raw data from gyroscope on the head and right shows means ± SD*

We have preliminary data showing that individuals with mTBI do not perform balance rehabilitation exercises in the same way as controls, despite similar instructions and ability to perform the task while working with the physical therapist. In our Rehabilitation Clinic, a physical therapist instructed 2 people with mTBI and 2 control subjects to perform a series of 3 common balance and vestibular exercises: gaze stabilization while standing, walking with head turns and quiet stance on foam with head turns. After all 4 people had learned the exercises, we later tested them, without coaching and without feedback, to perform the exercises, as they were meant to do at home. All participants wore a head-mounted Opal inertial sensor while performing the exercises. The two participants with mTBI had smaller peak-to-peak amplitudes and greater variability of rotational head velocity while performing the task compared to the control subjects (Fig. 5).

Head turns while walking may be a good indicator for recovery after mTBI. We have data on 25 young athletes with a sport-related mTBI (2 days post-injury) and 25 matched healthy controls. Adapting the protocol for the Dynamic Gait Index (DGI), participants were asked to turn their head side to side while walking. Using an Opal inertial sensor affixed to the head with an elastic headband, we found that individuals with acute mTBI rotated their heads with less velocity (3.7 rad/s versus 4.3 rad/s; p = 0.07) and had smaller head movements (0.91 rad versus 1.0 rad; p = 0.06) during this common rehabilitation and everyday task at the initial assessment (Fig 6). Following the resolution of their symptoms, participants improved and executed the head turns at a similar angular velocity compared to controls. These preliminary results suggest symptomatic individuals with mild mTBI preferentially choose slower rotational head velocities and can improve over time. We similarly expect participants in Aim II to be capable of rotating their heads faster than they preferentially choose. We expect they are capable of increasing the speed and amplitude of head rotation when quantitative feedback is provided to the physical therapist about their performance at home. The individuals presented in Fig 6 were very mild and all returned to their sport without the need for a physician visit or rehabilitation. In contrast, we expect the participants in our proposed study will be more impaired since they are seeking out physician evaluation of their symptoms.

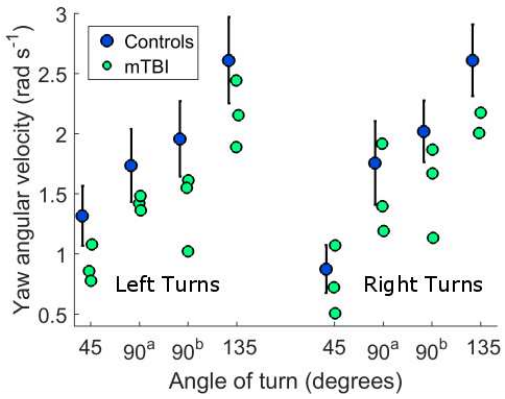


Figure 7. *Angular velocity of the head during left and right turns of various angles. Controls shown with mean ± SD. The individuals with mTBI (green) exhibited consistently less peak angular velocity of the head despite similar overall gait speed compared to controls. Two 90° turns were examined (King et al., pilot data)*

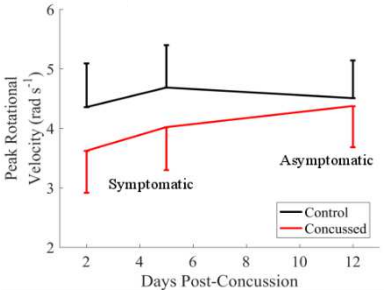


Figure 6. *Peak rotational velocities of the head during walking with head turns. When symptomatic, concussed athletes had slower angular velocities than controls. Peak rotational velocities increased to normal levels once symptoms resolved. (King et al., presented at Society for Neuroscience, 2016)*

Head coordination is altered during functional tasks of everyday living, such as walking and turning. We have preliminary data from 3 individuals with chronic mTBI and ongoing complaints of imbalance and 17 healthy controls walking around a marked course containing left and right turns of 45, 90, and 135 degrees (Data

obtained from currently funded DOD project # W81XWH-15-1-0620). While turning, the subjects with mTBI consistently rotated their heads slower than control subjects (Fig. 7) despite similar lumbar rotational velocities and overall speed of walking during a complex walking (navigation) task as quantified by inertial sensors affixed on the head, sternum, and lumbar area. These preliminary results suggest that mTBI influences the reorientation of the head during common ambulatory activities such as turning which could explain complaints of altered balance during complex everyday activities.

Combined, these results suggest that symptomatic people with mTBI show abnormal head movements during prescribed head turning tasks as well as in everyday mobility tasks such as walking in complex environments. Further, they show an inability to perform head exercises directed at increasing head movement during various activities suggesting insufficient vestibular recovery and poor ability to perform a home exercise program. We propose that recovery may be improved by objectively monitoring the quality of prescribed balance exercises. In Aim II, we expect that increasing the angular velocity and amplitude of the head movement through home monitoring of prescribed balance and vestibular rehabilitation exercises will improve functional mobility during complex locomotor tasks such as walking and turning.

Pilot data for Aim III

The primary goal of Aim III is to develop a novel sensor-based biofeedback system to provide real-time information to the physical therapist regarding head (amplitude and velocity) and trunk stability during the training phase of rehabilitation. To accomplish this goal, we will work closely with 1) APDM (a local small company that develops and commercializes inertial sensor systems to quantify human movement), 2) physical therapists from local practices (OHSU Outpatient Clinic, the Portland VA Rehabilitation Center and community practices) and 3) mTBI patients to develop clinically-useful tools for balance rehabilitation after mTBI.

