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Integrated cognitive and physical fitness training enhances attention abilities in older adults

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Abstract

Preserving attention abilities is of great concern to older adults who are motivated to maintain their quality of life as they age. Both cognitive and physical fitness interventions have been utilized in intervention studies to assess maintenance and enhancement of attention abilities in seniors, and a coupling of these approaches is a compelling strategy to buttress both cognitive and physical health in a time- and resource-effective manner. With this perspective, we created a closed-loop, motion-capture video game (Body-Brain Trainer: BBT) that adapts a player's cognitive and physical demands in an integrated approach, thus creating a personalized and cohesive experience across both domains. Older adults who engaged in two months of BBT improved on both physical fitness and attention outcome measures beyond that of an expectancy-matched, active, placebo control group, with maintenance of improved attention performance evidenced 1 year later. Following training, the BBT group's improvement on the attention outcome measure exceeded performance levels attained by an untrained group of 20-year-olds, and showed age-equilibration of a neural signature of attention shown to decline with age: midline frontal theta power. These findings highlight the potential benefits of an integrated, cognitive-physical, closed-loop training platform as a powerful tool for both cognitive and physical enhancement in older adults.

Introduction

Over the last decade there has been a surge of research aimed at improving cognitive abilities by harnessing neuroplasticity via cognitive training¹⁻⁵. The augmentation of deficient attention abilities is especially of interest for older adults, given well documented age-related declines in these abilities⁶⁻¹⁴, which are exacerbated in the presence of interference^{2,7,15-17}. Cognitive training as a whole has come under warranted scrutiny given consistent shortcomings in study design and outcomes: i) minimal extension of benefits beyond the training interventions themselves, ii) lack of appropriate control groups, and iii) absence of follow-up testing to assess sustainability of observed effects¹⁸⁻²⁰. However, there have been several notable examples of cognitive interventions enhancing non-trained cognitive abilities in older adults^{10,21-23}, with these findings aligning with systemic reviews supporting the utility of cognitive interventions in the older adult population²⁴⁻²⁶.

In contrast to the uncertainty surrounding the benefits of cognitive training, the utility of physical fitness interventions for older adults' general health has been well established. Fitness-based interventions have also been shown to benefit cognitive control abilities²⁷⁻³², with such findings hinting at the possibility that combining cognitive and physical training approaches may lead to greater cognitive benefits than either approach alone (although not supported to date³³⁻³⁶). The use of combined cognitive and physical interventions are especially compelling as a strategy to maintain both cognitive and physical health³⁷, given that such a pairing can be a time- and resource-effective approach for addressing multiple risk factors in older adults³⁸. Indeed, combined training has been shown to result in greater participant enjoyment compared to either sequential training³⁹ or physical exercise alone⁴⁰.

We have previously demonstrated that cognitive interventions using closed-loop, adaptive algorithms⁴¹ designed to target specific cognitive abilities in older adults can improve task performance and neural measures of cognition^{12,23,42-44}. These interventions, delivered as engaging video games, have shown positive effects not only with older adults, but in diverse populations⁴⁵⁻⁴⁸. Here we created a novel cognitive intervention for older adults (Body-Brain Trainer, BBT; **Figure 1**) that requires participants to perform full-body, physical movements in response to cognitive challenges that engage different cognitive control domains^{41,49}. As in our previous work^{42,50,51}, we integrated real-time adaptivity using closed loop mechanics for each cognitive ability being challenged. Given the movement demands of BBT, we also implemented an adaptive physical fitness challenge by using real-time heart rate data to

titrate game play for a personalized and integrated training experience across both cognitive and physical domains (see **Methods** and **Supplementary Materials** for more details on the BBT software).

In the present study, we sought to evaluate the primary question of whether BBT could improve measures of attention and physical fitness in older adults beyond that of an expectancy-matched, active placebo control group. We also interrogated the following secondary questions: what is the neural mechanism underlying positive cognitive effects, do any observed cognitive improvements persist one year later without booster training sessions, does BBT result in older adults achieving comparable levels to young adults on our primary outcome measure, and does this intervention affect other measures of cognitive control (working memory).

