Optimizing Cognitive, Environmental, and Neuromotor Stimulation in Traumatic Brain Injury

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JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Patients with a history of traumatic brain injury (TBI) are at elevated risk for Alzheimer's disease and related dementias (ADRD). Improvements in TBI treatment may mitigate this risk. The treatment of TBI, especially for those with chronic neuropsychiatric sequelae, is moving toward multi-modal approaches that include non-pharmacological interventions such as exercise and cognitive enrichment. Complex motor activities, which combine physical and cognitive demands, have been shown to have well established neurocognitive benefits. However, there are a lack of cognitive enhancing interventions that utilize these complex motor activities. Many adults with history of TBI face significant barriers to engaging in physical activity which limit their ability to participate in many neurocognitive interventions. This study seeks to address the need for novel TBI interventions optimized for adults with history of TBI by determining the effectiveness of an immersive computer game designed to integrating complex cognitive-motor processes. During this proposed 12-month study involving patients with history of TBI (n=66) we will examine cognition, independent function, mood and ADRD-related brain biomarkers after 12 weeks of a randomized intervention, as well as 9 months post-intervention to assess for durability of any benefits. We hypothesize that complex motor activities will improve cognitive health in adults with a history of TBI and that promising results would have implications for early intervention for those at risk for mild cognitive impairment and ADRD.

2. Objectives (include all primary and secondary objectives)

1) Primary Objective: To determine the efficacy of a complex cognitive-motor game, Bandit (intervention), on cognition, lifestyle, independent activities of daily living (IADL), activities of daily living (ADL), psychological and physical well-being, sleep, physical activities, and social networks in patients with past TBI in comparison to a Successful Aging Program (active control).
2) Objective 2: To examine mechanistic brain biomarkers of ADRD prior to and following 3 months of exposure.
3) Objective 3: To assess durability of any observed cognitive, lifestyle, and IADL benefits 9-months post-exposure.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Studies have shown that those with past TBI are at elevated risk for ADRD. The brain networks most impacted post-TBI, the prefrontal cortex (PFC) and the hippocampus, are also related to the pathological processes involved in ADRD. The PFC network helps with executive processes involved in the initiation, planning, coordination, and sequencing of actions toward a goal. Executive functioning is the cognitive domain found to have the strongest impact on functional outcomes after TBI. Research has also shown that loss of brain volume in the early stages of Alzheimer's disease is greater in the PFC than in other areas of the brain. The hippocampus is functionally linked to spatial navigation and memory through the consolidation of information learned as one physically moves from location to location. The hippocampus declines most precipitously with age and is further implicated in risk for dementia. These findings suggest that improving the treatment of TBI may be an important strategy for the early intervention of ADRD.

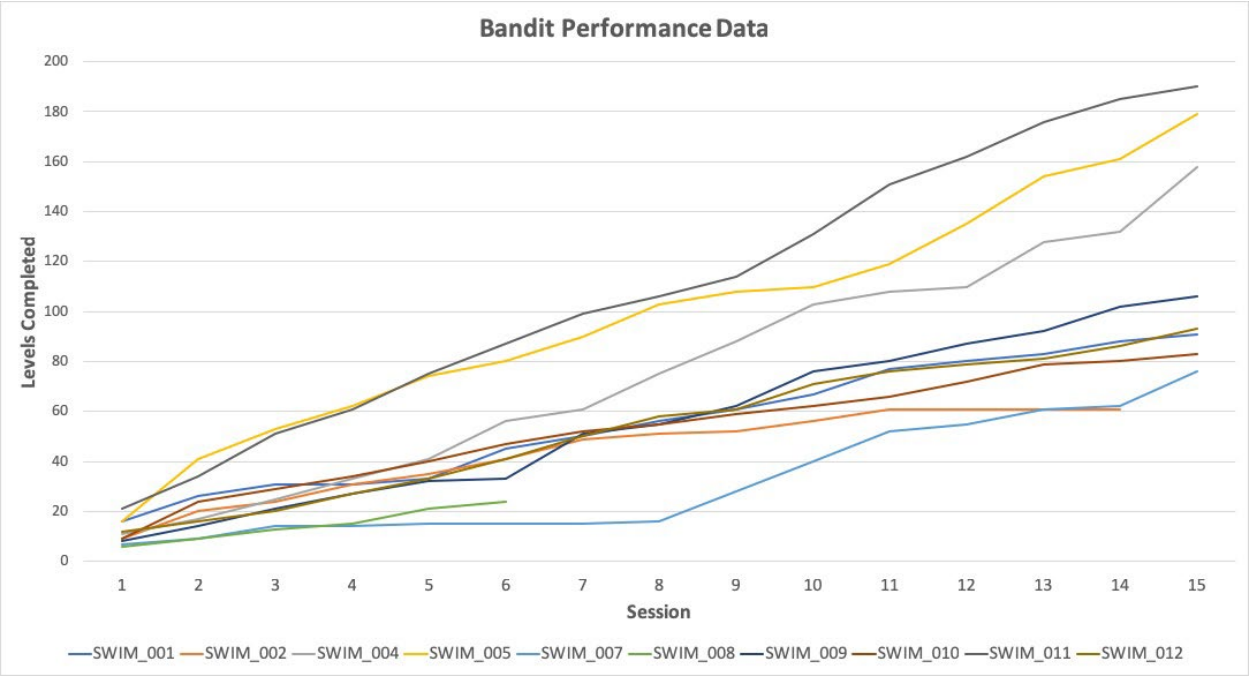
A growing body of research suggests that non-pharmacological interventions have the potential to provide powerful treatment options for those with chronic cognitive, mental and physical sequelae after TBI. Evidence shows that even moderate physical activity such as low-intensity walking improves neurocognitive health. Cognitive enrichment from various daily activities has also been found to have beneficial effects on cognition and risk for neurodegenerative disorders.

