CogXergaming to reduce fall risk among frail older adults: A Randomized controlled trial

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Sponsor: Midwest Roybal Center for Health Promotion and Translation

Version: 7

Date:01/26/21

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LIST OF ABBREVIATIONS

HIPAA	Health Insurance Portability and Accountability Act
ICF	International Classification of Functioning, Disability and Health
IRB	Institutional Review Board
PI	Principal Investigator
SOP	Standard Operating Procedure
PA	Physical Activity
MOCA	Montreal Cognitive Assessment
MOB	Matter of Balance
fMRI	functional Magnetic Resonance Imaging
MMSE	Mini Mental State Examination
VF	Verbal Fluency
CF	Category Fluency
DR	Digital Recall
AN	Analogies
RL	Repeated Letter
MA	Mental Arithmetic
AHA-BLS	American Heart Association-Basic Life Support
AED	Automated External Defibrillator

1.0 Project Summary/Abstract

Due to the age associated sarcopenia and reduced cardiovascular fitness, frail older adults experience significant decrease in physical function which comprises of mobility, endurance, muscle strength and balance control [1,2,3]. The impaired physical function results in poor quality of life and reduced community participation, leading to increased frailty and long-term disability [8]. Further, compared to cognitively intact frail older adults, cognitively impaired frail older adults experience greater deterioration of such physical function, specifically during dual-task performances (i.e., simultaneous performance of cognitive and motor task). This deterioration occurs due to increased cognitive-motor interference as a result of dual-tasking and is known to increase exhaustion among frail older adults [7]. Previous studies have used multicomponent training and have shown to improve physical function and maintain cardiovascular functioning [4,5,6]. However, the capacity of such interventions to improve cognitive function along with physical function is not known or unclear. Further, the concurrent comorbidities that occur along with psychosocial issues such as depression present as barriers and lead to reduced compliance to therapy leaving only a few of them to benefit from it [40,41]. Alternate forms of therapy such as exergaming with explicit cognitive training has shown promising effects in improving motor and motor function in disabled populations [38,39]. These studies use a cost-effective, off the shelf device such as Nintendo Wii or Microsoft Kinect to deliver the training which is easily available and clinically translatable. Further, such training has demonstrated increase in brain connectivity enhancing cognitive functions associated with balance control [10]. However, there is limited literature examining the effect of exergaming in older frail population and the efficacy of such training is unknown. Therefore, this study proposes a randomized controlled trial to examine the feasibility of CogXergaming program with an aim to improve locomotor-balance control, cognition, muscular system and cardiovascular fitness.

2.0 Background/Scientific Rationale

The population of adults aged 60 years and older has been growing with around half of the people older than 85 years estimated to be frail [14,15]. Age-related changes in multiple systems affecting balance, mobility, muscle strength, motor processing, cognition, nutrition, endurance and physical activity (PA) results in frailty [3]. Studies on frail older adults have reported improvement in mobility and functional level following exercise interventions [16]. Regular physical activity in this population has helped improve cardiovascular conditioning and quality of life, thus allowing these frail older adults a chance at independent living in the community [17,18,19,20,21]. In addition to physical comorbidities, the presence of psychosocial issues such as depression may act as a barrier to community participation. Several PA interventions have demonstrated limited long-term effect and sustainable behavioral change in this population [22,23]. An evidence-based fall prevention program called Matter of Balance (MOB) was developed to reduce fall risk and improve physical function and maximize activity participation in older adults [11,12,13]. Meanwhile, Exergaming, a task-specific interactive gaming, has been gaining attention as a novel therapeutic alternative that promotes motor recovery in healthy and disabled populations [24,25,26]. Exergaming involves repetitive-task specific exercises with movement execution feedback and motivation provided in real time [22,24,25,26]. Studies have shown Exergaming improved symmetrical weight shifting, multi-directional stepping, single-stance, rapid movement training and self-initiated postural weight shifts in the participants [27,28]. This anticipatory postural control training helps significantly improve balance control and mobility [8,24,26,27,28,29,30]. In addition to the physical function domains that underlie physical frailty, executive cognitive domain functions also predict late-life physiological impairments [31]. Thus, we postulate that PA facilitated through Exergaming and accompanied by simultaneous cognitive training is a novel approach to counter and inhibit frailty associated with physical function and cognitive decline.

3.0 Objectives/Aims

Aim 1: To test the feasibility (compliance and effectiveness) of cognitive-motor exergaming (CogXergaming) in the frail older adults and to compare the improvements in behavioral biomarkers in this group across balance, muscle fitness, cardiovascular fitness and global cognition to the group receiving the Matter of Balance training.
Hypothesis: Participants will respond well to CogXergaming training paradigm and demonstrate significant improvements in balance, muscular fitness, cardiovascular fitness and global cognition as compared to the Matter of Balance training group.

Aim 2: To examine the effect of CogXergaming on physical activity levels and quality of life measures post-intervention.
Hypothesis: The participants who received CogXergaming will demonstrate significant improvement in physical activity and quality of life post-training as compared to their own pre-training scores.
Aim 3: To examine the effect of CogXergaming structural and functional connectivity within the cognitive-motor areas pre and post training to establish effect size.
Hypothesis: Post-training, participants will demonstrate improved memory consolidation, attention, motor planning and execution compared to pre-training indicating improved functional connectivity within the cognitive-motor areas.

4.0 Eligibility

- Community dwelling frail older adults aged 60 years or above
- Can understand & communicate in English
- Ability to walk more than 30 feet with or without an assistive device
- Ability to stand 5 minutes without an assistive device (length of a Wii Fit game)

5.0 Subject Enrollment

A total of 120 participants will be enrolled in the pilot study (see Research Design and Procedures for details).
We will initially recruit the participants by posting flyers (approved by the Institutional Review Board) at Geriatric and internal medicine by contacting Dr. Tanjeev Kaur, giving presentations to potential participants at various exercise centers and senior homes. We will also use social media, such as Facebook, Twitter, etc. to post flyer for recruitment. As a part of recruitment procedure, we will not be accessing the EMRs, and will get referrals from different physicians for those who are potentially eligible to participate in our study. Our research staff team will travel to various locations to provide the background education about our study and explain the procedures through the study involved and will show them the consent form. The consent form will provide enough information about the study and the interested people will be asked to provide their contact information, which will be noted down on a sheet. Later, one of the researchers mentioned on the Appendix P will contact them for a telephone screening. Individuals making the initial contact looking at flyers will also undergo the same telephone screening question and will be asked where they heard/read about the study. The initial telephone screening would determine their general health condition, preliminary eligibility. They will be asked to choose a group that they prefer to participate which includes 3 options- **1) Group 1: In-person assessments and in-person training (where all the tests and training sessions will be conducted in the laboratory); 2) Group 2: In-person assessments and online training (where only the tests before and after training will be conducted in the laboratory and they**

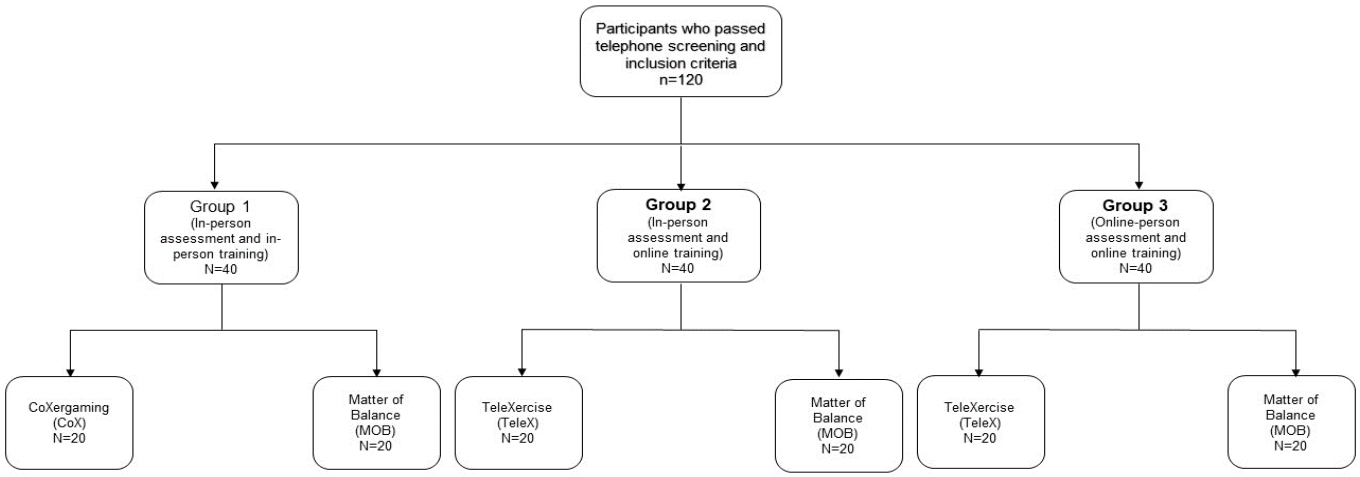
can do the 1-on-1 training online at home via zoom application); Group 3: Online assessments and online training (where all the tests and training will be conducted online via zoom application). Those who choose to be in Group 1 or Group 2, they will be screened for claustrophobia using the claustrophobia questionnaire (Napp, A. E. et al 2016) and individuals who score an average of 1.2 or less will be given the option of being included for fMRI study participation. Once he/she meets the inclusion criteria, they would be scheduled for an in-person laboratory screening at Room 415, B56 or 725 of the College of Applied Health Sciences building. The laboratory screening involves evaluating the individual's performance on various clinical measures balance, muscle strength, endurance and cognition. The participants will also undergo osteoporosis screening using an ultrasound device to measure their heel bone density. During the bone density testing, their heel will be squeezed by the rubber membranes of the testing apparatus. As a result, they will experience some pressure, and/or mild tingling, cold or warm sensation on the heel from the membranes or the gel used during the testing. While Group 3 will continue with online test measures followed by training sessions.