RESULTS

Participation and Study Overview:

To interrogate the posed questions, we performed a double-blinded, randomized, placebo-controlled study (registered on clinicaltrials.gov [NCT03032796]) where 49 healthy older adults (OA; mean age=68.5 +/- 6.3, 26 females) were randomly assigned to an intervention group (BBT: n= 24) or an active, expectancy-matched control group (Mind-Body Trainer (MBT): n=25, see **Supplementary Figure 1** and **Methods** for details). A total of 41 of these participants (BBT = 21, MBT = 20) returned 1-year after completing their intervention to assess for the presence of sustained cognitive benefits (a CONSORT figure describing participant enrollment can be found at **Supplementary Figure 2**). Details regarding improvements on the BBT training intervention itself can also be found in the **Supplementary Materials**, including **Supplementary Figures 3-6.**)

Sustained Attention:

Here we used a vigilance task as our primary cognitive outcome measure to assess the intervention's impact on attention abilities. This task was a customized Continuous Performance Task (CPT), which is a modified version of a well-validated sustained attention task, the Test of Variables of Attention (TOVA)⁵², used as an outcome measure in our previous intervention studies^{42,48,53} (**Figure 2a**). 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 techniques⁵⁴⁻⁵⁶. Importantly, this measure has been shown to reflect performance inconsistencies that are especially present in both healthy older adults and those with mild cognitive impairment⁵⁷, and has been used to support neural noise⁵⁸ and dedifferentiation⁵⁹⁻⁶¹ theories of cognitive aging.

Using a repeated measures ANOVA to evaluate change in CPT performance from pre- to post-intervention (see ‘Statistical methods’ in Methods), we found a significant time (Pre, Post) by intervention (BBT, MBT) interaction ($F_{1,45} = 7.49$, $p = 0.009$, Cohen’s $d = .79$), with performance improvements (i.e. a reduction in tau from pre to post) in the BBT group ($\Delta = +15.73$ msec improvement, $t_{23} = 2.29$, $p = 0.03$), but not in the MBT group ($\Delta = -6.46$ msec improvement, $t_{24} = -1.60$, $p = 0.13$; **Figure 2b**, and **Table 1** for values). When this measure was compared to a separate untrained cohort of young adults ($n=51$; **Figure 3**) who completed this task in a single visit, the BBT group did not show expected age-related performance differences at baseline; i.e., the BBT group exhibited equivalent performance to young adults ($t_{73} = .42$, $p = .67$; see **Table 1** for values). However, following training, the BBT group showed significantly lower tau (i.e., better performance) than young adults ($t_{74} = 2.20$, $p = .03$). Finally, in evaluating stability of performance gains over time, follow-up tests 1-year later revealed that neither group showed significant differences from post-training performance levels (BBT: $t_{20} = 1.61$, $p = .12$; MBT: $t_{19} = .34$, $p = .74$; see **Table 1**).

We also performed an exploratory analysis of attention (not part of pretrial registration assessments) to assess how a more challenging complex visual discrimination task with varying levels of distraction would be impacted by these interventions (see **Supplementary Figure 7a** and **Methods** for task details). The same pattern of results as described for CPT in terms of both the statistical interaction and follow-up tests 1-year later were observed on the complex visual discrimination task (see **Supplemental Materials and Supplementary Figure 7b**).

Neural Correlates of Sustained Attention:

In addition to measuring cognitive performance, participants also underwent electroencephalography (EEG) recordings during the CPT task to examine neural mechanisms that underlie performance changes from pre to post (i.e., improved ability to stabilize their attention as revealed by reductions in tau). Here we utilized the neural metric of midline frontal theta power, given that it has been associated with sustained attention abilities^{62,63} and is a sensitive marker of changes in attention abilities following interventions^{42,45,64}. A repeated measures ANOVA revealed a significant group by time interaction ($F_{(1,43)} = 6.61$, $p = 0.014$, Cohen’s $d = .74$; **Figure 2c**), with post-hoc paired-samples t-tests showing a significant increase in power following the intervention for the BBT group ($t_{23} = -2.77$, $p = 0.011$), but not

in the control group ($t_{20} = 0.79, p = 0.44$). Once again, the same pattern of results was also observed for the complex visual discrimination task using comparable EEG analyses (see **Supplemental Materials and Supplementary Figure 7c**).

When compared to the group of young adults, the older adult BBT group showed expected age-related reductions in pre-training theta power ($t_{56} = 3.10, p = .003$). After the intervention period, the BBT group's post-training power increased to a level equivalent to that of young adults ($t_{57} = .11, p = .91$, see **Figure 3**, and **Table 1** for values). With respect to assessing the stability of these changes 1-year later, neither group showed significant differences from their post-training levels (BBT: $t_{18} = 1.16, p = .26$; MBT: $t_{14} = .95, p = .36$; see **Table 1** for values).

