Protocol

Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercises (INHANCE)

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Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise (INHANCE)

Revision 6, Dated: October 19, 2022

Posit Science Corporation

INVESTIGATOR

NAME:_____
Signature:_____
DATE: _____

By signing here, the investigator acknowledges that he or she has reviewed and understands the protocol referenced above and agrees to comply with it. Additionally, the Principal Investigator's signature indicates that his/her site has not been the recipient of prior FDA 483 reports or other detailed audit findings. Any and all prior FDA 483 reports or regulatory warnings have been submitted to Posit Science Corporation prior to the commencement of this clinical trial.

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1. Title

Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise (INHANCE)

2. Principal Investigators and Key Staff

The trial is sponsored by Posit Science Corporation (PSC) and is funded exclusively by the National Institute of Aging. PSC will assist with posting flyers and ads online and serve as the coordinating and data management center. Key staff may be found below:

Principal Investigators

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Clinical Trials Manager

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Clinical Trials Manager
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3. Site Investigator and Study Site

The Site Investigator, listed below, will oversee participant recruitment, screening, and enrollment for this clinical trial. In addition, this study site will administer the assessments, provide training program orientation and support during training period, and complete the imaging required for this trial.

Study Site McGill University

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4. Overview

This study called INHANCE (*Improving Neurological Health in Aging via Neuroplasticity-based Computerized Exercise*) is a validation study to evaluate efficacy of two neuroplasticity-based, computerized cognitive training programs to improve neurological and neuropsychological health in older adults. Both the study and the training programs being investigated meet the criteria of **Non-Significant Risk**.

This study is registered in an online database for clinical trials that is run by the federal government. The purpose of this database is to serve as a resource with easily accessible information about publicly and privately funded research studies that are being done or have been done. This database will not include information that can identify participants that partake in the study. This listing is available to the public at http://clinicaltrials.gov.

5. Specific Aims

The primary objective of this study is to evaluate the impact of a targeted speed and attention training program to improve cognition in healthy older adults, as evidenced by standard measures of cognition, and positive improvements in the neuromodulatory cholinergic system as measured via positron-emission tomography (PET).

The primary outcome is to determine the extent to which a cognitive training program focusing on speed and alertness mechanisms leads to measurable brain changes within the cholinergic system at baseline and at post-intervention. We

will measure the FEOBV uptake through PET imaging.

Exploratory outcomes will include neuropsychological assessments to measure the cognitive and attentional abilities of participants prior to and after the training program. The assessments will evaluate important performance assets post-intervention and at a +3month benchmark after the training is complete. It will also include behavioral assessments of acetylcholinergic function. Heart rate variability and/or pupillometry will be measured during train-to-task assessments (and/or during the training exercises if extra time is needed).

6. Background

Americans are living progressively longer lifespans without a corresponding delay in the onset of dementia. This mismatch between longevity and brain health has led to an epidemiological crisis with over 5.5 million dementia cases in the U.S. alone and nearly 50 million cases worldwide.[1,2] The cost of care for this order of magnitude carries a steep economic price including resources of nearly one trillion dollars worldwide and $259 billion in direct care costs and $230 billion in dementia caregiver productivity losses to the U.S. alone—all of which are projected to increase as time unfolds.[1,2]

Dementia-related pharmacotherapies only mildly, non-selectively and temporarily amplify neurological function, and do not significantly delay the progression of Alzheimer's Disease and other dementias to their catastrophic end state. At the same time, across the past decade, non-pharmacological therapeutics have been shown to be efficacious for sustaining brain health, most notably forms of progressive computerized brain training that target positive brain health-related processes identified in brain function- and plasticity- related neurophysiological studies.[3–6] For example, a specific form of divided-attention speed-of-processing training called Useful Field of View training (UFOVt) was shown by independent researchers in the ACTIVE trial to reduce the risk of dementia onset by 28-48% over a decade-long follow-up period.[3]
A second form of training, developed via two SBIR-funded phase II programs (R44AG039965; R44NS071780), focuses on naturally upregulating neuromodulatory control machinery and is referred to as Tonic and Phasic Alertness Training (TAPAT), has now been shown to drive strong benefits in executive function,[7,8] skill acquisition,[9] spatial and non-spatial attention,[10–12] and sleep duration and quality,[13] driving neurological improvements that enhance UFOVt-driven gains.[9] In a recent pilot study in healthy older adults conducted at

McGill University, a limited epoch of training with TAPAT confirmed that it broadly upregulated forebrain acetylcholine (ACh) expression, as measured by PET-ligand imaging. This trial will seek to confirm these effects in a controlled setting to more completely understand the mechanism(s) by which UFOVt and TAPAT's attentional training so broadly enhance cognition. Given the importance of initiatives to identify alternative or adjunctive non-pharmacological therapeutics for the prevention and treatment of dementia (e.g., FINGER trial; US Pointer trial) the aims of the current project are of great importance: to further develop this approach to be adopted as a standard tool applied for the management of brain health in our older-age populations.

7. General Study Design

We will employ a double-blind, parallel-arm, active-controlled, randomized clinical trial design comprised of a treatment group, a computerized program that trains speed of processing and attention, compared to an active control group using executive function training in 90 healthy older adults.

Approximately 108 participants will be consented to ensure the successful completion of 90 participants (post 20% attrition). Participants will then complete the *Screening* (V0) assessments to determine eligibility. Following inclusion, participants will complete the *Baseline* (V1) assessments, PET imaging and structural MRI scan; participants will then be randomized into either the *Speed and Attention training* or the *Executive Function training* and will engage in approximately 35 hours of program use for the 10-week *Intervention Period*. Following the 10-week intervention, participants will complete a *Post-Intervention* (V2) assessment, and PET and MRI imaging to evaluate changes in cognitive function. Participants will then stop using their assigned program for 3 months and return for a *Follow-up* (V3) end-of-study assessment to evaluate the endurance of changes in cognitive function in the absence of further program use.

The protocol will be conducted in accordance with the protocol submitted to and approved by the Institutional Review Board prior to implementation.

8. Study Population

All subjects will be recruited in Montreal, Canada near McGill University where the FEOBV radiotracer is synthesized and administered. Selection of participants

is based on age and health status and is not based on gender or ethnic considerations, although these are expected to reflect the diverse population of Montreal. Every effort will be made to target a balanced enrollment.

9. Inclusion/Exclusion Criteria

Following informed consent, participants will be screened for the following inclusion/exclusion criteria.

Inclusion Criteria

1) Potential participant must be 65 years or older at the time of study screening.
2) Potential participant should achieve a score of ≥ 23 on the Montreal Cognitive Assessment (MoCA).
3) Potential participant must be likely able to complete all primary outcome measures in the judgment of the investigator.
4) Potential participant must demonstrate adequate decisional capacity, in the judgment of the investigator, and capable of to making an informed decision regarding their participation in this research study.
5) Potential participant must have the visual, auditory, and motors capacity to use the computerized intervention in the judgment of the investigator.
6) Potential participant must already have, be willing to obtain, or be willing to travel to locations with internet connectivity to complete intervention activities.
7) Potential participant must be able to communicate in either English or French.

Exclusion criteria:

1) Potential participant has an existing diagnosis of major or minor neurocognitive disorder at screening.
2) Potential participant answers 'yes' to:
   Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia-Suicide Severity Rating Scale (C-SSRS) or any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion *if the ideation or behavior occurred within 2 months from Participant's date of consent* (as recommended by the FDA for treatment trials.)
3) Potential participant scores >10 on the Geriatric Depression Scale – Short Form (GDS-SF).

