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Neuromodulation of Cognition in Older Adults

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1. Project Title

Neuromodulation of Cognition in Older Adults: The Stimulated Brain Study

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3. Abstract:

The current study will investigate methods for enhancing cognitive training (CT) effects in healthy older adults by employing a combination of interventions facilitating neural

plasticity and optimizing readiness for learning. Adults over the age of 65 represent the fastest growing group in the US population. As such, age-related cognitive decline represents a major concern for public health. Recent research suggests that cognitive training in older adults can improve cognitive performance, with effects lasting up to 10 years. However, these effects are typically limited to the tasks trained, with little transfer to other cognitive abilities or everyday skills. A pilot randomized clinical trial will examine the individual and combined impact of pairing cognitive training with transcranial direct current stimulation (tDCS). tDCS is a method of non-invasive brain stimulation that directly stimulates brain regions involved in active cognitive function and enhances neural plasticity when paired with a training task. We will compare changes in cognitive and brain function resulting from CT combined with active tDCS versus CT combined with sham tDCS using a comprehensive neurocognitive, clinical, and multimodal neuroimaging assessment of brain structure, function, and metabolic state. Functional magnetic resonance imaging (FMRI) will be used to assess brain response during working memory, attention, and memory encoding; the active cognitive abilities trained by CT. Proton magnetic resonance spectroscopy (MRS) will assess cerebral metabolites, including GABA concentrations sensitive to neural plasticity.

We hypothesize that:

1) tDCS will enhance neurocognitive function, brain function, and functional outcomes from CT, with combined CT and tDCS providing the most benefit;
2) Effects of tDCS on CT will be maintained up to 3 months following training
3) Neuroimaging biomarkers of cerebral metabolism, neural plasticity (GABA concentrations) and functional brain response (FMRI) during resting vs. active cognitive tasks will predict individual response to tDCS.

To date, no studies have examined combined intervention strategies using CT or optimization of learning and functional status through facilitation of active versus resting brain states in the elderly. The present study will provide a unique window into critical mechanisms for combating cognitive decline in a rapidly aging US population and novel methods for counteracting this looming public health crisis.

4. Background:

4.1. Public Health / Clinical Significance: **1)** Increased life expectancy has resulted in a marked increase of the older population. **2)** Cognitive changes occur with advanced age that affect functional and health status. **3)** While Alzheimer's and related neurodegenerative diseases cause the most dramatic cognitive disturbances in the elderly, cognitive aging occurs even among people considered to be neurologically healthy. **4)** Even mild neurocognitive disturbances affect people's daily functioning, health status, and quality of life. **5)** Alterations of brain structure and function occur as people reach advanced age, along with cerebral metabolic changes, that are associated with neurocognitive decline. **6)** Our preliminary data suggests that baseline cerebral metabolite (MRS) and functional neuroimaging (FMRI) indices are associated with baseline neurocognitive functioning and predictive of subsequent age-related cognitive decline and brain disturbances. **7)** There is a paucity of preventive and treatment

interventions for averting cognitive aging and enhancing cognitive function. **8)** Certain cognitive training (CT) approaches improve specific areas of cognitive performance, although their relative efficacy and mechanisms of action are not well understood. **9)** Most CT approaches do not generalize well to cognitive abilities beyond those being trained or to everyday functional abilities. Efforts are needed to improve the generalizability of CT. **10)** Methods exist which could potentiate CT (e.g., tDCS), but they have not been rigorously tested in RCTs.

4.2. Scientific significance. 1) While there is evidence that CT can improve cognitive functioning, the underlying mechanisms are not well understood. **2)** The efficacy of CT likely is dependent on the plasticity of neural systems. **3)** Evidence that certain types of neurochemical, electrical and behavioral stimulation potentiates synaptic plasticity and enhances learning has been demonstrated in laboratory animals. It is important to be able to measure these changes in humans during the course of learning such as that occurring with CT. Yet, in vivo human studies of these effects are difficult for obvious reasons. **4)** Functional (FMRI) and cerebral metabolic (MRS) neuroimaging indirectly assess changes in neural plasticity during cognitive tasks. Recent developments in MRS enable Gama Amino butyric Acid (GABA), the primary inhibitory neurotransmitter and an essential neurotransmitter for synaptic communication and associative formation, to be measured from brain regions of interest (ROIs) [1] [2]. GABA concentrations predict attentional control [1] and sensory discrimination [3,4], decrease with age[5] and yet demonstrate long-term increase with learning interventions.[2,6]. Functional connectivity measured by FMRI provides another potentially powerful approach for measuring these changes. Yet, these neuroimaging approaches have been employed to only a very limited extent in studies of the mechanisms of CT. Studies employing neuroimaging to assess CT outcome are needed. **5)** Many open questions exist regarding the brain's structural and functional connectivity in relationship to regional cerebral metabolites. Achieving better understanding of these relationships is important, since cerebral metabolic alterations may contribute neuropathology and perhaps even normal cognitive aging. **6)** Extensive research exists for each of these neuroimaging modalities in isolation for various diseases, but multimodal studies employing these approaches simultaneously are less common, particularly in studies of normal aging or CT. **7)** Various CT approaches exist, but only a few have been tested and shown to be effective in larger scale clinical trials (e.g., UFOV, dual N-back training). RCTs are needed to test the relative efficacy of these CT approaches, and whether there is value in using them in combination. **8)** Brain stimulation may potentiate neural plasticity based on animal studies. Most of these approaches have yet to be tested in conjunction with CT in humans. **9)** It is unclear whether optimal CT benefit is achieved by bolstering activation of brain regions necessary for the tasks to be performed. **10)** Individual differences exist in the ability of people to benefit from CT. These differences are not well understood. We will examine neuroimaging and behavioral factors that predict CT outcome and that may account for these individual differences. **11)** State-of-the-art neuroimaging analysis methods may yield insights into interactions among brain networks/systems, and ways to optimally integrate structural and functional connectivity with cerebral MRS and cognitive outcomes. **12)** We will employ state-of-the-art

statistical methods, extending predictive modeling and causal inference approaches for neuroimaging.