Fitness Measures

We assessed whether the BBT intervention led to measurable improvements in physical fitness measures beyond that of the control group by focusing on metrics of balance⁶⁵⁻⁶⁹ and blood pressure⁷⁰⁻⁷³, given their association with real-world health outcomes in older adults. Using a repeated measures ANOVA to test for differential group improvement over time, we observed a significant group by time interaction on a balance measure (i.e., the limits of stability test associated with risk of falling^{74,75}; $F_{(1,44)} = 8.37, p = 0.006$, Cohen's $d = .90$, **Figure 4a**); notably, the BBT group significantly improved on this stability measure ($t_{21} = -3.81, p = 0.001$) whereas the MBT group did not ($t_{23} = -0.81, p = 0.94$). With respect to blood pressure, a repeated measures ANOVA revealed a significant group by time interaction of diastolic blood pressure ($F_{(1,41)} = 9.32, p = 0.004$, Cohen's $d = .78$, **Figure 4b**), with the BBT group significantly decreasing their diastolic blood pressure after training ($t_{21} = 4.35, p = 0.001$) while the MBT group did not ($t_{20} = 0.68, p = 0.51$). See **Methods** and **Supplementary Materials** for details on systolic blood pressure as well as other exploratory physical fitness metrics.

Working Memory and Basic Response Time Assessments

We also explored whether BBT led to an improvement on a working memory task (described in trial registration as a secondary outcome) that has been shown to improve in previous intervention studies of older adults^{16,42,46,76} (see **Methods** for task details). A repeated measures ANOVA of tau using a within-subject factor of Session (Pre, Post) and a between-group factor of Study Group (BBT, MBT) did not demonstrate a Study Group x Time interaction for any of the three working memory conditions (no distractions, ignore distractions, attend to distractors), indicating that tau on this working memory test did not differentially change between study groups ($F_{(1,39)} \leq 0.95, p \geq .34$, see **Table 1** for no distractor

condition values). Similarly, independent t-test analyses showed that there was no group difference in performance post-training on any of the three conditions ($t_{(42)} \leq 1.46$, $p \geq 0.52$).

Finally, we administered a Basic Response Time (BRT) task as a measure of simple motoric response time to ensure that any differences observed between groups were not due to improvements in basic motoric speed (see **Methods** for task details). A repeated measures ANOVA with a within-subject factor of Session (Pre, Post) and a between-group factor of Study Group (BBT, Control) did not reveal an interaction, indicating that RT did not differentially change as a function of training between study groups ($F_{(1,40)} = 2.16$, $p = .15$, see **Table 1** for values). Similarly, there was no RT performance difference post-training between the BBT and MBT groups ($t_{(42)} = .44$, $p = .67$). This same analysis approach revealed the same outcome for RTV, with no observed interaction ($F_{(1,40)} = .31$, $p = .58$) or difference post-training ($t_{(42)} = 1.5$, $p = .13$). These results suggest that differences found on the primary outcome measures cannot be attributed to improvements in basic motoric speed or motoric variability.

DISCUSSION

Overview:

Here we demonstrate that an integrated cognitive-physical fitness intervention (BBT) improved measures of physical fitness, as well as objective measures of attention beyond an expectancy-matched, active placebo control group. After the intervention, their post-training cognitive performance reached comparable, and in one case superior, levels to younger adults, with these gains being maintained 1 year later. Here we discuss the implications of these findings and how they relate to other efforts aimed at improving cognitive function in older adults.

Physical, Cognitive, and Neural Enhancements:

Given the movement demands of BBT, it was unsurprising yet reassuring that engagement led to improved balance, consistent with results from other exergaming studies in older adults^{77,78}. However, this is the first study of its kind that also evidenced diastolic blood pressure improvements beyond a control group, suggesting that the adaptive fitness mechanics spurred a physiological benefit not previously seen before. BBT also had a positive effect on attention abilities in older adults, in alignment with other combined cognitive-physical intervention studies that evidenced enhanced attention in older adults^{33,35,79}. However, the benefits observed here were attained with a significantly shorter training regimen (8 weeks) compared to the majority of these other combined studies (typically between 12-16 weeks, with some lasting up to 30 weeks), and with much less logistical burden by the training in each

domain being integrated rather than split across different training days. Another key difference from previous studies was the incorporation of adaptivity, not just for cognitive challenges but also for physical fitness demands, which allowed us to titrate the physical training appropriately to each individual's fitness level. We hypothesize that the integration of the cognitive and physical training within a video game experience may have spurred the observed benefits after a relatively abbreviated intervention time.