All participants' information will be recorded in a database in the form of an excel sheet that will include the information of the participants eligible and those not eligible for study. For participants not eligible for the study, the reason for withdrawal or exclusion from the study participation as per the telephonic interview will be recorded. An excel file would be maintained to document the results of participants' initial telephone screening, osteoporosis screening, clinical assessment and laboratory dynamic stability test.

To minimize coercion and undue influence on the participants, the potential participants will directly call research coordinators in response to a flyer and/or other recruiting materials or by word of mouth. In case of interested participants referred by the physician or met at recruitment meetings, the researcher will collect the contact information and will initiate contact to perform a telephonic screening. Participation is voluntary and individuals' decisions will not be influenced by research personnel who conduct pre- or post-training assessments.

6.0 Study Design and Procedures

- This study will be a randomized controlled design.
- During the telephone screening, all the participants will be asked to choose a group that they prefer to participate which includes 3 options: Group 1: In-person assessments and in-person training; Group 2-In-person assessments and online training and Group 3- Online assessments and online training.

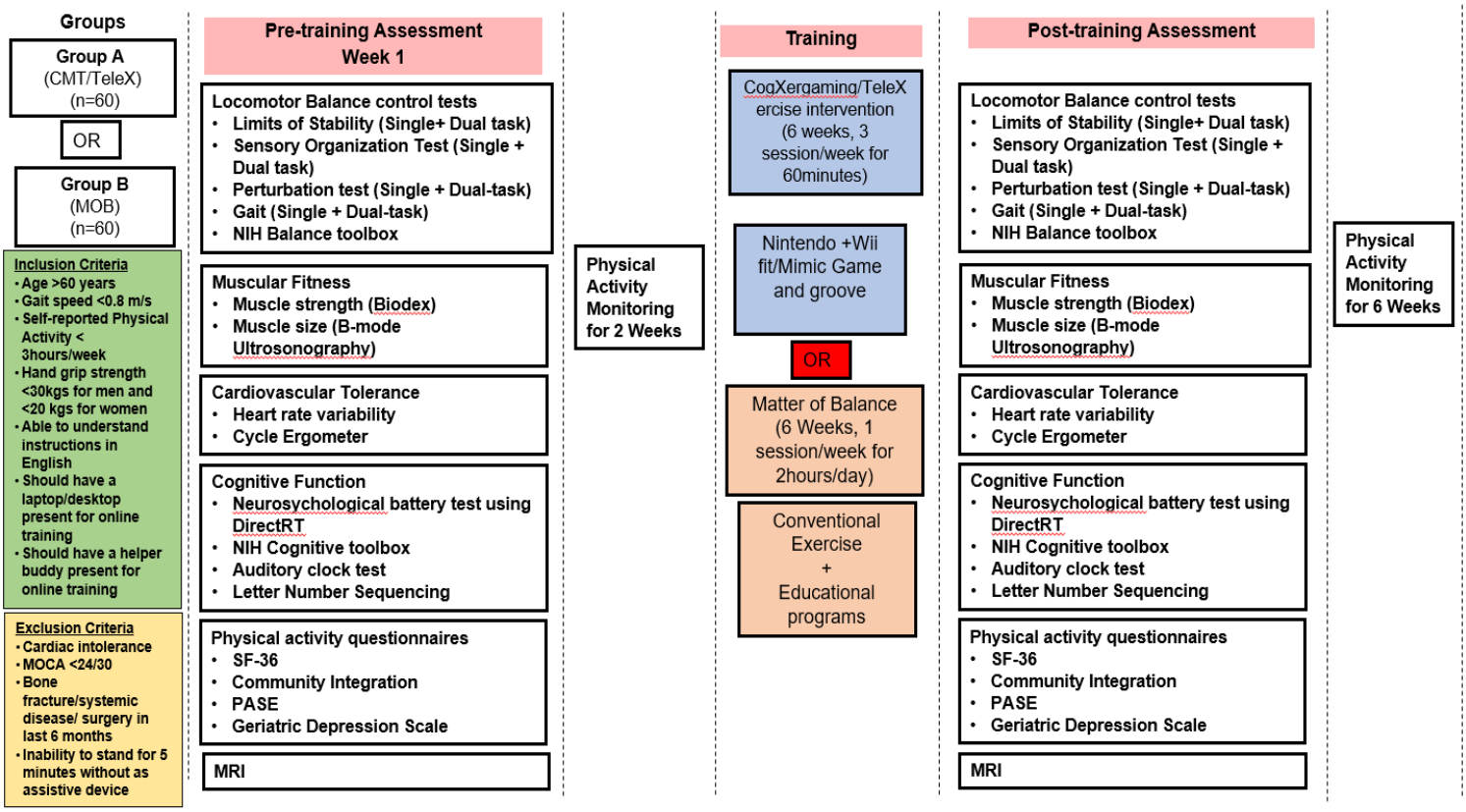


- Figure 1 above shows recruitment and distribution of participants into differenct groups based on the options given for assessment and training to the participants during telephone screening.
- After the participants are allocated to groups 1,2 and 3 depending on their choice, each participant from every group will be randomly assigned either Group A (CogXergaming) or Group B (Matter of balance) for training by flipping a coin.
- Al the participants will be undergo 1-on-1 testing and training.
- Study protocol will vary according to the groups that the participants choose to be in (Groups 1,2 or 3).
- **For Group 1 (In-person assessments and in-person training):** Group A (CoXergaming) will undergo a total of 8 weeks session with first week and last week comprising of assessment. 6-week training will be delivered using the Nintendo Wii-Fit gaming system and a pointer mouse. Participants will visit the laboratory 3 times a week for 6 weeks with each session lasting for 60 minutes (18 training sessions). During training session, participants will wear a gait belt and will be guarded by a research assistant for safety. On the other hand, if the Group 1 participant gets assigned to Group B (Matter of balance) then participants from Group B will undergo a total of 10 weeks session with first week and last week comprising of assessment. The participants will undergo an 8-week (one session a week for 2 hours/day, 8 sessions in total) structured intervention specifically designed to reduce the fear of falling and to increase the engagement in PA.

Test	Pre-test	CogXergaming/TeleXercise Intervention (6 weeks)																	Post-test
Session	1-4	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	1-3
Week	1	2			3			4			5			6			7			8

Test	Pre-test	Matter of Balance (8 weeks)								Post-test
Session	1-4	1	2	3	4	5	6	7	8	1-3
Week	1	2	3	4	5	6	7	8	9	10

Protocol design



- For Group 2 (In-person assessments and online training): The assessments will be performed same as Group 1 (in-person). For training sessions, Group A (CoXergaming) will be trained through TeleXercise intervention via zoom online application (details are provided in the intervention section) for 6-weeks. All participants will be undergoing 3 training sessions per week for 6 weeks (18 training sessions). Group B (Matter of balance) will also be trained online and will undergo an 8-week (one session a week for 2 hours/day) structured intervention specifically designed to reduce the fear of falling and to increase the engagement in PA.
- For Group 3 (Online assessments and online training): The assessments will be performed online during the first and the last week. The online pre and post

assessments would consist of assessing balance, gait, cognitive performance and physical activity online via zoom application (details provided in outcomes). For the training sessions, Group A (CoXergaming) will be trained through TeleXercise intervention via zoom online application (details are provided in the intervention section) for 6-weeks. All participants will be undergoing 18-training sessions over a period of 6 weeks. Group B (Matter of balance) will also be trained online and will undergo an 8-week (one session a week for 2 hours/day) structured intervention specifically designed to reduce the fear of falling and to increase the engagement in PA.

