Study Protocol Approved by UCSF Ethics Committee

IRB   10-04957

A video game to enhance cognitive health in older adults, children, and adolescents

"Characterizing the Synergistic Effects of Physical and Cognitive Training on Attention and Working Memory"

June 18 2022

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Recruitment Criteria

1. Males and Females, aged 55-80
2. Inclusion criteria
    a. English speaking
    b. Normal or corrected to normal vision and hearing
    c. Ability to complete cognitive tasks
    d. Ability to cooperate and comply with all study procedures
    e. General health/physical fitness allowing safe participation with BBT physical components
    f. Be within 2 standard deviations (SD) of age-matched controls on all five of the neuropsychological composite scores.
3. Exclusion criteria
    a. Neurological or psychiatric disorders
    b. History of stroke
    c. Prior head trauma
    d. Psychiatric illness
    e. Psychotropic medications
    f. Hormonal medications
    g. Cardiovascular medications
    h. Physical or mental conditions that interfere with daily activities
    i. Two or more composite scores exceeded 1.5 SDs.

Procedures

1. Screening for general inclusion/exclusion criteria
2. Consenting
3. Baseline outcome data collection
4. Cognitive control training intervention period
5. Return visit to UCSF for post-intervention outcome data collection
6. Return to UCSF for 1-year outcome data collection

Measures administered
1. CPT
2. Working Memory Task
3. Frontal Theta Power
4. Filter Assessment
5. Frontal Theta ITC
6. Diastolic Blood Pressure

Time commitment
- Consenting: 30 minutes based on individual reading speed and comprehension level
- Outcome assessments at baseline, 2-month, and 1 year time points: 2 hours
- Intervention training: 25-35 minutes 3-5x/week for 6-8weeks, depending on intervention arm assigned

Introduction

80

81   The augmentation of deficient attention abilities is especially of interest for older adults, given well

82   documented age-related declines in these abilities[1-9], which are exacerbated in the presence of

83   interference2[,10-13]. Over the last decade there has been a surge of research aimed at improving cognitive

84   abilities by harnessing neuroplasticity via cognitive training[13-17]. Cognitive training as a whole has come under

85   warranted scrutiny given consistent shortcomings in study design and outcomes: i) minimal extension of

86   benefits beyond the training interventions themselves, ii) lack of appropriate control groups, and iii) absence

87   of follow-up testing to assess sustainability of observed effects[18-20]. However, there have been several notable

88   examples of cognitive interventions enhancing non-trained cognitive abilities in older adults5[,21-23], with these

89   findings aligning with systemic reviews supporting the utility of cognitive interventions in the older adult

90   population[24-26].

91   In contrast to the uncertainty surrounding the benefits of cognitive training, the utility of physical fitness

92   interventions for older adults' general health has been well established. Fitness-based interventions have also been

93   shown to benefit cognitive control abilities[27-32], with such findings hinting at the possibility that combining cognitive and

94   physical training approaches may lead to greater cognitive benefits than either approach alone (although not supported

95   to date[33-36]). The use of combined cognitive and physical interventions are especially compelling as a strategy to

96   maintain both cognitive and physical health[37-39], given that such a pairing can be a time- and resource-effective approach

97   for addressing multiple risk factors in older adults. Indeed, combined training has been shown to result in greater

98   participant enjoyment compared to either sequential training[40] or physical exercise alone[41]. However, while the typical

99   protocol of alternating between physical and cognitive training has shown to have some cognitive benefits[34,35,41-43], this

00   cumbersome tactic requires a multitude of human and material resources. Alternatively, one resource-effective

01   approach in this arena has been the use of exergames; however, it remains unclear how effective such approaches are

02   at improving cognitive and physical outcomes in aging populations[44-49], leaving an open question of their overall utility.

