Title: Successful Aging and Enrichment (SAGE): Effects of Environmental Stimulation on Cognitive Health and Neural Plasticity

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Detailed Protocol

Successful Aging and Enrichment (SAGE): Effects of Environmental Stimulation on Cognitive Health and Neural Plasticity

Background and Significance

Increasing numbers of individuals are living into old age [1-3]. According to a recent UN report (2007), individuals over the age of 60 are the fastest growing age group on earth. They currently account for 700 million people around the world. By 2050, the numbers are expected to grow to 2 billion. The number of individuals projected to become demented is proportional to the growth in the aging population. Today around 25 million people suffer from dementia, a disease that is relatively rare before the age of 65. After 65, the proportion of demented persons in the population doubles every five years until 90+, when approximately half of that population suffers from this syndrome. The global cost of dementia care in 2009 has been estimated to $421.6 billion [4]. If nothing can be done to prevent, cure, or at least delay the incidence of dementia, the resources to take care of all demented individuals will constitute an enormous burden for many countries. Advancing our knowledge about factors that contribute to cognitive health among the elderly is thus both an important and urgent task. Models developed by Brookmeyer and colleagues [5] suggest that an intervention that could delay the mean onset of Alzheimer's Disease (AD) by ~5 years would lead to a 50% reduction in incident rates. Even a 1 year delay would be associated with a 10% reduction in incidence.

A large number of epidemiological studies have found that an active lifestyle contributes to cognitive health across the lifespan [6]. The protective factors reported include intellectual and physical enrichment activities; social activities and networks; awareness and concentration (mindfulness) practices; and cognitive activity. Some studies have indicated that these types of activities may also have a positive effect when performed late in life. Critics, however, claim that associations from epidemiological studies do not constitute a sound basis for conclusions about causality.

In 2010, a systematic review of potential factors that might prevent cognitive decline indicated that the quality of evidence was low for all reported factors, except for cognitive training, the main reason being lack of experimental validation in human studies [7]. More recently, one experimental study in humans found that physical exercise had positive effects on BDNF, an important marker of neural plasticity and cognitive health [8].

A common model to explain the possible effect of environmental stimulation on cognitive health involves its impact on reserve capacity [6, 9]. The basic idea is that a brain that has received more stimulation will have richer neural networks and greater capacity to develop new neural connections with learning (i.e., the stimulated brain will be more plastic). Another implication is that loss of function of part of a brain (e.g., due to underlying neurodegenerative disease, stroke, or trauma) can more easily be compensated for. On a cognitive level, reserve could also facilitate the development of alternative processing strategies or behaviors to compensate for difficulties in a particular area.

The evidence that physical stimulation, mental stimulation, and awareness (mindfulness) training may have beneficial effects on the brain and cognition is reviewed below.

Physical Activity

Studies of animals have indicated that exercise promotes neurogenesis and synaptogenesis. Exercise up-regulates the production of brain derived neurotrophic factor (BDNF) [10, 11]. BDNF is believed to help induce neurogenesis and promote survival and/or neuronal differentiation. It has also been linked to long-term potentiation necessary for memory formation. A Cochrane Database System Review [12] noted that 8 out of 11 randomized controlled exercise intervention studies reported that structured aerobic exercise interventions resulted in increased cardiorespiratory fitness of the intervention group, with an average improvement of approximately 14%. This improvement was associated with better performance on cognitive functions, including auditory attention (effect size 0.52), speed of information processing (effect size 0.26), and visual attention (effect size 0.26).

Physical activity and exercise has been associated with the enhancement of cognitive and brain function, and with a reduced risk for clinical dementia [13-22]. A recent review article published in *Nature Reviews: Neuroscience* [23] concluded that physical activity improved cognition in both normal older adults and patients with early AD. Although benefits were seen for a range of cognitive functions, there appeared to be disproportionate improvement in executive control (including planning, working memory, and multi-tasking). Particularly intriguing are the exercise intervention studies that have looked at effects on not only cognition but also underlying brain structure and activity. For instance, in a study reported by Colcombe and colleagues [24], older individuals who participated in an aerobic training group exhibited significant increases in the size of components of the prefrontal cortex and superior temporal lobes. In another study by the same researchers [25], more physically fit older subjects as well as those randomly assigned to participate in the aerobic fitness training group performed better on an attention task (more efficient response to conflicting cues on a flanker task). Moreover, functional magnetic resonance imaging (fMRI) revealed that older subjects exhibited greater neural activity in regions associated with attentional control (middle and superior frontal gyrus, superior parietal lobule) and less activity in the anterior cingulate cortex.

Cognitive Stimulation

There have been numerous studies comparing animals placed in “enriched” versus standard environments. An enriched environment often means a cage filled with potentially interesting objects and structures to explore. The opportunity for aging animals to interact with a more complex environment appears to influence neurogenesis , dendritic complexity, the capacity to compensate for injury, and and promotes cognitive abilities and the capacity to compensate for injury [26-30].

Morphometric MRI studies of the human brain have provided evidence that cognitive activity or training alters brain morphology of relevant structures, leading to an increase in cortical thickness. For example, comparisons of the MRIs of individuals learning to juggle versus those of control subjects reveal an increased size of bilateral mid-temporal grey matter and left posterior intra-parietal sulcus, structures associated with the visual processing of movement [31]. Similarly, comparisons of the MRIs of licensed London taxi drivers versus control subjects reveal increased volume of the posterior hippocampus believed to help mediate spatial memory [32]. fMRI has been used to examine the impact of cognitive training on older adults. For example, Erickson and colleagues [33] conducted a randomized, longitudinal dual-task training study in older subjects. They found that training improved task performance and was associated with an increase in asymmetric hemispheric activation (increase in left and decrease in right hemisphere activity within the ventral lateral prefrontal cortex (PFC), and a

decrease in age-related differences in the pattern of prefrontal activation). Logan and colleagues [34] found that training that emphasized semantic elaboration during a memory encoding task led to improved performance of older subjects. This was associated with increased activity of the PFC (especially the left ventral region), which, compared to young subjects, had been under-recruited at baseline, prior to training. Both studies suggest that the aging brain can exhibit plasticity that may be influenced by training and intervention programs.