4.3. Clinical and scientific background.

4.3.1. Cognitive aging and dysfunction affects health status, Quality of Life (QOL), and functional capacity. Brain dysfunction resulting from neurodegenerative disease or other medical condition adversely affects overall health status.[7-11] Even mild cognitive deficits affect QOL, diet, physical activity and other health behaviors,[10,12,13] and are often stronger predictors of health outcomes than other physical factors,[7] but typically receive less clinical attention. Accordingly, cognitive aging has considerable functional relevance.

4.3.2. Cognitive training. Various CT approaches enhance cognitive functioning in the elderly and remediate cognitive disorders. While improvements in cognitive performance are reported in many studies, this research suffers from a lack of well-conducted RCTs designed to determine the specific factors contributing to cognitive improvements. However, several approaches are effective in improving cognitive performance in the context of large RCTs. The ACTIVE study showed that CT improved cognitive performance and resulted in some generalization to other functional abilities.

4.3.3. Benefits of cognitive training. Various CT approaches exist. While improved cognitive performance is often reported, this research has suffered from a lack of well-controlled RCTs, experimental designs that did not enable the basis for effects to be determined, and limited transfer of training.[14-18] Yet, findings over the past decade (e.g., ACTIVE) suggest that certain CT approaches are effective for enhancing cognitive aging.[17,19-36] Significant cognitive and functional improvements occur in laboratory and home-based CT studies.[19,23,31,37-41] Effect sizes generally exceed d=1.0 immediately after CT, and even after 10 years (η^2 >0.6.). In ACTIVE,[22,24,32,36,42] people receiving CT outperformed those who were untrained, with normal cognitive aging attenuated. We considered and selected CT approaches based on consensus of our study team (Woods, Marsiske, Edwards, Czaja, et al.), and evidence supporting their effectiveness. Three types of CT training have been particularly effective in studies by our group and others: 1) UFOV; 2) N-back Working Memory; 3) Attention-arousal training, all available in the PositScience BrainHQ suite (See Miscellaneous Attachments for detailed descriptions/samples of each game.)

Attention/Speed of Processing

1. Hawk Eye- works on visual precision, which helps the brain perceive what you see quickly and accurately so that you can recall it better.
2. Divided Attention- requires the brain to focus in on and react to particular details—matching colors, shapes, and/or fill patterns—while at the same time dismissing competing information.
3. Target Tracker- is designed to help build divided attention by requiring you to track several items moving around your screen at the same time
4. Double Decision - requires visual search and selective attention to peripheral objects among distractors.[20] Difficulty gradually increases relative to object similarity, presentation rate, and distractor complexity and eccentricity.

Working Memory

1. To Do List Training- the brain hears a set of instructions, then uses its memory of those instructions to follow them in order. The instructions get longer and more complex over time at the task, making greater demands of your working memory systems.
2. Memory Grid - Auditory processing is one of the most important building blocks of memory. Only when you take in information with crystal clarity can the brain store it accurately and recall it clearly later. In Memory Grid, the task is to match cards representing syllables together.
3. Auditory Aces- Participant will be presented with auditory information about playing cards. The information is presented one card at a time. The task is to decide if the current card information matches the card information presented a specific number of steps back in the sequence.
4. Card Shark- N-back working memory task that varies on whether the current target matches stimuli presented 0-n steps before and presentation speed, leading to increased difficulty,[44,45] and age-sensitivity[46].

4.3.4. Generalization and functional outcome. Training transfer has been most studied and shown on UFOV. In ACTIVE, ten-year maintenance of UFOV training effects occurred with evidence of substantial transfer at 5 and 10 years. UFOV training resulted in fewer self-reported limitations of everyday activities,[24] higher locus of control [30] and perceived health-related quality of life, [68] better subjective health,[29] and less depression.[27] [68] At ten years, UFOV-trained people still reported less limitation in daily activities[36]. Self-reported driving cessation and archival accident records indicated lower odds of crashes and driving cessation for UFOV-trained elders at three,[25] five,[28] and ten-years post training.[35] In other RCTs involving greater sustained adaptive CT dosages (similar to the currently proposed study) superior performance and reaction times were found on a driving-simulator and also for instrumental activities of daily living (look up phone numbers, read pill bottles, etc.).[23] For the other two intervention components, near transfer to other cognitive tasks has been shown. N-back training transfers to matrix reasoning[44] and to sustained attention and self-reported cognitive function in older adults for at least three months post training.[48] Tonic/phasic attention training transfers to spatial selective attention and the temporal distribution of attention (attentional blink).[66]

4.3.5. Brain stimulation to potentiate training. Since the pioneering work of Penfield, it has been recognized that sensory, motor and cognitive functions could be altered via electrical stimulation of specific brain regions. In laboratory animals, brain stimulation represented an alternative approach to experimental lesions, enabling both the potentiation and inhibition of neural activity depending on where in the brain stimulation was applied. Until recently, most human brain stimulation studies involved neurosurgically implanted electrodes, which has obvious limitations for general clinical use. **Transcranial direct current stimulation (tDCS)** is a non-invasive brain

stimulation method that alters the sub threshold membrane potential of neurons, facilitates neural plasticity and learning, and increases regional blood flow while modulating local GABA concentrations during stimulation.[69-89] During tDCS, a weak electrical current is applied to the scalp that penetrates skin, bone, CSF and the meninges to stimulate underlying cortical and subcortical tissue.[90-95] tDCS applied to dysfunctional cortical regions improves performance on a variety of cognitive tasks.[96-99] Bilateral tDCS to the frontal cortices improves decision-making, attention and working memory performance in older adults.[100-103] Improvements from a single session of tDCS have been shown to last for up to five years in healthy adults.[104-108] Small pilot RCTs (n=20/group) pairing CT with bilateral frontal tDCS show significant and lasting improvement in older adults experiencing declining cognitive function.[108-112] Maintenance of these tDCS and CT effects have been shown to last beyond one year.[104,105,107,108,110] These studies demonstrate that CT combined with tDCS leads to lasting improvement in CT effectiveness for older adults and patients. Research suggests that increased regional blood flow and decreased GABA concentrations during tDCS facilitate the brain's neural plastic response to paired training tasks.[75,80,83,84,89,113-117] Pairing CT with tDCS to combat age-related cognitive decline holds great promise for older adults.