The cognitive benefits of physical exercise are evident. However, in adults with past TBI, there are significant functional and motivational barriers to engaging in physical activity which we seek to address in our study. Given that even a single TBI in an aging adult may increase the risk of cognitive decline, there is an urgent need for novel strategies optimized for this population.

Accumulating evidence points to complex motor activities, which combine physical and cognitive demands, as a promising way to train cognition. Despite the clear benefits, complex motor activities have been largely ignored as cognitive enhancers and there is a dearth of novel strategies that take advantage of the synergistic effects of integrating complex motor and cognitive interventions.

We propose a novel TBI intervention to enhance cognitive function, mobility and related functional and lifestyle activities by applying an immersive computer game that was designed for stroke patients. Action video games have been shown to lead to perceptual and cognitive benefits that extend well beyond the confines of the games themselves. These technologies have the potential to safely and simultaneously enhance executive function efficiency and motor control in ways that translate to enhanced community activity and independent function.

Dr. Michelle Carlson, co-I of this study, has successfully demonstrated the feasibility of implementing Bandit 1 hour/day, 3 days/week among older adults (n=16; mean age= 79) in an independent-living retirement community who exhibit varying levels of physical function and disability, including Parkinson's disease, COPD, and lower-limb amputation. Participants were 100% compliant and, as shown in the Figure below, most showed steady improvements in performance over game sessions, with the exception of one participant who discontinued due to vertigo from Meniere's disease. Anecdotal quotes from participants during and after game play include: "Bandit, you stinker, you're supposed to eat the shark on this level, not the fish!" and "This is 'sneaky exercise' because you're not actually thinking about how much you're moving..." We have recently completed focus groups with 100% compliance that confirm high levels of motivation to play Bandit. This pilot study motivates our proposal to extend this intervention to aging adults with past TBI to innovate intervention designs that use safe, video game technology to promote complex, integrated cognitive-motor behavior important to daily independent functions (e.g., shopping, driving, cooking).



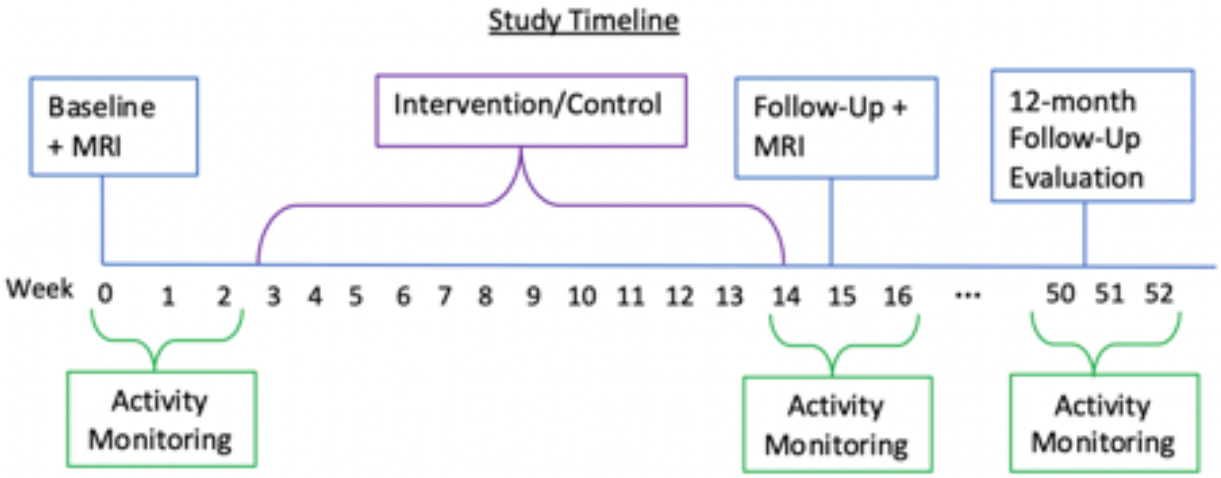
4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Study Design: Randomized Controlled Trial

Study Population: Patients 40 years of age or older with a remote history of TBI (>2 years) and evidence of mild cognitive impairment

Sequence and Timing of Study Procedures: See Study Design Figures below. All procedures listed after consent are research procedures. Enrollment will occur at the ABI and MATC clinics.



Patient Identification (in-person or remote)

- Potential participants are established patients of clinical PI, Dr. Peters and clinical co-Investigators.

- The research team will identify individuals that meet the inclusion criteria and no exclusion criteria for the study.
- When a patient of the PI or a co-investigator, during a future routine clinic visit, the patient's provider will evaluate each patient potentially eligible for the study and gauge interest. If there is interest, the provider will get the patient's approval for the research team to call the patient and will give the patient's information to the research team. The research team will then reach out to the patient to schedule the Recruitment and Consent Visit.
- Participants will be sent home with the following packet of information: (1) study consent form to reviewed during Recruitment and Consent Visit and (2) the COVID-19 Research Participant Risk Information Sheet.
- Collection of demographic and injury data will be collected prior to enrollment in the study as part of routine clinical care. In this way, eligibility for the study will be established prior to consent.
- No adjustments will be made to the standard of care in regard to medication or therapies the patient is receiving during the 12-week (3 month) intervention.