Formal cognitive training has been shown to improve measures of intellectual performance. For example, in a study by Ball and colleagues [35], older individuals (65-94 years old) were randomly assigned to one of three training groups for memory (verbal episodic memory), reasoning (problem-solving that follows a serial pattern), or speed of processing (visual search and identification), or to a control group. The initial intervention improved performance relative to baseline; however the improvement was limited to the cognitive realm that had been targeted. Improvements lasted through the 2 years of follow-up. Other studies also have supported the potential benefit of cognitive training in older adults [22, 36, 37]. Recently, there has been some evidence of transfer of improvement beyond the specific cognitive activity that was trained, especially when the training was directed at working memory and executive control [38-40].

Mindfulness Meditation

The literature indicates that there are two types of mindfulness. Each is comprised of pragmatic practices and psychological orientations. In relation to both types of mindfulness, Jon Kabat-Zinn refers to the pragmatic aspects of mindfulness as a "scaffolding" used to support the psychological orientations of mindfulness [41].

The first type of mindfulness is derived from ancient contemplative traditions (e.g., Buddhist meditation practices) [42]. Pragmatically, this first type can include the practice of taking a seated posture with the eyes closed or partially open, the practice of walking, or another pedestrian task, while silently focusing on observing somatic sensation, sensory stimuli (sound, smell), breath, mental activity, or emotional activity [43, 44]. The psychological orientation during this pragmatic practice is described by Kabat-Zinn as "paying attention in a particular way: on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment to moment" [45]. There is no attempt to alter perception, just to direct attention .

The second type of mindfulness has been pioneered by Ellen Langer and is concerned with shifting perspective, or "reperceiving" [46]. The pragmatic practice for this type of mindfulness is outward focused: one observes a person, thing, or idea. Psychologically, one is still oriented to non-judgment and moment-to-moment awareness, but, in addition, one is oriented to experience the person, place, or idea in novel ways [47].

There are several other integral components of psychological orientation in both forms of mindfulness. One is non-striving: instead of choosing a goal-oriented or competitive mindset, one cultivates an attitude of patience, compassion, and acceptance for what is happening in the present moment. Also, instead of a discriminating mindset, one chooses a mindset of inclusive curiosity [46]. Instead of seeking to avoid unpleasant experience or retain pleasant experiences, all experiences are seen as equally valuable [48]. We aim to include aspects of all of these components and practices in our mindfulness intervention.

There is evidence of the impact of mindfulness practice on attentional control and mental efficiency [49-54]. Both intervention and comparison studies of long-term meditators vs. non-meditators suggest that mindful meditation may alter brain structure and physiology [49-51, 55-61]. The literature also supports the feasibility of mindfulness training in older adults [62, 63].

To the best of our knowledge, the proposed study would be the first to experimentally compare the impact of different types of structured training programs on markers of cognitive and brain health in older adults.

Relevant Previous Research by the Project's Investigators

The proposed research is a collaborative effort between Linnaeus University, Vaxjo, Sweden and the Brigham and Women's Hospital, Boston MA. It brings together researchers who have been investigating different aspects of cognitive aging.

The proposed studies parallel on-going research at Sweden's Karolinska Institutet Alzheimer's Disease Research Center (KI-ADRC), headed by Bengt Winblad. Ann-Charlotte Granholm and Abdul Mohammed have previously cooperated on studies concerning the role of BDNF on cognitive function in older animals. Their previous findings from experimental studies on rats showed that environmental stimuli can have a positive impact on brain anatomy, behavior, and learning ability [64-66]. Environmental stimulation increased levels of BDNF [65, 67] in the hippocampus and cortex, two brain regions critically involved in cognitive functioning. Environmentally induced elevation of BDNF levels in experimental animals was related to enhanced spatial learning [66, 68]. It is unclear whether environmental stimulation in humans modifies neurotrophin levels or cognitive functioning. In humans, various types of stimulation are being considered as prime candidates (e.g., physical exercise and [69] cognitive stimulation [70]). However, which type of stimulation is most effective and whether the effects can be observed in elderly persons is unknown.

Bengt Winblad has reported that people with higher education are less likely to suffer from dementia [71], which has been interpreted as resulting from long-term intellectual stimulation. Moreover, such findings are consistent with the model of "cognitive reserve", which holds that capacities, in particular brain-involved capacities, that developed over time serve to mitigate negative effects of age- and disease-related changes in the brain. It was also found that individuals who had been living with another person as part of a relationship had lower risk of dementia in later life [72], which can be interpreted as a result of social and perhaps even intellectual stimulation. However, since both of these results come from epidemiological studies, we cannot ascertain a causal link with cognitive health. Even less can be said about possible functional factors behind this association. For example, is the cognitive health benefit associated with a long-term relationship due to the intellectual challenges of taking into account the views and needs of a partner? Or is the cognitive benefit due to the social/emotional consequences of living with someone?

The Laboratory of Healthy Cognitive Aging at BWH under the direction of Kirk Daffner has investigated curiosity (attention to the novel aspects of one's environment) and cognitive reserve in normal aging and neurological disease [73-82]. His lab has demonstrated that successful cognitive aging is strongly associated with increased engagement by novel stimuli, as measured by electrophysiological (event-related potentials) and behavioral markers [74]. The difference between high and average cognitive performers in attention to novelty increases with age [74]. However, even among cognitively successful

older adults (individuals in their upper 80s and 90s), cognitive resources may be insufficient to compensate for age-associated neural changes [81]. Greenwood and Parasuraman have argued that exposure to novelty, requiring the brain to adapt to changing demands, serves as a key factor in promoting brain plasticity and cognitive integrity [83].