4.3.6. Age-associated brain changes. It is well known that with advanced age, humans are vulnerable to neurodegenerative diseases that cause brain pathology, usually evident on post-mortem autopsy.[118-127] Though less pervasive, neuropathology is also relatively common in elderly adults without documented brain disease.[128]

4.3.6.1. Age-associated brain change on structural neuroimaging. Changes in structural brain volume and morphometry on MRI, along with specific abnormalities, occur with advanced age, particularly when there is vascular co-morbidity.[129-160] Raz et al. showed cortical and subcortical volume loss of .5 -4% per year across different cortical and subcortical regions in older adults without overt brain disease.[129,133,141,143,161] We have shown cortical and white matter volume loss across the lifespan in past large international studies.[146,147,162-167]

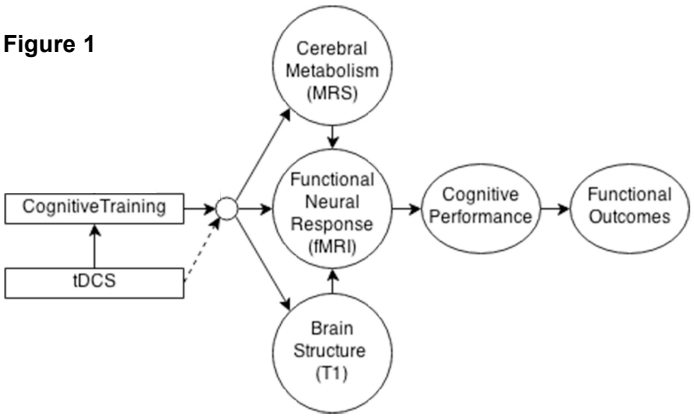
4.3.6.3. Functional neuroimaging provides a potentially powerful method for assessing healthy and abnormal brain functioning (see Cohen and Sweet, for a review[168])**.** FMRI is noninvasive, can be used in conjunction with structural MRI and MRS, and is sensitive to functional brain abnormalities.[153,157,169-179] It holds promise as a biomarker of cognitive aging, neural plasticity, and cognitive improvements following CT. Age-associated alterations in brain activation on FMRI during both rest state and active cognitive tasks have been demonstrated in many past studies. Unfortunately, the clinical potential of FMRI has yet to be fully realized, in part because many different paradigms have been employed across studies. Furthermore, longitudinal change in BOLD response as a function of aging has been examined in relatively few studies, and almost no large RCTs. Reduced cognitive reserve with aging has been linked to a number of FMRI effects, including HAROLD and PASA.[180-183] Chang et al. showed that cognitive reserve influences FMRI activation, with a reduced "dynamic range" of BOLD response during tasks relative to rest explaining this effect.[184-190] The concept of dynamic range is both important and useful, and will be discussed in greater detail when reviewing preliminary data (C4). ERP measures the speed at which the brain processes

cognitive information. These measures will provide markers of improvement in the temporal processing of information, a key element altered with age.

4.3.6.4. Cerebral metabolites (MRS): Proton MRS, which is sensitive to chemical compounds containing hydrogen, useful for measuring brain metabolites, including N-Acetyl Aspartate (NAA), choline (Cho), myo-inositol (MI), creatine (Cr), and glutamate-glutamine complex (Glx). Our group and others have shown that MRS abnormalities occur among people with a variety of age-related brain disorders, including neurodegenerative disease, cerebrovascular disease, and HIV[191-206], with reduced NAA and elevated MI associated with cognitive dysfunction and conversion to dementia. Elevated Cho and MI reflect inflammatory processes and glial and cell membrane disturbances, and are differentially associated with cognitive performance, clinical status, and also cortical, subcortical, and white matter volumes on MRI[204-211]. Thus, MRS is predictive of clinically significant neurocognitive dysfunction.[206,208-210]

GABA, the brain's principle inhibitory neurotransmitter,[212] is essential for synaptic communication and regulation of neuronal excitability,[213] and neural plasticity.[214-218] It plays a key role in learning and memory[219-235] and modulates other behavioral and affective functions, including executive control and attention.[236-238] Decreased cerebral GABA occurs with advanced age,[219,223,227,230] and GABA dysregulation occurs in neurological and psychiatric conditions.[49,239-267] GABA delivered to the frontal cortex and hippocampus in animals facilitates cognitive and working memory performance. GABA can now be reliability measured using proton MRS,[5,268-273] based on seminal work by Edden (consultant).[274-278] GABA provides an in vivo biomarker of neural plasticity in brain ROIs important for the cognitive functions to be trained in our study. [276 84]

Figure 1



A.3.8. Summary and Conceptual Model. Age-associated functional, structural and metabolic brain changes occur, even in the absence of frank neurodegenerative disease. CT holds promise for reducing the adverse effects of cognitive aging, enhancing neural plasticity, cognitive efficiency, functional capacity, and quality of life. In theory, CT benefits could be augmented by coupling it with other interventions that either increase neural plasticity. Yet, relatively few of these approaches have been tested in RCTs, and the mechanisms underlying their effects are largely unknown. Even less is known about the combined effects of CT with tDCS. Our preliminary data provides strong support for CT to combat cognitive aging, and also for the effects of tDCS on cognition and brain function. We hypothesize that CT leads to improvements in neural plasticity (GABA MRS) and functional brain response (FMRI). In turn, this can lead to improved cerebral metabolic health and structural brain preservation. Coupling CT with tDCS will increase neural plasticity in brain areas important for working memory, focused attention, and executive control, improve effectiveness of CT, and ultimately cognitive health (see Figure 1 for conceptual model).