4) Potential participant has been treated with a computer-based cognitive training program manufactured by Posit Science within 5 years of the date of consent.
5) Potential participant is participating in a concurrent clinical trial (involving an investigational pharmaceutical, behavioral treatment, medical device or other) that, in the judgment of the investigator, could affect the outcome of this study.
6) Potential participant is pregnant or breastfeeding.
7) Potential participant has claustrophobia or implantation with any medical devices above the waist that may concentrate radio frequency fields or have other medical issues that may frustrate participation in MRI imaging procedures.
8) Potential participant has medical illnesses deemed to interfere with participation in study activities and/or unstable and/or untreated conditions that may affect cognition, including substance abuse/dependence disorders, drugs that interfere with cholinergic function, ongoing chemotherapy or other cancer treatment.
9) Potential participant shows signs of intoxication due to current substance abuse (including alcohol and/or illegal drugs).

10. Recruitment

Study participants will be recruited from Dr. de Villers-Sidani's neurology clinic at the Montreal Neurological Hospital (MNH).

Recruitment methods may include public presentations about the trial, brochures and flyers that describe the study and include information regarding inclusion/exclusion criteria as well as mechanism for indicating interest and communicating desire to be contacted. Study recruitment materials will describe the opportunity to volunteer for a clinical trial to advance the science and treatment of age-related cognitive decline. The emphasis of the benefit will be on advancing science to assist others with age-related cognitive decline. Compensation will be described in appropriate terms that are not overemphasized relative to the remainder of the text. No indication of "free medical treatment" will be communicated.

All materials used for advertising or recruitment will have received IRB approval prior to implementation, and the study site will conform to recruiting standards established at the study site. The study staff will manage these efforts

and contact individuals that indicate interest. The aim of phone contact is to describe the study, answer any questions, and if the potential participant agrees, conduct phone screening.

PSC will assist posting recruitment ads and flyers online and will serve as a coordinating and data management site. PSC will directly manage and support this study in San Francisco, using standard and established methods.

11. Description of Informed Consent Process

Prospective participants will undergo a phone screen, which will include an overview of study details and a discussion of all risks along with questions to assess inclusion and exclusion criteria. Eligible individuals expressing interest in the study will be invited to the study site to complete the informed consent discussion, followed by a behavioral screening session, health questionnaire, and interview. The informed consent discussion will take place in a private room at the study site. Participants will be provided a copy of the IRB-approved consent form detailing the general purposes and procedures of the study. Study staff will provide detailed information about study requirements, offer all participants an opportunity to ask questions and provide clarification prior to signing the consent. Participants will be encouraged to take time to consider whether or not they wish to participate in the study and discuss with family prior to signing the consent. At the participant's request, study staff may be asked to 'step-out' of the room to provide privacy for such discussions. To participate in any of the proposed studies, an individual must be judged capable of understanding the nature of the research, risks and potential benefits. The consent form will clearly state that the participant may withdraw consent and stop participation at any time without penalty. All participants will be told that the purpose of the study is to evaluate the effectiveness of two different computerized training programs. Potential risks and benefits will be explained by the study staff, and the participants will be asked to sign the consent form. A member of the study staff will also sign the consent form. No study activities will take place prior to completion of the consenting process.

On the consent form, both the treatment and active control programs will be described as "computer-based activities designed to engage cognitive processing," and the goal of the trial will be described as "comparing two forms of cognitive remediation." The goal of this description is to ensure that if participants realize that they are engaged in a training experience that differs

from other friends or colleagues enrolled in the trial, that they will not assume that they are participating in an experimental versus control, thereby maintaining the integrity of the blinded study. We note that although we hypothesize that the active control executive function training will not be as effective as the training, they have been chosen for their face-validity: providing time-matched, online access to computer-based exercises.

The consenting study team member will inform participants about compensation for their participation in the study. Specifically, we will provide $30 USD ($40 CAD) for the *Baseline Visit* and PET/MRI Imaging (V1), $10 USD ($13 CAD) for every 10 training sessions completed (maximum of $70 USD ($91 CAD) for completing all 70 sessions) during the *Intervention Period*, $30 USD ($40 CAD) for completing the *Post-Intervention Visit* and PET/MRI Imaging (V2) and $30 USD ($40 CAD) for the end of study 3-month *Follow-up Visit* (V3). Participants who complete the study in its entirety will be reimbursed $160 USD ($211 CAD). Participants who complete the PET imaging at the Concordia PERFORM Centre will receive an additional $50 CAD for transportation reimbursement at each visit. Payment for assessment visits will occur following completion of that visit. In the event that a participant must repeat an assessment visit due to administrative assessment or study staff errors, participants may be provided additional compensation for that session. If the participant does not complete the study or withdraws early for any reason, the participant will only be compensated for the study visits and/or training sessions they have completed.

Participants will be offered a loaner tablet to complete their assigned training exercises but also given the option to train on a personal device if desired. For participants who are loaned a tablet, compensation for all study activities completed through the end of the *Intervention Period* will occur after the participant returns the loaned tablet to the study staff at the *Post-Intervention Visit* (V2). If, for any reason, participants are unable to meet with study staff in person to return the tablet, the participant will be sent a pre-paid label and box (if necessary) to return the tablet at no cost to them. Participants who withdraw from the study will be compensated for all study visits they have completed once the loaned tablet has been returned to the study staff. For participants who do not return the tablet, all forms of appropriate means and communication (e.g. phone contact, email, mailed letters) may be used to retrieve the study tablet. If a loaned tablet is not returned to the study staff upon the participant's exit from the study, the device may remotely deactivated so that it is unusable. Participants who do not return the tablet will be compensated for study-related

activities minus the cost of the tablet so that a replacement device can be purchased ($194 CAD).

One fully-executed copy of the informed consent will be provided directly to the participant, the original signed form will be retained in a secure manner at the study site and be available for inspection at the study site upon the request of representatives of the reviewing Institutional Review Board or other relevant regulatory agencies. The copy of the consent form taken home by the participant will include appropriate telephone and email contact information, including the Site Investigator and site's reviewing IRB.

Individuals with altered mental capacity who are otherwise not capable of providing independent consent, or who require a Legally Authorized Representative (LAR) to consent, are not eligible for to enroll in the proposed study. The informed consent form will be changed if increased risk or other adverse events, which will influence a person's willingness to participate or increase their risk of participation, are noted. In such cases, IRB review and approval will be obtained for the revised consent form and active participants will be re-consented.

12. Screening Procedures

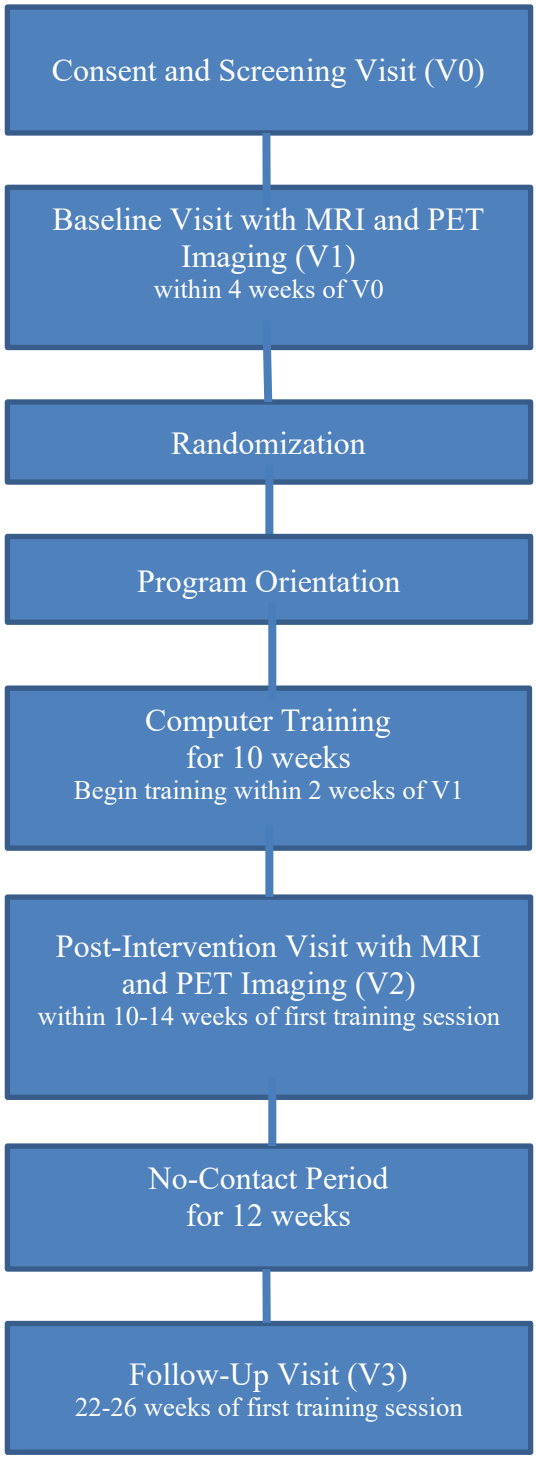
Following informed consent, potential participants will go through a set of structured interviews, short neuropsychological assessments, self-report questionnaires, and provide basic demographic information, medical and medication history to evaluate their suitability for the study given the inclusion/exclusion criteria. The following measures will be administered to participants at screening:

- Demographics, Medical History and Medications: A structured clinical interview will be used to collect key demographic (e.g. year of birth, age and education) and medical history information, including medical diagnoses or conditions that may be grounds for exclusion (e.g., neurocognitive disorders, chemotherapy treatment, current therapies (including enrollment in other clinical trials that may be grounds for exclusion), and current medications.
- Cognitive status will be assessed using the Montreal Cognitive Assessment (MoCA). Participants with scores lower than 23 may be indicative of compromised cognitive status and will not be eligible for enrollment.

- Depressive symptoms will be assessed using the Geriatric Depression Scale – Short Form. Participants with scores higher than 10 will not be eligible for enrollment. Participants who fail the GDS will be referred to a physician for appropriate treatment.
- Participants will be asked to complete the Columbia-Suicide Severity Rating Scale (C-SSRS); potential participants that answer 'yes' to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) or, any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion will be excluded from the study *if the ideation or behavior occurred within two months from Participant's date of consent* (as recommended by the FDA for treatment trials.) Participants excluded for this reason will be referred to a physician for appropriate treatment. Further, participants meeting these criteria at any time throughout the study will be asked to complete a final assessment, if appropriate, then withdrawn from the study and referred for appropriate treatment.

13. Study Flow and Procedures

Study Procedures: Participants will flow through the study in the following manner:



1. *Consent and Screening Visit* (V0)*:* Study staff will discuss study goals, activities, and requirements with the potential participant; complete the informed consent discussion, and if/when appropriate the potential participant will consent to join the study. Study staff will perform required inclusion/exclusion assessments. This visit will last approximately 1 hour.

2. *Baseline Visit (V1):* If the participant is eligible, the participant will complete the cognitive assessment battery and the pre-training PET and MRI recordings. This visit will last approximately 3 hours and may be split into 2 sessions, if needed.

3. *Randomization:* The participant will be randomized after the *Baseline Visit* and before the planned first day of the training program. Randomization will not take place until all Screening and Baseline data have been fully reviewed, residual data queries have been resolved, all EDC data fields have been fully monitored, and it has been verified that the participant has met all study eligibility requirements.

4. *Program Orientation*: The participant will attend a program orientation session so that study staff may orient them to the training program in person or remotely. The participant will also receive detailed

written information on how to perform the training program over the next several weeks. During this period, study staff will conduct weekly check-ins to answer questions and troubleshoot any issues.

5. *Intervention Period:* The participant will engage in assigned program for ~30 minutes per session, seven sessions per week, for 10 weeks (approximately three months after randomization to complete).

6. *Post-Intervention Visit* (V2): The cognitive assessment battery along with PET and MRI imaging will be completed following completion of the intervention period, approximately 3-months following initial enrollment. The participant will be informed that they will no longer have access to the intervention applications after this visit. This visit will last approximately 3 hours and may be split into 2 sessions, if needed.

7. *No-Contact Period:* Following the *Post-Intervention Visit,* the participant will be entered into a follow-up period lasting 3 months with no further program use. Study staff may connect with the participant once a month during this time to maintain engagement, but otherwise we do not expect study staff to be in contact with the participant during this period until it is time to schedule the participant's final appointment.

8. *Follow-Up Visit* (End of Study, V3): This assessment visit will be completed approximately 6-months following the initial enrollment. The participant will complete the cognitive assessment battery and will be formally exited from the study following this visit, concluding their participation in the study. This visit will last approximately 1.5 hours.

Retention

We will use a variety of proven retention strategies as detailed by Robinson et al. (2015)[166] such as a clear study identity, consistent contact study staff for scheduling, flexible appointment times and reminders, and financial incentives. In the consent process, we will stress that enrolling in the study involves a commitment to complete four-six in person visits (each lasting between 1-3 hours in which imaging may be performed and their perceptual and cognitive abilities will be assessed and questionnaires completed) and up to 35 hours of exercises. When scheduling visits, every effort will be made to accommodate participants' schedules. A minimum number of completed training sessions may be required for participants to complete the *Post-Intervention Visit* (V2). We will indicate for

each participant the best manner (e.g., email, phone, cell) and times to contact them to facilitate communication. Participants will be reminded before all scheduled testing visits by their preferred mode of communication of their appointment time. Participants who miss a visit will be contacted and requested to reschedule. A secondary contact person may be collected for each study participant to facilitate follow-up. Given our target populations, prior experience, and resources, we are confident we can meet or exceed our recruitment and retention goals.

Assessments. We will use neuropsychological assessments from those moderately distal from program use (e.g., standardized neuropsychological assessments of untrained cognitive functions) to those very distal from program use (e.g., assessment of functional abilities). This structure will allow the investigators to determine the degree of transfer of benefit to untrained modalities, including the extent to which improvements generalize to untrained functional ability and real-world experience (e.g., quality of life). All assessment forms will be translated to French for French-speaking participants.

The complete cognitive assessment battery will be performed at the *Baseline Visit* (V1), the *Post-Intervention Visit* (V2), and the *Follow-Up Visit* (V3 - End of Study). For a full list of all assessments and administration times, please direct your attention to *Appendix I* and/or the *Description of Assessments*. All assessments will be administered to all participants, those enrolled in both the treatment and active control interventions; alternate forms of the assessments will be used when available to mitigate test-retest effects. Study staff conducting the assessments at follow-up visits (V2 and V3) will be blinded to group allocation and will receive training by a member of the coordinating center and/or authorized study staff regarding appropriate administration of all measures, scoring and data reporting to ensure data quality. Performance on all measures will be scored, submitted into the study database, and monitored for accuracy and integrity by the PSC Data Monitor(s). Any discrepancies in scoring will be resolved by referring to the raw data collected during the assessment visit(s).

14. Description of Assessments

Neuropsychological assessments

Although there is no universally accepted standardized neuropsychological assessment battery for treatment trials in age-related cognitive decline, the trial will employ empirically validated assessment measures specific to age-related

cognitive decline. Collectively, we have chosen a battery based on five key criteria (when possible), including 1) existing standardization, to ensure reliable data collection procedures, 2) sensitivity to the cognitive decline typical of this study population, 3) normative data available for the normal aging population, 4) reasonable test-retest stability (i.e., to control for potential participant improvement through strategy learning over repeated measures) for use in a treatment trial with three repeated measures, and 5) good sensitivity to change following cognitive remediation.

Cognitive Assessments

Cognitive status will be assessed using the Montreal Cognitive Assessment (MoCA). The MoCA is a brief tool to assess general cognitive function. Each of the 30 components of the assessment is scored for a total of 30 points. The MoCA tests visuospatial/executive functioning, naming, memory, attention, language, abstraction, delayed recall, and orientation to time and place.[53] Participants must score 23 or above on the MoCA; those who do not meet this score criteria will not be eligible for enrollment.

The Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER)[54] includes series of tasks targeting inhibition, set shifting, fluency, insight, and planning. Available at http://memory.ucsf.edu/examiner. Participants will complete a subset of the EXAMINER (Flanker, Set-Shifting, Anti-Saccades). Confirmatory factor analysis supports both a one-factor model and a three-factor model, and these models formed the basis for an Item Response Theory (IRT)-generated Executive Composite score and Cognitive Control sore. Test-retest reliabilities range from .78 to .93. EXAMINER was designed to be applied in multiple ways. The EXAMINER allows researchers the ability to quantify each of the relevant domains.

Train-to-Task Assessments

This group of assessments serves as a positive control for task learning. We expect large improvements in the treatment group on these assessments because they have directly practiced these tasks. The data are relevant because individuals failing to make progress on train-to-task assessments may represent a subpopulation not treatable with this program, and individuals making strong progress may represent a subpopulation particularly amenable to treatment with this program. The two assessments in this group are closely modeled on exercises in the visual and cognitive control modules, and include visual speed of

processing, and cognitive control speed of processing. These assessments will be performed at *Baseline, Post-Intervention and Follow-up Visits*.

Mood Assessment

The Geriatric Depression Scale - Short Form (GDS-SF) will be used to assess mood. This assessment is A 7-minute 15-item self-report questionnaire to assess depression in older adults.[153,154] Participants must score 9 or less on the GDS-SF; those who do not meet this criteria will not be eligible for enrollment.

Suicidality Assessment

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to screen for and assess suicidal ideation. Those that do not meet inclusion criteria for this assessment will not be enrolled in the study. The C-SSRS will be repeated at the *Post-Intervention* and *Follow-up (end of study) Visits* to screen for any changes in suicidal ideation over the course of the study.

Behavioral Assessment

To assess for acetylcholinergic function, heart rate variability and/or pupillometry will be measured during train-to-task assessments (and/or during portions of the training if extra time is needed). The pupillometry acquisition will be carried out using Tobii Pro Glasses 2. The heart rate variability will be acquired using a wearable wrist band monitor.

Neuroimaging Assessment

The PET imaging will be conducted at the MNI and at the Concordia PERFORM Centre and MRI scan will be conducted exclusively at the MNI. A structural MRI will be acquired during the first scanning session to co-register the PET data with each individual's neuroanatomical brain image. Three-dimensional T1-weighted anatomical MR image volumes covering the entire brain will be acquired on a 3T Siemens Magnetom Prisma scanner with an 8 channels head coil (repetition time = 27 ms; echo time = 9.20 ms; between 176 and 192 sagittally oriented slices with a slice thickness of 1 mm; acquisition matrix = 240x256; field of view = 256 mm). Participants will be in the scanner for up to 20 minutes. Participants with self-reported claustrophobia or physician-reported implanted devices (e.g. pacemakers, cochlear implants, aneurysm clips, etc.) and pregnant women will be excluded from participating in the study.

To understand cholinergic status, PET imaging will be performed with a radioactive atom, FEOBV, which will be administered intravenously via a fine

needle-catheter inserted into an arm vein. Participants will have to wait for approximately 180 minutes for the chemical to be appropriately distributed in their brain. During this time, they should remain at rest, but will be able to use the washroom and walk around if necessary. The expected dose for 2 PET scans is estimated at 11-15.4 mSv and does not exceed the nationally accepted limits of 50 mSv/year. FEOBV is undetectable at 20 hours post-administration. No effect of the chemical can be detected in a given individual, since it is always administered in very small amounts (tracer dose). A physician is available if needed.

Participants will be positioned lying on their back in the PET machine and will be in the scanner for a total of 40 minutes A transmission study lasting 5 minutes will be performed using a source of [Cs137]. Subjects will then receive a slow push IV injection of 350-400 MBq of [^{18}F] FEOBV, a quantity that has been proven safe by Petrou et al (2014).[148] Subsequently, PET data will be acquired in 3D list mode and begin 3 h after injection, for a 30 min duration. The PET marker will be produced according to the method described by Mzengeza et al (2007).

FEOBV should be avoided in pregnant and breastfeeding women. Therefore, pregnant and breastfeeding women are excluded from the study. To mitigate the risk of contamination, up to 12 hours after the administration of FEOBV, a toilet should be used instead of a urinal, and the toilet must be flushed several times after use. Detailed safety information about FEOBV can be found in the Investigator's Brochure.

15.Randomization

Given the potential importance of demographic variables on response to speed and attention training, we will employ a minimization method of adaptive stratified randomization with a 1:1 allocation; the "platinum standard" of randomization methods when stratification is required[145] to minimize the imbalance between the number of participants in each group over factors known to influence performance. We will balance groups based on distribution of the ACh score and EXAMINER Composite score. The minimization method addresses the general problem ensuring stratification across multiple factors in small or moderate sized trials. The various imbalances are added together to give the overall imbalance in the study. Group assignment is then made at random with a heavy probability weighting (0.8) in favor of the group that would minimize imbalance. One participant out of two (50%) will do the speed and

attention computer program training, and one participant out of two (50%) will do the executive function computer program training.

Participant allocation cannot be performed until after the *Baseline Visit (V1)* and before the planned first day of program use. All Baseline data for each participant must be fully monitored, with all queries resolved, because allocation depends on obtaining data for the two prognostic variables.

16. Blinding

Un-blinded Site Roles: Unblinded study staff will provide support for participants using their assigned programs. Unblinded study staff will not be authorized to participate in assessment administration, scoring, evaluation, or follow-up of study participants after randomization. Only blinded study staff will engage in these activities.

Blinded Site Roles: All study staff responsible for the administration and scoring of participant assessments will remain blinded to participant treatment. Site Investigator will be required to complete a Delegation of Duties Form prior to the start of the study, indicating which activities individual study staff will be authorized to complete.

To prevent un-blinding, the following controls will occur at the study site level:

1. The cognitive training condition and the active control condition will be identified as "Treatment A" and "Treatment B."
2. Participants will be instructed and reminded not to discuss details related to their training program with study staff, colleagues, friends, or acquaintances.
3. Site Investigator and PIs will be instructed to not discuss details of either treatment arm with study staff.
4. Study site will be required to minimize the possibility of accidental un-blinding of the study staff (e.g. unintended viewing of training sessions).

17. Description of Protocol Devices (Software Program)

This study employs two computerized interventions: speed and attention training and executive function training. Participants will be asked to engage in the assigned training exercises for approximately 30 minutes per session, for 7 sessions per week, over 10 weeks. To address factors that contribute to non-

compliance we have incorporated several elements of flexibility in the training schedule to accommodate the challenges that older adults may encounter. These risks and associated accommodations will also be discussed with the participant.

- *Location of Use:* The computerized treatment and control programs allow participants to use the program at their residence or in clinic.
- *Fatigue:* Older adults may report symptoms of fatigue, and we expect that some participants may not be able to complete a full session in one sitting. To accommodate this issue, participants may choose to break the time into shorter segments, such as 15 min in the morning and 15 min later in the day. Participants can pause the sessions to take a break at any time and continue where they left off. The participant may discuss this with the study staff, who will work out a schedule that is feasible, given the participant's experience.
- *Variable Number of Total Sessions:* We expect that some participants will not be able to complete the minimum number of training sessions per week, every week. To accommodate this, we will explain to participants that the study will benefit from them doing as much program use as their schedule permits. However, if they need to reduce the number of sessions per week, the study staff will work with them to generate a feasible training schedule.
- *Cessation of Program Use While Continuing Participation in the Study:* In some cases, a participant may wish to stop or minimize use of the program going forward, while remaining in the study. Potential reasons for this decision might include a change in work circumstances, a change in residence, health issues, family/personal issues, or a lack of interest in program activities. However, the participant may want to meet their personal commitment to the basic scientific research of the study. In such cases, after discussion with the study staff, the participant will be permitted to cease using the program and be scheduled for a *Post-Intervention Visit (V2)* and *Follow-up Visit (V3)* at the appropriate time, given that the participant has met the minimum number of training sessions required to complete these follow-up visits.