If interest in novelty is both a marker and promoter of cognitive health, it is critical to determine if this process can be influenced through structured interventions involving cognitively stimulating activities, physical exercise, or mindfulness training. To our knowledge, the proposed study would be the first to systematically test this possibility.

Finally, work at BWH by Farzaneh Sorond has utilized transcranial doppler (TCD) studies to examine cerebral blood flow responses in healthy older adults [84-86]. TCD can determine the extent to which subjects are capable of enhancing cerebral blood flow in response to cognitive demands and whether these responses can be altered by experimental interventions. Neurovascular coupling reflects the link between regional synaptic activity and regional cerebral blood flow. Under normal conditions, cerebral blood flow and cerebral metabolic rate are coupled, with an increase in metabolic demand leading to an increase in blood flow. Dr. Sorond's lab has shown that compared to fast walking elders, those who are slow walkers exhbit impaired neurovasuclar coupling [84]. Another study demonatrated that the pattern of blood flow velocities in anterior and posterior circulations differ between healthy old and young subjects [85]. A recently published report indicated a strong link between neurovascular coupling and cogntive performance in older adults. In individuals with baseline impairments, there was improvementt in neurovascular coupling and cognitive funtion with regular cocoa consumption, which may be due to its antioxidant, anti-inflammatory, or cholinergic properties [86].

In summary, the current project engages experts from major research institutions that represent different perspectives (biological, pharmacological, psychological, clinical and epidemiological) and who bring experience using different methodological approaches,. The composition of this research team should facilitate an interdisciplinary approach to study factors of importance for maintaining brain health in later life. Together, we have published over 1,000 articles in the field.

Specific Aims

The overarching goal of the current study is to identify factors that promote neural plasticity and cognitive health in elderly persons.

The specific aims address the impact of different types of structured mental or physical stimulation over a 5 week training period on the following:

1. Biological markers of brain plasticity (e.g., BDNF)
2. Electrophysiologic markers (event-related potentials) of neural efficiency and capacity
3. Neuropsychological markers of cognitive performance
4. Vascular markers of cerebral health (e.g., neurovascular coupling using transcranial doppler)

Subject Selection

We aim to have 200 subjects complete the study. There are two sites: one at BWH and one at Linnaeus University, Vaxjo, Sweden, with 100 subjects participating at each site.

Subjects will be recruited at the two sites with the aim of obtaining a representative sample of healthy, elderly participants 65 and older in each country. At BWH, subjects will be recruited through several channels, including announcements in local newspapers and other available media; outreach to independent living communities; senior activity centers and organizations; and through existing databases for studies of healthy aging that exist at BWH.

To be included in the study, participants must:

1. Be 65 or older
2. Have ≥ 8 years of education
3. Be sufficiently fluent in the English language to understand instructions and perform the neuropsychological tests (as the purpose of the project is to study healthy aging)
4. Score above levels indicating possible cognitive impairment on the Mini Mental State Exam (MMSE) (≥ 26) [87]
5. Have an estimated intelligence quotient (IQ) score ≥ 90 based on the American National Reading Test (AmNART) [88]
6. Have a score within 2 SD of the age-appropriate mean on the short form of the Boston Naming Test [89, 90]
7. Have a score within 2 SD of the age-appropriate mean on the Logical Memory Subtest of the Wechsler Memory Scale—Third Edition [91]

Subjects will be excluded for any of the following reasons:

1. History of CNS diseases or major psychiatric disorders based on DSM-IV criteria [92]
2. Score of > 10 on the Geriatric Depression Scale [93]
3. Corrected visual acuity worse than 20-50 as tested by a Snellen wall chart
4. Severe hearing disability that would interfere with their ability to participate in the experiments (e.g., to hear instructions and participate in cognitive testing)
5. Medical conditions (e.g., heart or pulmonary disease) that would prevent them from participating in the physical exercise training program
6. Evidence of substantial functional decline based on interview questions and completion of a questionnaire based on the Clinical Dementia Rating Scale [94] by an informant who knows the subject well

Permission will be obtained from subjects to contact their primary care physicians (PCPs). PCPs will be asked to confirm that if their patient were assigned to the physical training condition, he/she could safely participate. Subjects will be excluded if their PCP does not confirm that they can safely participate.

All subjects meeting the inclusion/exclusion criteria will be entered in the study, regardless of race, ethnic background, or gender. Every effort will be made to actively recruit minorities and women to reflect the racial and gender composition of the age group studied.

We anticipate that subjects will reflect the current demographic composition of the Boston area, with approximately 12% from minority groups. In our prior studies on cognitive aging, ~17% of subjects were from minority populations (~10% of which were African American). Approximately 58% of our subjects

have been women (which reflect the demographics of a population of older subjects). We anticipate having a similar mixture of subjects in the proposed study.

Subject Enrollment

Phone Screen

Information about the study:
Potential subjects will be briefly informed about the study. We will explain that the purpose of the research is to identify factors that can help to promote cognitive and brain health in older adults. This will be accomplished through examining the impact of different training programs involving physical or cognitive exercises and activities. Potential subjects will be told that there are 4 different training programs: two programs involve cognitive training, one involves training in mindfulness (awareness), and one involves physical training. We will make it clear that participants do not get to choose the program, but will be assigned by chance (randomized) to one of these training interventions. All participants will come to Brigham and Women's hospital for a baseline assessment and for a post-intervention assessment, which will be the same regardless of the training program in which a subject participates. These assessments will include cognitive, brain wave, and biological measures of brain function and adaptation. Training will take place in the participant's own home over a 5 week period. They will be paid for their time and the cost of parking at BWH will be covered.

Information about the potential subject:
All potential subjects will be screened by phone, using a standardized telephone interview that reviews neurological, medical, and psychiatric conditions, and conducts a brief cognitive test.