5. Specific Aims:

Age-related cognitive decline has become a major public health concern. As the population ages, the number of older adults experiencing cognitive and functional disturbances has increased. There is currently a paucity of effective interventions to prevent or treat cognitive decline or to enhance brain function in the elderly. The proposed study will recruit a cohort from the state with the highest growth of older adults. We will employ an adaptive randomized clinical trial (RCT) to test whether the benefits of cognitive training (CT) can be enhanced by a combined adjunctive intervention aimed at increasing neural plasticity and optimizing readiness for learning: transcranial direct current stimulation (tDCS).

Current CT approaches have been shown to improve performance on trained tasks, with effects lasting up to ten years[32,33,36,279,280]. However, generalization of effects to other cognitive domains and everyday functioning has been a problem in the past. There is now compelling evidence that the elderly do experience functional improvements that persist long after initial training, though peoples' ability to derive such benefits varies. Combined interventions have rarely been examined and methods aimed at increasing neural plasticity and optimizing readiness for learning are only now beginning to be explored. The proposed study will test one theoretical approach for facilitating and optimizing CT effects on functional outcome. We will use an adjunctive physiological method to further stimulate task-related brain regions, directly enhancing neural responsivity/plasticity and ultimately learning. While theoretical rationales exist for each of these approaches, no studies to date have shown whether adjunctive administration can optimize learning and functional status in the elderly.

A randomized clinical trial will enroll 90 participants. Cognitively healthy elderly adults, age 65-90 will undergo either a CT intervention in combination with transcranial direct current brain stimulation (tDCS) or sham tDCS control. The CT intervention will employ a suite of adaptive training tasks from the POSIT Science Brain HQ[281]; a well validated CT method for enhancing cognitive functioning in the elderly. Participants will receive tDCS or sham/placebo prefrontal stimulation administered during training.

Participants will be assessed at baseline, after CT (2 weeks), and at 3-month follow-up. At each time point, a comprehensive neurocognitive, clinical and multimodal neuroimaging assessment of brain function, metabolic state, and brain structure will be conducted.

FMRI will be used to assess brain response during working memory, attention and memory encoding. Proton magnetic resonance spectroscopy (MRS) will assess cerebral metabolites, including gamma-aminobutyric acid (GABA) concentrations, sensitive to neural plasticity in task-associated brain regions.

The central hypothesis of this proposal is that tDCS will increase neural plasticity in task associated brain regions, facilitating effectiveness of CT and transfer to everyday function.

Aim 1. Determine whether neurocognitive improvement and longer-term functional outcome (as measured by "ecological assessment") are better when CT is coupled with tDCS, an intervention that will increase neural plasticity and augment training effects.

H1.1. Active tDCS combined with CT will amplify effects of CT on measures of attention, working memory, executive functioning, and learning efficiency, while sham tDCS will not.

H1.2. Active tDCS will enhance near and far transfer of CT, but sham will not evidence near or far transfer.

Aim 2. Determine whether CT combined with tDCS leads to greater functional and metabolic brain changes (FMRI, MRS). Effects will parallel Aim 1.

H2.1. Combined CT + tDCS will potentiate decrease activation in working memory and attentional (dorsolateral prefrontal cortex, medial frontal cortex, inferior parietal lobe, supplementary motor association cortex) brain systems, reflecting increased neural efficiency, while CT + sham tDCS will not.

H2.2 Cerebral metabolite alterations will occur secondary to CT and tDCS, with long-term increase in GABA and *N*-acetyl aspartate (NAA) concentrations, and decreased choline (Cho) and myoinositol (MI) concentrations in the frontal cortex and posterior parietal cortex. CT and tDCS will modulate MRS GABA in frontal areas. These effects will be specific to CT.

Secondary aim. We will examine which baseline factors (e.g., clinical, demographic, neuroimaging, cognitive) best predict individual differences in outcome.

6. Research Plan:

6.1. Experimental design. This study employs a randomized trial design with 90 participants. One factor with two levels [Factor 1 = stimulation type (active or sham) yields two cells. Thus, participants will be assigned to one of two conditions:

1: Active tDCS + CT
2: Sham tDCS + CT

CT has previously been established with strong effects on cognitive and functional outcomes. Some small clinical trials showed small to medium effects of tDCS in conjunction with CT.

Participants will be assessed at three primary time points during the study, plus one screening visit on the front end to be sure they meet all inclusion criteria for the study:

1) Informed Consent and Screening Visit
2) Assessment Visit #1- baseline pre-training;
3) Assessment Visit #2- post-2 weeks
4) Assessment Visit #3- three month follow-up after all training

(see Figure below for summary).

This design will enable longitudinal analyses of CT and tDCS effects. We will examine their effects on cognitive performance, functional and metabolic neuroimaging measures, and everyday functional abilities. At each assessment, we will obtain clinical and medical history, neurocognitive measures, and neuroimaging (structural MRI,

FMRI, MRS). All participants will undergo neuroimaging at baseline, following training, and at a three month follow-up.

Stimulated Brain Study

Screening	✓	✓	✓	✓			✓		
Assessment Visits 1-3 Activity Summary	Informed Consent Form	Medical History	Hearing and Vision Tests	Memory and Thinking Tasks	Computerized Daily Activity Tasks, like banking etc.	Physical and Medical Self Reports	MRI Screen-Form	NIH tool box	MRI Brain Scan Appt.
Visit #1 Baseline				✓	✓	✓	✓	✓	✓
Visit #2 After 2 weeks (10 days) of Training				✓	✓	✓	✓	✓	✓
Visit #3 Three month followup				✓	✓	✓	✓	✓	✓
Daily Lab Visits	Brain Training Games	Brain Stimulation/Sham	tDCS Sensation Questions						
Days 1-10	✓	✓	✓						

6.2. Study participants and randomization procedure. We will recruit 90 older adults (women = 45; age: 65-90 years). Study participants will consist of healthy individuals who have expressed an interest in taking part in an intervention aimed at optimizing and possibly preserving cognitive functioning and brain health. We will use web-based permuted block randomization to randomly divide participants into the four groups. People with pre-existing dementia, neurological brain disease, or meet criteria for a diagnosis of mild cognitive impairment (MCI) will be excluded, though people with subjective concerns about their cognitive functioning, who do not meet these criteria, may participate. Detailed inclusion/exclusion criteria can be found in Section 7.