Recruitment and Consent Visit (remote only)

- Research team will call interested patients via telephone or videoconferencing.
- Research staff will review the COVID-19 Research Participant Risk Information Sheet.
- Research staff will then explain the purpose of the study.
- Obtain informed consent and enroll the participant in research study.
- The previously provided physical consent form will be completed and returned to the study team (either via mail, email, fax, or during the pre-intervention evaluation visit)
- We will then schedule the visit for the pre-intervention evaluation.

Pre-Intervention Evaluation Visit (in-person)

- The day prior to the visit, research staff will call the participants to complete the COVID-19 clinical screening questions. If participants screen positive, the visit will be canceled.
- An initial evaluation, which will last approximately one hour, will be conducted in Hampton House Room 398, Bayview clinic, or Howard County General clinic where the potential participants are already seen clinically. The testing space can fit two occupants and the door has a window to view the participant.
- Universal masking will be used for participants and research staff. Research staff will use a face shield whenever a distance of 6 feet cannot be maintained. Cleaning protocols with occur as per CDC guidelines and only one research participant will be in the room on a given day (only one per cleaning).
- Evaluations will consist of a detailed review of the consent form, demographic survey, physiological measures (e.g., height, weight, blood pressure, pulse), physical function measures, cognitive tests, and surveys to evaluate knowledge, attitudes, and behaviors around technology use, well-being, sleep, lifestyle activities, physical activities, social networks, depression, health status, independent activities of daily living, and activities of daily living. All measures that can be completed remotely prior to visit, with the research assistant outside of the room, or with the research assistant greater than 6 feet from the patient will be.
- Participants will be asked to wear an Apple Watch paired with an iPhone and an Actigraph for 2 weeks prior to starting the intervention. Participants will be given hands-on education on the use of the these devices at baseline and provided on-call support while wearing them. For those who have an iPhone, we will offer to provide the iPhone or if they prefer, we can download the secure physical activity monitoring research app at no cost. This app does not collect personally identifiable information and can be easily removed from their iPhone.

- The pre-intervention MRI scan will be scheduled at this visit and completed prior to intervention start.

Intervention Visits (in-person)

- After 2 weeks of using the Apple Watch paired with an iPhone and Actigraph to measure baseline activity levels, participants will have their first intervention visit.
- The day prior to each intervention visit, research staff will call the participants to complete the COVID-19 clinical screening questions. If participants screen positive, the visit will be canceled.
- All intervention visits will occur at Hampton House Room 398, the Bayview clinic, or Howard County General clinic. Parking will be vouchered for participants, if applicable.
- Universal masking will be used for participants and research staff. Research staff will use a face shield whenever a distance of 6 feet cannot be maintained. Cleaning protocols with occur as per CDC guidelines and only one research participant will be in the room on a given day (only one per cleaning).
- During the first intervention visit:
    - Intervention Arm: Research staff will walk the participant through setup and use of Microsoft's Kinect system. The Edinburgh Handedness Inventory will be used to assess handedness. This is important to ensure that participants are performing the intervention with their dominant hand.

    - Active Control Arm: The first visit for the Successful Aging Program will include introductions, rapport building among the group of 5 participants maximum in this arm *(not to exceed JHU Safety Guidelines for COVID-19)*, and an overview and goal setting topic using the Prevention in Practice report from the 10-keys to Healthy Aging Program.
- Participants in the intervention will be given the option of completing either three 60-minute intervention sessions or two 90-minute intervention sessions (including 10 minute warm- up and warm-down) each week for 12 weeks (ranging from 24 to 36 sessions, total). This option allows the participants to minimize their exposure outside of the home when traveling to and from the intervention site. The active control arm will have one session each week for 12 weeks.

Heart rate will be objectively assessed during the game using the heart rate sensor on the Apple Watch. We have modeled our intervention on numerous cognitive and physical exercise interventions in older adults, often conducted over a 12-week interval (see Report From the Institute of Medicine, 2015; Blazer, D., Yaffe, K., Karlawish, J. *JAMA.* 2015;313(21):2121-2122; Sprague, S., Freed, C., Webb, Philips, J, & Ross, L The impact of behavioral interventions on cognitive function in healthy older adults: A systematic review, Ageing Research Reviews, 2019). Additionally, a recent meta-analysis of randomized trials of active "exer" video games in clinical and non-clinical cohorts suggests that they can improve executive functions, processing speed and visuospatial abilities (Stanmore, E., Stubbs, B., Vancampfort D., de Bruin, & Firth, J. The effect of active video games on cognitive functioning in clinical and non-clinical populations: A meta-analysis of randomized controlled trials, Neuroscience and Biobehavioral Reviews 78 (2017) 34–43).

Post-Intervention Visit (in-person)

- The day prior to the visit, research staff will call the participants to complete the COVID-19 clinical screening questions. If participants screen positive, the visit will be canceled.
- Immediately after completing 12 weeks of the intervention or active control, a follow-up evaluation will occur in Hampton House Room 398, the Bayview clinic, or Howard County General clinic. This visit will last ~1 hour.
- Universal masking will be used for participants and research staff. Research staff will use a face shield whenever a distance of 6 feet cannot be maintained. Cleaning protocols with occur as per

CDC guidelines and only one research participant will be in the room on a given day (only one per cleaning).