Eligible subjects interested in participating will be asked to assent to being randomized to one of the four training programs, which will be recorded on the phone screen in-take form.

Permission to Contact a Potential Subject's PCP
Eligible subjects will be informed that one of the interventions is a physical exercise training program that involves a mild to moderate degree of exertion. All subjects will need "permission" from their PCPs indicating they can safely participate in physical exercise.

Potential subjects who remain eligible and interested after the phone screen will be mailed a form to sign that will be sent to their PCP authorizing them to complete it. The form will include a brief description of the physical exercise program and ask the PCP to state whether or not it is medically safe for the person to participate in such a training program, if he/she were assigned to it. We will include a stamped, addressed envelope for subjects to mail the form back to us in.

After we receive written authorization from the potential subject, we will contact the PCP's office, fax the form, and provide our secure fax number where the completed form should be sent back. After receiving the completed form from the PCP, we will contact the potential subject to let her/him know if she/he is eligible to participate. If eligible, we will schedule the pre-intervention assessment, where informed consent will be obtained and additional screening procedures and baseline testing will take place (see below).

Randomization

Subjects will be randomly assigned to one of 4 conditions (3 experimental, 1 active control), which will be determined prior to the first visit so that the appropriate informed consent form can be completed:

1. Cognitive training using Cogmed (Pearson ®)

2. Awareness ("mindfulness") training

3. Physical exercise training using an interactive video platform

4. Active control condition using the non-adaptive Cogmed program

We plan to continue to recruit subjects until all 4 arms of the protocol are filled.

Study Procedures

Pre-Intervention Assessment
The initial screening evaluation will take place over two half-day sessions, each lasting 3 to 3.5 hours in a designated room in the Laboratory of Healthy Cognitive Aging, Center for Brain/Mind Medicine, BWH, 221 Longwood Avenue, Boston, MA.

The sessions can be completed over one or two days, depending on the subject's preference.

Pre-Intervention Assessment Session 1
The first session will include completion of informed consent, a medical history, demographic information, including socioeconomic status (SES), survey questionnaires, and tests of visual acuity.

Screening Evaluation (for inclusion/exclusion)

Cognitive Screen

- *The Mini-Mental State Examination (MMSE)*, a broad cognitive test on memory, spatial ability, memory and orientation, commonly used to screen for cognitive impairment [87]
- *American National Adult Reading Test (AmNART)*, a test of word pronunciation that provides an estimated IQ [88]
- Logical Memory I and II, Wechsler Memory Scale—Third Edition, a test of verbal memory [91]
- *Boston Naming Test (Short-form, 15-items)*, a test of confrontation naming [89, 90].

Depression Screen
Geriatric Depression Scale [93]

Neurological/Physical Evaluation
Subjects will undergo a structured neurological examination. Height and weight will be obtained to calculate BMI. Visual acuity will be measured (Snellen wall chart).

Gait
Gait will be assessed through a procedure in which subjects walk 10 meters under two conditions:

1. Single task (walking at a comfortable pace)
2. Dual task (walking at a comfortable pace while simultaneously counting backwards by 3's, beginning with a 3 digit number told to the subject)

Every trial involving serial 3's will start from a different three digit number to reduce learning effects. Subjects will be given an opportunity to carry out an untimed practice trial. Under the dual task condition, subjects will be instructed to perform as well as they can on both tasks (i.e., no specified prioritization). Each condition will be done 2 times, with the order counterbalanced across subjects. The first and last meter (gait start up and slow down) will not be counted in the measurements.
Time to walk 8 meters and number of steps taken will be measured. Under the dual task, we will also track how many numbers are generated while carrying out the serial 3's task (both correct and incorrect responses). In addition, the single task of counting backwards by 3's for 20 seconds will be tested twice in a seated position (once prior to and once after the gait testing).

Informant Questionnaire

Subjects will select someone who knows them well (family member or friend) to complete a set of questionnaires. One questionnaire will provide information about a person's level of functioning (based on the Clinical Dementia Rating Scale [94]), and another will inquire about a person's level of engagement (Apathy Scale [95]). The questionnaires will be enclosed with a letter explaining how to complete the forms. We will provide a stamped, addressed envelope to return the quesionnaires to us. A backup plan will be to mail these materials directly to the informant selected. This would occur if the materials were misplaced or if the subject requests us to do so. Informants will be compensated for their time by a $10 check that will be mailed to them.

Outcome Measures (Dependent variables measured at baseline and after the 5 week intervention)

- *Cambridge Neuropsychological Test Automated Battery* (CANTAB), a computerized assessment of cognitive functions:
    - CANTAB Paired Associate Learning (PAL) – assesses visual memory and new learning
    - CANTAB Attention Switching Task (AST) – measures cued attentional set-shifting
    - CANTAB Reaction Time (RTI) – measures speed of response to visual target when the stimulus is either predictable (simple RT) or unpredictable (choice RT)
    - CANTAB Spatial Span (SSP) – assesses working memory
    - CANTAB One Touch Stockings of Cambridge (OTS) – a test of non-verbal reasoning
- *Trail Making Test*, Parts A and B, tests of visual attention and task switching [96]
- *Digit Symbol Coding, WAIS-IV*, a test of processing speed [96]
- *Controlled Oral Word Association Test (COWAT)*, a test of verbal retrieval and word generation [97]
- *Categorical Fluency* (a test of rapid retrieval of semantic knowledge) [97]

Subject Questionnaires

Self-report about race and ethnicity
Self-report of socioeconomic status
International Physical Activity Questionnaire (IPAQ) (www.ipaq.ki.se) [98]
Handedness questionnaire [99]
Apathy Screen [95]
Need for Cognition Scale [100]
Mindful Attention Awareness Scale [101]

Quality of Life Scale (QOL) [102]
Pittsburgh Sleep Quality Index [103]
SF-36(tm) Health Survey [104, 105]

Pre-Intervention Assessment: Session 2
Session 2 will start in the ERP laboratory at 221 Longwood Avenue.