03   We have previously demonstrated that cognitive interventions using closed-loop, adaptive algorithms[50]

04   designed to target specific cognitive abilities in older adults can improve task performance and neural measures of

05   cognition[12,23,51-53,] with some evidence of these effects persisting well after the intervention period[51,54]. These

06   interventions, delivered as engaging video games, have shown positive effects not only with older adults, but in diverse

07   populations[55-58], with previous work highlighting the possibility of returning performance on measures of cognitive

08   control to young adult level.[5,51] Here we created a novel exergame intervention for older adults (Body-Brain Trainer,

09   BBT; **Figure 1**) that requires participants to perform full-body, physical movements in response to cognitive challenges

10   that engage different cognitive control domains[50,59]. As in our previous work[51,60,61], we integrated real-time adaptivity

11   using closed loop mechanics for each cognitive ability being challenged. Given the movement demands of BBT, we also

12 implemented an adaptive physical fitness challenge by using real-time heart rate data to titrate game play for a

13 personalized and integrated training experience across both cognitive and physical domains (see **Methods** and

14 **Supplementary Materials** for more details on the BBT software).

15   In the present study, we sought to evaluate the primary question of whether BBT could improve measures of

16 attention and physical fitness in older adults beyond that of an expectancy-matched, active placebo control group. To

17 the best of our knowledge, this design is noteworthy given that the use of expectancy matching[62] has been absent in all

18 previous efforts examining cognitive benefits from combined approaches, including those studies designed to evidence

19 potential synergistic effects through mechanistic control groups (see **Supplemental Materials** for a brief treatise

20 describing our rationale for utilizing this particular control group). We also interrogated the following secondary

21 questions: what is the neural mechanism underlying positive cognitive effects, do any observed cognitive improvements

22 persist one year later without booster training sessions, does BBT result in older adults achieving comparable levels to

23 young adults on our primary outcome measure, and does this intervention affect other measures of cognitive control

24 (working memory).

25

26   **METHODS**

27 **Participants:**

28 The study was approved by the Committee on Human Research at the University of California, San Francisco, and

29 retrospectively registered on ISRCTN registry [ISRCTN [66423499] to distinguish the goals and approach taken here from

30 those of the 'parent' registration (clinicaltrials.gov submission NCT03032796). This study was designed to gauge the

31 feasibility and potential efficacy of using the BBT intervention compared to an expectancy matched active placebo

32 group, for a subsequent mechanistic trial exploring synergistic effects of a combined intervention versus individual

33 components alone (as described in the 'parent' clinicaltrials.gov submission). For continuity and cohesion, we used the

34 same primary (CPT) and secondary (Working Memory Task) outcome measures listed in the parent clinicaltrials.gov

35 registration. Furthermore, here we also examined a subset of the exploratory outcomes listed in the parent registration

36 (blood pressure, event-related spectral perturbation derived from EEG) as well as two new exploratory measures (Filter

37 Task, Limit of Stability Assessment). 49 healthy, older adult (OA) individuals consented to participate in this study. OAs

38 were randomly assigned (block size of 5) to a training group (body-brain trainer; BBT; N=24, mean age=68.8 +/- 5.9, 13

39 females) or an active, expectancy-matched control group (mind-body trainer; MBT; N=25, mean age=68.20 +/- 6.75, 13

40 females). All participants were from the San Francisco Bay Area and recruited through online and newspaper

41 advertisements. All participants had normal or corrected-to-normal vision, had no history of stroke, traumatic brain

42 injury, or psychiatric illness, were not taking psychotropic, hormonal, or cardiovascular medications, and did not have

43 any physical or mental conditions that may interfere with their daily activities (e.g., migraine headaches, substance

44 abuse, neuropathy. Similar to our previous work, all participants reported playing less than 2-hours of video games per

45 month, and completed a general health questionnaire reviewed by the study team assessing each individual's current

46 state of physical fitness to ensure that they could safely engage with the physical aspects of the BBT platform. All

47 participants gave written informed consent, and were paid $15/hour for their in-lab and at-home participation. All

48 participants were encouraged to not change any aspects of their daily routine (e.g. to change exercise habits) for the

49 duration of the study.