- This post-intervention evaluation will repeat the same physiological measures, physical and cognitive function measures and surveys completed during the initial evaluation. All measures that can be completed remotely prior to visit, with the research assistant outside of the room, or with the research assistant greater than 6 feet from the patient will be.
- Participants will be outfitted with the Apple Watch paired with iPhone and Actigraph to wear again for 2 weeks post-intervention. Participants will be asked to either bring the devices to their next clinic appointment or return the watch via mail in a pre-paid package.
- The post-intervention MRI scan will be scheduled at this visit and subsequently completed.

Post-intervention MRI, even in this short interval, has been used to show evidence of change in other studies. Some of the main studies in this realm were conducted by Co-I, Dr. Michelle Carlson. These studies have incorporated functional and structural MRI and show short-term, intervention-specific changes in relevant brain biomarkers (e.g., hippocampus, prefrontal-cortical circuits and executive functions) (e.g., Carlson MC, Erickson KI, Kramer AF, Voss MW, Bolea N, Mielke M, et al. Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. The Journals of Gerontology Series A, Biological Sciences and Medical Sciences. 2009;64(12):1275-82; Draganski, Gaser, Busch, Schuierer, Bogdahn, & May. Changes in grey matter induced by training, *Nature. 2004.* vol 427, pp 311–312; Colcombe, S., Kramer, A.F., Erickson, K.I., Scalf, P., McAuley, E., Cohen, N., Webb, A., Jerome, G., Marquez, D., & Elavsky, S. Cardiovascular fitness, cortical plasticity, and aging. *PNAS,* March 2, 2004 101 (9) 3316-3321).

9 Months Post-Intervention Visit (in-person)

- The day prior to the visit, research staff will call the participants to complete the COVID-19 clinical screening questions. If participants screen positive, the visit will be canceled.
- Participants will have a third cognitive and functional evaluation 9 months post-intervention (12 months post-baseline) to test the potential durability of any benefits observed immediately post-intervention.
- Universal masking will be used for participants and research staff. Research staff will use a face shield whenever a distance of 6 feet cannot be maintained. Cleaning protocols with occur as per CDC guidelines and only one research participant will be in the room on a given day (only one per cleaning).
- This evaluation will include the same physiological measures, cognitive and physical function measures, surveys and 2-week Apple watch to wear paired with an iPhone and Actigraph as completed at baseline and post-intervention. All measures that can be completed remotely prior to visit, with the research assistant outside of the room, or with the research assistant greater than 6 feet from the patient will be. After those two weeks, the participants will be asked to either bring the watch to next clinic appointment or return the watch via mail in a pre-paid package.

MRI protocol:

MRI scans will be performed on a 3T Philips scanner housed in the F.M. Kirby Research Center for Brain Imaging at the Kennedy Krieger Institute. This is a research dedicated MRI facility that contains two 3T Philips scanners. The sequences to be completed for this study are as follows:

Structural Scans:

- MPRAGE sequence (repetition time = 8 ms, echo time = 3.6 ms, FOV = 256 mm, matrix = 256 × 256, slice thickness = 1 mm; 200 slices). Acquisition time 6 min 58 sec.

- Fluid-Attenuated Inversion Recovery (FLAIR): The FLAIR structural scan will be an T2 sequence with a 1 × 1.19 × 1.20 mm^3 resolution with 160 slices over an FOV of 256 × 256× 256 mm with TR/TE = 11000/2800 ms. The total scan time will be 5 min 8 sec.
- High-resolution Hippocampus: A high-resolution structural acquisition with a limited field of view covering the bilateral hippocampus is completed using a T2 sequence with TR/TE = 8020/54 ms, a resolution of 0.4x0.4x2.0 mm over a FOV of 179x179x60 mm. The SENSE acceleration factor = 2. The total scan time is 5 min 36 sec.
  T2 STAR sequence will be a .8 × 1 × 4 mm^3 resolution with 44 slices over an FOV of 256 × 256× 205 mm with TR/TE = 650/20 ms. Acquisition time 4 min 29 sec.

DTI Scan:

- The DTI scan will be a transverse multi-slice spin echo, single shot, echoplanar imaging sequence, with a resolution of 2.00 × 2.00 × 2.00 mm^3 resolution with 80 slices over an FOV of 256×256 ×256 mm with 10861/87 ms. Acquisition time 8 min 05 sec.

Functional MRI:

- Resting-state fMRI: The resting state functional MRI (rs-fMRI) scan uses a 2D echo planar imaging sequence with a SENSE acceleration factor = 2, TR/TR = 3000/30 ms, flip angle = 90° with a 3.4x3.4x3.4 resolution over a FOV of 217x217x162 mm. SPIR is used for fat suppression. A total of 200 times points are collected for a total scan time of 10 minutes.
- Flanker task fMRI: Whole-brain functional data will be acquired with T2*-weighted echoplanar images (repetition time = 1500 ms; echo time = 30 ms; slice thickness = 4 mm/1 mm gap; 30 slices, interleaved acquisition; flip angle = 70°; matrix = 64 × 64; FOV = 240 mm). Data will be acquired in a single run of 578 volumes. Acquisition time 14 min 40 sec.

b. Study duration and number of study visits required of research participants.