APDM has experience in adapting wearable sensors for real time feedback on gait (i.e. step length and arm swing). APDM, together with our Balance Disorders Laboratory, has a current grant to support developing a biofeedback system for gait training (Phase I SBIR Grant R43AG056012; NIA). For this project, patients wear sensors on the feet, wrists and trunk while walking using a non-portable, laptop-based, biofeedback prototype (Fig. 8). APDM has developed and validated various innovative algorithms that use wearable inertial sensors to provide objective measures of gait and balance in patients with movement disorders. These algorithms have been developed to automatically collect and then analyze data offline. The algorithms use inertial sensors attached to the feet and lumbar segment to identify temporal events of the gait cycle including loading response, mid/terminal stance, pre-swing, and swing phases. In addition to gait events, the algorithm characterizes gait and dynamic balance with more than 20 spatial and temporal metrics. During Aim III of this project, we will develop and validate new algorithms to characterize head and trunk kinematics during movement without a laptop (Fig. 8).

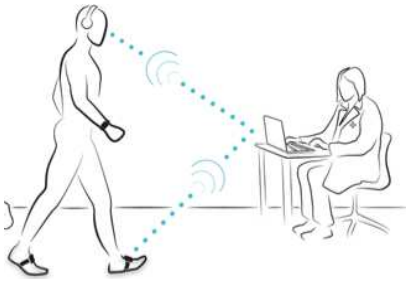


Figure 8. *Current APDM feedback prototype using a laptop with auditory feedback.*

4. Study Design

This study is an interventional study on people with mTBI with two nested arms. Arm 1 examines whether initiating interventional physical therapy earlier improves outcomes compared to the standard of care. Arm 2 is nested within Arm 1, and examines whether added information about the quality of prescribed exercises performed at home and obtained from inertial sensors further improves outcomes. A third arm of the study is to develop a system capable of delivering real-time feedback on the quality of prescribed exercises to improve outcomes.

5. Study Population

The proposed interventional study (Aims I and II) will involve 160 human participants for intervention, all of whom who have sustained a mild traumatic brain injury (mTBI) and have complex, multisensory system impairment and complaints of imbalance and 10 subjects for validation. Aim III will involve a total of 80 human participants: 25 subjects who have sustained an mTBI with balance and/or vestibular deficits and 50 healthy control subjects and 5 physical therapists. The Oregon Health & Science University (OHSU) Concussion Management Clinic currently sees 1,200 new concussion patients per year and the primary care clinics at OHSU see approximately 3,000 mTBI patients per year.

a. Number of Subjects

The proposed interventional study (Aims I and II) will involve 160 human participants for intervention, all of whom who have sustained a mild traumatic brain injury (mTBI) and have complex, multisensory system impairment and complaints of imbalance and 10 mTBI subjects for validation. Aim III will involve a total of 80 human participants: 25 subjects who have sustained an mTBI with balance and/or vestibular deficits and 50 healthy control subjects and 5 physical therapists. A subset of (approx. 100) healthy adults will be tested to validate and provide normative data with the updated testing protocol.

b. Inclusion and Exclusion Criteria

Inclusion criteria for Aims I and II: Participants may be either Veterans or non-Veterans and must: 1) have a diagnosis of mTBI based upon VA/DoD criteria (Control and Prevention 2014, Defense 2015), 2) be between 18-60 years-old, 3) be within the acute or post-acute stage (< 12 weeks post-concussion) according to the VA/DoD clinical practice guidelines (Group 2016), 4) be able and willing to come to OHSU for physical therapy and perform home exercise program daily for 6 weeks, 5) have no or minimal cognitive impairment; a score between 0 and 9 on the Short Blessed test, and 6) have a SCAT sub score of 1 or higher on balance, dizziness, nausea, headache, or vision AND a minimum total score of 15.

Inclusion criteria for Aim III: The physical therapists we will recruit to test and provide feedback on the system will 1) have experience in neurologic rehabilitation and 2) be naïve to the APDM mobility Lab system. The patients with mTBI may be either Veterans or non-Veterans and must: 1) have a diagnosis of mTBI based upon VA/DoD criteria (Control and Prevention 2014, Defense 2015), 2) have continued complaints of imbalance, 3) be any time point out since mTBI, 4) be able and willing to test the system and provide structured feedback. The control subjects we will include may be either Veterans or non-Veterans and must be between the ages of 18-60 years-old.

Exclusion criteria for all categories: Participants must NOT: 1) have had or currently have any other injury, medical, or neurological illness that could potentially explain balance deficits (e.g., CNS disease, stroke, greater than mild TBI, lower extremity amputation), 2) meet criteria for moderate to severe substance-use disorder within the past month, as defined by DSM-V, 3) display behavior that would significantly interfere with validity of data collection or safety during study, 4) be in significant pain during the evaluation (5/10 by patient subjective report), 5) be a pregnant female (balance considerations), 6) have past history of peripheral vestibular pathology or ocular motor deficits, 7) be unable to abstain for 24 hours in advance of testing in the use medications that might impair their balance, and 8) any condition or behavior that would interfere with comprehending the consent form and/or following directions.

c. Vulnerable Populations

No vulnerable populations (pregnant women, fetuses, neonates, children, or prisoners) will be included in this study.

d. Setting

All aims will take place at OHSU and at the VAPORHCS and recruitment may also occur at community clinics around Portland. VA and OHSU activities: All data collected at the VA will be collected at the National Center for Rehabilitative Auditory Research by a VA investigator including an audiologist and/or a research assistant. OHSU data will be collected at the Balance Disorders Laboratory, School of Nursing and Vestibular clinic by an OHSU investigator including an audiologist and/or a research assistant. All OHSU work will be done on OHSU time, under the OHSU portion of the approved protocol. The rehabilitation intervention will be done in the Balance Disorders Laboratory.