The attention-based improvements reported here are comparable to those found in other aging intervention studies from our group that utilized different closed-loop adaptive mechanics to improve attention both with²³ and without distraction⁴². Attention improvements documented using the same CPT task have also been observed in a recent meditation-based intervention study in younger adults⁴⁸. This convergence of attention improvements emerging from different types of closed-loop interventions in older adults and other populations is particularly compelling^{46,80-82}. Indeed, the results from these studies suggest the potential for individuals to select their preferred digital treatments without concerns about differential efficacy.

While there is ample evidence that combined interventions in older adults can have positive effects on overall cognitive function⁸³⁻⁸⁶, few studies have included neuroimaging assessments to examine the underlying mechanisms of improvements observed^{36,87,88}. Studies involving such combined approaches have reported increased cerebral glucose metabolism in frontal and sensorimotor regions³⁶, enhanced fMRI resting state functional connectivity between frontal and temporal regions⁸⁸, and increased fMRI resting state synchronization at temporal and cerebellar regions⁸⁷. These findings highlight distinct neural metrics involving 'task-free' measures across different brain regions associated with improved cognitive performance, as brain-behavioral correlations were observed in each study. Here, we observed that the activation of a frontal top-down network accompanied improved attentional performance without external distraction, as well as increased trial-by-trial neural consistency that corresponded with improved attentional focus when distractions were present. These findings are aligned with our previous work in older adults evidencing similar top-down theta power enhancements following a closed-loop video game intervention (NeuroRacer)⁴², as well as improved theta coherence following a distraction training intervention in both older humans and rats²³. Thus, empirical support exists for the idea that midline frontal theta is an especially sensitive marker of attentional control changes in intervention studies⁶⁴.

Comparisons to young adults and long-term maintenance of benefits:

The present findings offer a mixed interpretation of whether the observed attention-based improvements were a remediation of age-related deficiencies or the intervention enhanced non-deficient processes. The older adult BBT cohort exhibited age-related deficits in midline frontal theta power that increased to levels equivalent to young adults after training, unlike the control group. However, the BBT cohort showed comparable performance levels at baseline (CPT tau) to the young adults, although after training they were significantly better than their younger counterparts. Previous studies have evidenced age-related declines on these same metrics^{42,89}. The current results support a compensation effect^{90,91}, given that improvements in the BBT group led to performance levels exceeding that of younger adults and suggest that integrated cognitive and physical approaches designed to augment plasticity in neural systems may have the potential to remediate certain aging deficits^{23,92}.

Other work has suggested that combined interventions may have a particular advantage with respect to long-term maintenance of observed benefits⁸⁶. We offer evidence here demonstrating that each group had comparable performance levels at the 1-year mark compared to levels attained immediately post-training. These findings should be considered with caution given that very few intervention studies targeting cognitive control abilities have evidenced persisting effects well past the initial treatment period⁹³⁻¹⁰⁰. Indeed, our own work failed to realize the persistence of the more distant transfer effects several years later⁶⁴, and even here the sensitivity of these measures one year later is unclear. While it has been argued that the value of these types of interventions are dubious without the demonstration of sustained benefits beyond the initial treatment period^{101,102}, we posit that these findings better highlight the potential utility of incorporating additional booster sessions for sustaining benefits.

Conclusions:

Here we observed that BBT led to improvement in the ability of healthy older adults to stabilize their attention from moment to moment on a vigilance task beyond that of an expectancy-matched, placebo control group. Beyond the methodological approach used here, these results are highly relevant for older adults given the steady advancement of innovative approaches designed to help these individuals with their cognition and physical fitness. The present findings are consistent with recent meta-analyses highlighting the positive effects of combined interventions on cognitive function^{83,86,103,104}, with accompanying physical benefits supporting the use of such technology to realize meaningful benefit in both cognitive and physical domains. Thus, comparable combined cognitive and physical interventions may be a viable time- and resource-effective approach for older adults to maintain (or even enhance) both their cognitive and physical health.

Limitations:

There are several limitations with the present study that are important to note. First, this work does not directly interrogate whether BBT leads to beneficial effects beyond those achieved with training cognitive or physical abilities in isolation. Several studies and meta-analyses have already interrogated this question³³⁻³⁶, with these works suggesting that the combined approach does not appear to yield synergistic effects beyond cognitive training alone. Furthermore, due to the experimental design, we cannot directly assess how much of the observed attention improvements can be attributed to the individual physical and cognitive training components incorporated in BBT. Indeed, both cognitive interventions and physical fitness training have been shown to induce attention improvements and positive functional changes in the prefrontal cortex (i.e. increased task-based activations)^{99,105,106} in line with present findings. Our goal here was to assess if there was value in an integrated approach beyond that of an expectancy-matched placebo control group, as a positive result sets the stage for a future trial directly examining the mechanistic contributions of training each domain in isolation.