Blood Samples
Subjects will be escorted to the phlebotomy lab at the BWH Center for Clinical Investigation, 221 Longwood Avenue, which is in the same building as where our offices are located. They will be given the opportunity to sit quietly in the waiting area for ~10 minutes before being escorted to a phlebotomy room. Blood samples will be taken via a cannula inserted into a vein by a BWH phlebotomist. Approximately 35 ml of blood will be collected.

Approximately 10 ml of blood will be prepared according to the method recommended by the Granholm Laboratory, Medical University of South Carolina.

In brief, one vacutainer tube with ~10 ml of whole blood is collected. This collection of blood will yield eight Eppendorf tubes with about 0.5 ml of serum in each. Another Eppendorf tube will contain the buffy coat (if available), and the vacutainer tube will contain the blood clot.

In the event that the BWH Center for Clinical Investigation is unavailable for blood processing and packaging, the sample will be taken to the Clinical Trial Center at BWH, where processing and packaging will be completed.

After freezing / storage, four of the Eppendorf tubes of serum, as well as one Eppendorf tube containing buffy coat, and the vacutainer tube containing the clot will be sent on dry ice by overnight mail to the Lotta Granholm Laboratory, Basic Science Building 410, 173 Ashley Avenue, Medical University of South Carolina, Charleston, South Carolina 29407.

The remaining four Eppendorf tubes of serum will continue to be stored at BWH until the Granholm Lab confirms receipt of the specimens. If the Granholm lab does not require these tubes, they will be transported to the De Jager Lab at Brigham and Women's Hospital and stored at BWH/Harvard-Partners Center for Genetics and Genomics, New Research Building, Rm 164 (see below).

To prepare the serum, the blood first stays for 30 minutes at room temperature and is then centrifuged (at 4° C) for 10 minutes. The serum is then collected in a separate polypropylene container, mixed by inverting several times, and finally distributed into eight Eppendorf tubes, with 0.5 ml of serum in each. These will be kept frozen in Ziplock bags at -70° to -80°. The clot and the buffy coat (if available) will also be frozen and sent to the Granholm Lab.

Additional blood will be collected and stored for future analyses, if/when additional funding becomes available. Approximately 5 ml will be collected (EDTA tube) for potential genetic analysis (identifying genetic variants that may impact age-related cognitive decline), and 20 ml will be collected (Lithium heparin tube) for purification and cryopreservation of peripheral blood mononuclear cells (PBMCs) from which epigenetic factors and markers of immune function can be derived. Preparation of blood products will be done by the

De Jager Lab at Brigham and Women's Hospital, and stored at BWH/Harvard-Partners Center for Genetics and Genomics, New Research Building, Rm 164. In the future, stored blood products may be sent for analysis at the Broad Institute at MIT or similar facilities that collaborate with BWH researchers. The informed consent forms will seek permission to store blood samples indefinitely for future study.

ERPs

Subjects will then participate in ERP experiments while data on brain waves are being collected. An ActiveTwo electrode cap (Behavioral Brain Sciences Center, Birmingham, UK) will be used to hold to the scalp a full array of 128 Ag-AgCl BioSemi (Amsterdam, The Netherlands) "active" electrodes whose locations are based on a pre-configured montage. Electrodes are arranged in equidistant concentric circles from the 10-20 system position Cz. In addition to the 128 electrodes on the scalp, 6 mini bio-potential electrodes will be placed over the left and right mastoid, beneath each eye, and next to the outer canthi of the eyes to check for eye blinks and vertical and horizontal eye movements. EEG activity will be digitized at a sampling rate of 512 Hz.

During the experimental protocols, visual or auditory stimuli will be presented. Participants will be asked to respond to designated stimuli by button press or foot pedal. Visual stimuli will include simple geometric shapes, letters, and complex figures that are presented on a high resolution monitor. Auditory stimuli will be presented binaurally at between 75dB SPL and 90dB SPL through high quality headphones.

The protocols will assess electrophysiological responses to novelty processing (subject-controlled novelty oddball task), working memory/attention (n-back task), and visual and auditory perception (visual and auditory evoked potential studies). Before beginning any new experimental condition, subjects will be given step-by-step explanations of what to do. Subjects will participate in practice trials. A brief break will occur between each block, and longer breaks will take place between each experimental condition.

Subject-controlled Novelty Oddball Task: The experimental procedures for the Novelty Processing Task are analogous to the ones described in published reports [74, 75]. Two hundred and fifty line drawings, white on black background, will be presented in 5 blocks of 50, each at the center of a high-resolution computer monitor. All stimuli will subtend a visual angle of approximately 2.75° along their longest dimension. There will be three categories of visual stimuli: 1) a repetitive Standard Stimulus (a triangle)--70% frequency, 2) a Target Stimulus (upside down triangle)--approximately 15% frequency, and 3) Novel Stimuli, randomly drawn from a set of unusual/unfamiliar line drawings (e.g., impossible or fragmented objects) shown only one time each--approximately 15% frequency, many of which come from the collection of drawings that have been used by Kroll and Potter (1984) [106] and Kosslyn et al. (1994) [107]. Stimuli will appear within a fixation box, subtending a visual angle of approximately 3.5° x 3.5°, that remains on the screen at all times. Participants will be told that the study is investigating how people look at different kinds of line drawings. They will be viewing a set of drawings and can look at each picture for however long or short they like. They control the viewing duration by pressing a button (with their dominant hand) that leads to the erasure of the current stimulus and the onset of a blank screen, followed by the presentation of the next stimulus. Participants will be told that they will not be asked questions about the drawings at the end of the experiment. Also, participants will be told to respond to the designated target stimulus by pressing a foot pedal (ipsilateral to the button press). Instructions will indicate that accuracy is more important than speed.