Participants will be enrolled for 12 months depending largely on availability of research equipment and scheduling of close-out visit. There will be three pre-intervention visits (recruitment and consent, pre-intervention evaluation, MRI), 24 to 36 intervention visits (intervention arm) or 12 Successful Aging Program visits (active control arm), and three post-intervention visits (immediate post-intervention evaluation, MRI, 9 month post-intervention evaluation). Participants will be encouraged to engage in all study visits; however, they will be allowed to choose the number of follow-up visits they attend, without penalty.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Any study team members not directly involved in the intervention administration will be blinded to study arm assignment. We anticipate two research staff being involved in the intervention administration and these staff will be different than staff administering any of the testing / evaluations.

It is important to include a control in this study because the video game being evaluated is designed to be multi-modal through integrated, complex cognitive and physical activity. To better isolate the impact of this multi-modal approach relative to physical exercise alone, it is important to compare any benefits of Bandit play to the benefits of the Successful Aging Program with an integrated placebo exercise component. .

In order to minimize bias in the assessment of outcomes of the two treatment arms, the study greatly benefits from blinding the research team as much as possible. Given the nature of the study, the participants will not be blinded.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A. No adjustments will be made to the standard of care in regard to medication or therapy during the study.

e. Justification for inclusion of a placebo or non-treatment group.

The Successful Aging Program will be used as the active control group for this study. This program is an active health education intervention (approximately 60 minutes long) based on staff attention both through lectures from the Prevention Research Center 10 Keys to Successful Aging materials on a variety of topics related to older adults. A short instructor led program (5-10 minutes) of upper extremity stretching exercises (a "placebo exercise") will be performed during each class to help foster adherence without directly affecting the study outcomes. In addition to the 60 minute in-person instructor led group, participants will be encouraged to spend two hours a week on take-home activities from the 10-key participant workbook and/or work on their personal health goals. We feel this group is necessary to account for the treatment effect caused by frequent visits and exercise alone.

f. Definition of treatment failure or participant removal criteria.

If the participant no longer wishes to be enrolled in the study, they will be excused with no consequence to their ongoing treatment and physician care. Subjects who become suicidal or develop problems that require aggressive treatment during the course of the study will be withdrawn, and followed at their established clinic, if appropriate care can be provided on an outpatient basis. If outpatient care is not appropriate, the clinical PI (Dr. Peters) will be responsible for admitting subjects.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants no longer wishing to take part in any component or all of the study can leave without penalty at any time. This will not impact the medication or therapy they are receiving as standard of care. The participants relationships with providers at their respective clinics will not be affected by their participation or non-participation in the study.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- English speaking
- 40 years of age and older
- History of at least one remote TBI (>2 years ago) of mild, moderate, or severe severity as diagnosed by Veteran's Affairs / Department of Defense (VA/DoD) criteria. TBI history will be obtained using the Ohio State University TBI identification (OSU-TBI-ID) form.
- Ability to perform most IADLs without physical assistance (e.g., no canes or walkers because person needs both hands to participate)
- Ability to dedicate 3 hours per week for about 12 weeks—approximately 20 to 26 hours of total time—to the study, including no upcoming surgeries, travel, or other events that would interfere with ability to complete study.
- Ability to give informed consent and understand the tasks involved
- Ability to complete MRI scan, including ability to lay in scanner for one hour
- Complete COVID-19 vaccination with copy of vaccination card provided to study team.

Exclusion Criteria:

- Presence of dementia defined as a telephone Montreal Cognitive Assessment Score (t-MoCA) score≤15.
- Presence of diseases associated with gross motor abnormalities that restrict ambulation (e.g., stroke with paresis, multiple sclerosis, amyotrophic lateral sclerosis, cerebellar or spinal cord disorders, peripheral nerve disorders, severe rheumatic or osteoarthritic disorders, limb amputation);
- Untreated major mental illness that may preclude successful completion of the study (e.g., major depressive disorder, anxiety disorders, etc.)
- History of physical or neurological condition that interferes with study procedures or assessment of motor function (e.g., epilepsy, severe arthritis, severe neuropathy, Parkinson's disease).
- Current diagnosis of color blindness.
- Social or personal circumstances that interfere with ability to complete 12-14 weeks of training sessions and follow-up evaluation.
- Inability to sit in a chair or stand and perform upper limb exercises for one hour at a time.
- Physical function and daily activities impacted by a recent experience such as surgery that could confound effects related to the intervention.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The immersive video game being tested in this study is called Bandit, developed by neurologist Dr. John Krakauer and the KATA engineers in the Brain, Learning, Animation, and Movement Lab at Johns Hopkins. Bandit provides an oceanic environment in which the individual's arm movements control a simulated dolphin. The neuromotor effects of this game have been designed to be used in the clinical setting to rehabilitate arm and hand function following stroke. The game has further been modified to a Kinect-based system and piloted for play in non-laboratory settings among community-dwelling adults. The game offers a unique combination of skilled arm movements plus varying levels of cognitive challenge. In this way, the individual's arms are challenged the same way the legs would be when walking in a complex, outdoor environment. Importantly, the participant "plays" while standing, thus engaging the whole body in this novel multisensorial experience.

We hypothesize that using cognitive training and physical fitness in a regimen of complex skill development will benefit the central nervous system networks that mediate executive and motor functions. Additionally, the promotion of complex neuromotor movement in aging adults with TBI through this intervention, would improve and maintain independent daily functional and physical activity, such as driving and shopping in complex and changing environments.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Interim (Futility) Analysis.