6.1 Participant Screening

Inclusion Criteria

- Walking speed <0.8m/s
- Self-reported Physical activity <3 hours/week
- Hand grip strength <30 kgs for men & <20 kgs for women (this will be assessed only for participants who come for in-person assessment)
- Not on any sedative drugs
- Can understand & communicate in English
- Ability to walk more than 30 feet with or without an assistive device
- Must have either a desktop computer/laptop/tablet with access to internet (only for participants who choose to go for online assessments and/or training)Must have a helper buddy assistance (only for participants who choose to go for online assessments and/or training). The helper buddy will be asked to stay in the same room throughout the online assessment and online training sessions. The helper buddy will not participate in any other way throughout the research procedures. In case of any adverse event, we will follow the adverse event protocol. The session will be immediately concluded, and the participant will be provided all the necessary support by the helper buddy while the research personnel stays online to ensure the participant is taken care of. The participant will be asked for symptoms and the type of discomfort he/she is experiencing. The adverse event will be immediately reported to the PI and the participant will be asked to visit his physician or doctor to seek medical attention in case the symptoms persist for more than a day. In case of emergency, like chest discomfort, the helper buddy will be asked to call 911 immediately
- ***2-minute step in place test or walk around:*** The participant is asked to stand up straight next to the wall with the heart rate/O2 monitor plugged in to the index finger. The subject then marches in place or walks around the room (with health coach able to see them on the screen) for two minutes. *On completion, the health coach will obtain the heart rate and oxygen saturation. If the HR exceeds 85% of age appropriate HR max and O2 saturation falls below 90% then they will be excluded from the study.*

Exclusion Criteria

- Participants will not proceed with the study if any of the following occurs at baseline measurement: 1) HR > 85% of age-predicted maximal heart rate (HRmax) (HRmax = 220 – age), 2) systolic blood pressure (SBP) > 165 mmHg and/or diastolic blood pressure (DBP) > 110 mmHg during resting), and/or 3) oxygen saturation (measured by pulse oximeter) during resting < 90% (only for participants who choose to go for in-person assessment and/or training). For The blood pressure criteria is only for participants who choose to go for in-person assessment and/or training which will be measured in laboratory (Group 1 and 2). To serve good for safety in group 3 (online assessment and online training), we will mail O_2 saturation monitors along with heart rate monitors. Participants will not proceed with the study if at baseline measurement HR > 85% of age-predicted maximal heart rate (HRmax) (HRmax = 220 – age) (only for participants who choose to go for online assessments and/or training). If excluded and the participant wants to participate in the study, they would need to obtain a physician consent.
- Unable to stand for 5 minutes without an assistive device (length of a Wii Fit game)
- Uncontrolled acute medical/surgical, neurological or cardiovascular disease
- History of bone fracture or significant other systemic disease or surgery in the last six months
- Moderate to severe cognitive impairment (MOCA <24/30)
- Specific to MRI participants: Self-reported presence of pacemaker, metal implants other than orthopedic implants, and/or Claustrophobia, cataract surgery (lens not compatible to the MRI confirmed by the MRI technician)
- Do not have either a desktop computer/laptop/tablet with access to internet (only for participants who choose to go for online assessments and/or training)
- Do not have a helper buddy to assist or provide physical support (only for participants who choose to go for online assessments and/or training)
- Participants who cannot understand and communicate in English will be excluded due to instructions for training and protocol being provided in English.

6.2 Intervention

Group A – CogXergaming
[For Group 1(in-person assessments and in-person training)]

CogXergaming based cognitive-motor balance training will be delivered to group A using the commercially available Wii-Fit Nintendo and a mouse in conjunction with cognitive training. All participants will undergo 18 sessions of training in a tapering manner for six weeks with 60-90 minutes of training per session, i.e., 3 sessions each week till the 6th week. Each session will be divided into 3 sub-sessions, where each sub-session will consist of playing 4 to 6 games in conjunction with cognitive task. All the games will be performed using a Wii-Fit balance board in front of a TV screen. At the beginning of each session, 10 minutes of warm exercises will be provided that includes self-stretches, lunges, squats, high stepping and chair rises. The participant

will play four of the six balance board games Table tilt, Tightrope, Soccer, Balance bubble, Light Run and Basic Step (each game is max 1.5 minutes). The Light Run and Basic Step is a challenging game which will be replaced by any of the 2 games aced for 2 consecutive sessions. Each game will be superimposed with any 3 of the 6 cognitive tasks (word list generation consisting of verbal fluency (VF) and category fluency (CF), digit recall (DR), analogies (AN), mental arithmetic (MA), repeated letter (RL). In the VF and CF task, Participants will be asked to recite as many words as they can, from a given category or an alphabet (e.g., participants will be asked to say as many names of "animals", "fruits" or words from a given alphabet letter, such as "S"). In the digit recall task, the participant will require to repeat the digits the research personnel told (e.g., please repeat the digits 153, and the participant is expected recite the 3 digits). Participants will be asked to respond to analogies asked, e.g., "Bird is to fly, and fish is to ____". In the mental arithmetic task, the participant will be asked to mentally calculate and provide an answer to the math equation given, e.g., 4+2=? the participant is expected to reply "6". In the repeated letter task, the participant is simply asked to repeat only a specific letter and not repeat all the letter, e.g., please repeat the letter "A" only when you hear me say "A" and ignore all the others, the personnel will start saying a series of letter- B N O A, and the participant is expected to respond "A". The cognitive tasks will be randomized making sure that all the cognitive tasks are played with all the games. The cognitive and balance board game scores will be noted on the scoring sheet for each session. The cognitive and physical demand will be assessed after each game in the sub-session across the 12 sessions via NASA TLX [32]. The NASA TLX scores will be collected on an iPad/iPhone using the NASA TLX application and the data will be exported in the form of .csv file. Participants will be asked to rate their level of exertion on the Borg scale after each sub-session to determine the fatigue level of the training [33]. Blood pressure (BP) and heart rate (HR) will also be monitored prior to and after each sub-session. A total 10 minutes rest interval between every sub-session will be mandatorily provided. In case of any fatigue noticed or the participant demands a break, they will be seated back in a chair and their vitals will be monitored to ensure safety. The rest intervals will be used to obtain HR and blood pressure for safety monitoring. The projected total time spent on intervention is estimated to be 60 minutes (10 minutes warm-up + 30 minutes Exergaming + 20 minutes break). A physical therapist will provide external assistance (contact guard support) or guided movements and monitor any adverse reactions (changes in perceived exertion, cardiovascular monitoring etc.). All participants' compliance will be calculated at the end of the 6 weeks of training.

Group A – CogXergaming in the form of TeleXercise intervention
[For Group 2 (in-person assessments and online training) & Group 3 (online assessments and online training)]

The TeleXercise intervention proposes to deliver exercises via exergaming-based animation videos combined with or without explicit cognitive exercises delivered by a research personnel monitoring the intervention. All the online training sessions will be carried out on one-on-one basis. Participants will need a desktop computer/tablet or smart phone of their own with access to internet on which the commercially available application will be installed. Research personnel will set up meeting invites and send them links via their preferred receiving mode (SMS or email). Once the research personnel admits all participants into the room via the secure link the research personnel will start the intervention. The research personnel will launch the **Mimic-Game-&-Groove application** on their computer and share their screen with the participants. Participants have to turn their videos on for the research personnel to see them. The audio will be kept in mute by the health coach and once the participant tries to talk or show any discomfort he/she will unmute in any unanticipated event The intervention consists of participants mimicking the exercises that are shown in form of games and dances on their screen (similar to exergaming but being passive rather than interactive). The participants will not receive knowledge of performance or knowledge of results like in traditional exergaming; however, after each session, they will receive a brief feedback by the health coach, 1) qualitative based on the movements, 2) quantitative based on their heart rate max (intensity achieved) and the number of steps per session (measured via wearable sensors/smartphone). Participants will receive the TeleXercise intervention for three times per week for 6 weeks (18 sessions) with each session lasting about 1 hour and 30 minutes, including warm-ups, rests, and a cool-down. Training will consist of 20 minutes of warm-up –joint mobility, walking, and stretching exercises of moderate intensity, and cool-down- low-intensity stretching exercises and 1 hour of TeleXercise. A wearable device provided will measure the heart rate and physical activity during the course of training. They will be asked to read out the Heart rate and number of steps before the training begins (which will be displayed on the wearable device). Furthermore, after each set of exercise, they will be asked to note down their heart rate and number of steps displayed on their watch and when asked they should report it to the research personnel. Participants must be below 85% of the age predicted maximum heart rate to continue testing and training. All participants will be provided with a feasibility questionnaire and their compliance will be recorded at the end of the 4 weeks of training. Participants are provided with a set of balance exercises, which are demonstrated via animated avatars. The balance exercises includes non-interactive balance games (stepping forward, backward, sideways), Tai-Chi, Weight shifting (to right leg, left leg and practice distributing equal weights on both the legs), Aerobic (stepping in place), dance, strength, and stretching. Please see the figure below

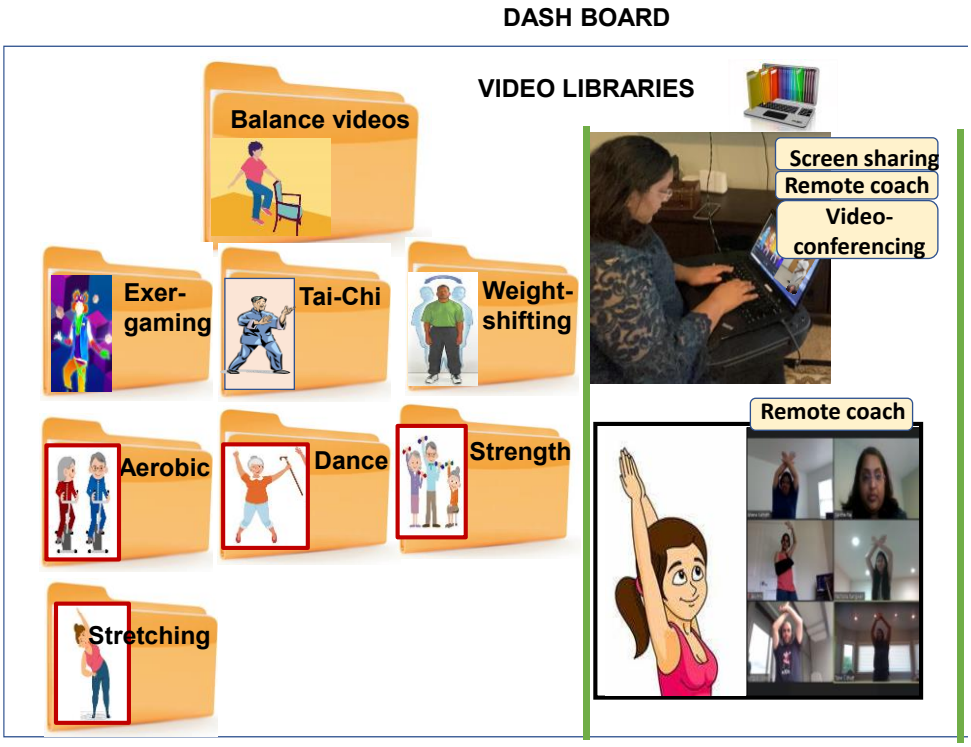


Figure 1.