Adaptation during COVID- 19 restrictions: During this time we will implement virtual visits or over the phone visits instead of in-person. This includes recruitment, screening, and all modified testing and rehabilitation sessions. No VA participants or VA data will be collected during this time.

e. Recruitment Methods

Aim I & II: Participants will be recruited from 3 primary sources; 1) OHSU Family Medicine clinic, 2) OHSU Concussion Clinics, and 3) community clinics. Subjects will be screened for Aim I & II through medical records by RA's and MA's for upcoming visits to clinics. Subjects interested in participating will receive a phone screening to determine basic eligibility. After passing initial eligibility screening they will be invited to come in for consent and comprehensive medical history screening. This study will use an Epic BestPractice Advisory (BPA) to recruit potential participants. Researchers will work with ITG to identify potential participants based upon the above eligibility criteria. Researchers will provide the list of inclusion and exclusion criteria and ITG will build the BPA in Epic based on these criteria. During a clinical interaction in Epic, if a patient meets the criteria built into the BPA, an Epic In Basket message will be sent to the study contact containing a link to the patient's medical record. Study staff will contact identified patients to determine if they are interested in participating in the study. Once the BPA has identified a patient, it will not fire again for that same patient. *Recruitment methods may include websites such as the OHSU Study Participants Opportunities page; newsletters; advertisements; flyers and other printed study materials; social media; institutional communication and events; presentations; and outreach at community events.*

Prep to Research:

Epic records for patients identified through the Epic BPA will be queried for eligibility and will be contacted by study personnel about the study. ResearchMatch.org will be used as one of the recruitment tools for this research study/protocol. ResearchMatch Volunteers will be contacted through ResearchMatch.org. Included with this submissions is a study recruitment message that will be sent to potential study volunteers."Aim III: Participants (physical therapists, mTBI patients and control subjects) will be recruited from 4 primary sources; 1) OHSU Rehabilitation Center 2) VAPORHCS (Rehabilitation and NCRAR Departments) 3) local outpatient physical therapy clinics in Portland and 4) the community (non-VA clinics). Physical therapists will be recruited from OHSU, the VA and the community. Once physical therapists from OHSU, the VA and the greater community have been recruited, they will be the ones to identify the potential mTBI patients for this Aim. To do this they will ask the patient if they are interested in learning more about participating in a 1-hour session to try the biofeedback sensor system. If the subject is interested, the physical therapist will give the subject the research assistants contact information and the subject will directly contact the research assistants. For all Aims, once potential subjects have been identified, research assistants will be responsible for the rest of the recruitment process, including further explanation of study details, screening and obtaining informed consent. The research assistant will ask prescreening questions on the phone to determine if the person is an appropriate candidate for the study. If the person meets all inclusion and exclusion criteria, the research assistant will schedule the candidate for the initial 1-hour appointment with the physical therapist and this will occur at OHSU in our Balance Disorders Laboratory. This 1-hour session will occur outside of the PTs regular clinical hours. Healthy controls will be recruited from the community and OHSU, using posted flyers. These flyers will be posted at community centers, fitness centers, and around the OHSU area. No flyers will be posted at the VAPORHCS.

Aim I & II: subjects will be compensated on a graduated scale to encourage retention. The first visit consisting of vestibular and oculomotor tests will be compensated $40. The second session, consisting of the baseline mobility and further oculomotor tests, will be compensated $60. The post-therapy mobility and oculomotor session will be compensated $80, and the retention mobility and oculomotor session will be compensated $100. Participants will be compensated $10 dollars per visit for each rehabilitation session. There is a maximum of 5 testing sessions, and approximately eight rehabilitation sessions. Subjects randomized into the standard of care intervention will be tested for mobility and oculomotor at both baseline and prior to starting their physical therapy. Therefore, the standard of care group will have an additional session for which they will be compensated $60. If a subject does not complete all parts of a session they will be compensated a prorated amount for their time based on the compensation for that session. People who complete all sessions for Aim I & II will be compensated $275 if they are randomized into the early intervention group, or $335 is they are randomized into the standard of care group.

Adaptation during COVID- 19 restrictions: Participants will be compensated $10 for rehab, $20 for modified Day 1, and $30 for modified follow up testings. People that complete all modified sessions will be compensated up to $190.

Home monitoring: Participants will be compensated $10/per day for approx. 7 days= $70. This will take place at two different time points during the study for a maximum compensation of $140.

Aim III: Physical Therapists will be compensated $100 for their time in training as well as testing. Both people with mTBI and healthy controls will be compensated $25 for the 60-minute long session

f. Consent Process

After a phone screening for inclusion/exclusion criteria by our research assistants, subjects who come in for testing will be presented with the appropriate consent form (either for Aims I & II, or for Aim III) that explains the nature of the study and the possible risks and benefits of the experiment, as well as Health Insurance Portability and Accountability Act (HIPAA) privacy information. The consent form also informs the subjects that they may withdraw from the study at any time without penalty. Subjects will be given privacy and ample opportunity to read, ask questions, and when satisfied document their consent to participate by signing the informed consent form. Consenting will take place at the subjects' respected location depending on their status as a Veteran or civilian. We will obtain a joint OHSU/ VAPORHCS Institution Review Board (IRB) to facilitate the process between sites.

Adaptation during COVID- 19 restrictions: We will provide consents to eligible participants through the Docu-Sign System. A link with the OHSU informed consent form (ICF), OHSU repository consent, and OHSU HIPAA authorization will be sent to the participant's preferred email address. A study team member will call the participant and discuss study details within the forms just like they would in-person. The study team member obtaining consent will be able to answer any questions the participant may have during this time. After the participant has signed all forms the person obtaining consent will also be sent a Docu-Sign link to sign as well. Once both parties have signed the documents the study coordinator will receive an email and will save these documents to a secure OHSU server. The participant will also receive a copy of the signed documents.

Mental Capacity:

Subjects suffering from mTBI may have minimal cognitive impairment but must be able to follow instructions and comprehend the consent form. Control subjects will be excluded if they are cognitively impaired.

Ongoing Consent:
Due to the length of this study, ongoing consent will not be considered for individuals participating.