6.2.1. Experimental Design Considerations and Limitations: CT Approach. The POSITScience BrainHQ treatment program was selected because it 1) provides specific training tasks directed at three essential cognitive domains tied to our aims and hypotheses (attention, working memory, executive control) that correspond with the neurocognitive and functional neuroimaging measures to be studied; (2) is shown to produce significant cognitive and functional improvements with good effect sizes in past RCTs (ACTIVE) with up to 10 year durability and transfer of training to measures of self-reported everyday functioning; 3) provides a "cognitive treatment engine[282]" which alone has a very highly likelihood of yielding significant cognitive and functional improvements, enabling us to test the augmenting effects of tDCS; and 4) is computerized, well standardized, and efficiently implemented.

Combined CT. We selected a combined CT approach rather than testing one specific training task: 1) This would optimize CT treatment effects for this primary intervention, providing a strong and reliable engine of change with which to examine effects of tDCS; 2) This approach enables us to affect several related cognitive functions that are strongly dependent on neural plasticity of the frontal cortex; and 3) This approach would maximize participants interest and motivation versus a single task that could become boring.

tDCS. Brain stimulation provides a means of directly augmenting CT effects. tDCS was selected from possible alternatives (e.g., transcranial magnetic stimulation) based on research and data by Woods (PI), Hamilton, and Bikson (consultants), including its safety profile, ability to facilitate neural plasticity, and potential for application outside of research settings. Frontal stimulation was chosen based on prior and preliminary studies demonstrating significant impact on attention, working-memory, and other cognitive abilities to be trained during CT. 2mA tDCS was chosen based on prior research demonstrating that this parameter excites, rather than inhibits, activity in stimulated neurons. [283]

NIH Toolbox. A battery of neurocognitive tests was selected that could be completed in 1.5 hrs for all participants. A battery was selected that would enable optimal assessment of attention, executive functions, and working memory, but would also include some measures of learning and memory, and to a lesser extent other cognitive functions. We use the NIH Toolbox-Cognitive as a core element of this assessment, as it: 1) Can be completed in 30 minutes; 2) Is computerized and well standardized with norms from a large national cohort of older adults; 3) Provides both accuracy and response time measures; 4) Emphasizes the cognitive domains of relevance to the study; and 5) Has been the subject of considerable focus and investment by NIA. This study provides an ideal vehicle for implementing this battery. We supplement the Toolbox with measures to provide more coverage of working memory, attention, learning and memory.

Stimulated Brain Surveys, Measures, Tasks and Activities
Screening Visit:
Informed Consent Process
Inclusion/Exclusion Screeners NACC UDS, Words in Noise (NIH-TB), Visual Acuity (NIH-TB), Colorblindness, MRI Screener, WTAR (optional: Mock MRI, MRI Measuring Device) Drug List review for inclusion/exclusion prescriptions
Baseline Computerized Tasks Posit Science Composite Baseline **Psychological Measures** BDI, Computer experience survey
Demographic Information **Medical History Form**
Assessment Visits: BL, POST, F/U
Neurocognitive Assessment HVLT-R, STROOP, Trails A/B, BVMT-R, Digit Span, Timed Activities of Daily Living, COWA, PASAT, CALCAP **Baseline Computerized Tasks** Posit Science Baseline, NIH Toolbox, Functional Activities of Daily Living,
Psychological Measures SF-36 Quality of Life, PSQ, STAI, BDI, AS, Computer experience survey, Expectations of brain training questionnaire, Expectations of brain stimulation questionnaire
Physical Measures PROMIS Measure, tDCS Sensation Questionnaire, Grip Strength
Mulitmodal Neuroimaging **MRI Brain Scan** Baseline, Post, Three Month Follow-up
Training Interventions:
Cognitive Training 5 hours per week (Posit Brain HQ 2 weeks) Posit Baseline Measure/weekly
tDCS Brain Stimulation (once per day for 10 days) tDCS Stimulation Survey/daily Electrode Drift Measurement

Neuroimaging measures. We will focus on functional (FMRI) and cerebral metabolic (proton MRS) indices for two reasons: 1) These modalities are most linked to and likely sensitive to CT-associated neural plasticity and brain changes; and 2) Changes in these domains are likely to occur over the course of training compared to structural neuroimaging measures. We include active FMRI tasks related to the cognitive functions to be trained, as well as a passive resting state condition to examine the DMN. With respect to MRS, we use a single voxel method to achieve optimal sensitivity and will measure from two ROIs (frontal and posterior cingulate) corresponding to task and resting state associated brain areas. Along with Creatine (Cr), we will examine cerebral metabolites sensitive neuronal loss and membrane disturbances (NAA, GLx), and pro-inflammatory processes (Ch, MI). We will also measure cerebral GABA concentrations using a state of art MRS approach that will reflect neural plasticity in ROIs. The MRS indices will be examined for Aims 2. We will also collect FLAIR imaging data to assess white matter hyperintensity load, as a possible predictor of treatment response (secondary aim)

6.3. Procedural sequence. The sequence and flow of the assessments to be conducted at baseline and each subsequent assessment is shown below. We describe participant recruitment and retention strategies in the Human Subjects section. We will inform potential participants about the study, and obtain their consent. We will then screen for inclusion/exclusion criteria and schedule them for baseline assessment visit #1 evaluation. All following assessments are identical otherwise.