Each game will be superimposed with any 3 of the 6 cognitive tasks (word list generation consisting of verbal fluency (VF) and category fluency (CF), digit recall (DR), analogies (AN), mental arithmetic (MA), repeated letter (RL). In the VF and CF task, subjects will be asked to recite as many words as they can, from a given category or an alphabet (e.g., participants will be asked to say as many names of "animals", "fruits" or words from a given alphabet letter, such as "S"). In the digit recall task, the participant will require to repeat the digits the research personnel told (e.g., please repeat the digits 153, and the participant is expected recite the 3 digits). Participants will be asked to respond to analogies asked, e.g., "Bird is to fly and fish is to ….". In the mental arithmetic task, the participant will be asked to mentally calculate and provide an answer to the math equation given, e.g., 4+2=?, the participant is expected to reply 6. In the repeated letter task, the participant is simply asked to repeat only a specific letter and not repeat all the letter, e.g., please repeat the letter "A" only when you hear me say "A" and ignore all the others, the personnel will start saying a series of letters- B N O A, and the participant is expected to respond "A". The cognitive tasks will be randomized making sure that all the cognitive tasks are played with all the games. The cognitive and physical demand will be assessed after each game via NASA TLX (20,21). The NASA TLX is a numerical 20 point-scale and participants will respond to the cognitive and physical demand questions accordingly. Participants will be asked to rate their level of exertion on the Borg CR10 scale to determine the fatigue level of the training (22,23). In case of any fatigue noticed or the participant demands a break, they will be asked to sit back in a chair and they will be asked to monitor their vitals and report to the remote research personnel to ensure safety. All participants compliance will be calculated across the training sessions

Group B – Matter of Balance training [For Group 1(in-person asssessments and in-person training) and Online version for Group 2(in-person assessments and online training), Group 3(online assessments and online training)]

Participants will undergo matter of balance training for 8 weeks (one session a week for 2 hours/day). The program emphasizes practical coping strategies that include group discussions, mutual problem solving, exercises to improve strength, coordination and balance, and a home safety evaluation. The program will be offered by graduate and post-doc research associates in the UIC Physical Therapy Department who will be certified A Matter of Balance (AMOB) coaches. The details of the exercise intervention are provided in the manual attached. Similar intervention for AMOB training will be provided online for participants in Group 2 and Group 3. All the online training sessions will be carried out on 1-on-1 basis.

6.3 Safety

Safety during in-person procedures: Participants will be wearing a safety harness system during the laboratory pre- and post-tests performed on motorized equipment such as the Balance Master and treadmill. For clinical tests, participants will be secured with a gait belt and will be allowed to use their assistive device (if using one) with close monitoring by the researcher or clinician. During the training sessions, the participants will also wear a gait belt, and external assistance (contact guard support) will be given for safety.

Safety during online procedures: Participants will be provided with a heart-rate, oxygen saturation and physical activity monitor which will be mailed to them after telephone screening. *To further ensure safety, 2 additional steps will be followed prior to participation in the study:*

1) *If the participant's resting O2 saturations is < 90% and heart rate is >85% of age predicted maximal heart rate, they will be excluded or given the option of obtaining physician consent to be included in the study. The health coach will monitor participant's resting heart rate and O2 saturation at the beginning of every testing/training session and at regular intervals during the training.*
2) *We will remotely administer 2-min walk test (shortened version of 6 min walk test) during the online assessment session for Group 3 (online assessment and online training). In this test, participants will march in spot or around the room (with health coach able to see them on the screen) in front of the health coach for 2 minutes with the pulse oximeter on. On completion, the health coach will obtain the heart rate and oxygen saturation. If the HR exceeds 85% of age appropriate HR max and O2 saturation falls below 90% then they will be excluded from the study.*

   For the testing procedure as well as the training procedure research personnel will engage with one participant only. During every zoom meeting, participants will not

proceed with any further testing or intervention if HR exceeds 85% of HRmax, or an increase in HR > 20 bpm of the resting HR. These measures will be recorded with the heart rate monitors sent to the participants. The tests included in the protocol were selected after a thorough discussion with 5 physical therapists who have been engaging and delivering telerehabilitation over the last 4 months of suspended in-person services. All tests are considering safe, reliability and validity of the tests and those that are easy to administer via telerehab. The remote research personnel will monitor the heart rate throughout the sessions. In addition, the test will be stopped if the remote research personnel observes any of the following signs occur during testing indicating cardiovascular intolerance: marked dyspnea, pallor, volitional fatigue, and imbalance during training. Furthermore, subjects will be asked to alert the remote research personnel and the helper buddy if they experience any discomfort such as tightness in the chest, excessive sweating, pain in chest, light headedness or dizziness, headache, and nausea. The test will be stopped if any of the above symptoms is reported by the participant during testing and training. Participants will also be required to place a sturdy chair approved by the remote research personnel in front of them for support, if needed throughout the training session. The helper buddy must be present to assist or provide physical support if needed during the procedures.

We will use an application called “Zoom” for our online screening an intervention. This zoom application will be HIPAA compliant version of ‘Zoom’ for all the sessions. This service includes access and authentication measure, all communications are safeguarded with end-to-end AES-256-bit encryption, and the platform integrates with the Epic electronic health record network to support healthcare workflows. Additionally, Zoom has “conduit exception” which means the application does not have access to personal health information (PHI). ‘Zoom’ does not have access to identifiable PHI and protects and encrypt all audio, video, and screen sharing data. Participants will only use the link provided by the research personnel, which would have: https://zoom.us/ followed by a long string of numbers, letters both capitalized and lower-case. For every testing/training session, we will be providing a new link to the participants to maintain security with only the research personnel having the rights to admit. No personal health information will be asked or recorded during these meetings.

6.4 Outcomes

Assessment: The following tests will be administered as baseline and post-intervention.
Table 1: Assessment variables for Groups 1 and 2 (In-person assessment) and Group 3 (Online-assessment)

Group 1 and 2 Assessments (In-person assessment)	Group 3 Assessments (Online Assessment)
Balance - Intentional balance control (Limits of stability test) (single and Dual task conditions) - Postural control (sensory organization test) (single and Dual task conditions) - Reactive balance control (Stance perturbation test) (single and Dual task conditions) - NIH balance Toolbox (Standing balance test)	**Balance** - 30-second chair stand test - Four-step square test - Sharpened Romberg's - One leg stance test
Gait - GaitRite mat (single and Dual task conditions) - NIH Balance toolbox (4m walk Gait speed test)	**Gait** - Tinetti Performance Oriented Mobility Assessment
Muscular fitness - Isokinetic Dynamometer - B-mode Ultrasonography	-
Cardiovascular fitness - Heart rate variability - YMCA submaximal cycle Ergometer test - NIH Balance toolbox (2-minute walk endurance test)	**Cardiovascular fitness** - 2-minute step in place test
Cognitive performance - Neuropsychological battery tests - NIH cognitive toolbox - Auditory clock test and letter number sequencing (single and Dual task conditions)	**Cognitive performance** - Neuropsychological battery tests - NIH cognitive toolbox - Auditory clock test and letter number sequencing (single and Dual task conditions)
Physical activity and motivation - Smartphone (Android/iphone)	**Physical activity and motivation** - Smartphone (Android/iphone)

- Wearable sensor - Quality of life (SF-36) - Physical activity scale for the elderly - Intrinsic motivational index	- Wearable sensor - Quality of life (SF-36) - Physical activity scale for the elderly - Intrinsic motivational index
fMRI scanning	-

Aim 1: Balance and Gait tests:

Balance:

For In-Person Assessment (Group 1 and 2)

Intentional balance control

Intentional postural sway will be examined via the Limits of Stability test protocol (Single task – ST) on the Balance Master (National Instruments etc.) and will also be examined while concurrently performing an oral trail making task, i.e. letter-number sequencing (dual-task condition, dual - DT) and /or Auditory Clock Test. The Equitest is a special equipment consisting of metal frame embedding forceplates with a surrounding visual display. Participants will be in a harness for their safety in case they get unsteady during any of the conditions inducing a sensory conflict. This will take about 15 minutes.