Consent for individuals with Legal Authorized Representative (LAR):
Subjects with an LAR must be meet all inclusion criteria to participate in the research study. If all inclusion criteria are met the Legal Representative must complete an IRB approved 'Application & Certification for Waiver or Alteration of the HIPPA Authorization requirement' prior to participation in the study. This study will follow all rules and regulations of Title 10 United States Code Section 980 (10 USC 980).

6. Procedures Involved

Aim I & II

We will ask subjects their preferred contact method for appointment reminders (email, text message, or phone call). We will send participants IRB approved text/email templates for each appointment dependent on where their testing location is (VA or OHSU).

All testing visits will take approximately 3-4 hours and will take place at either OHSU or at the Portland VA (NCRAR). During the first two initial testing sessions over two days, participants will complete questionnaires to help identify how they perceive their problems, as well as undergo clinical tests of vestibular function and balance and gait. We will place five small (Apple Watch size) motion sensors on their waist, feet, trunk and head to measure balance and gait, and then will use a Neurocom platform to measure balance during a variety of sensory conditions. The platform moves and the participant stands as still as they can. They will be secured in a harness to eliminate the chance of falling. We will then have you perform several balance and gait assessments such as standing on one leg, tandem stance and feet together as well as walking tests such as continuously walking for approximately two minutes. If rehabilitation does not begin immediately, there will have one additional balance and gait testing session just prior to beginning rehabilitation. The two follow up testing sessions after the conclusion of rehabilitation will include the balance and gait testing but not the vestibular testing. The first follow up session will occur immediately after the 6 weeks of rehabilitation and the second follow up session will be an additional 6 months later.

Vestibular and cognitive testing session:
The vestibular and cognitive testing session will involve a standard clinical battery of vestibular and oculomotor tests. All vestibular testing will be performed by an audiologist. Vestibular testing is a part of standard training of audiologists and testing as described here will be performed by a practitioner with a particular specialization and experience in vestibular testing. These tests will include:

Hearing Tests:
Your ears will be examined with an ear light to check for wax, substances or other conditions that might interfere with the tests to be conducted. Next a soft ear-tip will be placed in your ear canal opening and you will sit quietly while small changes in ear canal pressure are made. You will then be asked to listen very carefully and respond to tones of different pitches and loudness levels. These tests will take approximately 15 minutes to complete.

Oculomotor, positional and other vestibular tests:
Some vestibular tests require you to wear electrodes on your neck and face and listen to relatively loud sounds for short amounts of time while contracting your neck or eye muscles. For the other vestibular tests you will wear video eye goggles that track your eye movements either while you are seated in an upright chair that rotates from left to right or while being positioned laying down on an exam table. During the laying down positioning tests you will guided to move from sitting to laying down while the audiologist monitors your eye movements with the video goggles. For testing in the chair, you will be in a lightproof booth wearing video

goggles and first asked to follow a red dot as it moves in different ways. You will wear a seatbelt and be provided with a headset so you can communicate with the examiner outside the booth. The final chair tests involve it moving back and forth at different speeds while the examiner monitors your eye movements. Together these tests will take approximately an hour and a half to complete.

Cognitive Testing:
Participant will complete the Automated Neuropsychological Assessment Metric test, a computerized neurocognitive test. This test will take about 40 minutes to complete.

Mobility and Coordination testing session:
The following tests and procedures will be performed a maximum of 4 times, depending on which physical therapy group participants were randomized into. Throughout this session, participants will wear 5 inertial sensors: 2 at the feet, 1 on the waist, 1 on the trunk, and 1 on the head to record the movements of each body segment. The sensors record accelerations, angular velocities, and orientation data and wirelessly transmit these data to a computer located across the room. No PHI / PII or identifiable data is included in this transmission.

Clinical and dynamic measures of balance, mobility and coordination: Participants will perform the Balance Error Scoring System consisting of 30 seconds of standing quietly in various conditions. They will also perform the mini-BEST, a standard clinical test of mobility that measures different elements of balance such as walking and going from sit to stand. They will also complete a complex turning task that involves motions similar to everyday movements around a home, where they will perform several walking turns in order to navigate a marked path multiple times. The time taken to complete the course will be recorded, and inertial sensors will record body movement. Eye tracking glasses will be worn and record the motion of the eyes during turning. Additionally, a 2-minute walk test will be performed at 1) a comfortable pace, 2) a comfortable pace while performing a secondary cognitive task. Clinical and instrumented assessment will occur simultaneously using a stopwatch and the inertial sensors. Participants will also wear eye tracking glasses to monitor the stability of their vision with respect to body movements. These tests will take approximately one and a half hours.

Oculomotor function and coordination: The coordination between participant's eyes and head will be assessed using a clinical assessment of vestibular and oculomotor function (Vestibular/Ocular-Motor Screening for Concussion – VOMS). Participants will wear the inertial sensors described above and the eye tracking glasses described above and then be asked to follow the researcher's finger in various configurations. Your vision will be screened using eye charts to test how clear letters are on a chart while seated and while moving your head. The researcher will ask then to report symptoms after each test. These tests will take approximately 15 minutes to complete.

Central Sensorimotor Integration (CSMI) Testing: Participants will be tested on a modified Research NeuroCom platform where they will stand on a force plate to record postural sway. The surface and / or visual surround will move while the participant is instructed to maintain their balance. Participants will wear a safety harness attached above to prevent a fall in case a loss of balance occurs. Participants will complete several trials of different perturbations (e.g., visual surround moving, platform moving, both moving). This test will take approximately 40 minutes to complete.

Questionnaires: These tests help to identify how participants perceive their problems.

Short Blessed Test (SBT): This questionnaire takes approximately 5 minutes and evaluates basic cognition and memory.