6.4 Cognitive Training. CT will involve up to 10 hours of training over 2-weeks (10 days). At the screening visit, post 2-week intervention and the 3-month follow up visit, participants will complete a 20-minute composite measure of the cognitive training

tasks. *Training platform*. CT employs a PositScience BrainHQ suite via its researcher portal. These tasks are web-based and multi-platform (i.e., Windows, Mac). Participants will be randomly assigned to training on 4 tasks focusing on working memory or 4 tasks focusing on attention/speed of processing. Participants will be required to have a specific viewing distances. Study interventionists will provide daily performance summaries. The rationale and task demands for each component were described earlier (A.3.3). These CT are commercially available (www.positscience.com), with well-documented protocols/manuals (See Appendix 1) and thus not described in detail here. (See miscellaneous attachments for specific game descriptions.) *Hardware*. Participants will complete CT on computers located at Clinical Translational Research Building. *Support:* Participants will have the opportunity to ask questions, and will be instructed on the various computer tasks. No special technical skills or experience are required A support phone number will be available if participants have questions arise between study visits.

6.5. Transcranial Direct Current Stimulation:

Bilateral Frontal tDCS: A Soterix Clinical Trials Direct Current Stimulator will apply 20 minutes of 2.0mA direct current through two biocarbon rubber electrodes encased in saline soaked 5cm^2 sponges (8cc of 0.9% saline solution) which then may be covered with electrode paste, and placed over the frontal cortices at F3 and F4 (10-20 system). Based on our well-established computational modeling workflow (C.4.1), F3/F4 stimulation delivers a broad pattern of frontal stimulation (see C.4.1d). Current inflow will occur on the right (F4), and outflow on the left (F3). Impedance quality will be ≤10kΩ to insure proper stimulation of brain tissue.

Sham tDCS: Sham stimulation is performed with the same device and all procedures will be identical except for the duration of stimulation. Participants will receive 30 seconds of 2 mA of direct current stimulation at the beginning of the session. Participants habituate to the sensation of tDCS within 30-60 seconds of stimulation. This procedure provides the same sensation of tDCS without the full duration of stimulation, making it a highly effective sham procedure. Blinding: The device has built in RCT double blinding protocols. Soterix will communicate only with Dr. Wu (Co-Mentor/statistician) to de-identify data for analyses.

Physiological Recording: During stimulation sessions participants will be asked to wear a special wristband that will be used to record physiological information such as pulse.

3D Head Models of Electrode Placement and Electrode Drift Measurement: We will take a brief set of images of the participant's head after the electrodes are placed to make sure that the electrodes are in the correct location. These images will be used to create a 3D model of the participant's head that will give us accurate information about where the electrodes were placed. In addition, we will physically measure any change in the electrode positioning over the course of the stimulation session to allow for assessment of quality control changes due to electrode drift. This is done by placing a mark at the bottom corners of each electrode and using a tape measure to measure the difference in electrode location at the end of the session. Ideally, no drift should occur and thus

measurement allows for use of a drift coefficient in statistical analyses of between participant differences in response.

6.6. Neuroimaging Methods. We will conduct neuroimaging on a Philips Achieva 3.0 Tesla research dedicated scanner with an existing research agreement. Scanning will take approximately 1 hour to acquire: 1) Structural MRI (T1, DTI), 2) FMRI (EPI-BOLD), 3) Proton MR Spectroscopy (MRS).

MRI Acclimation Protocol Options: Participants may have the MRI Measurement Tool (See MRI Measurement Tool Appendix in Misc. Attachments) demonstrated for them to visually see the size of the inside of the chamber of the MRI Scanner. Participants may be asked to try the device on themselves to gain a greater understanding of the size constraints related to the MRI Scan, and to give them a chance to experience the snug fit inside the core of the scanner. If participants cannot fit in the measurement device, they will be excluded from the study.

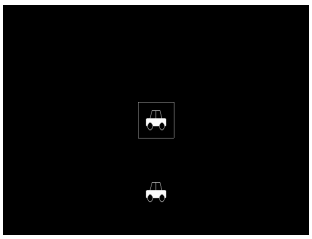
The participant may also be offered to make a visit to the Mock MRI Scanner (See Mock MRI Appendix in Misc. Attachments), located in the UF Dental Tower Ground floor, DG-73) to see if they are completely comfortable with the scanning process, and if they can realistically tolerate the size constraints. This can also be a time to discover if claustrophobia will be a limiting factor and exclusion for participation. If there is no concern regarding fit, or claustrophobia, this part may be skipped.

6.6.1. FMRI paradigms. We will present the two FMRI tasks (2-Back, Spatial-Temporal Attention) using E-Prime 2 software (Psychology Software Tools, Inc., Pittsburgh, PA), with the video signal on a screen behind the participant's head. The screen is viewed through a double-mirror attached to the head coil. An MR-compatible piano-key response box attached to the stimulus presentation computer will collect performance data. We will apply a cushioned-pillow head stabilizer to minimize head movement during scanning.

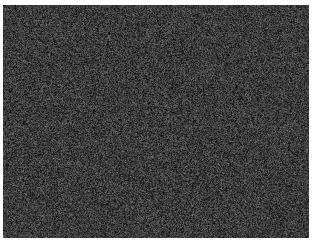
2-Back. *This task will measure brain changes due to our N-back training.* We will assess verbal working memory on a 2-Back task, as in past studies[153,157]. Consonants are visually presented for 500ms with an ISI=2500ms. Participants determine if each stimulus is the same or different from previously stimuli, responding by binary button press (yes vs. no). Executive control, phonemic buffering, and sub-vocal phonemic rehearsal are required. 0-back and 2-Back conditions are alternated in a block design with two 5-minute runs of eight blocks (consonant lists), with four blocks of the 0-Back and four blocks of the 2-Back. *0-Back: F*our blocks of nine consonants of random case and order (33% targets). Yes-no responses are made if targets that match stimuli occurring two earlier. 2-*Back:* Four blocks of 15 consonants (33% targets) will be pseudorandomly presented across the visual field. Accuracy and RT are recorded.
The useful field of view (UFOV) fMRI task. Task will involve participants making decisions about where on the screen they saw a previously displayed object. Participants are presented two images simultaneously, one in a central box, and another outside the box. These images disappear very quickly and are replaced by a "noise" screen, similar to a scrambled television signal. Then participants are asked where they saw the object (a car) outside the box (e.g., up, down, left, right, etc.) and

what object was inside the box (either a car or a truck). The participants will respond using buttons on a response box. After participants have answered they are presented a fixation cross and wait until the next trial begins. Time between trials is randomized and jittered in accordance with best practice event-related fMRI design. The task duration is approximately 17 minutes. Examples of the stimuli are below.