Several of these options in aggregate are likely to lead to variation within a group with regard to the total number of sessions completed and may cause an imbalance between the number of sessions completed between the treatment and control groups. Although this is not ideal, we believe that this is the correct approach given that such flexibility will allow more participants to join the study (compared to no program use flexibility) and may produce less drop-out. In

addition, this approach has the value of more closely mimicking real-world use of the program, increasing the prospective validity of the study. We will continuously monitor the distribution of completed sessions and will consider modifications to the protocol (see Modifications to the Protocol) if it appears that this flexibility is causing meaningful between group differences to emerge. The data analysis plan is generally robust to variations in number of sessions completed (see Data Analysis Plan).

Each study participant will be remotely supervised by the study staff. They will have phone contact up to three times in the first week to ensure a smooth start, and at least once per week for the following weeks. Contact with participants may be adjusted depending on each participant's needs. During the no-contact phase, participants may be called once a month to maintain engagement with the study. Based on our previous experiences with in-residence trials, we have developed protocols and training that will allow the study staff to establish rapport with participants, identify and tend to any barriers to program use or compliance (such as establishing reminders to train or reducing distracters in the environment), and to provide feedback and support around performance.

Speed and Attention training

This program combines UFOVt and TAPAT in an approximately 35-hour training schedule delivered over a 10-week period (approximately 30 minutes per session, 7 sessions per week, for a total of 70 sessions).

UFOVt. The goals of UFOVt are to improve the visual system's ability to divide attention under rapid temporal conditions, and to progressively expand the field of view under observer command. In this exercise, users must discriminate a visual stimulus presented in the center of gaze while locating a target in the periphery in very rapid succession, both presented at progressively briefer display durations (see Figure 1A). The primary *adaptive dimension* is the duration of the visual stimulus presentation (determined by 80% criterion accuracy on a trial-by-trial basis). As a user gets trials correct, those durations decrease, making the task more difficult and driving the brain to extract the information more rapidly; conversely as the user gets trials incorrect, those durations increase, making the task easier. *Engagement of neuromodulatory systems* is driven by wrapping the exercise in a game format in which users trigger the start of the stimuli (engaging cholinergic selective attention systems), are presented with multiple varying stimuli over time (engaging noradrenergic novelty detection systems), and earn positive, unexpected, surprising, and fun rewards when trials

are correct (engaging dopaminergic reward systems). There are a total of 40 unique levels of UFOVt which vary in the eccentricity of the peripheral target, the discriminability of the central targets, and the contrasts between background and foreground stimuli.

TAPAT. The goals of TAPAT are to amplify the response power of modulatory control machinery controlling attention to improve the individual's intrinsic regulation of alertness, executive control, mood, and learning rate. TAPAT was first invented by Department of Veteran affairs neuroscientists and co-inventors Dr. Thomas Van Vleet and Dr. Joseph DeGutis (U.S. Patent 13/068,850; VA Ref: 08-0156). The training approach is specifically designed to elicit two well-characterized, intrinsic properties of the attention- and alertness-control machinery of the brain: *tonic* and *phasic* alertness. Tonic alertness refers to the ongoing state of intrinsic readiness that fluctuates on the order of minutes to hours, and is intimately involved with sustaining attention and also provides the cognitive tone necessary for performing more complicated functions such as working memory and executive control.[122,123] Poorly sustained attention is characterized by low amplitude, noisy tonic responses in locus coeruleus (LC) neurons.[93] In contrast, phasic alertness is the rapid modulation in alertness due to any briefly engaging event, and is vital for operations such as orienting and selective attention.[122] Normal aging is marked by a progressive declines in tonic alertness and in both tonic and phasic responses in both LC neurons and acetylcholine-expressing neurons in the nucleus basalis (NB) in this exercise task setting. With their 'exercise' by intensive, repeated engagement, there is an up-regulation of trophic factors (primarily EGF) that result in a strong increase in the functional status of LC, NB and the VTA.

TAPAT is an innovative variation of a continuous performance training strategy that targets sustained attention by requiring users to remain alert and engaged while responding to stimuli and ignoring foils. Users must remember a target image presented at the start of the trial after which a continuous stream of images (target or foil of unequal presentation probability) are interleaved with variable ISIs to promote vigilance (see Figure 1B). The task is to press the response button for all non-targets ("GO") and withhold responses for all targets ("NO-GO"). The primary *adaptive dimension* is the duration of the inter stimulus presentation (determined by 80% criterion accuracy on an image-by-image basis); an adaptation to induce greater response control. There are 40 unique levels of TAPAT that vary in the discriminability between targets and foils, the ratios of targets and non-targets, the categorical nature of the stimuli presented, and the attractive powers of distractors. With this design, participants must

sustain attention over long periods of time, respond to successively presented stimuli in a consistent manner (i.e., low RT variability), and inhibit the proponent motor response when an anticipated target is presented (i.e., high target accuracy). These conditions, again, very strongly engage both LC and NB neuronal populations.

Executive Function Training

In this RCT trial, participants in the active control arm will play previously vetted and popular casual video games for an overall duration that is time-matched to the intervention. These games are designed to *not* actively engage the neural systems that underlie aging. With this kind of control, the current study will be able to assess convergent validity (i.e., that exercises that should improve cognitive function, in fact do) and discriminant validity (that exercises that should not improve cognitive function, in fact don't). We will use control games that are designed to be a face-valid approach to cognitive training, that can be described to participants as a valid approach for improving brain health in aging, and that support a matching of the expectation-based influence on performance in neuropsychological outcome measures.

We shall carefully match the experimental treatment program and the alternative control program in overall program use intensity, modality (visual), mode of delivery (supervisor portal), time-spent attending, delivery of rewards, and overall engagement; and provide a comparison group that matches the experimental treatment group on the aforementioned attributes but without the key elements specific to improving the neuro-modulatory control of the brain. Variety and novelty are critical to maintaining participant engagement in the control group. Two games will be selected to appear per session from a larger set. Here are some examples of the games below:

- Lineup Four: Line up four chips in a row before your opponent.
- Bricks Squasher II: Move a paddle and bounce the ball to destroy the bricks.
- Gems Swap: Form a line of 3 or more identical gems by swapping their positions.

These internet-delivered computerized exercises are fully developed, widely believed to be cognitively beneficial, are applied in graded levels in training, and are rated E (for everyone) by the Entertainment Software Rating Boar.

18.Laboratory Specimens

There are no laboratory specimens collected for this study.

19. Sample Size Justification

We have statistically powered the study to detect a between groups Cohen's d effect size of 0.50 on our co-primary outcome measure, calculated as the between group difference in the treatment effect means (post-assessment score minus pre-assessment score) divided by the pooled standard deviation of the observed test-retest reliability. This effect size translates, for example, in an improvement of 5.8 points (on an IQ-like index score) within the treatment group versus an improvement of 1.0 point within the active control group, with both groups showing a variance of 10 points (2/3 of a standard deviation, as observed in other composite cognitive performance data) from pre-assessment to post-assessment. Recently published studies that examined the efficacy of TAPAT in participants with acquired brain injury (n=40) documented effect sizes of 0.75[10] and 0.69[45] on the composite attention measure; we believe this is a reasonable estimate of the plausible effect size in this trial. Also, a recent meta-analysis of the effect size of cognitive rehabilitation documented an average between groups effect size of 0.3[163] in the population of studies used to support the practice guidelines for cognitive rehabilitation.[164,165] We base our power analysis on the less-sensitive neuropsychological co-primary, to ensure we have the power to detect both co-primary effects. Based on this analysis, we plan to enroll 108 participants assuming 20% attrition, to achieve a maximum of 90 completers in the trial.

20. Data Analysis

The data analysis plan *a priori* defines a primary intent-to-treat (ITT) population, a set of secondary evaluation populations, a single primary outcome measure, a set of exploratory outcome measures, a single primary evaluation time point, a secondary evaluation time point, a primary statistical analysis methodology, a criterion for statistical significance, and guidance for the interpretation of results.