50

51 **Neuropsychological Battery**

52 Prior to experimental testing, all participants were evaluated on 3 measures probing for cognitive impairments and

53 depression (the Montreal Cognitive Assessment (MoCA[110]; minimum score of 26; the Geriatric Depression Scale (GDS)[111];

54 the PHQ-9[112]) as well as nine neuropsychological tests. These nine tests were subdivided into related domains and

55 composite scores of each were calculated for each of the following:

56   1. Immediate Memory – consisted of the five immediate recall trials from the California Verbal Learning Test

57   (CVLT-II) [113]

58   2. Delayed Memory – the long delay free and cued recall trials as well as the Recognition measure from the CVLT-II

59   3. Processing Speed – Digit Symbol task (citation), Executive Composite-DKEFS Trails Condition 2 (numbers only) [114]

60   4. Cognitive Flexibility (Task Switching) – DKEFS Trails Condition 4 (number-letter switch)

61   5. Fluency - Verbal Fluency (Animals [115], D- Words (MoCA)

62

63 Color vision deficiency was assessed with Ishihara's Tests for Colour Deficiency[116]. To be included in the study, all

64 individuals were required to be within 2 standard deviations (SD) of age-matched controls on all five of the composite

65 scores. Participants were also excluded if two or more composite scores exceeded 1.5 SDs. This procedure provided a

66 thorough characterization of the cognitive status of each OA participant in multiple domains while simultaneously

67 ensuring that their cognitive faculties were comparable to that of their age-matched peers. All participants tested within

68 two SDs of the normative values established for each of these measures.

69

70 **Study Design:**

71 For those participants randomized to the BBT group, they were asked to come to Neuroscape at UCSF 3 days per week, 1

72 hour per visit (36min of on-task training time per session, 24 minutes allocated for warm up/cool down/breaks) for 8

73 weeks (24 hours total, 14.4 hours of actual training time). Each of these visits were accompanied by an onsite trainer to

74 facilitate the training experience for the participant and ensure that training was being completed in a safe manner. For

75 those participants randomized to the MBT group, they were loaned an iPad tablet (9.7 inch screen size; 1024 x 768

76 screen resolution) for their training session following their 'Pre-training' assessment, and were instructed to train with

77 their assigned task at home for six weeks, 5-days per week, with 30-minute training sessions per day, for a maximum of

78 thirty 30-minute training sessions (15 hours of training total). All MBT participants were instructed to train sitting down

79 with the tablet on a flat surface, such as a table, in a location with minimal external distraction.

We used a study design that involved several layers of blinding: i) data was collected by a group of research associates who were blinded to the identity of the intervention group, ii) data analysis (which was anonymized to conceal intervention group identity) was performed by a different group of researchers, and iii) participants were blinded to the group assignment following randomization procedure, which was done prior to the first participant visit to the lab. Blinding began at the point of recruitment, where all participants were informed that they were being recruited for a study designed to test the efficacy of software interventions for improving cognition in a variety of domains. Neither the BBT nor the MBT participants were aware of the other group or the task that they trained with. Both groups were administered the same instructions and brief overview of the goals of the study, namely to determine if the training game could improve cognitive abilities. Thus, all participants were told that they were part of an active intervention to improve their cognitive abilities (see below for details on how we established matched expectancy[117]). Finally, one study coordinator was informed of the treatment assignments, as their role was solely to provide technical and other support during the training.

All participants reported to our UCSF Neuroscape laboratories prior to training ('Pre-training' session) and following the completion ('Post-training' session) of training (1-week grace period from start/end of training) to compete a battery of cognitive and physical outcome measures to assess training-related changes. Participants were invited to return to the laboratory 1 year after their post-training outcome assessment to evidence which, if any, positive training effects persisted in the cognitive domain. Over the course of the study, 3 participants in the BBT group and 2 participants in the MBT group voluntarily withdrew from the study, resulting in the complete pre- and post-training data sets from 24 BBT participants and 25 MBT participants. One additional participant had a non-training related adverse event which caused them to withdraw from the study prior to be randomized to a group. We were unable to collect EEG data from three participants at pre-training due to equipment malfunctions, and, due to technical issues with photodiodes, we were unable to time-lock the EEG to the event onsets for several other participants (n= 4 at pre-training, n= 4 at post-training). There was one participant who did not return for their post physical assessment.