Postural Control

Sensory organization test will be administered using the Equitest equipment. This test quantitatively assesses the participant's ability to use visual, proprioceptive and vestibular inputs for maintaining their posture in quiet standing. The test will be administered under single and dual-task (simultaneous performance of motor and cognitive tasks) conditions. The test will take approximately 10 minutes to complete. Participants will be in a harness for their safety in case they get unsteady during any of the conditions inducing a sensory conflict.

Reactive balance control

Reactive balance control will be examined via the stance perturbation test under single and dual-task conditions (simultaneous performance of letter number sequencing task or auditory clock task). The participant will be prepared with 29 Helen-Hayes passive reflective markers placed on several joints on the body (knee joint, ankle joint, wrist, shoulder, hip, sacrum, neck). The participant will be in a harness and instructed to stand shoulder width apart on the Active Step Treadmill making sure both his feet are on the treadmill belt. The harness provides support making sure the participants knee do not land on the treadmill surface and avoid injury. A 3-D motion captures cameras will be used to capture the body kinematics and cortex software for collecting the data will be used. Prior to the experiment, the participant will be educated about what will he be experiencing once the test starts and will be instructed to respond naturally when an

unexpected perturbation occurs. After the participant attains a comfortable stance position on the treadmill belt, a sudden unannounced slip-like or trip-like perturbation will be induced, and their responses will be recorded. During the dual-task condition, the participant will be provided with the cognitive task at the beginning and any time after the participant begins to respond to the cognitive task, a slip-like or trip-like perturbation will be induced to the participant. Another research personnel will always guard the participant during the test as a safety precaution.
For analysis purpose, their kinematic data will be run through a customized MATLAB code for computing the required variables for analysis.

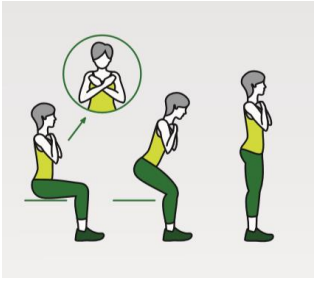
NIH balance toolbox

Locomotion and Balance measures of the NIH Balance toolbox will be used to assess their clinical balance scores via the NIH toolbox application using the iPad and iPod. The locomotion test involves 4-meter walk gait speed test. The total time taken to complete the 4-meter walk will be noted on the iPad. This test will take about 3 minutes to complete the task. The standing balance test involves maintaining stance position without losing balance at five different positions (eyes open on a solid surface, eyes closed on a solid surface, eyes open on a foam surface, eyes closed on a foam surface, eyes open in tandem stance position on a solid surface). The iPod will be clipped on the gait belt which will be buckled around the participants' waist. This test will take 7 minutes to complete the tasks. The participant will wear a gait belt throughout and a research personnel will be around to provide contact guard support during this test. Two-minute walk test will be conducted on a 60 feet walkway. In this test, the participant will be asked to walk up and down the 60 feet walkway for two minutes. The total distance covered will be recorded in a chart provided by the application on the iPad.

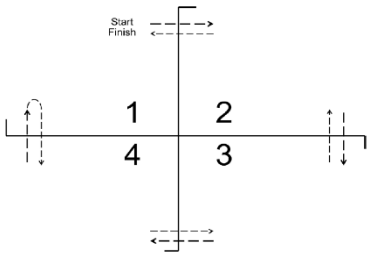
For Online Assessment (Group 3)

Balance will be determined with the following tests:

1) **30-second chair stand test**. This test is conducted to assess leg strength and endurance. Participants will be asked to stand in front of a sturdy chair and monitored by the remote research personnel during the test. The participants will be instructed to sit in the middle of the chair. Place their hands on the opposite shoulder crossed, at the wrists. Keep their feet flat on the floor and back straight with arms against their chest. Then the following instruction "On "Go," rise to a full standing position, then sit back down again. 6. Repeat this for 30 seconds" is provided to conduct the test and assessed by the research personnel remotely. This test is easy to perform and requires a sturdy chair (available at every home) and will be performed in front of the camera during the zoom meeting for the research personnel to monitor and collect the required data.



2) To test the dynamic balance and to assess the person's ability to step over objects forward, sideways, and backwards, a **Four-step square test** will be used. The participants will be instructed to stand in square 1 facing square 2 (see fig below). The participants are instructed to step as fast as possible into each square in the following sequence: 2,3,4,1,4,3,2, and 1 and required them to step forward, backward, and sideways to the right and left. Participants will be provided with the following instruction ""Try to complete the sequence as fast as possible without touching the sticks. Both feet must contact the floor in each square. If possible, face forward during the entire sequence." The research personnel will instruct and monitor the participants remotely and note the time the participants took to complete four-step square test. This requires a removable tape to be pasted on the floor (which will be mailed in case they do not have a tape at home). The test is easy to be performed by individuals and does not require any other special equipment to measure their performance.



3) To assess the static balance of participants in sensory integration taxing condition, they will be assessed on **Sharpened Romberg** (27,28). Participants will be shown on the screen the positions they need to stand in and will be assessed by the remote research personnel. Further the participants will also be assessed on **One-legged Stance test** to assess static postural and balance control (27,29). Participants will be instructed the following" Stand on one leg, place your arms across your chest with your hands touching your shoulders and do not let your legs touch each other. Look straight ahead with your eyes open and focus on an object about 3 feet in front of you. Ideally do this with the shoes off." Remote research personnel will assess the performance of the participant. This test does not require any equipment and is safe to administer remotely.

All these tests will be performed on single and dual task conditions. Under dual-task conditions, concurrently performed with an oral trail making task, i.e., letter-number sequencing (dual-task condition, dual - DT) and/or Auditory Clock test. The participants will be asked to place a sturdy chair in front of them for their safety in case they get unsteady during any of the above tests.

Gait function

For In-person Assessment (Groups 1 and 2)

Subjects will be asked to walk on the GAITRite, an electronic mat (CIR Systems, Inc., Sparta, NJ, USA). It consists of sensors embedded into 12 × 2 feet mat which measures spatial and temporal gait parameters via the accompanying GaitRite software (GaitRite Gold, Version 3.2). Dual-task performance will also be performed while walking.

For Online Assessment (Group 3)

Gait assessment (walking stance, walking pattern, step symmetry, trunk) of **Tinetti Performance Oriented Mobility Assessment** will be evaluated remotely to assess gait problems in older adults (30,31). A safe area visible to the research personnel remotely will be chosen and only then the test will be administered. During this test, the research personnel will ensure that he/she is constantly visible in the screen and measure the time taken to complete the test

Muscular Fitness

For In-Person Assessment (Groups 1 and 2)

Participants will be tested for lower extremity muscle strength and muscle size using isokinetic dynamometer. The Peak muscle torque/power generated by biodex software and Muscle cross sectional area will be examined.

Muscle cross-sectional area: For this, the participant will be asked to stand in a comfortable relaxed position. The midpoint of thigh will be marked for measuring the muscle thickness of quadriceps femoris. B-mode Ultrasonography via Sonosite M Turbo machine will be used to measure this muscle thickness with a 5 Hz scanning head. The scanning head will be pretreated with water-soluble transmission gel to provide contact on the marked surfaces without compressing the skin surface. Then, the transducer head will be positioned perpendicular to the longitudinal axis of the quadriceps for which the machine will provide with ultrasound images and electric calipers will be used for noting the muscle thickness.

Cardiovascular exercise tolerance

For In-Person Assessment (Groups 1 and 2)

Participants' Heart rate variability will be tested during all laboratory measures using the Polar ProTrainer 5 RS 800CX GPS. We would compare the change in indexes of heart rate variability over the period of training.

YMCA submaximal cycle Ergometer test: Prior to testing, the participants will be asked to notify the research personnel if they experience any discomfort such as nausea, dizziness during testing. The participants will pedal on the cycle ergometer for 1 minute as a warm-up without resistance at a rate of 50 revolutions per minute (rpm). The participant will continue to pedal at 50 rpm with increased resistance (25 Watts- Fist workload). We will record the heart rate at 2 and 3 minutes. If the difference between the heart rate at 2nd and 3rd minute are greater than 5, the participant will continue for another minute and we will then record the heart rate at 4 minutes. Based on the steady-state heart rate (HR) reached, we will increase the workload for the second stage or workloads beyond the fourth stage and/or increase the intensity by 25 watts (0.5 Kp) until the termination heart rate is reached (85% of age predicted max). The participant will cool down after the last stage has been completed.

For Online Assessment (Group 3)

2-minute step in place test: The participant is asked to stand up straight next to the wall while a mark is placed on the wall at the level corresponding to midway between the kneecap and top of the hip bone. The subject then marches in place for two minutes, lifting the knees to the height of the mark on the wall. Resting is allowed and holding onto the wall or a stable chair is allowed. Stop after two minutes of stepping. The remote research personnel records the total number of times the right knee reaches the tape level in two minutes.