N-Back Task: The experimental procedures for the N-Back Task are analogous to the ones described in a previous report [108]. Subjects will perform a verbal *n*-back paradigm in the visual modality with three levels of difficulty (0-back, 1-back, 2-back). Stimuli will consist of letters of the alphabet, white on a black background, presented at the center of a high-resolution computer monitor for 200 ms, in pseudo-random order. Under each *n*-back condition, subjects were shown a series of 300 letters, divided into three blocks. For each level of *n*-back, 75% of trials will be non-matches and 25% of trials will be matches. Subjects will be instructed to respond only to match letters (button press on a game controller). Subjects will be told to respond as quickly as possible without sacrificing accuracy. The interval between the onset of consecutive visual stimuli will be fixed at 2200 ms. The hand used for button press and the order of *n*-back level will be counterbalanced across subjects.

Evoked Potentials:
Visual evoked potentials: Subjects will be view a series of checkerboard stimuli (4° visual angle) flashed to the right or left visual field (presented at 1-9 Hz) while they fixate on a dot at the center of the screen.

[74]ERP Recordings
ERP data collection and analysis will follow published reports by Daffner et al. (2012) [109]. An ActiveTwo electrode cap (Behavioral Brain Sciences Center, Birmingham, UK) will be used to hold 128 electrodes to the scalp. EEG activity will be digitized at a sampling rate of 512 Hz.

ERP Data analysis
EEG data will be analyzed using ERPLAB and EEGLAB [110] toolboxes that operate within the MATLAB framework. EEG epochs for different stimulus types will be averaged separately. Although many event-related potentials (ERPs) will be measured, the focus of analysis will be on the P3b component, which reflects categorization/memory updating and the P3a component, which reflects orienting/executive control. The size of these components serves as an index of the amount of resources allocated to perform the task, and the latency of the component serves as an index of processing speed.

Transcranial Doppler (TCD)
Information about blood flow using transcranial doppler (TCD), a non-invasive technique, also will be collected during an n-back task and in response to flashing checkerboard stimuli. TCD recordings will be done either before or after the ERP experiments.

Neurovascular coupling reflects the link between regional synaptic activity and regional cerebral blood flow. Under normal conditions, cerebral blood flow and cerebral metabolic rate are coupled, with an increase in metabolic demand leading to an increase in blood flow. Neurovascular coupling will be indexed by changes in bilateral middle cerebral artery blood flow velocities during the n-back task.
A 2-MHz, pulsed flat transcranial Doppler probe (MultiDop, DWL) will be placed over each temporal bone. The signal on both probes will be range gated to a depth of 45 mm to 60 mm, to insure insonation of the M1 segment of the middle cerebral artery. Once the signals are maximized, the probe will be fixed in place for the duration of the test using a Velcro headband that will be placed over the ERP electrode cap. Localization and determination of the proper artery and position will be performed according to standard techniques. Normally, in about 1 out of 5 older people, these blood vessels cannot be tested.

Baseline physical activity monitoring (accelerometry)
For the week between Session 2 at BWH and the start of the structured intervention in the homes of subjects, they will be asked to wear an accelerometer that is fitted snuggly around the waist using the

elastic waistband and is placed over the right hip. Subjects will be asked to wear the accelerometer while awake during 7 consecutive days, except during water based activities since the accelerometer is not waterproof. This will provide baseline data on the level of physical activity/movement in which subjects are engaged.

Accelerometry provides a physiometric measure of motor activity. The accelerometer is a lightweight, small (matchbox sized) non obtrusive device that measures and records accelerations. The accelerometer output is digitized by a twelve-bit Analog to Digital Convertor (ADC) at a rate of 30 Hz. Once digitized the signal passes through a digital filter that band-limits the accelerometer to the frequency range of 0.25-2.5 Hz. The frequency range detects normal human motion and rejects changing accelerations within the passband.

Interventions – General Features and Overview

All of the interventions will include the following features: the duration will be ~35 minutes per day, 5 days/week, over a 5 week period. A member of the research team will visit the subject's home to introduce the training program, and carefully review how to use the appropriate software on a computer, which will be loaned to subjects while they participate in the project. If the subject's home does not have internet access, the tablet provided will include prepaid wireless internet access. The team member will be present during a practice run to facilitate the process and address any concerns.

Subjects will be instructed to carry out the training sessions during the same part of the day (e.g., early morning), and to set up a routine in which they will not be disturbed by phone calls or visitors. Individuals will be told not train more than once a day. They will be encouraged to maintain their other activities and not substitute the training stimulation for another activity in which they have been routinely engaged.

For both cognitive and physical training, subjects will begin with a level they can easily manage. The difficulty will be slowly increased as their performance improves (due to training effects), with the aim of keeping the subjective effort approximately constant and moderately challenging through the 5 weeks. Similarly, for the mindfulness training, the meditations and tasks will become more self-directed and challenging during the 5 week course.

A member of the research team will communicate with each subject on a weekly basis (via phone call or email, whichever mode of communication is more convenient for the subject) to provide feedback and address any questions or concerns. Subjects will also be encouraged to contact the research team at any time they have questions or concerns. Data will be monitored for potential breaks, interruptions, and unusual performance fluctuations.

1. Cognitive training using Cogmed (Pearson ®)

During the initial session, a member of the research team will visit the subject's home and introduce the subject to the Cogmed training program (www.cogmed.com). Individuals will start at the same low difficulty level. As training proceeds, task difficulty will be individually adjusted based on performance by increasing/decreasing the number of items individuals have to remember, such that a participant reaches approximately 60% correct per day for each task. Each training session will start at the task difficulty level where the participant ended in the previous session. Performance and reaction time data will be continuously recorded while subjects are doing the task, and these data will be sent via the internet to the research team after each session. A member of the research team will communicate with

each subject on a weekly basis (via phone call or email) to provide feedback and address any questions or concerns.