Intervention Descriptions:

BBT paradigm: BBT is comprised of three modules, with each targeting a different aspect of cognitive control: visual search tasks for attention (with increasing distraction), spatial span/multiple object tracking tasks for working memory, and a task-switching paradigm targeting goal management/cognitive flexibility abilities. There are also three different tasks with ascending difficulty within each module, such that advancing to the next level engages a fresh challenge while maintaining interest (for example, a change from a spatial span condition to a multiple object tracking condition with working memory demands). Comparable to our previous work using cognitive measures alone[51,60,61], here we integrate real-time adaptivity for both the cognitive and physical aspects of the gameplay. For each cognitive task, difficulty scales on a trial-by-trial basis, with a correct trial performed within a thresholding-determined response window leading to shorter response window by 10msec, and an incorrect trial leading to a lengthening of the response window by 30msec

14   (thus, a 1"up"/3"down" staircase). These cognitive adaptive algorithms are designed to assure participants remain at an

15   ~80% rate of accuracy, a level that is not too easy nor too hard, so that it is enjoyable and engaging. <u>For the physical</u>

16   <u>training</u>, difficulty is tied to the demands associated with the distance an individual must travel for a given response and

17   the amount of time allocated to complete this response. These movement-related aspects are directly responsive to

18   whether heart rate is below/within/above a predetermined heart rate window to ensure a moderately intense workout

19   that does not impede the ability to perform the cognitive task. For example, if one is playing the game *below* their

20   assigned heart rate range, the software will automatically increase the distance that the participant must move to

21   respond with their hands/feet on each trial until their heart rate is within the specified range. Training sessions are

22   linked, such that the next session begins at the level attained at the end of the previous session. Participants are

23   provided two types of feedback: 1) real-time feedback – indicating whether the participant successfully detected or

24   classified the target and 2) punctuated feedback – participants advance through a series of "levels" that are reported at

25   the beginning and end of each run.

26

27   **BBT Module Descriptions**

28   (i) BBT Attention. This module demands an active scan of the screen in search of a target, much like traditional visual

29   search tasks[118]. This module involves a constantly evolving amount of cued information as well as number of

30   incongruent distracting elements, such that participants experience less cued information while experiencing more and

31   more distracting elements as they advance. Participants are required to quickly identify the direction of a probe target

32   that is facing at a right angle (up, down, left, right), and are aided by the presence of directional cue indicating in which

33   location of the screen the target will appear amongst distracting elements. Responses are made by reaching their hands

34   to indicate the direction of the probe, with the additional physical challenge of running in place if the target is up or

35   down. Prior to each level, participants completed a thresholding session to determine the optimal starting point from

36   both a cognitive and physical perspective. After completing their initial 7 training sessions, participants advance to LEVEL

37   2 of this module which entailed facing a greater challenge: here they encountered an increase in the number and

38   salience of distracting elements, including the presence of congruent distractors, as based on their performance on the

39   previous trial. After completing 14 training sessions, participants moved on to LEVEL 3 of this module: here participants

40   performed the same task as before, but now without the aid of a directional cue. Participants only receive game points

41   when they correctly perform a given trial faster than the predetermined, personalized threshold determined at the

42   beginning of each level to optimize the attentional engagement.

43

44   (ii) BBT Working Memory. This module engages spatial working memory resources similar to the Corsi block task[119-121],

45   requiring individuals to memorize an additional stimulus following two consecutive correct responses, with two

46   consecutive incorrect trials leading to one element being subtracted. Participants memorize the location of objects on

47   screen followed by a 5-7 second delay period during which the participants perform a directed physical movement, with

a correct response leading to a greater number of potential targets to be memorized on the next trial (and vice versa).
Responses are made with both hands and feet by reaching/kicking targets, with additional physical challenges (making a
woodchopping motion) occurring during the delay period. Prior to each level, participants completed a thresholding
session to determine the optimal starting point from both a cognitive and physical perspective. After completing 7
training sessions, participants are asked to also memorize and report the sequential order in which the targets originally
appeared on the screen (LEVEL 2), thus increasing the spatial working memory load. After 14 training sessions,
participants perform a working memory/multiple object tracking task that requires memorizing and tracking the targets
as they become invisible and move amongst a sea of moving objects (LEVEL 3). Participants receive game points when
they correctly complete a working memory trial faster than a predetermined, personalized threshold so as to challenge
the underlying cognitive working memory circuitry.