Second, while we observed improvements on distinct measures of attention, as in previous work, improvements did not emerge on a working memory outcome measure as it did in previous intervention-based studies^{42,46} (see **Supplementary Materials**). One possible explanation for this result is that BBT disproportionately engaged attention-based circuitry during training, given that both working memory¹⁰⁷ and cognitive flexibility abilities^{108,109} call upon attentional resources for their successful utilization. Thus, attention abilities were engaged during each BBT module across the entire intervention periods. This interpretation, while speculative, is consistent with previous work that targeted cognitive flexibility and observed improvements on the same outcome measures used here (CPT and the working memory task), as well as on the same neural measures⁴².

METHODS

Participants:

The study was approved by the Committee on Human Research at the University of California, San Francisco, and registered on clinicaltrials.gov [NCT03032796]. The present study directly examined the intervention and expectancy matched placebo arms described in the registration, with the collection of the two mechanistic control arms planned for a future RCT. 49 healthy, older adult (OA) individuals consented to participate in this study. OAs were randomly assigned to a training group (body-brain trainer; BBT; N=24, mean age=68.8 +/- 5.9, 13 females) or an active, expectancy-matched control group

(mind-body trainer; MBT; N=25, mean age=68.20 +/- 6.75, 13 females). All participants were from the San Francisco Bay Area and recruited through online and newspaper advertisements. All participants had normal or corrected-to-normal vision, had no history of stroke, traumatic brain injury, or psychiatric illness, were not taking psychotropic, hormonal, or cardiovascular medications, and did not have any physical or mental conditions that may interfere with their daily activities (e.g., migraine headaches, substance abuse, neuropathy; see **Supplemental Materials** regarding our neuropsychological assessment protocol). All participants reported playing less than 2-hours of video games per month. All participants gave written informed consent, and were paid \$15/hour for their in-lab and at-home participation.

Study Design:

For those participants randomized to the BBT group, they were asked to come to Neuroscape at UCSF 3 days per week, 1 hour per visit (36min of on-task training time per session, 24 minutes allocated for warm up/cool down/breaks) for 8 weeks (24 hours total, 14.4 hours of actual training time). Each of these visits were accompanied by an onsite trainer to facilitate the training experience for the participant and ensure that training was being completed in a safe manner. For those participants randomized to the MBT group, they were loaned an iPad tablet (9.7 inch screen size; 1024 x 768 screen resolution) for their training session following their 'Pre-training' assessment, and were instructed to train with their assigned task at home for six weeks, 5-days per week, with 30-minute training sessions per day, for a maximum of thirty 30-minute training sessions (15 hours of training total). All MBT participants were instructed to train sitting down 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 expectancy¹¹⁰). 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 complete 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^{42,50,51}, 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 (thus, a 1"up"/3"down" staircase). These cognitive adaptive algorithms are designed to assure participants remain at an ~80% rate of accuracy, a level that is not too easy nor too hard, so that it is enjoyable and engaging. For the physical training, difficulty is tied to the demands associated with the distance an individual must travel for a given response and the amount of time allocated to complete this response. These movement-related aspects are directly

responsive to whether heart rate is below/within/above a predetermined heart rate window to ensure a moderately intense workout that does not impede the ability to perform the cognitive task. For example, if one is playing the game *below* their assigned heart rate range, the software will automatically increase the distance that the participant must move to respond with their hands/feet on each trial until their heart rate is within the specified range. Training sessions are linked, such that the next session begins at the level attained at the end of the previous session. Participants are provided two types of feedback: 1) real-time feedback – indicating whether the participant successfully detected or classified the target and 2) punctuated feedback – participants advance through a series of “levels” that are reported at the beginning and end of each run. We describe each module in greater detail in the **Supplementary Materials**, as well as the pre-training calibration procedures undertaken to personalize the experience for each participant.

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 work⁴⁸. 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.