Cognitive Function

For In-Person Assessments (Groups 1 and 2)

1) Neuropsychological battery of tests: This will be administered using DirectRT software [34] which has been validated and is a reliable tool to determine cognitive functioning. The participant will be provided with a pair of headphones with an attached microphone for his responses to be audio recorded. A keyboard and mouse will be provided for use during the games as required. 1) Visual Stroop test is a demonstration of interference in the reaction time of a task. In this test, the participant will be asked to read the ink color in which the word is printed and not read the word. 2) Category Fluency Task: This task assesses semantic fluency and requires the participant to recite as many words he can pertained to the category heard, e.g., animals, boys' names, and fruits in one minute. 3) Verbal Fluency Task: In this test, the participant will be asked to recite as many words as possible from the letter cue heard, e.g., "A". 4) Reaction time task: The participant will be asked to hit a number on the keypad corresponding to the position of the yellow dot on the screen. 5) Paired Associated Learning: In this task, the participant is instructed to observe numbers with their positions on the grid which will appear for only a few seconds, and when the cue, i.e., a specific number from the grid is given, the participant is expected to respond to the position the number was on the grid he observed. 6) Spatial Working Memory: The participant is asked to use the mouse to click on the red boxes to find a star. He will be instructed to avoid clicking on the boxes he already found the star in and find the stars in all the boxes for the game to progress. The game consists of 3 levels and the level progresses with the level of difficulty. The game will not progress if he does not complete that level given. 7) Auditory stroop task: The participant will hear words "High" and "Low" at high or low pitches. His/her task is to respond to the pitch of the word and not repeat the word. The responses will be audio recorded.
2) NIH cognitive toolbox [35,36,37] measures will be used to determine the change in the cognitive function. It is a standardized test widely used which is highly reliable and valid to use among the mild cognitively impaired older adults administered via the iPad using the NIH Toolbox application. All the responses will be recorded by the iPad and

scores will be generated accordingly which can then be exported via excel sheet. 1) Picture sequence memory test: This test evaluates the episodic memory of the individual. The participant recalls a series of pictures in a particular manner described before. For example, the participant is shown pictures about how to go camping. A series of pictures are shown on building a tent to fishing. For the test, the pictures are jumbled, and the participant is expected to place those pictures in the same order described. The number of adjacent pairs of pictures placed correctly will score a point. The scores are application generated. 2) Flanker inhibitory control and attention test: In this test, the individual is instructed to click on the arrow on the keyboard that matches the direction of the middle arrow in the stimulus given on the screen. Accuracy of the responses are recorded, and the scores are application generated. 3) List Sorting Memory test: The test is divided into two subsets to evaluate working memory. The participant will be shown a picture of animals. For the first subset, the task for the participant is to name the animals from smallest size to the largest size. The second subset involves a category of food along with pictures of animals. The task of the participant is to say the food first and then name the animals from smallest size to the largest size. The accuracy of the participants' response will be recorded by the application. 4) Dimensional Change card sort: This test involves three subsets assessing executive functioning. For the first subset, the participant is expected to choose the same shape of the stimulus provided, for example, if the stimulus given is a boat, and for the answers from which the participant is supposed to choose is given as rabbit and boat, he is expected to click on the boat. In the second subset, the participant is expected to click on the object that matches the color of the stimulus and avoid clicking on the same shape. The last subset involves playing the first and the second subset together in a randomized order generated by the application. 5) Pattern comparison Processing speed test: This test involves the participant to hit the yes or no button depending on the pictures provided look the same or not. Similarity of shapes of objects, colors are provided as stimulus. This test evaluates the processing speed of cognitive functioning.

3) Auditory Clock test: The participant will hear times of day. His/her task is responding yes if both the hour and minute hands are on the same side of the clock face and respond no if the hands are not on the same side of the clock face. The responses will be audio recorded.

4) **Letter number sequencing:**

For Online Assessment (Group 3)

For all the cognitive tests, the research personnel will share his/her screen to input the cues. The responses will be recorded and saved for data analyses. **Visual Stroop**-

Visual Stroop test is a demonstration of interference in the reaction time of a task. In this test, the participant will be asked to read the ink color in which the word is printed and not read the word. **Auditory Stroop**- The participant will hear words "High" and "Low" at high or low pitches. His/her task is to respond to the pitch of the word and not repeat the word. The responses will be audio recorded. **Flanker inhibitory control and attention test**- In this test, the participant is instructed to verbally respond right or left that matches the direction of the middle arrow in the stimulus given on the screen. Accuracy of the responses are recorded. **List Sorting Memory test**- The test is divided into two subsets to evaluate working memory. The participant will be shown a picture of animals. For the first subset, the task for the participant is to name the animals from smallest size to the largest size. The second subset involves a category of food along with pictures of animals. The task of the participant is to say the food first and then name the animals from smallest size to the largest size. The accuracy of the participant's response will be audio recorded. **Dimensional Change card sort**- This test involves three subsets assessing executive functioning. For the first subset, the participant is expected to say the same shape of the stimulus provided, for example, if the stimulus given is a boat, and for the answers from which the participant is supposed to choose is given as rabbit and boat, he is expected to say "boat". In the second subset, the participant is expected to say the object that matches the color of the stimulus and avoid naming the shape. The last subset involves playing the first and the second subset together. **Pattern comparison Processing speed test**- This test involves the participant to say the yes or no depending on the pictures provided look the same or not. The similarity of shapes of objects, colors are provided as stimulus. This test evaluates the processing speed of cognitive functioning.

Aim 2: Physical Activity (PA) Level

For In-Person Assessment (Group 1, 2 & 3)

Physical activity will be monitored using a wearable device or a smartphone to track the number of steps performed weekly pre and post the intervention. Participants will also be asked to visit the lab bi-weekly to upload their data upload.

Questionnaires such as **Physical Activity Scale for elderly** will be self-reported by the participant. Also, number of steps per session will be assessed using participants smartphone. For participants who have iPhones with IOS platform we shall use the "Health" application, and data will be retrieved in excel format by the use of "Qs access" application. For participants with Android phones, the "Google Fit" application will be downloaded on the phone, and data retrieved in excel format from participants' google account through the website "*https://takeout.google.com/*". Participants will be educated on how to email their data. Participants will be provided with a step-by-step upload

information sheet for iPhone and Android and be guided by the remote research personnel if needed any further help. All these applications are free of charge to participants and researchers. Additionally, a wearable sensor (Fitbit) would be mailed to them to their address and the physical activity (# of steps) will be recorded during the training sessions.
The Fitbit Sensor can track steps (walking & running), distance (km & miles), calories burned, exercise time and heart rate. It also stores up to 30 days of daily activity records. There is no risk involved in using Fitbit sensor as a physical activity monitor. Once they receive the sensor, they would be asked to wear it around their wrist and charge the sensor as required. After the completion of the study they would be required to mail back the sensor provided to them. A self-addressed stamped envelope will be provided to the participants to accomplish sending the same

Quality of Life: This will be assessed using the SF-36 questionnaires. Social community interactions will be assessed by the Community Integration questionnaires, The Physical Activity Scale for the Elderly will assess self-reported engagement in PA and the Geriatric Depression Scale will assess depression levels.

Motivation – Motivation index found to correlate highly with compliance will be evaluated by the 37 item self-report Intrinsic Motivational Inventory (Measures participants' Interest/Enjoyment of a target activity, and their Perceived-Competence, -Effort, and the activity's Value/Usefulness. These measures will be obtained after the intervention is completed.

AIM 3: Magnetic Resonance Imaging (MRI):

For participants interested in in-person assessment and (Groups 1 & 2) who are willing to be present in-person for the MRI scanning. The participants from both the intervention groups (A and B) willing to undergo MRI scanning will be invited to UIC center for Magnetic Resonance Research for fMRI scanning center located at 2242 W. Harrison St. Chicago. IL. 60612. Image acquisition will be performed in a 3T and 1.5T Magnetic resonance scanner (MR 750, GE healthcare, Milwaukee). A part of the research group Dr. Michael Patrick Flannery will perform the work for scanning the participants for fMRI.
During the functional MRI (fMRI) session, the following protocol will be followed for assessing the changes in the structural and functional connectivity pre- to post-intervention. Prior to the MRI scanning session, the entire protocol will be administered for familiarization of the protocol to be followed in the scanner. The participant is aware of the cognitive task and instructions will be provided again once he is in the scanner. The participant will be made to practice clicking the yes and no button for responding

during the fMRI protocol. A resting period of 8 minutes prior to the imaging process will be provided so that the person is relaxed and has got adjusted to the environment.
1) Rest for 8 secs. 2) Auditory clock test- The participant will hear times of day. His/her task is to respond by clicking yes button if both the hour and minute hands are on the same side of the clock face and click no, if the hands are not on the same side of the clock face. 3) Rest. 4) Action observation- The participant will observe a Wii-fit Game in the screen. 5) Rest 6) Mental Imagery with eyes open- The participant will be instructed to imagine that they are playing the game while a scene from the Wii-fit game is projected in front. 7) Rest. 8) Action observation and mental imagery- The participant will be asked to observe a video of a Wii-fit game and will be instructed to imagine that they are playing the game. 9) Rest. 10) The participant will be instructed to close his eyes and imagine that they are performing the game observed before. 11) Rest. 12) The participant will be instructed to observe the game while he simultaneously responds to the auditory clock test. 13) Rest. 14) The participant will be instructed to observe and imagine playing the game projected while he simultaneously responds to the auditory clock test. 15) Rest.