2. Awareness (mindfulness) training

During the initial session, a member of the research team will visit the subject's home and introduce the subject to mindfulness techniques. For this training, subjects will participate in a series of mindfulness exercises. Before the start of each session, subjects will log-on to a secure password-required website. Each session will consist one fifteen minute guided mindfulness meditation that we will label "Mindfulness Meditation Session", and 3 six minute guided Mindfulness-in-Action tasks such as "mindful listening", "mindful observing", and "mindful walking," which we will label "Mindfulness Task 1", "Mindfulness Task 2", etc. The meditation and tasks will become increasingly more self-directed over the 5 weeks; the degree of guidance will decrease to keep the subjective effort approximately constant and moderately challenging through the 5 weeks.

The mindfulness meditations will be narrated by one guide and the tasks will be narrated by a different guide. We will have 7 mindfulness tasks in total, whose order of presentation will be counterbalanced across sessions: 1. mindful observing of place, 2. mindful eating, 3. mindful observing of object, 4. mindful observing of person, 5. mindful walking, 6. mindful listening, and 7. mindful writing with the non-dominant and dominant hand.

At the end of each session, participants will write brief reflections stored via the website (e.g., an estimate of the amount of time subjects experienced their thoughts as wandering) both as an integral part of the mindfulness process and as a means of increasing the likelihood that subjects fully participate in each session. Each session will be structured as follows: Login, Mindfulness Meditation Session, Mindfulness Task 1, Mindfulness Task 2, Mindfulness Task 3, Write Log Reflection, Logout.

Login and logout times will be recorded to keep track of a subject's participation. A member of the research team will communicate with each subject on a weekly basis (via phone call or email) to provide feedback and address any questions or concerns.

3. Physical exercise training using an interactive video platform

Subjects will participate in a structured physical exercise training program that aims to progressively increase their level of activity over the 5 week training period. During the initial session, a member of the research team will visit the subject's home and introduce the subject to the different aspects of the training program (e.g., interactive video, accelerometer). An interactive video will be used to present a structured exercise program. This interactive video is being created with exercise physiology specialists in Sweden. It will run using an application on the computer (connected to a monitor or TV screen if possible).

Each training session will begin with warm up/stretching exercises, followed by a series of aerobic exercises, with breaks every few minutes. The aerobic exercises will be followed by a cool down/stretching period.

Aerobic exercises will include relatively low impact activities like walking, jogging, or running in place, which will aim to put limited demands on balance. Each exercise will be explained and demonstrated in the video. All exercises can be done standing, sitting, or next to a chair that provides balance support as demonstrated in the videos. After the first session, for each subsequent session the difficulty level will start at one level below the previous session's average difficulty level (e.g. if they exercise at the most difficult level for most of the time during one session, the next session will start at the medium difficulty level). Each exercise will be explained and demonstrated in the video.

There will be a water break every 8-10 minutes and an Exertion Check-In Break every 3-4 minutes. At each Exertion Check-In break, subjects will push one of 3 buttons to rate their perceived level of exertion ("Too Easy", "Somewhat Hard", "Too Hard"). If they choose "Too Easy", the next set of exercises will be a bit faster. If they choose "Too Hard", the next set of exercises will be a bit slower. If they choose "Somewhat Hard", the next set of exercises will stay at the same level. Subjects are told that the goal is to work at a level that requires a modest degree of effort, where they feel stimulated and like they are working hard, but not so hard that they feel dizzy or short of breath.

If they want to make the exercise easier or harder anytime, they can press the "Pause" button on the computer screen and choose "Too Easy" or "Too Hard".

If they would like a short break, they can also press the "Pause" button on the computer screen. When they are ready to start again, they can press the "Resume" button.

If they need to stop the exercise completely they can press the "Pause" button and then press "Start Over Later".

If, for some reason, they feel unable to carry out a particular exercise (e.g., inability to bend a knee because of arthritis), they will be able to press the "Pause" button and then the "Skip Exercise" button on the computer that will trigger the display and demonstration of an alternative exercise (e.g. Step Touch instead of Skipping).

For the five weeks of the exercise training, during all waking hours –except during water- based activities- subjects will wear an accelerometer, as described earlier. The accelerometer will provide measurements of the intensity of physical activity during the exercise training and allow us to chart the degree to which it increases over the 5 week program. At least once a week subjects will connect the accelerometer to an adapter attached to the computer. This will allow the accelerometer to be recharged and allow research staff to upload the, the activity data via the internet to our laboratory at BWH. Subjects will be given feedback about the amount of "activity units" that they have accrued during the training sessions, which will be automatically added to a log for their review that is stored on the computer. This will provide additional feedback to subjects about their progress and can serve to encourage them to increase the number of activity units per session over the course of their 5 weeks of training. A member of the research team will communicate with each subject on a weekly basis (via phone call or email) to provide feedback and address any questions or concerns.

4. Low level of cognitive training using the Cogmed program (which will serve as an active control condition)

Individuals in the control group will participate in the same computerized Cogmed training program as described above. The main difference is that for the control group task difficulty will remain at the same low starting level, rather than increasing over time. The instructions given to subjects will be identical to the ones used in the cognitive training intervention. During the initial session, a member of the research team will visit the subject's home and introduce the subject to the Cogmed training program (www.cogmed.com). As with the active training group, performance and reaction time data will be continuously recorded while subjects are doing the task and these data will be sent automatically to the research team after each session. A member of the research team will communicate with each subject on a weekly basis (via phone call or email) to provide feedback and address any questions or concerns.

Post-Intervention Assessment

Shortly after completing their 5 week intervention program, subjects will return to our BWH Lab at~~,~~ 221 Longwood Avenue, Boston, MA for 2 half-day sessions. Every effort will be made to have the subjects return to the Lab within 2 days of completing the training program.