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. For the present study, we adapted the task for use with EEG recordings, which requires many trials with an actual response, and also facilitates the examination of ex-gaussian tau, a non-parametric measure of distribution skewing of response times¹¹¹⁻¹¹⁴. A key factor that led to our decision to use this particular metric stems from recent work demonstrating that the relationship between behavioral variability and inattention is driven by the tail of the ex-Gaussian distribution of response times (which is indexed by tau) rather than variability in the normal distribution component¹¹⁵. In this task, participants maintain fixation on a central crosshairs and grey squares are shown on a black background at the top or bottom of the field of view. Stimuli are presented frequently at the top of the screen as a 4:1 ratio of targets to nontargets and participants are instructed to only respond to these stimuli. Participants completed 2 blocks of 125 trials with 100 targets per block, yielding 200 total targets and 50 non-target trials.

Working memory fidelity task. We used a delayed recognition working memory paradigm designed to measure changes in participants' ability to maintain an accurate mental representation of items in working memory either in presence or absence of distracting or interfering information. We have used

versions of this task in numerous previous studies^{16,42,46,76}. To summarize briefly, this paradigm consisted of three different conditions that were presented in blocks: 1) no distraction (ND), 2) Ignore distractor (ID, distractor was present, but participants were informed that the distractor was to be ignored), and 3) Attend Distractor (AD, participants were required to make a judgment about the interfering stimulus). Each run was preceded by an instruction slide informing the participant which condition they would be performing. Each trial began with the presentation of a face displayed for 800 ms, followed by a delay period (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), and the presentation of a face probe (1 s). The participants were instructed to make a match/nonmatch button press response at the probe as quickly as possible, without sacrificing accuracy. This was followed by a self-paced intertrial interval (ITI). The experiment was programmed in E-Prime (<https://pstnet.com/products/e-prime/>) and the stimuli were presented on a CRT monitor.

Basic response time task. Here we administered a basic response time (BRT) task as a measure of simple motoric response time to ensure that any differences observed between groups were not due to differences in basic motoric quickness. Basic motor speed was assessed in the form of a simple target-detection task during their pre-training assessment, to ensure that any training-related enhancements in performance were not attributed to a general motoric speed increase, but rather to enhancements in cognitive control processes. On this task participants pressed a keyboard button as quickly as possible upon the appearance of a circle at the center of the screen (50 trials). Average response time (the time between the target appearance and button press) was assayed as a unit of basic motor speed¹¹⁶.

Complex visual discrimination amid distractions. For this exploratory measure of attention in the presence of variable distraction (considered exploratory given that it was not described in our clinicaltrial.gov submission), we used a custom Filter Task¹¹⁷ (**Supplemental Figure 7a**) to assess how well participants were able to identify targets in the presence of task-irrelevant information^{48,118,119}. The experiment was programmed in MATLAB's psychophysics toolbox (<http://psychtoolbox.org/>) and the stimuli were presented on a CRT monitor. In this task, participants must attend to an array of different numbers of items (either 1 or 3 red rectangles) with or without the presence of 2 visual distractors (2 blue or green rectangles): set size 1 no distractors (1 total item), set size 1 with distractors (3 total items), set size 3 no distractors (3 total items), set size 3 with distractors (5 total items). Half of each of the trials for each condition began with a cue indicating the participant should attend to either the left or the right side of the screen. The procedure for 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 sample set from one of the four

conditions was shown for 200ms followed by a 900 ms blank delay and then a probe set containing the same number of red rectangles as in the sample in either the same orientation or with a single rectangle of altered orientation (50% of each). The probe screen remained visible until participants responded with a “Yes” or “No” button press indicating whether or not one of the attended rectangles changed orientation. Participants completed 8 blocks of 80 trials, yielding 160 trials per condition. Participants were instructed to respond as fast as possible without sacrificing accuracy. As in our previous work⁴⁸, we focused on Response Time Variability (RTV) as our measure of interest here.

Neural Cognitive Control Assessments:

EEG Recordings. Neurophysiological data were recorded during each cognitive control assessment using an active two head cap (Cortech Solutions) with a BioSemiActiveTwo 64-channel EEG acquisition system in conjunction with BioSemiActiView software (Cortech Solutions). Signals were amplified and digitized at 1024 Hz with a 16-bit resolution. Anti-aliasing filters were used and data were band-pass filtered between 0.01–100 Hz during data acquisition. For each EEG recording session, a 1 × 1-inch white box was flashed for 10 ms at one of the corners on the stimulus presentation monitor at the start of each trial. A photodiode (<http://www.gtec.at/Products/Hardware-and-Accessories/g.TRIGbox-Specs-Features>) captured this change in luminance to facilitate precise time-locking of the neural activity associated with each sign event. During the experiment, these corners were covered with tape to prevent participants from being distracted by the flashing light.