1) Both objects are presented simultaneously



2) Noise Screen



Resting State. Participants will also be asked to rest for 6 minutes while functional data is being collected to assess resting state activation.

6.6.2. Proton MRS: GABA-edited spectra will be acquired using the MEGA-PRESS experiment, from 1 voxel (medial frontal). 9 minutes duration. Spectra will be analyzed using the Gannet package for the batch analysis of GABA-edited MR spectra, quantifying GABA concentration relative to water, correcting for voxel CSF fraction. OFF spectra will also be analyzed using LCModel to give concentrations for additional metabolites NAA, Glx, Cho, MI, and Cr. Analyses. Cerebral MRS metabolite concentrations will be derived from spectral analysis[295] With unsuppressed water FID at TE=30ms used for eddy-current correction. Time domain MRS ratios will be derived normalized for Cr. A double-exponential decay will be fitted to the water amplitudes at the 7 echo times. The signal amplitudes of brain tissue and CSF will be derived (corrected for T2 decay), with brain water signal used to correct for partial CSF volume. MRS Quality Assurance: GABA-edited MR spectra will be visually screened, and additionally spectra with a fitting residual of over 10% will be accepted for further analysis. The concentration measures for the additional metabolites will be accepted with an LCModel Cramer-Rao lower bounds (%SD) of less than 20%, a reliable estimate for a particular metabolite for group comparisons[295]. Scans resulting in spectra that do not meet quality criteria will be repeated. Past studies showed intra-subject variability of ~10% for GABA and 3-5% for other MRS peaks. Line width and signal-to-noise resonance ratios are plotted over time (brain, phantom) to monitor spectral

quality; inter- and intra-subject variability assessed by correlation and Bland and Altman plots.[412,413]

6.6.3. Structural MRI. High-resolution whole brain axial gradient-echo MPRAGE 3-D T1-weighted images will be acquired for volumetric and cortical thickness analyses and FMRI. Analyses: Volumetric indices will be obtained for total gray and white matter, FreeSurfer ROIs[296-298], and a priori ROIs (MRS, FMRI).

6.6.4. **FLAIR**. Fluid attenuated inversion recovery (FLAIR) images will be acquired to assess white matter hyperintensity load (i.e., white matter damage). Volumetric and whole brain analyses of data will be used to look at region specific versus global levels of white matter load.

6.7. Neurocognitive and Psychological Assessments: Assessments will include a neurocognitive battery (approximately 180 minutes in duration, see list attached in Miscellaneous documents, and listed below. The battery consists of standardized, well-established neurocognitive measures with strong reliability and validity [304]. Each is widely used in clinical neuropsychology and in Dr. Cohen's (Primary Mentor) research over the past 20 years. Our goal is to assess global cognitive ability (NIH-Toolbox: cognitive module), and specifically attention-executive functions, working memory, processing speed, and learning-memory. These are domains affected by aging[24,31,146,305-314] and will also tap the domains assessed by FMRI (Aim 1). Psychological measures are those commonly used in cognitive training paradigms, such as to gain greater understanding of the relation of things like depression, anxiety and apathy to the cognitive training intervention, and the resulting effect on memory and thinking. The BDI-II has a high risk of identifying severe depression and suicidality. The measure will be monitored carefully to identify and mitigate any risk to persons that are identified as at risk. The PI will be informed immediately, and a referral to Clinical and Health Psychology Clinic will be made right away for the participant. The PI or study staff will contact the participant directly to advise them of the concern, and assist with any intervention that may need to be referred. The State-Trait Anxiety Inventory(STAI) has medium risk to identify anxiety disorders and the same protocol will be followed if a participant is identified to have severe anxiety disorders that require medical treatment or referral to a Clinical and Health Psychology appointment for treatment. The National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS), a comprehensive neuropsychological battery will be used to assess dementia/MCI in older adults. The NACC UDS is comprised of several neuropsychological tests including the Montreal Cognitive Assessment (MoCA), Craft Story Immediate and Delayed Recall (similar to the WMS Logical Memory), Benton Complex Figure Task Immediate and Delayed Recall, Number Span Forward and Backwards, Category Fluency, Trails A & B, The Multilingual Naming Test (similar to the Boston Naming Task), and Letter Fluency. The UDS takes approximately 45 minutes to administer. Score corrections are provided for age, sex and education.

6.7.1. Physical activity, QOL, PROMIS self-reported health assessment. We will administer the*, Medical Outcomes Study Short Form-36 (SF-36: v.* 2.0, a widely used QOL measure), and the PROMIS self report measures at each assessment.

The PROMIS measures assess change in self-reported cognitive and physical function. [321] [321]. Change in self reported physical and mental health status correlate with QOL and mental and physical health status. [322,323] [324] These measures will serve as important assessments of interventions influence on everyday life.

Screening Visit
Informed Consent
MRI Screener
Medical History/Prescription Drugs
Drug Exclusion List Review
NACC UDS
Words in Noise (NIH-TB), Visual Acuity (NIH-TB), Color Vision
WTAR
Posit Composite Baseline Game Testing (0%-79% range)
BDI
Computer and Technology Use Questionnaire

Assessment Visits #1,2,3
NIH Toolbox
HVLT-R
BVMT
Stroop Test
Trails A & B
COWA
Apathy Scale
SF 36 Quality of Life
PROMIS self-report
Digit Span
Pittsburgh Sleep Questionnaire
Pain Questionnaire
BDI/STAI
PASAT
CALCAP
Expectation of brain stimulation questionnaire
Expectation of brain training questionnaire

Daily Check In
tDCS Stimulation sensation questionnaire

7. Possible Discomforts and Risks:

Potential Risks.