PROMIS Item Bank v1.0 (Satisfaction with Participation in Social Roles – Short Form 4a): This questionnaire asks four questions related to how satisfied they are with social roles in the past 7 days. It takes approximately 2 minutes and will be given at the same time as the SCAT-2.

IPAQ (International Physical Activity Questionnaire- Short Form): This questionnaire takes approximately 5 minutes and asks intensity and type of physical activity performed in the last 7 days.

Dizziness Handicap Inventory (DHI): This questionnaire takes approximately 10 minutes and asks if participants become dizzy while performing various tasks.

PTSD Checklist (military or civilian version depending on service): This questionnaire takes approximately 10 minutes and is a list of problems and complaints some people have in response to stressful life experiences.

Sports Concussion Assessment Tool – 2 (SCAT-2): This questionnaire and balance screen takes approximately 10 minutes and asks people to rate 22 different symptoms on a scale between zero and six. This symptom questionnaire will be administered weekly by survey (REDcap) or by telephone, depending on the participant preference.

Neurobehavioral Symptom Inventory (NSI): This questionnaire takes approximately 10 minutes and goes through commons symptoms after traumatic brain injury (such as nausea and blurred vision) and asks them to rate symptoms.

Insomnia Severity Index (ISI): This questionnaire quantifies a participant's difficulties sleeping in the last two weeks on a scale of 0-4. It takes approximately five minutes.

Headache Impact Test- 6 (HIT-6): This questionnaire measures one's ability to function in everyone life (work, school, home and social situations). This questionnaire takes five minutes.

Quality of Life After Brain Injury (QOLIBRI): This questionnaire takes approximately 10 minutes and will ask them to rate your quality of life before and after concussion.

Concussion Symptom Subtype Inventory (CSSI): This questionnaire takes approximately 10 minutes and asks you to rate if you have had specific symptoms within eight categories at two points in time – before your injury and now.

Patients Global Impression of Change (PGIC): This single questionnaire takes approximately 1 minute and will ask people to rate how they perceive their health has changed over the course of treatment on a scale of 1-7.

Home monitoring: A subset of participants will be given an inertial sensor to wear at home for a period of time (i.e. 7 days) to follow their activity recovery at home.

Adaptation during COVID- 19 restrictions: Modified procedures during this time will be for study team members to ask questionnaires (listed above) over the phone or through a virtual visit. Participants will be emailed a PDF of the questionnaires for them to review while the study team member asks them to subjectively rate their symptoms.

Intervention: After participants are enrolled in the study, they will be randomly assigned to begin physical therapy immediately (approximately 2 weeks after their physician appointment) or within the standard of care timeline (approximately 8 weeks after their physician appointment). This randomization will be found on a pre-assigned list that was generated prior to their enrollment. This randomization will be performed in RedCap by a

statistician using the Randomization Module to ensure half the participants receive the early intervention and half receive the standard of care timeline. Rehabilitation will last for 6 weeks with approximately one physical therapy session per week. During these sessions, the participant will be evaluated by the physical therapist and will perform exercises around commonly impaired areas such as balance performance, head movement, and aerobic exercise capability. They will be expected to do a home exercise program that is tailored to their ability level and you will either do this home portion as it is commonly prescribed or while using a wearable sensor to track head and trunk movements. They will be progressed in their rehabilitation program according to standard practice and by ability level. See appendix for specific details of intervention.

Functional Near Infrared Spectroscopy:

Functional Near Infrared Spectroscopy (fNIRS) is a noninvasive, mobile brain imaging modality that allows for reliable measures of cortical activity. Prefrontal cortex activity data will be collected on a subset of participants using a wireless portable, continuous-wave, functional 8-channel fNIRS system (OctaMon, Artinis Medical system) on the first and last rehabilitation session when performing aerobic exercise on the treadmill (Figure 9).

Figure 9. fNIRS measurements during rehabilitation

Adaptation during COVID- 19 restrictions: A study team member will send or deliver the wearable sensor technology to the subject's home. No physical contact will occur with patient. The physical therapist will do all rehabilitation intervention through a virtual visit. The home exercise program will be tailored to their ability and level.

Post testing: After the conclusion of physical therapy, subjects will be retested two times on the gait and balance testing but not the vestibular testing. The posttest session will occur after the 6 weeks of physical therapy. The follow-up session will be an additional 6 months later and will encompass the same testing protocol as the posttest session.

Home Monitoring:

Participants may be sent home with wearable sensors at pre-physical and post-physical therapy time points and wear the sensors for approx. 1 week. The wearable sensors will be worn for a minimum of 8 hours each day and collect the participant's activity and mobility metrics.

Videotaping: Testing session may be videotaped for use in data checking and educational purposes. We will not videotape if the participant requests not to be videotaped. It is not a requirement of the study. We will use the photographs and videos in research publications and educational materials, in these cases we will use a black box over the participants face to hide their identity.

Aim III

Physical therapists will be trained to use the biofeedback sensor system and will be asked to try the system and provide feedback to the researchers and company (APDM). They will also be asked to evaluate the system with 5 of their patients who have balance deficits and mTBI. Specifically, they will use the device to provide feedback during 3 specific vestibular exercises: gaze stabilization (head turns), walking with head turns and standing on foam with eyes closed and turning the head. Feedback will be either auditory or visual from the motion of the head and/or trunk. People with mTBI will be asked to try the biofeedback system and provide feedback to the researchers and company (APDM). People without mTBI will be asked to perform specified exercises that require head movements during standard balance and vestibular exercises in order to obtain normative values

to incorporate into the patient report forms. All of these sessions will occur at OHSU in the Balance Disorders Laboratory.

Questionnaires:
Health Screening Questionnaire: This questionnaire will take approximately 15 minutes to complete, containing questions about participant age, sex, race/ethnicity, and a comprehensive look at health history and symptoms.

mTBI (concussion) Screening Questionnaire: This questionnaire will take approximately 15 minutes to complete and contains questions about injury, severity, treatment and history to determine eligibility.