An interim-analysis will be performed on the primary outcomes when 1/3rd (n=22) of patients have been randomized and have completed the 12 weeks of study intervention and post-intervention follow-up visit. The interim-analysis will be completed by a statistician blinded from the treatment arm. The statistician will report to the independent data safety monitoring board (DSMB). The DSMB will have unblinded access to all data and will discuss the results of the interim-analysis. The DSMB will decide on continuation of the trial. If the DSMB feels a case of futility is present, they will discuss with the investigators, and IRB if necessary, to decide on continuation of the trial.

b. Primary outcome variable.

Primary Objective, Primary Outcomes:

Objective #1, Primary Outcomes

Cognitive outcomes: We will assess executive function, psychomotor and perceptual speed, and verbal learning and memory. Four tests will be administered: the Trail Making Test (TMT), the Stroop Test, the Pattern Comparison Test, and the Rey Auditory Verbal Learning Test (RAVLT). The TMT is comprised of two timed parts, A and B, that requires participants to connect numbers in an ascending sequence (Part A measures psychomotor speed) and in ascending alphanumeric sequence, numbers and letters (Part B measure executive function). The Stroop test requires one to name as quickly and accurately as possible the color of ink that color-words are presented in (e.g., "red" presented in blue ink) and assesses one's ability to inhibit a well-practiced response (word reading) in favor of a less-practiced response (inhibitory executive function). Perceptual speed will be assessed using the Pattern Comparison Test, requiring one to compare as many pairs of 32 line drawings as possible in 30 seconds and to determine whether members of each pair are similar or different. Verbal learning and memory will be assessed with the RAVLT which is comprised of 3 presentations and 3 recalls of a 15-word list as well as a 20-minute delayed recall of the word list.

Physical Mobility outcomes: Performance-based measures of mobility will be performed using the Short Physical Performance Battery (SPPB). Measures include:

- Walking speed, both usual and rapid pace, over a 4 meter course.
- Ability to rise from low chair without using arms.
- Balance: Functional reach and static stands: side-by-side, semi-tandem and tandem.

Grip Strength will be measured with a dynamometer and captures upper limb muscular strength.
Self-reported whole-body physical and mental tiredness will be measured using the Pittsburgh Fatigability Scale.

IADL outcomes: Self-reported measures of physical function performing Independent Activities of Daily Living (IADLs)
ADLs outcomes: Self-reported measure of physical function performing Activities of Daily Living (ADLs).

Objective #2, Primary Outcome

Brain MRI Volumetrics: We will obtain 3-T volumetric data on a research-dedicated Philips 3 Tesla (T) scanners using previously described methods. We will obtain various volumetric measures, including:

hippocampus, amygdala, mediotemporal cortex, orbitofrontal cortex, striatum, total gray matter, and total white matter using standard software packages including Freesurfer, SPM and MRICloud.

Objective #3, Primary Outcome:

Same as primary objective, primary outcome

c. Secondary outcome variables.

Primary Objective, Secondary Outcomes:

Activity outcomes: The following physical activity will be assessed with an Apple Watch paired with iPhone and an Actigraph:

- Summary metrics include: total counts/day (amount); total minutes of activity/day (duration); total bouts of activity/day (duration); levels of activity intensity (sedentary to vigorous) and accumulated time within each activity level.
- We will additionally include a novel, validated metrics, including active (non-rest) time and variability, intensity of movement and daily time- stamped, or diurnal, patterns of low, moderate, and vigorous activities.
- The following data on heart rate will be assessed using the heart rate sensor on the Apple Watch: - Summary metrics include: BPM –beats per minute; resting HR (non-intervention); on-intervention HR; HR variability (Standard deviation of all HR intervals, Standard deviation of the averages of HR intervals in activity bouts.

N*europsychiatric Symptoms*: The following data will be collected to assess for neuropsychiatric symptoms:

- The Patient Health Questionnaire-9 (PHQ-9) depression scale will be used for depression screening measures.
- The Neuropsychiatric Inventory–Questionnaire (NPI-Q) will be used to provide a brief assessment of neuropsychiatric symptomatology.

Lifestyle and Physical Activity: The following questionnaires will be given to assess lifestyle and physical activity.

- The Lifestyle Activity Questionnaire (LAQ) will be used to measure frequency of participation in everyday activities (e.g., cooking, reading, gardening, etc.).
- The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire will be used to measure weekly frequency and duration of numerous lifestyle physical activities normally undertaken by older adults such as walking, housework, aerobics, and hiking.
- The Life Space Questionnaire will be used to assess the spatial extent and frequency with which older adults move within their communities over the past week.
- Early Enrichment Lifestyle Activities Questionnaire will be used to assess total and variety of cognitively enriching activities that respondents engaged in prior to adolescence.

Well-being: The following will be used to assess psychological and physical well-being.

- The Self-efficacy questionnaire will be used to measure self-efficacy in eight domains using a Likert scale.
- The Social Ties Checklist will be used to assess one's social environment and perception of social network in relation to their perceived emotional and social support.
- The Geriatric Depression Scale will be used to assess depression in older adults.
- The Satisfaction with Life Scale will be used to assess life satisfaction and includes 5 items on a 7-point Likert Scale with higher scores indicating greater life satisfaction.