7.0 Expected Risks/Benefits

Potential Risks: Pertaining In-Person assessment and training
Reactive balance control: During the stance perturbation test, there is a slight risk of falls and injury (e.g., a muscle pull at shoulder or leg, muscle at the back).

Training sessions: As the training sessions involve high intensity training, the initial sessions may cause some muscle soreness in the lower limbs which may cause some discomfort during the first week of training, which will then be settled once the training sessions progress.

MRI scanning: The participants may experience discomfort as they are in an enclosed place with a loud noise generated during the MRI procedure. The participants will be given ear plugs to eliminate the MRI generated noise.
All participants will be monitored throughout the MRI scanning procedure through a camera while he/she is in the MRI scanner. They will be instructed that if any kind of discomfort is experienced to let us know immediately.

Preventing falls during the stance perturbation test (SPT) and limits of stability test (LOS): For both intentional and reactive balance control experiments, all the participants would be asked to wear a full-body protected harness to prevent any part of the body other than the feet contacting the treadmill belt (SPT)/force platform (LOS). The harness has adjustable shoulder and leg straps and will be attached to an overhead metal arch

that will allow the participants to perform movements freely having neither the knees nor hands from touching the treadmill belt/force platform. During the threat to balance control in stance position during the reactive balance control experiment, the safety harness will hold the participant and prevent him/her from falling. During the past several years, in more than 500 experimental sessions for both young and older adults conducted by the research team, similar harness systems have successfully protected Participants from injury following induced slips during standing or walking tasks. The harness system incorporates a number of safety features designed to limit the peak forces applied to the body, thereby minimizing the risk of injury upon a fall into the harness. The full-body harness is padded and provides support over a large contact area (>1500 cm2), primarily in regions that are able to withstand larger forces without injury (*i.e.* the pelvis and buttocks). Shoulder suspension of the harness provides protection against both forward and backward falls, with negligible risk of straps entanglement. Finally, the extent of body descent before harness assistance begins is limited (15 cm on average), very carefully calibrated and controlled. Our calculations indicate that, during a worst-case fall into the harness, an individual who weighs 1000 N would be Participated to a peak pressure of < 0.3 MPa, well below the stress threshold for even a moderate muscle contusion (1.9 MPa), requiring no medical treatment.

Preventing falls during training sessions: There is also a risk of balance loss and falls while participating in the actual balance training on the Wii-Fit balance board. For that reason, participants will always be made to wear gait belt and supervised by a research personnel mentioned in Appendix P during the training sessions. Blood pressure and heart rate will be monitored prior to the training session, after each sub-session (completion of 4 games). Participants will be given a chair to sit back after each sub-session (completion of 4 games - approximately 10 minutes considering each game played for 1.5 minutes) or if he/she feels tired during the game (i.e., ≥ 15 on Borg scale for perceived exertion) or if the blood pressure is beyond normal limits (i.e. > 85% of age-predicted maximal heart rate). More than or equal to 15 on the Borg scale of perceived exertion indicates that the intensity of the physical activity performed was high and that it gives an idea to the research personnel that the participant would need to slow his movements down. Additionally, if at any point the heart rate, blood pressure, drops or rises above the pre-determined acceptable limits, the session will be terminated. Participants will be asked to inform the experimenter about any of the symptoms including marked breathlessness, excessive sweating, pain in chest, or fatigue. The research personnel will observe for any changes in participant's facial expression indicating anxiety or discomfort. In case of any discomfort, the session will be terminated, and the time of the training session will be noted.

Preventing injuries from training: The proposed setup incorporates several precautionary features, evolved through a decade of research, against such injuries. To further reduce the risk of injury, all Participants will undergo a series of stretching and warm-up exercises at the start of the experiment and training. A physical therapist or an exercise specialist on the team will conduct these procedures. Stretches will encompass all major muscle groups of the lower limbs and trunk. Warm-ups include activities such as walking, lunges, squats, high stepping and chair rise.

Potential Risks: Pertaining Online assessment and training

Clinical test related risks

1. The clinical balance tests performed pre-and post-intervention would present with a mild risk of losing balance while performing the activities. Subject would be remotely monitored by the research personnel and also asked to place a sturdy chair in front of them while performing these assessments.
2. The walking tests (2-minute step in place test and the training may be led to some amount of fatigue.
3. During the cognitive assessment which tests memory, attention, comprehension etc., participants may experience some disappointment if they are unable to perform a certain task.
4. The answering falls and physical activity questionnaire may have some questions about personal health information and daily physical activity habits and the subjects may be some discomfort while answering those questions.
5. During assessment and training sessions of Group 2 and 3, we will ask the "helper buddy" to note what the participant may be feeling. Incase of events like shortness of breath, excessive sweating, fatigue or muscle crams- the session will be stopped and the participant will be discontinued from the study

Figure 2: Adverse event protocol

Privacy related risk

6 Further, as all the tests will be performed in a home-based setting via online interface wherein the researcher personnel would be performing the assessments and training remotely, therefore at any point in time there is a potential for breach of privacy and confidentiality.

Potential Benefits:

Study participants will receive bone health status, balance performance from their osteoporosis screening and other physical ability tests. Such information can allow them to take any necessary preventive measures. In addition, this cognitive-motor exergaming is expected to promote significant benefits on reducing fall-risk by improving function of both the balance control and cognitive functions. Further, it delivers training via a low cost off-the shelf virtual gaming console for providing

repetitive, engaging and meaningful, task-orientated training. It also examines if the training-induced effects cause plasticity in the cognitive and motor control areas and networks in the brain. If participants demonstrate no gains, the training offered will maintain their optimal physical functioning and not result in any deterioration.

8.0 Data Collection and Management Procedures

The overall goals of data management are to ensure: 1) that the collected data is properly documented and accurately entered; 2) the confidentiality of the participant data is maintained giving access to the primary investigators for retrieving data and exporting to statistical packages.A codebook will be created consisting of Prior to data collection and entry, a codebook will be created which will contain the variable names, descriptions, and value codes of each variable/item collected during the study. Following development of the codebook, a database will be created in Microsoft Excel to facilitate data entry. The program permits logic checks on input and checks for invalid entries. One research staff member will enter all data separately, and another researcher will verify the data entry to identify any mismatching data values, variable names, or observation numbers thus, to eliminate data entry errors. Several data quality checks will also be conducted, including descriptive statistics and graphic plots to detect outliers and influential observations. All computer data will be stored in a password-protected network server with back-up scheduled every midnight. The original raw data will be stored in a locked cabinet accessed only by key project personnel. The motion analysis data would be backed up on a portable hard drive and stored in a locked cabinet accessed only by key project personnel.

Each laboratory session will be recorded with a video camera system for further analysis of body responses. The 3D motion cameras will detect small ball-shaped markers that is placed on different parts of the body, including the feet, ankles, knees, hips, shoulders, elbows, and wrists to represent body movement. Each session will also be recorded on a videotape using a camcorder. Only the investigators related to this project will have access to these files. The videotape or its reproduction may be used for research purposes such as publication in scientific journals or presentations at educational or scientific meetings and teaching purposes in the future. All the videos are taken from the side and back, where no facial feature will be identifiable. Thus, the participant would not be recognizable by a stranger without other identification from the record. ID codes will be at a single office and in a locked file. They will be destroyed along with the videotape of the experiment 2 years after completion of the entire project. Only the personnel directly related to the project will have access to the videotape, which is kept in a locked office. Only the Principal Investigator and one research team member have the access key, and there are no duplicate keys.

For Group 1 and 2: All the details described above will be used for data collection and storage.

For Group 3 (online assessments and online training: Data including assessment measures (online assessment procedures are described in assessment section) will be

collected via HIPAA complaint 'Zoom' version (described in 'Safety' section). The participants performance will be scored on observational basis which will be noted on hard copy of the trial record sheet for testing. During the training sessions, the participants will read out their heart rate and number of steps which is displayed on their wrist monitor to the research personnel after every sub-session and the research personnel will note this down on the hard copy training sheet. The participant will be informed prior to recording the testing and training sessions to ensure that he/she is aware of it. Their consent for video recording is mentioned and clarified in the informed consent that videos will be recorded if they participate in the study. However, they can opt out of their videos being used for education purposes or conferences. The video files will be in the form of mp4 and this will be used for analysis purposes. No personal health information or contact information will be recorded to ensure participants privacy. Each participant will be denoted with a subject number and testing and training video files will be directly stored under subjects specific denoted number.

9.0 Data Analysis

All the data analysis will be performed at 1919 W Taylor St. Room 415, B-56 using the SPSS Inc., (Armonk, NY). Also, see the section "Statistical Considerations".

10.0 Quality Control and Quality Assurance

For quality control and assurance, all the study related procedures will be performed by trained and experienced personnel. All research personnel will take the CITI and HIPAA training courses along with regular training to ensure safety of the custom designed equipment. The raw data will be checked by the PI immediately after data collection.