(iii) BBT Task Switching. This module challenges cognitive flexibility resources by requiring participants to rapidly switch
their focus based on distinct rules, much like a traditional task-switching paradigm[122-124]. Here a morphing algorithm is
used to titrate the perceptual similarity of the target presented, such that a correct trial makes a subsequent exemplar
morph more similar to the probe presented (and vice versa). Participants are presented with exemplar objects along
with a target, and move their hands to the target object that is most similar to the exemplar presented. For example,
when a greenish-blue target appears, participants decide whether the image is more GREEN or more BLUE. The target
changes its degree of likeness to each exemplar following each trial, with each correct response morphing the probe
towards an indistinguishable 50/50 ratio of each exemplar (and vice versa). Prior to each level, participants completed a
thresholding session to determine the optimal starting point from both a cognitive and physical perspective. After
completing 7 training sessions, the presented probes now have features that integrate two rule bases (Level 2, e.g. both
Color and Shape, so a BLUE square), creating greater cognitive demands, similar to interference generated by a Stroop
task. Finally, after 14 training sessions, participants perform the same task, but the exemplars now spawn in random
locations across the screen, heightening the cognitive demands further by requiring visual search (LEVEL 3). Participants
receive game points when they perform a trial as fast or faster than a predetermined, personalized threshold to
pressure underlying goal-management circuitry.

BBT cognitive and physical training calibration
For each cognitive task, difficulty was initially determined through a pre-training assessment to determine an optimal
training threshold, then scaled on a trial-by-trial basis throughout the training experience. The associated physical
challenge for each cognitive task was driven via motion capture of one's hands and feet, where the distance that an
individual had to reach/kick to respond during the cognitive task was directly tied to a participant's predetermined
optimal training heart rate. For example, if an individual's heart rate was below their training window, then the distance
an individual had to traverse to respond on a given trial increased.

8

This continuous cognitive scaling occurred in parallel with an adaptive cardiovascular challenge, with a pre-training VO_2 max assessment determining an optimal training window with respect to one's heart rate using indirect calorimetry[125] to calculate a more precise level of cardiovascular fitness for each individual. More specifically, this involved participants completing a treadmill graded exercise VO_2 Max test to subsequently determine an individual's maximal heart rate, which subsequently was used to determine the heart rate percentiles (60-70% of one's max HR, 70-80% of one's max HR, etc.) at which participants would train at during the BBT training experience. This predetermined heart rate window was used as a baseline comparator against one's current heart rate, with the responses needed for a given cognitive task scaled to be closer or further away than a previous trial without impeding the ability to perform the cognitive task.

MBT battery:

To mitigate any potential placebo effects brought on by participant expectations, we identified a suitable active control condition based on participant predictions of potential training-related gains as in our previous work[58]. We identified a set of three commercially available iOS apps (**Supplementary Figure 1**) that were matched to our BBT program in terms of expectation of improvement on our cognitive outcome measures (see below for description of the statistical selection process). Those apps were a language learning app (Duolingo; www.duolingo.com), a Tai Chi app (Tai Chi Step by Step; www.imoblife.net), and a logic games app (100 Logic Games; www.andreasabbatini.com/LogicGames.aspx). For Duolingo, participants were given a choice of which language they wanted to learn from those available on the app. Within the app, we set a 10 min training time per day. During training, the app takes users through a series of modules that increase in difficulty and are only unlocked sequentially following completion of an earlier module. Modules are organized topically (e.g., Food, Animals, Phrases, etc.) and each module contains listening, speaking, vocabulary, and translation tasks and culminates with a topic quiz. At the end of each lesson the app provides a progress report showing learning "streaks" and the accumulation of "lingots" (Duolingo currency). These feedback features are meant to keep participants motivated. For Tai Chi, users simply open the app and select from a series of modules that provide detailed and easy-to-follow instructions on how to perform many basic, intermediate, and advanced Tai Chi movements and is geared toward beginners with no Tai Chi experience. Each description can be read or listened to and is accompanied by an animation. Users were instructed to then practice the exercise themselves several times after each lesson. The logic games app is comprised of a series of "puzzle sets" that revolve around a particular theme and which get progressively more difficult as people advance. The puzzles are similar to the