- The Positive and Negative Affect Schedule will be used to assess affect and consists of two 10-item scales to assess positive and negative affect.
- The PROMIS Sleep Disturbance and PROMIS Sleep-related Impairment Questionnaires will be used to assess perceptions of sleep quality, depth, restoration, alertness, sleepiness, tiredness, and functional impairments.
- The Media and Technology Usage and Attitudes Scale will be used to assess use of technology-based media and related attitudes toward this usage.

Health Status: The following questionnaires will be administered to assess health.

- The EuroQOL 5-Domain (EQ-5D) is a six-item questionnaire to evaluate mobility, pain/discomfort, anxiety/depression, self-care, and usual activities.
- The SF-36 is a 36-item self-report questionnaire that assesses eight domains of health status.

Objective 2, Secondary Outcomes

Brain MRI DTI: DTI parameters (FA, MD, RD, AD) will be assessed in 20 predefined regions of interest (ROI) from the JHU ICBM-DTI-81 WM atlas. Mean values of each DTI parameter for each ROI will be measured.

Brain MRI rsfMRI: rsfMRI data will be analyzed using both seed-based (by generating 6mm spheres that will be placed in regions of interest) and group independent component analysis (utilizing Group ICA Toolbox (GIFT, MIA Lab, University of New Mexico)).

Task-related fMRI: The Flanker task will be employed to assess inhibitory control in regions of the prefrontal cortex, anterior cingulate cortex and occipital cortex (Colcombe and Kramer, 2004). These regions have been associated with neural plasticity in response to a multi-modal intervention by the PI Dr. Carlson (Carlson et al., 2009).

Fluid Attenuation Inversion Recovery (FLAIR): We will a FLAIR MRI sequence which is used to detect traumatic brain lesions.

Peak Expiratory Flow (PEF): PEF will be used to assess pulmonary function. Using a peak flow meter, we will quantify PEF by asking the participant to inhale as deeply as possible and then exhale, as hard and fast as possible, into the peak flow meter. PEF is a surrogate measure of cardiorespiratory fitness. This will allow us to investigate whether the physical activity intervention improved pulmonary function and potentially cardiorespiratory fitness. Poor PEF has also been associated with increased risk of cognitive decline. Therefore, we would like to examine whether baseline PEF or changes in PEF may be related to baseline cognition or post-intervention changes in cognition.

Note: Given ongoing concerns about COVID-19 and forced expiration, we will require all participants to have received a full course of COVID-19 vaccination. This is reflected in the inclusion criteria for the study. Additionally, the PEF procedure will be completed in a clinical space with approved ventilation.

d. Statistical plan including sample size justification and interim data analysis.

Sample Size: The power calculation for this study is based on the study by Kramer et.al (2018) and our clinical experience. In the quasi-experimental pilot clinical trial of using dual-task (cognitive and physical) exercise intervention for training in cognitive function, Kramer et. al found effect sizes of 0.91 in intervention arm and 0.75 (SD=0.33) in the peddler arm for Stroop test when using Congruent Correct-Incongruent Incorrect Metric scale. The effective sample size for the proposed trial would suggest a total evaluable sample size of 66 with alpha set at 0.05. This sample estimate represents a feasible target given

the number of patients with TBI seen at the clinical sites and given what is feasible for us to complete the study visits in the time provided through Department of Defense (DoD) grant funding.

Data Analytic Plan:

- Definition and selection of dataset: Using an Intention-to-treat (ITT) design, all randomized participants will be included and followed up as available. The per-protocol (PP) population111 will include all participants in the ITT population who do are compliant with study treatment as defined by >70% session exposure. Baseline demographic and clinical characteristics, including time since TBI, severity, medical comorbidity, and post-concussive symptoms will be included as covariates in the ITT dataset. Pre-post intervention benefits will be assessed using both ITT and PP datasets.
- Basic exploratory analyses will first be conducted, including checking of distributional assumptions, assessment of relationships among covariates, and missing-value multiple imputations.
- Continuous variables will be described by using mean, standard deviation, median, minimum and maximum, and 95% confidence interval for parameter estimation. Graphical display (spaghetti plots) of the outcome scores will also be generated for the 4 visits (baseline, 3 months, 9 months and 12 months) by group. Category and count variables will be described using frequency or proportions.
- Analyses will be conducted using STATA 11.2 (StataCorp, Texas, 2009) or R 2.13.2(2011). All statistical tests will be judged for significance based upon a two-sided p-value of less than 0.05.

e. Early stopping rules.

- If it is deemed that the participant requires a higher level of care (inpatient hospitalization), they will be removed from the study.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

We do not expect any anticipated adverse outcomes for the study participants. The risk is minimal and therefore no harm is expected to be done to participants.

Risk associated with study involvement: As this study includes research as part of standard clinical care, there is a minor risk of unintentional release of protected health information. Risks in regard to assessments are limited to boredom, fatigue, and frustration. Additionally, given the time spent outside of their homes, participants risk exposure to COVID-19.

Risk associated with magnetic resonance imaging (MRI): MRI can damage or heat implanted or worn metallic objects or jewelry. It can also interfere with the proper functioning of implanted devices (e.g., pacemakers). In the setting of TBI, increased intracranial pressure (e.g., from a subdural hematoma) would be a contraindication for lying flat in the MRI machine for an extended period of time. Lastly, the MRIs will be reviewed for incidental findings, which can be psychologically troubling or lead to need for further work-up, which can be financially, emotionally, and logistically difficult for patients.