During these sessions, we will repeat the following measurements, as described in the section on pre-intervention assessment:

Collection of blood
Cognitive Testing (CANTAB subtests, *Trail Making* Test, Parts A and B, *Digit Symbol Coding, WAIS-IV*, *Controlled Oral Word Association Test (COWAT))* [96, 97]
Completion of questionnaires
Neurologic/gait assessment
ERP studies
Transcranial doppler studies

Subjects will be paid for their time, as follows:

Pre-intervention evaluation session 1	$60
Pre-intervention evaluation session 2	$60
Structured intervention	$30/week for 5 weeks
Post-intervention evaluation session 1	$60
Post-intervention evaluation session 2	$60
Completion of all study components	$60

Subjects who choose to discontinue participation will be paid for their time in a prorated manner. Check request forms will be sent to BWH (accounts payable) and a check will be mailed to the address designated by the subject. During the evaluation session, the cost of parking will be covered by a voucher applicable to any BWH parking facility.

Biostatistical Analysis

We will mainly use MANCOVA methods to compare the different conditions while controlling for various background factors, such as age and baseline cognitive performance. Cognitive change scores will be the main outcome variables. In addition, we will analyze changes from baseline in BDNF levels, gait score neural activity, as measured by ERPs, and degree of vascular coupling, as measured by TCDs.

In separate analyses, we will investigate whether various cognitive domains (e.g., executive functions, memory) are differentially affected by different types of stimulation. We will also perform separate analyses for closer investigation of how age, education, intelligence and mood may modify the experimental effects.

Risks and Discomforts

During the Intervention Programs only subjects whose primary care doctor indicate are safe to engage in in the physical exercise training program will be able to participate in the study (even if they are randomly assigned to one of the non-physical exercise intervention programs). In the physical exercise training program, perceived level of effort will be carefully monitored and subjects who report their perceived exertion to be hard will be instructed to decrease their level of effort. During the initial visit to the subject's home, the study staff will prepare a card that includes the name and phone number of the subject's PCP, in case medical issues arise.

During all of the structured intervention phases, study staff will be regularly communicating with participants to answer questions, address concerns, and try to augment a subject's level of comfort with the training activity.

Physical fitness training for 35 minutes, titrated to a moderate level of effort, is generally safe and often recommended for healthy adults. During exercise, there is a risk of fatigue, dyspnea, palpatations, and muscle cramps or aches. Following exercise, there is a risk of muscle, joint, or back discomfort. While exercising, individuals with heart disease are at risk for chest discomfort/angina.

Subjects will be told that if they experience symptoms, they should stop exercising. If they experience chest discomfort, they should contact their primary care physician. If the chest discomfort is severe, 911 emergency medical services should be called and the subject should be taken to a hospital emergency room for evaluation. For other symptoms, they should page the research team.
The PI, a physician, will review the symptoms with the subject and help determine whether further medical assessment is appropriate. As a safety measure, subjects can only participate in this study if approved by their primary care physician.

Cognitive training poses no serious clinical risks for participants. The cognitive exercises may cause some degree of frustration or fatigue. The subject may stop the testing at any time or decline to answer any question.

Awareness training poses no serious clinical risks for participants. It may make some individuals feel fatigued or frustrated.

During the interview, neuropsychological testing, and ERP paradigms, subjects may become anxious, frustrated, or fatigued. The study staff consists of trained individuals who will attempt to make subjects as comfortable as possible. Although it is hoped that subjects will answer all of the questions, they may

skip over any questions that they choose not to answer. A subject may experience some tiredness or restlessness during the experimental tasks. If so, the subject can take a break or discontinue the testing.

Obtaining a blood sample by inserting a cannula into a vessel is a routine and safe procedure. However, complications can occur, such as bleeding, bruising, and feeling dizzy/lightheaded. There is a small risk of infection, and of fainting. Bloods will be drawn by experienced phlebotomists.

There are no serious risks associated with the collection of electrophysiological (ERP) data. The cap with electrodes fits snugly and may cause minor discomfort. If so, the investigator will try to adjust the fit. Different sized caps will be available to facilitate a comfortable fit. There is a small risk of minor skin sensitivity, chapping, or drying associated with the conductive gel. Also, there is a slight risk for infection at an electrode site, if the skin is injured during the procedure. The electrode gel itself may leave the hair untidy. However, it is water-soluble and will wash out easily. Electrodes around the eyes and behind the ears are attached with stickers and may cause slight discomfort upon removal.

There are no known serious risks associated with measuring blood flow using Transcranial Doppler (TCD) Ultrasound. The headband that holds the ultrasound camera may cause minor discomfort. The technician carrying out this study will be experienced and try to adjust the fit to make it as comfortable as possible. During the n-back task, a subject may experience some fatigue or restlessness. If so, the subject can take a break or discontinue the testing.

There are no known serious risks associated with measuring movements using accelerometry. The band around the waist that holds the device fits snugly and may be experienced by some as uncomfortable. If so, the band can be adjusted to make it more comfortable.

There are no known serious risks associated with measuring heart rate using the using the Polar device. The band around the chest that holds the device fits needs to fit snugly may be experienced by some as uncomfortable. If so, the band can be adjusted to make it more comfortable.

Potential Benefits

Evidence to date would suggest that participating in cognitively or physically stimulating activities may promote brain health. However, there are no proven benefits to subjects who participate in this study. The results may benefit others by elucidating mechanisms that contribute to successful cognitive aging. These results may be useful in developing rational interventions aimed at preserving cognitive and functional status in older individuals

Monitoring and Quality Assurance

The Principal Investigator and Co-Investigators will report any and all serious and non-serious adverse events to the IRB within a timely manner.

Study personnel must immediately report to the PI any adverse events from this study. All adverse events will be reviewed by the PI and reported to the Partners Human Research Committee (HRC) in accordance with ICH Guidelines.

The PI will be responsible for monitoring and assuring the validity and integrity of all of the data, for monitoring the day-to-day activities of all study procedures, and for the adherence to the IRB-approved protocol. The PI will maintain a tracking log to reflect all adverse events regardless of relationship or expectedness and submit the updated log each year during the IRB renewal process.

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