The **primary ITT population** is defined as all participants who complete the first training session. Note that this includes all randomized participants except those who drop/withdraw post-randomization and pre-training.

The **primary outcome measure** assesses FEOBV uptake as measured through PET ligand imaging at baseline and at post-intervention.

The **exploratory outcome measures** are:

- MRI Imaging
- EXAMINER executive composite score
- Useful Field of View (UFOV) score
- Tonic and Phasic Alertness (TAPAT) score
- Heart rate variability
- Pupillometry

The **primary analysis time point** is the post-intervention assessment. The **secondary analysis time point** is the follow-up assessment.

The **primary statistical analysis methodology** is a linear mixed model approach. We will first compare treatment and active control groups in the ITT population to determine if any differences in baseline demographic, characterization, outcomes variables, or total program use time remain after the randomization process. Any such factors that show trend level significant differences ($p < 0.1$) will be noted and used as covariates in the linear mixed model analysis. We will examine the data from each outcome measure using a linear mixed model with group and time as fixed factors, site as a random factor, and co-variates as necessary from the baseline analysis. Missing data will be handled with an iterative maximum likelihood procedure to optimally estimate model parameters. The key value for significance will be the group by time interaction factor for the model.

The **criterion for statistical significance** is $p < 0.05$. Results with $p < 0.1$ will be described as trends.

To evaluate the efficacy of speed and attention training, we will conduct the analysis based on the baseline and post-intervention data.

Finding a significance level of $p < 0.05$ on the FEOBV primary outcome measure will support the statement that the intervention increases acetylcholine upregulation and will support the statement that the intervention improves generalized cognitive function in the population.

To evaluate requisite dosing and endurance of effects following completion of speed and attention training we will conduct the analysis based on the baseline, post-intervention and follow-up assessment data. We will conduct confirmatory analyses based on the (1) baseline and post-intervention (completion) assessment

data to evaluate the magnitude of change (further increase or asymptote), and the (2) post-intervention (completion) and follow-up assessment data to evaluate the endurance of the change (further increase or decline).

Exploratory analysis will test for effects in exercise-based progress as well as by domain (e.g., sustained attention, processing speed) to determine the unique benefit of each exercise (UFOVt, TAPAT) to influence a) progress in the alternate exercise, b) performance in measures of generalization and c) complimentary effects (i.e., how progress across exercises affect outcomes). Additionally, we will measure whether improvements on certain components of the training program or programs (e.g., improvements at inhibiting one's response to target stimuli) are associated with the executive composite score and/or ligand binding executive or functional performance scores (as well as individual assessment measures). This could indicate whether certain patterns of training improvements are related more to improvements in attention, executive control, speed of processing or other. These analyses will be evaluated after correcting for multiple comparisons (e.g., Tukey's HSD).

21. Data Management

Data collected in this study may include paper forms for consent forms, self-report questionnaires, psychometrician-administered structured interviews, and neuropsychological or functional assessments. All study-related data will be recorded into a secure, web-based electronic case report form (eCRF) at study site through LORIS. This system meets all relevant privacy and security standards for electronic clinical trial data entry and storage, as well as the Health Insurance Portability and Accountability Act (HIPAA) standards for confidentiality and privacy.

Following consent, each participant will be assigned a standardized Participant Identification Number (PIDN) composed of digits to identify the study and 3 digits to identify the participant. The digits will begin with "001" for the first consented participant and ascend thereafter. All eCRF data entry will be de-identified, using the PIDN and not the participant name, but will include identifying information in the form the date of the assessment administration, age and potentially other dates associated with the data collected.

The study site will enter eCRFs directly into the study database. There is no transfer of data between study site and Sponsor outside of this mechanism

during the study. Sponsor staff will interact frequently through phone and email throughout the study to accomplish the quality goals of the data management process through the below process:

Periodic analysis of each data field (across all cases) will be performed to examine the expected distributions of data, and to identify outliers for possible data mistakes. Attention will be paid to the following:

- *Data Cleaning:* All eCRFs are automatically subjected to initial checks for omitted data and data inconsistencies. These deficiencies are required to be resolved at the point of data entry to prevent errors from entering the system.
- *Data Editing:* Each data record is evaluated on a regular interval. Any discovered error is then referred to the Site Investigator Designee by email, telephone, or secure communication through the Electronic Data Capture system via the Data Monitor. The Site Investigator Designee will review the queries and make the corrections through the eCRF system. All such changes are automatically logged to allow a complete audit trail and recovery to any point in the change log if required.
- *Data Update:* The cycle of data edit will be ongoing until all the data are clean. If further data entry or source documentation errors are discovered during the study site visit the corrections will be made at that time through the eCRF system.
- *Data Back-up*: The eCRF system employs an automatic continuous replication system to ensure that all data including change logs and access logs are replicated to two independent remote servers. At any point, the system can emit the entire store of eCRFs as paper CRFs for offsite storage or auditing if required.

We will take all standard and appropriate steps to protect the privacy and confidentiality of participants in this trial. At enrollment participants will be assigned a PIDN as described above, and all study data collection derived from that participant will be coded by PIDN. All eCRF pages, including those with demographic as well as assessment data, will have the PIDN on them rather than the participants' name. No personally identifying information will be shared with PSC, except for dates of assessments, dates training exercises are completed, year of birth, other dates associated with the data, and age. The eCRF system runs on remote servers not physically accessible to any study staff (including PSC staff); all electronic access to the eCRF system is logged and regularly reviewed for any inappropriate access. All study related paper materials will be

stored in locked file cabinets inside of locked rooms when not in use. All participant use of the study programs (treatment and control) will use a login based on the PIDN, and study programs will not collect or store any personally identifiable information, except for dates that training exercises are completed on the device or on PSC servers.

This protocol includes the administration of the Columbia-Suicide Severity Rating Scale which may result in the collection of sensitive information that may require reporting to state or local authorities. If study staff become aware of specific issues outside of the ordinary data collection procedures (e.g., spousal abuse) they will follow established procedures already in place designed by their specific site and appropriate for their local jurisdiction to report such knowledge.

22. Confidentiality

Participation in research may involve a potential loss of privacy. All records and documents pertaining to participation in this study will be handled as confidentially as possible.

All information, if collected on paper, will be kept in areas of limited access available to approved study staff only. Data keys will be stored separately and securely. Electronic data will be password protected and securely stored.

Representatives of the Sponsor, the reviewing Institutional Review Board, and the NIH will be permitted to audit study-related data and related materials. Personally identifiable information will not be used in any study reports or publications; data contained in these will only be presented or published in aggregate form.

Mobile app usage will be kept secure: We are aware that mobile app use can pose some confidentiality hazards to users and hence put in place several important safeguards to minimize potential risks.

Participants will be provided a de-identified log-in to access the computerized training program. The program will not capture, collect, transmit or store personally identifiable data, except for dates that training exercises are completed. De-identified data will be encrypted and will not reside on the device but will be transferred immediately with no personal identifiers, except for dates. Data collected through the computerized program does not include geographic

location data. IP address data is stored only in memory and in request logs, and is used for technical support and troubleshooting, but not persisted with the participant's data. Data are uploaded using SSL over encrypted channels to secure servers every 30 seconds. Therefore, security of electronic data is ensured at the level of the server, the user, and the database.