EEG Preprocessing. Preprocessing was conducted using the EEGLAB software¹²⁰. Noisy channels were identified 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 ($\pm 100 \mu V$) were removed.

Midline Frontal Theta Analyses. Midline frontal theta (4-7Hz) power (mft Power) has been implicated in sustained attention abilities^{42,121-123}, including correlating with RTV across the lifespan¹²⁴, 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^{23,42,45,48,64}. 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^{42,45,48,64}.

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^{74,75} as well as a physiological measure of fitness and health (diastolic blood pressure)⁷². 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)¹²⁵, with MAP being an important predictor of cardiovascular disease¹²⁶⁻¹²⁸. 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 performance¹²⁹.

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 ($t_{89}=-1.84$, $p=0.069$, with the MBT intervention showing a trend towards having greater expectation of improving on this measure than the BBT group) and the Filter tasks ($t_{89}=-0.682$, $p=0.50$). 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 ($t_{36}=1.26$, $p=0.21$, MBT mean=5.0, BBT mean=5.4) and the Filter tasks ($t_{36}=0.64$, $p=0.53$, MBT mean=5.0, BBT mean=5.3).

Statistical Analysis Approach:

Analyses were conducted by researchers who were blind to group membership. To test for training effects on each of the collected outcome measures, we used an repeated measures ANOVA approach as in our previous work^{42,53}. Statistically, no between-group differences were observed for at baseline involving: (1) age ($t_{47}=0.35$, $p=0.73$); (2) gender ($t_{47}=-0.15$, $p=0.88$); (3) CPT performance ($t_{45}=1.84$, $p=.07$); (4) Filter task performance ($t_{46}=1.34$, $p=.19$); (5) mft power ($t_{44}=1.70$, $p=.10$); (6) mft ITC ($t_{41}=1.11$, $p=.28$); (7) limits of stability ($t_{44}=1.05$, $p=.30$); (8) diastolic blood pressure ($t_{43}=1.77$, $p=.08$). For those measures that showed a trend towards a group difference at baseline (CPT performance, mft power, and blood pressure), we performed an analysis of covariance (ANCOVA) with post-training performance as the dependent variable, pre-training performance as the covariate, and group as the fixed factor. Our reasoning for using this approach is that this analysis accounts for variation around the post-test means

that arises from the variation where participants began at pretest¹³⁰. Using this approach, we observed a nearly significant group difference following training for the CPT task ($F_{(1,46)} = 3.85$, $p=0.056$), a significant group effect for mft power ($F_{(1,44)} = 4.35$, $p=0.043$) and a significant group effect for diastolic blood pressure ($F_{(1,42)} = 6.93$, $p=0.012$), supporting the assertion that the reported ANOVA effects were not driven by trending baseline differences between groups. For post-hoc analysis of the within-group changes, we performed two-tailed, paired-sample t-tests on each group separately to test for significant differences between each testing session. We report Cohen's d for all significant ($p < .05$) and trending ($p < .10$) ANOVA results, using the Hedges and Olkin correction¹³¹ for small sample bias.

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Author Contributions:

J.A.A. and A.G. designed the experiments; J.A.A., R.A.S., C.R. and A.G. developed the BBT software; J.V., A.S., C.G., C.T. collected the data; J.A.A., J.V., A.S., C.G., and C.T. analyzed the data; and J.A.A., J.V., A.S., and A.G. wrote the paper. All authors discussed the results.

Competing Interests statement:

A.G. is a co-founder, shareholder, BOD member, and advisor for Akili Interactive Lab, a company that produces therapeutic video games.

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Table 1. Group means and standard deviations for each primary measure at each timepoint for each group.