more well-known Sudoku puzzles, but provide a more engaging experience with colorful icons, unique rule sets for each theme, and increasing difficulty. For each puzzle, users are given a task (e.g., plant trees according to specific rules), a time limit, and several hints that they can unlock. Participants were instructed to spend approximately 10 min with each app each training day (5 days per week for 6 weeks). For Duolingo, the time was set internally in the app. For the other two apps, participants self-timed their training, and they recorded their time on a training log. All participants completed the MBT intervention at home using an iPad Mini 2 (iOS version 8.2; Apple) that was supplied by the UCSF Neuroscape Center. On the day they were given their iPad to begin training, participants were also provided an instructional binder with instructions on how to play, a calendar for recording notes and comments throughout their training experience, and were given e-mail support throughout the intervention period. Throughout the intervention period, technical support for the iPads and all software was provided via e-mail, phone, and in-person contact, when needed.

Because these apps were commercial apps and not designed to send data to our server, we took additional steps to track compliance in the MBT group. On the day they were given their iPad to begin training, participants were also provided an instructional binder with instructions on how to play, a calendar for recording notes and comments throughout their training experience, and were given e-mail support throughout the treatment period. They were instructed to try to split their time equally among the three apps. Upon completion of the training, researchers confirmed the participants' logged training times.

Behavioral Cognitive Control Assessments:

Attention without distraction. A custom continuous performance task (CPT) designed in Presentation (http://neurobs.com) was used to assess vigilance without distraction. This tool is a modified version of a well-validated vigilance task (**Figure 2a**), the Test of Variables of Attention (TOVA), that we have used as an outcome measure in previous intervention studies. As our metric of interest, we focused on the ex-gaussian tau of response times, a non-parametric measure of distribution skewing that quantifies attentional lapses by examining the distribution of long response times. Several studies have demonstrated a clear advantage of this measure over traditional measures of response time (although we report on traditional metrics of response time and response time variance in the **Supplemental Materials**) given that it explains a greater proportion of variance without needing to employ data trimming techniques[126-128]. Importantly, this measure has been shown to reflect performance inconsistencies that are especially present in both healthy older adults and those with

43 mild cognitive impairment[129], and has been used to support neural noise[130] and dedifferentiation[131-133] theories

44 of cognitive aging.

45   For the present study, we adapted the task for use with EEG recordings, which requires many trials with

46 an actual response, and also facilitates the examination of ex-gaussian tau, a non-parametric measure of

47 distribution skewing of response times[134-137]. In this task, participants maintain fixation on a central crosshairs

48 and grey squares are shown on a black background at the top or bottom of the field of view. Stimuli are

49 presented frequently at the top of the screen as a 4:1 ratio of targets to nontargets and participants are

50 instructed to only respond to these stimuli. Participants completed 2 blocks of 125 trials with 100 targets per

51 block, yielding 200 total targets and 50 non-target trials.

52

53 *Working memory fidelity task.* We used a delayed recognition working memory paradigm designed to measure changes

54 in participants' ability to maintain an accurate mental representation of items in working memory either in presence or

55 absence of distracting or interfering information. We have used versions of this task in numerous previous

56 studies[11,51,56,78]. To summarize briefly, this paradigm consisted of three different conditions that were presented in

57 blocks: 1) no distraction (ND), 2) Ignore distractor (ID, distractor was present, but participants were informed that the

58 distractor was to be ignored), and 3) Attend Distractor (AD, participants were required to make a judgment about the

59 interfering stimulus). Each run was preceded by an instruction slide informing the participant which condition they

60 would be performing. Each trial began with the presentation of a face displayed for 800 ms, followed by a delay period

61 (3 s), the presentation of a face stimulus as a distractor in the ID and AD conditions (800 ms), a second delay period (3 s),

62 and the presentation of a face probe (1 s). The participants were instructed to make a match/nonmatch button press

63 response at the probe as quickly as possible, without sacrificing accuracy. This was followed by a self-paced intertrial

64 interval (ITI). The experiment was programmed in E-Prime (https://pstnet.com/products/e-prime/) and the stimuli were

65 presented on a CRT monitor.