23. Disposition of Data

The following study records will be retained by the study site for a minimum of two years following the conclusion of the study:

1. Signed participant informed consent forms
2. Supporting documentation of all adverse events
3. Completed eCRFs
4. Study related correspondence and study reports

The sources of the research material will be data collected strictly for research purposes. Subjects will be carefully screened for contraindications prior to participation. All data are coded so as not to identify any given participant. Hard copy data from the diagnostic and assessment interviews will be stored in a locked file cabinet in a safe location at the study site with limited access by authorized study staff and/or kept in a safe location on password protected computers in locked offices. Data from diagnostic interviews and assessment visits will be also be recorded in LORIS, a secure, web-based software application designed to support data capture for research studies. LORIS is designed to comply with GCP and HIPAA-regulations. A list of names, addresses, and telephone numbers of all participants will be stored on a password-protected document and/or paper in a locked file cabinet at the study site with limited access by authorized study staff for purposes of contacting the individual participants. The information that will be solicited during the screen includes: demographic information, medical history, medication use, cognitive status based on the MoCA, depressive symptoms based on GDS-SF, and suicidal ideations and behaviors based on C-SSRS. The types of data collected will be: self-report data concerning neurological status and behavioral data from cognitive tasks.

Study staff will comply with the requirements (i.e., the enrolling institution) data storage and disposition policies at the conclusion of the record retention period.

24. Sharing Research Results

The final data set from the proposed lifestyle intervention study will include self-reported demographic and health data, raw and composite scores on neuropsychological measures, and PET/MRI data regarding the efficacy of each treatment intervention and combined effects in our normal aging population.

These data will be broadly shared with the research community and lay persons through the conventional scientific publication process in the following steps:

Conference Presentations
Following the completion of the trial and execution of the data analysis plan, the interpretation of the data by the research team will be presented at conferences. We expect to write 3-5 abstracts on results from our primary and secondary analyses for relevant scientific meetings.

Initial Scientific Papers
As specified by the *a priori* hypotheses in the data analysis plan, we anticipate writing 3-10 scientific manuscripts covering (1) the comparison of the effectiveness of each intervention on neuropsychological assessments, (2) the comparison of the effectiveness of each intervention on FEOBV uptake as measured through PET imaging, (3) the correlation between the magnitude of the training effect on neuropsychological and FEOBV binding, and (4) the comparison of the short-term and enduring effects on cognition and neuromodulatory outcomes. We also plan secondary analyses of key moderators (e.g., age, sex, ethnicity, baseline cognitive performance, baseline FEOBV values) to assess individual differences in outcomes. These will be submitted to and published in relevant peer-reviewed journals.

Following Scientific Papers
Following the completion of the *a priori* data analysis plan, we will make the complete data set available to McGill investigators to conduct further post-hoc exploratory analyses. Any relevant results will be submitted to and published in relevant peer-reviewed journals.

Data Archive
Two years after the completion of the trial, we will deposit the complete raw data set, including MRI and PET data, in a freely-available, open-source platform that has been vetted and approved by the institution. Imaging data will be defaced to

protect patient confidentiality. The designated database for this trial will serve as a locked repository, appropriate for academic researchers not affiliated with the trial to conduct further confirmatory or exploratory analyses. We will wait two years in order to allow completion of the main analyses before the data is made available to non-affiliated investigators.

There are no pre-existing agreements that will limit data sharing. Data analyses, publications, and public sharing will proceed in the order described above. To protect participant privacy, no study publications or publicly available data sets will include personally identifiable information.

25. Foreseeable Risks, Risk Management & Emergency Response

The following foreseeable risks will be discussed with potential participants during the *Consent and Screening Visit (V0)*, as will the following measures taken to minimize such risks:

- *Screening interview and self-report measures*. Participants may feel uncomfortable answering sensitive questions about their neurological condition and medical history during the screening interview or on self-report measures. Participants will be reminded that their participation in the study is voluntary and that as such, they are not required to complete any assessments, may skip individual questions or assessments, or withdraw from the study entirely.
- *Discomfort During Assessments and Training*. Computerized assessments and training may be fatiguing or frustrating for some individuals. To minimize this potential discomfort, breaks are encouraged and scheduled within the session. If a participant appears to be under undue strain, testing sessions are discontinued.
- *Lack of Assessment Feedback*. Participation in this study does not include feedback to participants on their individual assessment results, as the assessment battery is not intended to be the type of comprehensive battery that would be used to guide treatment. Though participants are informed of this policy during consent, some participants may find the lack of feedback to be frustrating. Any participant interested in such comprehensive assessment will be referred to their Primary Care Physician.
- *Risks of Email Communication*. This study will rely on the use of email communication between study staff and research participants as part of their participation in the clinical trial. study staff are expected to email

participants about their upcoming appointments, provide weekly updates on program usage, or communicate other important study information, including the instructions for completing study activities remotely. Participants may also ask questions of study staff using email. There are risks associated with email communication, and these risks increase when emails are sent without an encryption service. Risks of sending or receiving unencrypted emails include, but are not limited to:

  - Others can intercept messages
  - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages
  - A copy of the message may be saved on a device or computer system, even if it is deleted
  - If an email address is not typed correctly, it can be sent to the wrong person
  - Emails can spread computer viruses
  - Others may be able to access messages on devices that were lost, stolen, or thrown away
  - If a user changes emails without notifying study staff, they may miss communications.

- *Loss of Privacy*. The most significant risks to the participants are those that would follow a breach of confidentiality and the disclosure of clinical information. Participation in any research study, including this one, may involve a loss of privacy, and absolute confidentiality cannot be guaranteed. Procedures designed to maintain data confidentiality include (1) formal protocol training sessions for all study team members emphasizing the importance of confidentiality, (2) adherence to specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants. One reason for breaching confidentiality is that, under certain jurisdictions, study staff are required by law to report cases of physical or sexual abuse to local law authorities; and another is that despite all procedures, an error may occur. To mitigate this risk, all data collected on paper will be kept in locked file cabinets and accessible only to authorized study staff. Except for dates of assessments, dates that training exercises are completed and dates associated with other data collected, no personally identifying information will be shared with PSC. Only the unique ID number, assigned by the study staff, will represent

participants during participation in the study. To facilitate tracking, a document securely stored in a locked filing cabinet or a password-protected computer file will be maintained containing the identity of participants, their ID numbers, and contact information. Electronic data will be password protected and stored on a secure network. All data keys will be stored separately and securely. Only study staff will have access to the study data. No participant names will be used in study reports or publications.

- *MRI Imaging:* Subjects will be exposed to a strong magnetic field and radio waves, however no long-term negative side effects have been observed for this type of imaging. The scan is noisy and subjects may feel uncomfortable. They will be provided with ear plugs to block out the noise. Subjects may experience claustrophobia. They will be in constant communication with the MRI technician and will be provided with a "call button" if they do not feel well and would like the procedure to stop. Subjects will answer an MRI screening questionnaire to confirm they do not have any MRI contraindications (Pacemaker, aneurysm clip, heart/vascular clip, prosthetic valve, metal prosthesis, pregnancy or intention to become pregnant, metal fragments in body, or transdermal patches).
- *PET Imaging*. Participants will be positioned lying on their back in the PET machine and will be in the scanner for a total of 40 minutes.
  A transmission study lasting 5 minutes will be performed using a source of [Cs137]. Subjects will then receive a slow push IV injection of 350-400 MBq of [18F] FEOBV, a quantity that has previously been demonstrated to be safe by Petrou et al (2014)[188]. Subsequently, PET data will be acquired in 3D list mode and begin 3h after injection, for a 30 min duration. The PET marker will be produced according to the method described by Mzengeza et al (2007)[189].
  During the PET imaging sessions, subjects may feel a stinging sensation at the time of the catheter insertion into the vein. Moreover, the prolonged immobility on the couch may also be a source of restlessness and discomfort for some participants. PET imaging involves the injection of specific agents (FEOBV) not normally present in the human body. Like any other chemical or pharmaceutical compound, these agents have a potential to produce undesirable or allergic reactions. However, such reactions have never been observed with the doses to be used in this study. Given that FEOBV is a radioactive compound, this means that subjects will be exposed to a small dose of radiation (measured in

milliSieverts, or mSv), above what one individual is usually exposed to in daily life (natural radiation in the environment, cosmic rays, etc.), or for medical reasons (diagnostic X-rays, radiation therapy, etc.). Most of the radioactivity will be gone from the body after a few hours. The risk which is alluded to when discussing risk associated with radiation exposures of the level seen in PET scanning is that of developing a cancer at some point in the future, which would not have developed otherwise. As a general concept, it is known that radiation increases the risk of developing cancer over certain doses. However, because of the very small doses used for PET imaging, this has never been observed. The risk is therefore low.