Physical Therapists Questionnaires:
System Usability Questionnaire: This questionnaire takes approximately 5 minutes and ask them to rate the APDM Mobility Lab system for ease of use and user friendliness.

We will ask Physical Therapists about their general practice and experience.

7. Data and Specimens

a. Handling of Data and Specimens
Data on gait, balance, eye movements, vestibular and oculomotor function, and questionnaires will be collected and stored on our secure OHSU database. All data will be entered by research personnel and stored indefinitely.

b. Sharing of Results with Subjects
The results generated in this study are experimental in nature and will not be shared with study subjects.

c. Data and Specimen Banking
Laboratory Evaluations: Not applicable. This study does not propose to collect or store human specimens.

Data will be de-identified with a unique subject ID that on the PI and RA will be able to link the ID to the person. Subject information and study data will be stored behind a locked office in a locked cabinet at OHSU (if paper) or behind a secure Oregon Health & Science University (OHSU) firewall on network drives requiring password authentication (if electronic). If being stored at the VA, it will be kept on the secure VAPORHCS network folder (King17370) or in locked cabinets in locked office P5F-153 bldg 104 (if paper). Data will be stored at OHSU in our secure database and may be used for future research. We will also ask permission from our subjects to be maintain their data in our Balance Disorders Laboratory repository (eIRB# 7797).

As required by the DOD, we will upload de-identified data to Federal Interagency Traumatic Brain Injury Research Informatics System (FITBIR) quarterly. The data will have no PHI uploaded and only quantitative data will be uploaded.

8. Data Analysis

Analysis of oculomotor data: We will use eye tracking along with inertial sensors on the head and trunk to examine how well the subjects is able to maintain a stable gaze, particularly in the horizontal and vertical VOR conditions, by examining average eye velocity throughout the condition. Secondary measures will be the cross-covariance between eye velocity and head angular velocity.

Analysis of postural sway data: Postural sway will be automatically quantified in the ML direction using APDM software during each stance condition by calculating the RMS around the mean acceleration (acc), a metric representing sway dispersion (APDM 2013). Our primary measure for this test will be the averaged ML RMS during the Instrumented Modified BESS using an inertial sensor to measure linear acceleration of the body since

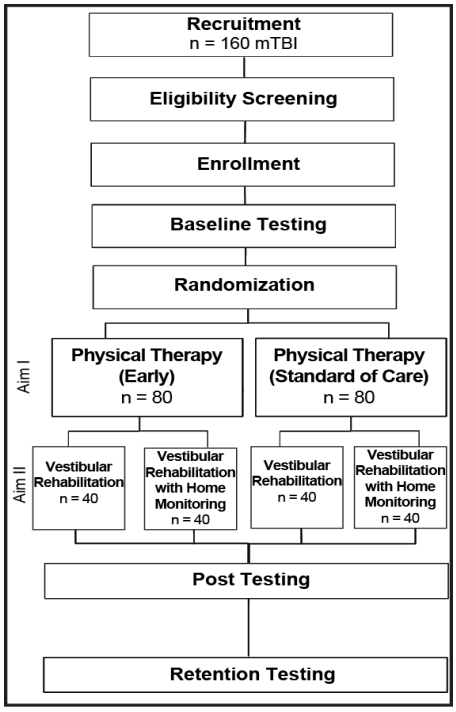
this test could classify mTBI best in our previous study (King et al., under review). Other temporal and spatial metrics such as sway velocity, frequency and jerkiness will be simultaneously collected for secondary analysis. Analysis of head stability during gait: Our primary measure during gait will be the lumbar to head attenuation of acceleration quantified by the attenuation coefficient (Iosa, Mazzà et al. 2010). The attenuation coefficient quantifies the amount of acceleration that is dissipated when moving from inferior to superior body segments. It is calculated using the ratio of head RMS acceleration to lumbar RMS acceleration, with a larger attenuation coefficient indicating more acceleration was dissipated from the lumbar to the head. Wireless eye tracking goggles during each trial will be analyzed to obtain secondary measures including the cross-correlation and time lag between eye, head, and trunk rotational velocities. The eye tracking glasses and head sensor will be used to quantify change in visual field and the quality (amplitude, symmetry, smoothness of head movement) of purposeful head turning, respectively, when participants are asked to walk while performing head turns.

Analysis of complex turning: Head, sternum, and lumbar mounted inertial sensors will quantify the angular velocity of reorienting segments, specifically of the head, trunk, and pelvis. The primary outcome will be the peak axial angular velocities head for each turn. Mobile eye tracking glasses will quantify the reorientation velocity and timing of the eyes with respect to the head. Eye-to-head, head-to-trunk, and head-to-lumbar sequential timing, along with peak axial angular velocities of the trunk and pelvis, will be calculated from the inertial sensors as secondary outcomes.

Analysis of CSMI data: The primary outcome measures are the parameters derived from a model-based interpretation of CoM sway evoked by pseudorandom stimuli (Table 4). The procedure for calculating these parameters is to (1) calculate CoM angular displacement from experimental measures of hip and shoulder displacement on each test trial, (2) use Fourier methods to calculate a frequency response function, FRF (Pintelon and Schoukens 2001), and (3) adjust parameters of a model of the balance control system using a constrained optimization algorithm until the model-derived FRF optimally matches the experimental FRF (Peterka 2002, Peterka 2003).