66

67 *Basic response time task.* Here we administered a basic response time (BRT) task as a measure of simple motoric

68 response time to ensure that any differences observed between groups were not due to differences in basic motoric

69 quickness. Basic motor speed was assessed in the form of a simple target-detection task during their pre-training

70 assessment, to ensure that any training-related enhancements in performance were not attributed to a general motoric

71 speed increase, but rather to enhancements in cognitive control processes. On this task participants pressed a keyboard

72 button as quickly as possible upon the appearance of a circle at the center of the screen (50 trials). Average response

73 time (the time between the target appearance and button press) was assayed as a unit of basic motor speed [138].

74

75   *Complex visual discrimination amid distractions.* For this exploratory measure of attention in the presence of variable

76   distraction (considered exploratory given that it was not described in the parent clinicaltrial.gov submission), we used a

77   custom Filter Task[139] (**Supplemental Figure 7a**) to assess how well participants were able to identify targets in the

78   presence of task-irrelevant information[58,140,141]. The experiment was programmed in MATLAB's psychophysics toolbox

79   (http://psychtoolbox.org/) and the stimuli were presented on a CRT monitor. In this task, participants must attend to an

80   array of different numbers of items (either 1 or 3 red rectangles) with or without the presence of 2 visual distractors (2

81   blue or green rectangles): set size 1 no distractors (1 total item), set size 1 with distractors (3 total items), set size 3 no

82   distractors (3 total items), set size 3 with distractors (5 total items). Half of each of the trials for each condition began

83   with a cue indicating the participant should attend to either the left or the right side of the screen. The procedure for

84   each trial began with a 750 ms fixation cross following by a right/left cue (200ms) and then a 300 ms blank ISI. Next, a

85   sample set from one of the four conditions was shown for 200ms followed by a 900 ms blank delay and then a probe set

86   containing the same number of red rectangles as in the sample in either the same orientation or with a single rectangle

87   of altered orientation (50% of each). The probe screen remained visible until participants responded with a "Yes" or

88   "No" button press indicating whether or not one of the attended rectangles changed orientation. Participants

89   completed 8 blocks of 80 trials, yielding 160 trials per condition. Participants were instructed to respond as fast as

90   possible without sacrificing accuracy. As in our previous work[58], we focused on Response Time Variability (RTV) as our

91   measure of interest here.

92

93

94   **Neural Cognitive Control Assessments:**

95   *EEG Recordings*. Neurophysiological data were recorded during each cognitive control assessment using an

96   active two head cap (Cortech Solutions) with a BioSemiActiveTwo 64-channel EEG acquisition system in

97   conjunction with BioSemiActiView software (Cortech Solutions). Signals were amplified and digitized at 1024 Hz

98   with a 16-bit resolution. Anti-aliasing filters were used and data were band-pass filtered between 0.01–100 Hz

99   during data acquisition. For each EEG recording session, a 1 × 1-inch white box was flashed for 10 ms at one of

00   the corners on the stimulus presentation monitor at the start of each trial. A photodiode

01   (http://www.gtec.at/Products/Hardware-and-Accessories/g.TRIGbox-Specs-Features) captured this change in

02   luminance to facilitate precise time-locking of the neural activity associated with each sign event. During the

03   experiment, these corners were covered with tape to prevent participants from being distracted by the flashing

04   light.

05

06   *EEG Preprocessing*. Preprocessing was conducted using the EEGLAB software[142]. Noisy channels were identified

07   upon initial visual inspection, were removed from the data, and interpolated using a spherical spline

interpolation, using the average signal of the surrounding channels to reconstruct the data in the removed channel. The data were then down-sampled to 1024 Hz to reduce the computational demand without losing any important information in the data. A finite impulse response filter with a high-pass cutoff of 1 Hz was applied to remove drift, and then a low-pass filter at 40 Hz was applied to remove high frequency noise. Ocular correction was performed by using ICA to isolate and remove activity induced by eye-blinks and lateral eye movements from the signal. The data were then re-referenced to the average signal of all channels. Epochs of -1000 ms to +1000 ms were generated for each stimulus type for subsequent analyses. Epochs containing excessive peak-to-peak deflections (±100 μV) were removed.