	BBT	MBT	Young Adult
Primary Measures			
<i>cPT (tau) Assessment (msec)</i>			
Pre-Training	72.5 (39.7)	52.2 (31.2)	68.1 (29.4)
Post-Training	55.8 (19.0)*	58.7 (39.4)	N = 51
1-Year	59.1 (17.4)	57.9 (30.4)	
<i>Frontal Theta Power during CPT (dB)</i>			
Pre-Training	0.77 (1.85)	1.67 (2.27)	2.11 (1.43)
Post-Training	2.28 (2.68)*	1.30 (2.20)	N = 34
1-Year	1.80 (2.25)	1.05 (1.11)	
Secondary Measures			
<i>Diastolic Blood Pressure (mmHg)</i>			
Pre-Training	78.72 (5.25)	76.23 (5.91)	(n/a)
Post-Training	73.00 (5.68)*	77.52 (6.32)	
<i>Limit of Stability Assessment (balance; m/s)</i>			
Pre-Training	3.88 (1.34)	4.29 (1.26)	(n/a)
Post-Training	4.59 (1.26)*	4.30 (0.99)	
<i>Working Memory Task, No Distractor Condition[#] (tau)</i>			
Pre-Training	29.7 (14.1)	24.1 (10.0)	(n/a)
Post-Training	26.0 (12.0)	24.2 (12.0)	
<i>Basic Response Time (mean RT; msec)</i>			
Pre-Training	409.1 (83.3)	372.4 (63.3)	(n/a)
Post-Training	390.7 (74.2)	373.6 (79.0)	
Exploratory Measures			
<i>Filter (RTV) Assessment, Set Size 3 (msec)</i>			
Pre-Training	544.1 (229.3)	470.8 (138.9)	409.5 (162.5)
Post-Training	412.6 (148.9)*	459.2 (107.2)	N = 51
1-Year	487.0 (297.7)	378.2 (123.0)^	
<i>Frontal Theta ITC during Filter (PLV)</i>			
Pre-Training	0.24 (.09)	0.28 (.09)	.25 (.06)
Post-Training	0.28 (.11)†	0.26 (.09)	N = 34
1-Year	0.23 (.05)^	0.21 (.08)^	

[#] = Performance on No Distractor condition shown, with similar results observed (not reported) on the Attend Distractor and Ignore Distractor conditions.

* = Post-training performance significantly different than Pre-training performance († = p = .08)

^ = Post-training performance significantly different than 1-Year performance

Note that no significant difference at baseline was observed between groups (see Statistics for details).

Figure 1. Body-Brain Trainer (BBT) platform. a, Image of participant playing BBT. Highlighted is the use of a heart rate monitor to assess and adapt the physical intensity of game play in real-time, as well as the Microsoft Kinect™ motion capture technology used to collect responses with one's hands and/or feet based on the cognitive task presented on the monitor, and adapt the cognitive difficulty of each game in real-time. b, Image of the task switching module. c, Image of the attention module. d, Image of the working memory module.

Figure 2. CPT task. a, Stimuli and protocol for the attention without distraction (CPT) task. b, Bar graphs illustrating the group mean change in ex-gaussian tau (pre - post, with + values demonstrating improvement in tau over time) for each group, with the dashed line (1-year diff = pre - 1-year) illustrating the change in tau at the 1-year mark. c, Bar graphs and topographic plots illustrating the group mean change in midline frontal theta power (post - pre) for each group, with the dashed line on the bar graphs illustrating the change in power at the 1-year mark (1-year - pre). The dashed circle on the topographic plot illustrates the electrodes where statistical analyses took place. * = $p < .05$. Error bars represent s.e.m.

Figure 3. Comparison of BBT and MBT performance versus younger adults.

	BBT Pre-Training	MBT Pre-Training	BBT Post-Training	MBT Post-Training
CPT (tau)	=	↑	↑	=
CPT (mfTheta Power)	↓	=	=	=

↓ => performance significantly lesser than that of young adults

↑ => performance significantly better than that of young adults

= => performance equivalent to that of young adults

Green = Significant improvement from pre-training

Red = Significant decline from pre-training

Figure 4. Improvements in Physical Outcomes Assessments

a, Limits of Stability (LoS) assessment on the NeuroCom balance manager system^{132,133}. The LoS is a center-out postural stability test that serves as a basic balance quantification metric. During this task, increases in movement velocity have been associated with decreases in fall risk in older adults¹³⁴. b, There was a significant group x time interaction in movement velocity of the LoS task ($F_{1,40} = 7.814$, $p = 0.008$, partial eta squared=0.163). The BBT group showed a significant increase from pre to post ($t_{18} = 4.53$, $p < 0.001$), whereas the control participants showed no difference ($t_{22} = -1.02$, $p = 0.32$). Note there was no difference at baseline between groups ($t_{43} = 1.77$, $p = .08$.) c, Diastolic blood pressure assessment. Diastolic blood pressure is a predictor of overall physical health and has been found to be decreased through exercise interventions^{135,136}. d, There was a significant group x time interaction ($F_{1,40} = 8.43$, $p = 0.006$). The BBT group showed a significant decrease from pre to post ($t_{19} = 4.31$, $p < 0.001$), whereas the control participants showed no significant change following their intervention ($t_{21} = 0.46$, $p = 0.65$). Note there was no difference at baseline between groups ($t_{44} = 1.05$, $p = .30$).

Supplementary Files

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