PSC does not provide compensation for research-related injuries and will not reimburse or pay medical expenses for the treatment of research-related injuries.

Participants will be encouraged to report any adverse effects occurring during the duration of the study to the point of contact within study staff. Although there is little chance for a study-related emergency, study staff are required to follow institutional standard operating procedures for obtaining emergency care or treatment for adverse effects requiring such. All participants will be told how to contact study staff in the case of an emergency.

26. Potential Benefits

The following benefit will be described to participants:

Benefit to Science: Results from this study will directly benefit the basic and applied science of brain plasticity. Understanding if the scientific design principles of speed and attention drive superior outcomes to executive function games will provide considerable insight to scientists working on cognitive training research.

27. Sponsor Staff

PSC will serve as the data management and coordinating center for this clinical trial.

Key staff at PSC include:

- Co-Principal Investigators (Dr. Thomas Van Vleet and Mouna Attarha) are responsible for the overall design of the study protocol and data analysis plan as well as the eventual publication of the result (with input and authorship from all investigators). Drs. Van Vleet and

Attarha are also responsible for the execution of the study protocol, including coordinating activities with all PSC and study staff participating in the trial.

- Study Coordinator (Sarah-Jane Grant) are responsible for assisting the PIs with the execution of the study protocol, overseeing data management, and ensuring IRB compliance. They will also be responsible for monitoring all submitted data for consistency and integrity. Ms. Grant will also be responsible for discussing all qualifying criteria with study staff, leading virtual training sessions, and holding meetings. They will be responsible for ensuring that the study site meets regulatory compliance requirements and executes the protocol, as IRB approved.

Dr. Van Vleet, Dr. Attarha, and Ms. Grant disclose a conflict of interest: all are paid employees of PSC and shareholders and could benefit if this training program is shown to be an effective treatment in this trial.

This conflict will be mitigated by ensuring that the complete investigator team, including Dr. Van Vleet, Dr. Attarha, and Ms. Grant, and other study staff have joint and overlapping responsibility for the design of the protocol, the execution of the protocol, the *a priori* design of the data analysis plan, the execution of the data analysis plan, the interpretation of the study results, and the authorship of publications emerging from the study. In addition, this conflict of interest will be disclosed to all study participants, and through standard mechanisms for all publications.

28. Withdrawal from the Protocol

Study participants may withdraw from the study at any time, for any reason, or for no stated reason. We anticipate that a common reason for study withdrawal will be the time required to use the program. For participants seeking to withdraw for that reason, we will offer the alternative of discontinuing use of the program and, if appropriate, scheduling and completing the follow-up visit(s). The data analysis plan is structured so that their data will be valuable even if they do not complete the intended number of sessions. Participants who still wish to withdraw following that option will withdraw. Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by arranging for team members to conduct an informational interview with the participant to understand the reasons for study withdrawal and identify

any issues with study conduct or adverse events that are relevant and arrange study compensation for sessions that the participant completed.

In rare cases, an investigator may decide to prematurely discontinue a participant's involvement in the study for any of the following reasons:

a) Safety,
b) Participant non-compliance,
c) A change in circumstance that would prevent completion of protocol-required assessments or intervention activities,
d) Participant relocation to an area that, due to great distance, would prohibit a participant from receiving follow-up at the study site,
e) Participant displays inappropriate behavior toward study staff members,
f) Loss of funding, or;
g) A clinical determination, by the investigator, that continuation in the study is not in the participant's best interests.

Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by arranging for the study staff to recover the tablet (if it has been issued to the participant), conducting an informational interview with the participant to understand the reasons for study withdrawal and identify any issues with study conduct or adverse events that are relevant, and arrange study compensation for sessions that the participant completed.

29. Modifications to the Protocol

Any significant changes to the protocol, including changes to inclusion/exclusion criteria, changes to assessments, changes to recommended levels of program use, changes that could potentially increase risk to study participants, and additions or removals of study site(s) will have to be approved by the grant recipients/PIs (Thomas Van Vleet, Mouna Attarha, PSC). Any such changes will also be discussed with and approved by the Institutional Review Board in the form of a protocol amendment prior to implementation.

30. Protocol Deviations

Protocol deviations will be noted and recorded by study staff (Site Investigator, Clinical Coordinator, Study Coordinator, Psychometrician, or Trainer) if they detect the deviation, or the Study Data Monitor if they detect the deviation during a study site visit. All protocol deviations will be reviewed by the PIs

(Thomas Van Vleet and Mouna Attarha) monthly and must be signed off by the Site Investigator; any such deviations suggesting systematic problems with the protocol procedures as implemented by the study site will be reviewed and corrective action determined and implemented by the study site.

31. Reporting of Unanticipated Adverse Device Effects & Problems

This is a minimal risk protocol. There is no significant risk to using the programs in this study, beyond the minor discomfort and tedium risks of using computerized software. There is greater, though still minimal, risk associated with FEOBV exposure and PET imaging as noted above.

An event that is serious must be recorded on the case record and requires expeditious handling to comply with regulatory requirements. If a participant becomes ill or injured as a direct result of participation in the project, necessary medical care will be made available. Any adverse events attributable to the study activities and/or program use will be reported to the reviewing IRB in a timely manner, if applicable. The NIH Project Officer will be informed of any actions taken by the IRB as a result of such adverse events. In the unlikely case of study-related serious adverse events, an interim analysis will be performed to determine whether a change in the risk/benefit ratio has occurred. If so, this change will be brought to the attention of the reviewing IRBs for review, current and future participants will be notified of this change and stopping rules will be considered.

We will also conservatively follow guidelines for medical devices (i.e., computerized cognitive training) in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in The Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with, a device. Furthermore, an effect is classified as an UADE if it is judged by the investigator to be a serious problem associated with a device that related to the rights, safety, or welfare of participants. We will operationalize this definition of a serious problem as one that result in any of the following outcomes: death, life-threatening situation, inpatient hospitalization atypical of the participant's diseases condition, persistent or significant disability/incapacity; or any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health or the health and well-being of all participants enrolled in the study. The study team will ask about any UADEs during each contact with participants and will be alert to any volunteered UADEs. All

UADEs will be documented and will be classified by the investigator to their degree of seriousness and their relationship to the study software. All UADEs, whether or not we believe them to be related to the protocol, will be reported to the IRB according to the study site's IRB procedures and to PSC as soon as possible, but in all cases within 3 working days of the event.

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Appendix I. Table of Assessments

	Consent and Screening Visit (V0)	Baseline Visit (V1) within 4 weeks of V0	Program Orientation and Intervention Period for 10 Weeks begin training within 2 weeks of V1	Post-Intervention Visit (V2) within 10-14 weeks of first training session	No-Contact Period for 12 Weeks	Follow-Up Visit (V3) within 16-22 weeks of first training session
Informed Consent	X					
Inclusion and Exclusion Criteria	X					
Demographics	X					
Medical History	X					
Medications	X					
MoCA	X					
GDS-SF	X					
C-SSRS, Baseline	X					
MRI and PET Imaging		X		X		
EXAMINER		X		X		X
Train-to-Task Assessments with HRV and Pupillometry		X		X		X
C-SSRS, Since Last Visit		X		X		X
Medications, Since Last Visit		X		X		X
Adverse Effects		X		X		X
Randomization*		X				
Program Orientation			X			
Computer Training			X			
Weekly Phone Check-In			X			
UADE	Complete as needed					
Study Exit	Complete when participant exits study					

*Randomization will take place after all Screening and Baseline data have been fully reviewed, residual data queries have been resolved, all EDC data fields have been fully monitored, and it has been verified that the participant has met all study eligibility requirements.