Sample size calculation for Aims I and II:

Sample size estimation for the efficacy of early versus later physical therapy intervention on patient-reported outcomes (Aim I) was derived from a published study evaluating the effects of early initiation of balance exercises after acute, peripheral vestibular balance disorders as measured by the Dizziness Handicap Inventory (DHI) (Jacobson and Newman 1990, Bamiou, Davies et al. 2000). Patients who presented for treatment within six months of the onset of vertigo had lower DHI scores following physical therapy compared to those who waited longer (22 versus 51, Mann-Whitney, p=0.007, Cohen's d=0.432). This significant difference in symptomatic outcome based on the effect of physical therapy latency is expected to be at least as profound in the proposed cohort given this study investigates the effects of an even earlier initiation of physical therapy, than the six or more-month latency of the described study. Assuming the effect size between early and late therapy initiation observed in the literature is equivalent in magnitude to the effect size expected in the proposed cohort, a significant effect of time would still be observed at α=0.05 with 80% power with a sample size of 36 per group, for both the wearable sensor group and standard physical therapy regimens.



Study design for Aims I and II

We demonstrated the resolution of symptoms in very mild mTBI was associated with increased head rotation during walking with head turns (Fig. 6). Power analysis for the secondary outcome (head-turn velocity) was derived from our pilot data assessing improved head velocity over time. In an mTBI cohort, a significant rate of change was observed with increasing head-turn velocity over time (N=26, t=4.07, p<0.001, Cohen's d=0.798, Fig. 6). With the same sample size of 36 per group, a significant effect of early versus later intervention would still be observable at α=0.05 with 80% power, if there is at least a 56% difference in the effect size (d=0.446) between the two time-course arms for either intervention group. Similarly, this effect size could also be observed to be statistically significant between the feedback-enhanced intervention and standard exercise regime within either the time to rehabilitation cohorts. Assuming a dropout rate of ~20% over the study period, the expected effects sizes would be found to be significant with a final recruitment of 40 subjects for each of the four groups; totaling 160 people with mTBI for aims I and II combined.

Primary outcome: DHI The final sample for Aims I and II will consist of four distinct groups: A) early rehabilitation using wearable sensors at-home, B) early intervention with traditional at home exercise program, C) late rehabilitation using wearable sensors at-home, and D) late intervention with traditional at home exercise program. Linear mixed-effects models will be used in an intention-to-treat design to assess the continuous rate of change in DHI over time in each group. Mixed-effects models will be used to account for within-subject correlation in the repeated measurements across time while addressing any missing data due to dropouts or absentee visits. An on-treatment comparison will also be leveraged, using ordinary least squares to model to bulk change in study outcomes from baseline to study exit for all subjects completing the study.

To compare the effect of early versus late intervention, the main effect of time (Aim I, comparing groups AB to CD) will be assessed in the mixed-effects model. To compare the effect of rehabilitation with home monitoring versus standard-of-care rehabilitation, the main effect of treatment will be assessed in the mixed-effects model (Aim II, comparing groups AC to BD). To compare whether the effect of at-home monitoring is different between early and late rehabilitation, the interaction between time and treatment will be evaluated using the mixed-effects model. Beyond the main effects of time, treatment and their interaction, individual contrasts among groups will be considered using an ANOVA framework to compliment mixed-effects regression model.

Mixed-effects models will also incorporate covariates found to influence study outcomes, including, but not limited to, age, gender, vestibular function. For the intention-to-treat mixed-effects models, an unstructured error covariance structure will be utilized and parameters will be estimated using restricted maximum likelihood procedures. Missing data points in the analytical sample are considered missing at random and the above approach is sufficient under this assumption. Results will be considered significant at α=0.05 with Holm-Bonferroni adjustments to correct for multiple comparisons among the various outcome measures. Model fit and integrity will be examined using a combination of formal fit criteria and visual inspection of residual plots.

Secondary Outcome measures will be assessed using the mixed-effects models as described above to determine the effect of time and treatment on each outcome. To determine the meaningful change of head stability metrics after rehabilitation, the minimal detectable change of our novel outcome measures presented in Table 2 such as attenuation coefficient, cross-covariance of eye, head, and lumbar movements, peak axial rotational velocities, and sequential timing of reorientation will be calculated. Minimally clinically important difference for these novel measures will also be calculated using an anchor-based approach where clinically meaningful difference is based on PGIC.

9. Privacy, Confidentiality, and Data Security

Identifiers: Subjects will be assigned a coded study identification (ID) number generated after written informed consent has been obtained. The subjects' name and unique ID number will be recorded in an electronic file, stored on a password-protected secure drive. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information. Data collection forms will be labeled using unique study ID numbers and will not have personal identifiers.

Confidentiality: To ensure and protect the privacy of the study subjects and to maintain confidentiality of the data, the following activities for data and safety monitoring will be in place for the study: 1) A detailed plan will be approved by the Institutional Review Board (IRB) before recruitment begins, 2) Data will be coded upon collection with the key to the code held separately from the data and accessible only to IRB approved study personnel who need to know. Subject information and study data will be stored behind a locked office in a locked cabinet at OHSU (if paper) or behind a secure Oregon Health & Science University (OHSU) firewall on network drives requiring password authentication (if electronic). If being stored at the VA, it will be kept on the secure VAPORHCS network folder (King17370) or in locked cabinets in locked office P5F-153 bldg 104 (if paper). The representatives of the US Army Medical Research and Material Command (USAMRMC) are eligible to review study records. The persons who are authorized to use and disclose the data from this study are the approved investigators, other research professionals at OHSU who are participating in the conduct of this research protocol, and the OHSU/Veteran Affairs (VA) IRB. All data will be safeguarded in accordance with Health Insurance Portability and Accountability Act (HIPAA). The knowledge of any pending compliance inspection/visit by the USAMRMC, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, warning letters, or actions taken by any Regulatory Agencies, including legal or medical actions, and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to OHSU and/or the Portland VA Human Research Protection Office, and to the Department of Defense and/or USAMRMC. Representatives from USAMRMC are eligible to review study records upon request. Data collected in this study do not include any sensitive information, such as history of communicable diseases that are required to be reported to state or local authorities.