Midline Frontal Theta Analyses. Midline frontal theta (4-7Hz) power (mft Power) has been implicated in sustained attention abilities [51,143-145], including correlating with RTV across the lifespan[146], that can evidence the engagement of the prefrontal cognitive control processes during a given task. This particular marker has also demonstrated a level of sensitivity in revealing changes following a digital intervention in multiple studies[23,51,54,55,58]. Time series were created by resolving 4-40 Hz activity using a fast Fourier transform (FFT) in EEGLAB in epochs from -1000 to +1000msec. Midline frontal theta total power analyses (evoked power + induced power) across trials from the vigilance task was conducted by resolving 4–40 Hz activity using a fast Fourier transform in EEGLAB, with these values subsequently referenced to a -900 to -700 pre-stimulus baseline (thus relative power (dB)). After mft relative power was computed, we specifically interrogated a predetermined cluster of frontal electrodes (Fz, FPz, AF3, AF4, and AFz) at the time window of maximum power, as this is the same approach that we have previously utilized in several intervention studies interrogating mft power changes[51,54,55,58].

Physical outcome measures:

To capture changes in physical fitness due to training during the study, all participants underwent a comprehensive physical outcomes assessment in addition to the cognitive assessments described above. Our targeted outcome measures were a senior-specific measure of stability indicative of fall risk[76,77] as well as a physiological measure of fitness and health (diastolic blood pressure)[74]. Our decision to focus on diastolic (rather than systolic) blood pressure was based on diastolic blood pressure being a proportionally larger contributor to mean arterial pressure (MAP)[147], with MAP being an important predictor of cardiovascular disease[148-150]. Descriptions of each exploratory fitness measure evaluated, including systolic blood pressure, are described in

the **Supplemental Materials;** note that these measures came from the Senior Fitness Test (SFT) to assess global physical performance[151].

Training-related expectancy ratings:

In an effort to identify an expectancy matched placebo versus the BBT intervention, we first compared expectancy on 10 different apps to BBT in a sample of 261 participants (Female=135, mean age=33.5). Each participant was randomly assigned to view a video of BBT or one of 10 potential apps (n= 15–30 individuals per app) which we did not hypothesize would improve cognitive abilities. They were then asked to rate the extent to which the presented intervention would lead to improvements on these outcomes, using a Likert scale measuring 1 (no improvement) to 7 (a lot of improvement). Following this first round of testing, we selected the three apps that had the highest expectancy matching scores, and subsequently collected new expectancy data in a sample of 76 young adults to assess the level of expectancy involving the combination of these three apps (n=37) versus BBT (n=39). Here we found no differences in participant expectations of improvement on our CPT task (t_{74}= 0.24, P = 0.62, 95% CI: −1.3 to 0.77) or on our filter task (t_{74}= 0.55, P = 0.16, 95% CI: −0.30 to 1.8), suggesting that we had comparable expectancy on this battery of control apps as compared to the BBT intervention with respect to our cognitive control outcome measures.

To determine if these expectancy findings held with older adults, we had 91 older adults complete this same expectancy survey. These older adults were shown a recording of either the BBT (n=46, mean age=64.4, Female=28) or the MBT (n=45, mean age= 63.2, Female=31) interventions and subsequently shown a video describing our cognitive outcome measures. We observed no significant difference between interventions in terms of participant expectations of improvement on the CPT (independent t-test: t_{89} =-1.84, p=0.069, with the MBT intervention showing a trend towards having greater expectation of improving on this measure than the BBT group) and the Filter tasks (independent t-test: t_{89} =-0.682, p=0.50). To ensure that these findings extended to the present study, we asked all BBT and MBT participants to complete a comparable version of this survey after they had completed their first few days of training on their assigned intervention to see if their experience led to different expectancy-based perceptions. This was motivated especially by the fact that the MBT training experience was distinct from the BBT training experience in that they completed their training at home on a tablet by themselves, whereas the BBT group trained at a laboratory on a large screen TV in the presence of a trainer. Once again, we observed no significant difference between interventions in terms of participant expectations of improvement on the CPT (independent t-test: t_{36} =1.26, p=0.21, MBT mean=5.0, BBT mean=5.4) and the Filter tasks (independent t-test: t_{36} =0.64, p=0.53, MBT mean=5.0, BBT mean=5.3).