Vulnerable Subjects: In some instances, older adults are considered a vulnerable population. There are some risks associated with driving to appointments and exposure to hospital environment.

b. Steps taken to minimize the risks.

Mitigation of risk associated with study involvement: All study personnel are trained in general principles of informed consent, confidentiality, and privacy requirements. A study team investigator will be available by cell phone to speak to staff, subjects, or prospective subjects regarding preventing harm and minimizing risk. Participants may choose to discontinue participation in any portion of the study and continue participation in other components of data collection. If the patient ever has concerns or discomfort arises, the patient may contact the study physician at any time. We have made all elements of the protocol that can be completed remotely so. We will give participants the opportunity to complete 24 longer intervention visits rather than 36 shorter to minimize exposure during travel.

Mitigation of risk associated with data storage: Quality-conscious personnel will be recruited and undergo comprehensive training and supervision to aid with adherence to ethical standards. Each member will sign a statement indicating knowledge and understanding of the above and voluntarily disclose potential conflicts of interest. De-identified information will also be used with data entered online via REDCap (http://project-redcap.org/). The REDCap database will be hosted and backed up on secure servers. Analytical datasets will be stored on Johns Hopkins Box (JHBox). JHBox is a secure cloud-based file sharing service which enables people to collaborate and share information within the research team. All analysis will be undertaken on JH computers. Information will be stored in locked cabinets and offices accessible to study personnel only. Individual's data collected through assessments (e.g., surveys, tests, activity) will not be shared with participating centers without the direct consent of the person.

Mitigation of risk associated with MRI: An MRI patient screening form will be completed by our research assistant at time of enrollment. The proposed study will utilize the clearance protocol currently used at the local institution. Older adults are more likely to have indication for clearance prior to MRI scan and we have developed a screening protocol with this in mind. The neuroradiologist on the study will review all MRI scans for incidental findings. Results will be given to the participant's physician if they choose. Otherwise, we will disclose the finding directly to the patient.

Mitigation of other risks associated with study procedures: All personnel involved in collecting and handling biological specimens are to follow appropriate precautionary procedures currently recommended by the Centers for Disease Control and Prevention. Shipping of specimens, if needed, will be done in compliance with federal regulations.

c. Plan for reporting unanticipated problems or study deviations.

All study personnel are trained in general principles of informed consent, confidentiality, and privacy requirements. In addition to comprehensive training and close supervision throughout the study, staff will be reminded of their duties and responsibility to participants, each other, and the public in adhering to high ethical standards in the following: interacting with participants and each other, protecting the privacy of participants and confidentiality of records, collecting accurate and reliable data, and adhering to principles for the analysis and reporting of data. The PI will be available by cell phone to speak to staff regarding preventing harm and minimizing risk. In order to preserve confidentiality, consents and contact information, which contain personal identifiers, will be stored separately from data collection assessments. All information will be stored in secured online servers and locked cabinets and offices accessible to study personnel only. The PI will communicate IRB guidelines and regulatory correspondence to staff during training and throughout the duration of the study. Any issues that violate IRB guidelines will be reported immediately to the PI in charge of the study who will resolve and report to the IRB within 10 days.

Participant identifying information will be destroyed within two years after the completion of the study. Unanticipated problems or study deviations will be reported to JHH IRB

d. Legal risks such as the risks that would be associated with breach of confidentiality.

While we do not expect any breaches, any events occurring during the study will be reported to the PI. The PI will coordinate directly with the participant if a problem requires additional care and will immediately report any problems or deviations to the IRB within 10 days. Any unanticipated problems or study deviations during at data collection will also be reported by the program coordinator. The study program coordinator will be available by cell phone to speak to participants and will periodically check in with participants regarding technology package use. Any issues will be reported immediately to the PI who will resolve and report to the IRB within 10 days. There are legal risks such as risks associated with loss of data and associated breach of confidentiality. However, to mitigate these risks, study data will be stored in a secure HIPAA complaint database (REDCap) and only de-identified data will be analyzed.

e. Financial risks to the participants.

Although there are no direct financial risks, if there are abnormal MRI or other study findings, this may lead to further medical workup and financial cost.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Benefits to the participant: There may or may not be benefits to subjects who participate in this study. The participant will receive a thorough neuropsychiatric evaluation and brain MRI at no charge. Participants will also have access to the study physician should they have study or non-study-related health concerns. Should the gaming intervention improve cognitive health as we hypothesize, the patient will have reaped these benefits during the study. If the control arm has interest in trying the intervention, they will also be given that opportunity after the study has convened. Based on the minimal risks of the study and potential benefits, this study has a favorable risk-benefit ratio for participants.

Benefits to society: Benefits to society will include important information that will add to the current body of knowledge on associations between TBI and ADRD. Our study will also contribute to the body of knowledge on complex motor activities as neurocognitive enhancers, for which there are very few studies despite its promise as an intervention strategy. We also hope to introduce a novel, low-risk intervention using complex motor activities in the treatment of TBI. We also customized this intervention to be appropriate for the aging population, a population which is excluded from involvement in current neurocognitive rehab treatments due to physical limitations.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will receive $70 at each evaluation (Baseline, Follow-Up, and 9-month Follow-Up). Parking is vouchered for participants. Where budget allows, the study team will make efforts to reimburse participants for travel expenses deemed to be a barrier for participation, such as use of rideshare apps.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There are no monetary costs to participants who take part in this study. All study materials, procedures, and human resources will be directly paid for by the study grant.