Data capture, verification and disposition: Data will be gathered from questionnaires and instrumented assessments, and entered into the web-based Research Electronic Data Capture system (REDCap) and into the OHSU Balance Disorders database. REDCap is a secure electronic database administered by OHSU. Hard copies of these records will be stored behind a locked office in a locked cabinet at OHSU or if at the VA on the secure VAPORHCS network folder (King17370) or in locked cabinets in locked office P5F-153 bldg 104 (if paper). The de-identified Mobility Lab data will be collected on a password-protected and data-encrypted laptop computer and

uploaded after each test session to an OHSU secure server, where the Balance Disorders database is located. The computer that will store the project database will be protected by current network security behind OHSU firewall. An institutional computer account and password will be required to access the computer storing the recruitment database and the images. In addition, the REDCap database is password protected, and only project personnel approved by Dr. King will be given access. Any hard-copy research records and consent forms will be stored in a locked file cabinet within a locked, secure office. Hard-copy and electronic research records will be kept for seven years, in compliance with HIPAA, or one year after publication, whichever is longer. VA record will be keep indefinitely or as directed by the VA standards. All identifiers will be removed at the completion of the study and it will not be possible to link the data to individuals after that time.

Adaptation during COVID- 19 restrictions: All data collected over the phone or through virtual visit will be recorded on REDCap and stored on a secure OHSU server, which only study team members have access to. The study team member and participant will do all remote virtual visits over a secure Wi-Fi network.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

See the Data and Safety Monitoring Plan form for details.

11. Risks and Benefits

a. Risks to Subjects

Information that identifies participants will be used in this study and shared with research staff and non-VA researchers. A breach in confidentiality and a resulting loss of privacy could result in monetary loss due to identity theft. However, the research team will make every effort to protect private health information and guard against any loss of privacy.

Musculoskeletal injury -There is a low risk of joint, tendon, or muscle pain, inflammation, or swelling during or after a testing session of gait and balance. The risk is reduced by use of well-trained assistants and also by the mild nature of the gait, balance and vestibular testing.

Exacerbation of symptoms - There is a low risk that existing symptoms such as dizziness will become worse by performing the tests and performing rehabilitation.

Emotional Distress- Some of the questions asked may be personal or embarrassing. People may refuse to answer them if they don't want to. Also, they may learn information about their balance and walking and that could be upsetting to them.

Falls- The balance and walking tasks may cause them to lose their balance or fall. However, our trained research assistants will walk alongside them at all times for safety. All safety measures will be taken to ensure a secure and comfortable environment. People will be allowed to take a break from the balance and walking tasks whenever necessary. For balance testing on the force plate, people will be secured in a harness for safety.

Nausea- There is a risk during some of the vestibular testing that some people will experience nausea and or dizziness, in which case we stop the test immediately.

Wearable sensor system- The wearable sensors worn on the body are commonly used in other laboratory studies assessing balance and gait. There is no identifiable information stored on these sensors. These sensors are non-invasive and may cause minimal discomfort, no greater than wearing a headband, wristwatch or belt.

Biofeedback sensor system- These sensors used for biofeedback are the same as the sensors in the wearable sensor system. There is no identifiable information stored on these sensors. These sensors are non-invasive and may cause minimal discomfort, no greater than wearing a headband, wristwatch or belt.

Other Risks: There is a small risk that people may experience some ear discomfort when having your ears examined and with wearing earphones during testing. Possible temporary discomfort may be experienced during preparation and placement of the electrodes on their skin. This is rare and lasts only a short period of time. Some tests require wearing video goggles over the eyes, these may also cause discomfort.
All sounds will be presented at levels where there is minimal risk of damage or discomfort. The vestibular-evoked potential tests involve the presentation of brief but loud sounds, if they find the sounds too loud we will stop the tests.

b. Potential Benefits to Subjects

Subjects and physical therapist will be compensated for their participation in this study. Subjects who participate in Aim I and Aim II will receive free physical therapy. Subjects may or may not personally benefit from being in this study. However, by serving as a subject, they may help us learn how to benefit patients in the future. All rehabilitation will be provided free of charge.

Short-term impact: Anticipated outcomes in the short term are to facilitate evidence-based recommendation for timing of physical therapy intervention for mTBI, particularly for those with complaints of imbalance. Based on results from this project and the expected benefits of early physical therapy, we expect patients with mTBI will have faster and more consistent referrals to physical therapy, thereby facilitating faster recovery. We expect the short-term impact will be immediately addressed within OHSU clinics who see patients with mTBI. Another short term impact will be mTBI-specific protocols implemented into the commercially available APDM Mobility Lab system. These test protocols will be readily available for researchers and clinicians.

Long-term impact: Our long term goals for this project are to produce more evidence-based rehabilitation and to ultimately improve care after mTBI. We believe that implementation of the findings from this research can be readily adopted into military protocols for post-mTBI care and have the potential to produce more long-term efficacious balance rehabilitation. An important long term impact of this work could clarify best practices for the rehabilitation of balance deficits by providing evidence regarding when to initiate rehabilitation and by producing protocols for utilizing wearable sensors in assessing and treating balance deficits after mTBI. We expect the use of wearable, inertial sensors will progressively increase throughout clinical, field-side or in-theatre environments as technology becomes less expensive and more widely accepted. This project will result in a portable, wireless, and easy-to-use product for physical therapists to use when training complex balance and vestibular rehabilitation exercises. The use of wearable sensors, as proposed in our project, is gaining momentum in the civilian and military populations as a method to detect mTBI. Yet, the use of inertial sensors in rehabilitation settings for clinical care is still lacking. This project will produce a system with wearable sensors to augment rehabilitation by providing feedback on the quality of head and trunk movements that are difficult to quantify visually. We anticipate that implementing this system will significantly improve the efficacy of rehabilitation following mTBI, reduce the chronic effects of mTBI and improve quality of life after mTBI. More effective rehabilitation will also lower the economic burden of mTBI on health care costs.