11.0 Data and Safety Monitoring

There will be a dual data and safety monitoring plan in place. One which is monitored by the research team itself and the second which is monitored by a Data and Safety Monitoring Board/Committee (DSMB).
The Principal Investigator (PI) Dr. Tanvi Bhatt will be responsible for ensuring participants' safety daily. In addition, other individuals the Safety Officer in conjunction with a Data Safety Monitoring Roybal Center Committee will act in an advisory capacity to monitor participant safety, evaluate the progress of the study, to review procedures

for monitoring the confidentiality of the data, the quality of data collection matter, management, and analyses.

For monitoring participant safety during the testing and training sessions, Participants will be asked whether they are feeling any pain or any kind of distress at regular intervals. Participants' heart rate (HR), blood pressure (BP) and blood oxygen levels will be monitored before and after testing, and before, after and during training session. The experiment will be stopped if any discomfort noticed and the HR > 20 bpm of the resting HR or blood oxygen drops below 92% or systolic BP exceeds > 20 mmHg of the resting state or if the diastolic BP exceeds > 15 mmHg from the resting state. There will always be two people in the experiment area to guard the participant if required. There is always a first aid kit available in the lab for use in case of any minor injury. We also have an AED for emergencies and at least one of the investigators during any experiment will be AHA-BLS (American Heart Association - Basic Life Support) certified for health care providers. In addition, we do regular harness checks to ensure that it is not damaged. Also, the participants will be called 2 days after the testing session and will be asked to inform the research personnel if there is any discomfort during the intervention period.

Adverse Event and Serious Adverse Event Collection and Reporting

An adverse event is defined as an undesirable and unintended result of therapy, intervention or interaction experienced by a participant in a research study. We will monitor adverse events, reports by participants during the intervention and maintenance phases of the study and reasons for drop out. All field staff who work directly with participants will be required to notify the PIs of any unanticipated problems/adverse events immediately upon discovery. If an adverse event is recorded during the intervention session, the session will be concluded, and the event reported to their physician and to the investigators.

Participants who report the event and will notify the University IRB. The PIs will immediately notify the Data Safety Monitoring Board and the University Institutional Review Board.

The relationship of the adverse event as not related, possibly related or definitely related will be determined using standard criteria for clinical trials and any additional guidelines used/ developed by the Data Safety Monitoring Board and the University Institutional Review Board.

<u>Possible - to qualify, the adverse event must meet 2 of the following conditions:</u>

1) Has a reasonable temporal relationship to the intervention,
2) Could not readily have been produced by the Participant's clinical state,

3) Could not readily have been due to environmental or other interventions,
4) Follows a known pattern of response to intervention,
5) Disappears or decreases with reduction in cessation of intervention.

Probable - to qualify, the adverse event must meet 3 of the following conditions:
1) Has a reasonable temporal relationship to the intervention,
2) Could not readily have been produced by the Participant's clinical state,
3) Could not readily have been due to environmental or other interventions,
4) Follows a known pattern of response to intervention
5) Disappears or decreases with reduction in cessation of intervention.

Definite - to qualify, the adverse event must meet at least 4 of the following conditions:
1) Has a reasonable temporal relationship to the intervention,
2) Could not readily have been produced by the Participant's clinical state,
3) Could not readily have been due to environmental or other interventions,
4) Follows a known pattern of response to intervention,
5) Disappears or decreases with reduction in cessation of intervention

Protection against Study Risks.

Informed Consent Process.

A copy of the consent form approved by UIC IRB will be provided to the potential participants to follow verbal description and to read on their own. Research assistant or research personnel will describe the study procedures verbally including testing, training, potential risks and benefits. Potential participants will be given time to read the consent form and may ask any questions regarding the study to clarify the misunderstandings. Individuals interested in participating at this point will be asked to sign two copies of the written consent form and will be provided with one copy for their use.

Protections against Study Risk. We believe that there is a minimal risk of injury to the participants in this study. These risks include a slight risk of muscle soreness associated with increased physical activity or stretching during training sessions, and a leg or shoulder muscle pull, and leg or back sprain due to expose to unexpected slip-perturbation during the testing session. There may also be the risk of anxiety due to the slip test. In case of any injury, participants will be encouraged to (a) consult their primary health care provider before initiating any new physical activity; and (b) perform physical activities at a pace that is comfortable for them and in a way that is consistent with any recommendations from their medical providers. Other risks include the following:

- While performing the blood pressure test, the cuff squeezed may elicit some discomforts.
- The clinical balance tests present a mild risk of losing balance while performing the activities.
- During the cognitive assessment, which tests memory, attention, comprehension, etc., may cause some disappointment and/or anxiety if they are unable to perform a certain task.
- The falls and physical activity questionnaire may have some questions about personal health information and daily physical activity habits, may be uncomfortable answering those questions. In that case, they have the option not to answer those questions.
- Further, as all tests will be performed in a laboratory setting wherein the research personnel will be performing the assessments and training, there is a potential for breach of privacy and confidentiality at any time.
- There may be risk of loss of confidentiality due to participation in this study.

To ensure confidentiality of all data, all participants will be assigned a numerical code and their data will be stored with the same corresponding code. Any identifying information that corresponds to the code number will be stored in a separate and double password-protected file. Access to this file will be limited to the PI and study research assistant/coordinator. Personal or private identifiable data will not be stored on portable devices. Data in paper format, such as consent documents, will be stored in locked file cabinets in a locked office and will only be accessible by immediate project personnel.

All coded electronic data will be stored and secured via password access on the Institute for Health Research and Policy (IHRP) protected server. The IHRP server systems are in a climate controlled locked room that is accessed by ID card. The hardware is protected by several APC UPS systems. The IHRP network uses Windows 2008 R2 Active Directory to control access to files and folders. The system is firewalled off from the rest of the university. The network is a private IP based system that permits us to restrict sensitive machines from connecting to the internet. There is no wireless access directly into the IHRP system. Encrypted backup tapes are stored off-site with Iron Mountain. Data analysis will be conducted with the use of coded data, thereby greatly reducing the chance of inadvertent disclosure.

All project staff will be required to be current in training in Human Research Participants protection sponsored by the University of Illinois at Chicago. The staff will also receive additional training on confidentiality by the principal investigator.

We do not anticipate any serious adverse events or distress as a result of participating in the proposed research. Any concerns will be immediately reported by the principal investigator. The Principal Investigator is a clinical psychologist and will provide training on identifying and responding to emotional distress in participants. For medical emergencies, staff will be trained to immediately call 9-1-1.

Frequency of Data and Safety Monitoring/ Safety Officer (SO) Reports.

The PI will meet semiannually with the DSM Committee, either in-person or by teleconference call to review study progress, data quality, and participants' safety. Written summary reports will be submitted twice a year and will include a detailed analysis of study progress, data and safety issues. Dr. Susan Hughes will serve as chair of the committee, and as SO for any adverse event reports. Other members will include David Marquez, PhD (Kinesiology), Margaret Baumann, MD (Medicine), and Laurie Ruggiero, PhD (School of Public Health).

The PI will be informed of serious adverse events as soon as they occur and will notify the *SO* within 24 hours of notification. In addition, serious adverse events will be reported to the UIC IRB with their established protocols.

12.0 Statistical Considerations

Counting for the attrition rate of 20% of most of the interventions with frail older adults, we expect to use data of 96 participants with 16 participants in each subgroup (Group 1A and B; Group 2A and B; Group 3A and B) for data analysis. To determine the effect of training using Exergaming, pre-post changes of balance, cognitive, gait and cardiovascular measures will be examined by ANCOVA. Results of the study from a sample size of 96 will enable us to conduct power analysis to plan for a larger scale RCT.

13.0 Regulatory Requirements

13.1 Informed Consent

Oral consent will be obtained over the telephone during the initial phone screen. Those who are eligible and elect to participate will be provided with a written informed consent document (approved by the University of Illinois at Chicago IRB). Consent will then be obtained by the research coordinators. All study participant documents will be available in English. The consent form will explain all procedures, risks, and benefits of the study. The study Participant will

communicate their intention to leave the study clearly too any study staff personnel, and their confidentiality will not be breached. Participants will receive a signed copy of the informed consent document. Informed consent form for each group will be separate so as to avoid any confusion for the participant. For Group 1 and 2, informed consent will be obtained in person in the laboratory. For Group 3 (online-assessments and online-training informed consent process will occur remotely (online) using REDCap. The PI holds an account through which participants will be provide their Informed consent via e-sign. This process will be explained via 'Zoom meeting' to walk them through every process.

13.2 Participant Confidentiality

Participants' confidentiality would be maintained as all the identifying information will be de-identified using an alpha-numeric code at the time of enrollment and the Participant specific unique code will be used for all the data collection purposes. All study records will be kept confidential by using a numerical code. A participant will not be identified personally in any report of the results. We will keep the identifying information at a centralized single location which will be locked, and it will be destroyed after the completion of the entire project. Only those who are active members of the research team will have access to the raw data. This research doesn't involve the use and disclosure of protected health information.

13.3 Unanticipated Problems

Any unanticipated problems will be reported to the IRB by submitting a "Prompt Report" form.

14.0 References

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