There are minimal risks associated with participation in this study. The potential risks are as follows:

Magnetic resonance imaging (MRI). MRI is a procedure that allows doctors to look inside the body by using a scanner that sends out a strong magnetic field and radio

waves. This procedure is used routinely for medical care and is very safe for most people, but you will be monitored during the entire MRI scan in case any problems occur. The risks of MRI as detailed in the Informed Consent are:

- The MRI scanner contains a very strong magnet. Therefore, you may not be able to have the MRI if you have any type of metal implanted in your body, for example, any pacing device (such as a heart pacer), any metal in your eyes, or certain types of heart valves or brain aneurysm clips. Someone will ask you questions about this before you have the MRI.

- There is not much room inside the MRI scanner. You may be uncomfortable if you do not like to be in close spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system, and, in the event of an emergency, you can tell them to stop the scan

- The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of patients. You will be given earplugs to reduce this risk, and headphones for added protection.

- If you are a woman of childbearing potential, there may be unknown risks to the fetus. Therefore, before you can have the MRI, you must have a pregnancy test.

- If an obvious abnormality is discovered during your MRI scan, you will be informed about it by the research team, you will be provided with a copy of your MRI scan and we will encourage you to see your primary care physician. MRI will only be done for research purposes in this study.

- You will be monitored very carefully while in the scanner, and repeatedly checked to ensure comfort.

There is a risk of introducing metal into an MRI environment. However, the MRI compatible transcranial direct current stimulator contains no materials that respond to the MRI environment. Thus, the risks associated with undergoing MRI while receiving stimulation are the same as transcranial electrical stimulation outside the MRI scanner.

Transcranial direct current stimulation. Transcranial direct current stimulation is considered safe but a small number of people do experience some side effects. The most common side effects are itching and tingling or mild discomfort at the area of stimulation, and headache. Other possible side effects include dizziness and nausea. Whenever an electrical stimulation is applied to the body, it could possibly cause a seizure or abnormal heartbeat, but this has never occurred with the transcranial direct current stimulation parameters used in this study.

Although there is no known risk to pregnancy, there may be unknown risks and all women of child bearing potential must have a negative pregnancy test prior to stimulation.

Cognitive Training. There is a risk participants will find cognitive training on the computer challenging, fatiguing, and/or boring. Research staff will explain what to do and how to perform the training tasks tests during your initial study visit. Participants will also have access to a 24-hour help line should you have trouble working with the training computer.

Neurocognitive and Functional tests. There is a risk that you will find cognitive and functional tests challenging, because it may be difficult to remember the things that you are asked to remember or have trouble hearing or seeing some of the sounds and pictures presented on the computer screen. You may skip any tests you do not wish to complete. Research staff will explain what to do and help you take the tests during your study visit.

Questionnaires. There is a risk that you will find questions on the questionnaires uncomfortable to answer. You may skip any question you feel uncomfortable answering.

Other possible risks to you may include fatigue due to the testing. Should this occur, you can take a rest-break at any time or you may discontinue the testing at any time. If requested by the participant, multiple test days are possible.

When being tested some people may develop anxiety. If these tests make you anxious we can stop the testing.

Researchers will take appropriate steps to protect any information they collect about you. However, there is a slight risk that information about you could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass you, or possibly affect your insurability or employability. Questions 17-21 in this form discuss what information about you will be collected, used, protected, and shared.

This study may include risks that are unknown at this time.

Participation in more than one research study or project may further increase the risks to you. If you are already enrolled in another research study, please inform one of the research team members listed in question 3 of this form or the person reviewing this consent with you before enrolling in this or any other research study or project. If you are currently participating in another study using transcranial direct current stimulation or transcranial magnetic stimulation, you will be rescheduled so that your participation in the current study does not overlap with your participation in the other study.

Adequacy of Protection against Risks.

Recruitment and Informed Consent. All study participants will provide written informed consent. Persons will be recruited from the CAM-CTRP research registry, community outreach, or community agencies. Participants will also be recruited at community events with IRB-approved flyers, and participants will have the option to confidentially provide name, phone number, and email if they wish to be contacted by the study team to determine study eligibility. The contact information will be securely stored during the

event and immediately stored in the Woods Lab per study data safety management plan. People interested in participating in the study will call the CAM-CTRP study recruitment coordinator. Potential participants interested in hearing more about the study will be provided information about the study. Persons will then indicate their agreement to participate by signing the informed consent document.

Our inclusion and exclusion criteria are designed to minimize risks to participants.

Inclusion criteria*:* 1) Men and women; 2) Age: 65 to 90 years; 3) English speaking; 4) Physically mobile; 5) working memory function between 0-75th percentile determined by screening results on the POSIT Baseline Cognitive Training computerized tasks.

Rationale: (1) The age range is selected to include a higher proportion of persons with possible concern about cognitive deficits (2) The language requirement will avoid difficulties with interpretation of cognitive results; (3) the mobility requirement is required because participants will need to be able to participate in neurocognitive testing and MRI testing at different locations; 4) the working memory function requirement is needed to avoid randomized groups from being biased by over-representation of extremely high (e.g., super agers) working memory function in a particular group and to include a representative sample consistent with the “typical” cognitive aging profile in US.

Exclusion criteria*:* 1) Neurological disorders (e.g., dementia, stroke, seizures, traumatic brain injury). 2) Evidence of dementia (NACC UDS scores of 1.5 standard deviations below the mean for age, sex and education adjusted norms in a single cognitive domain on the task). 3) Past opportunistic brain infection 4) Major psychiatric illness (schizophrenia, intractable affective disorder, current substance dependence diagnosis or severe major depression and/or suicidality. 5) Unstable (e.g., cancer other than basal cell skin) and chronic (e.g, severe diabetes) medical conditions. 6) MRI contraindications (e.g., pregnancy, claustrophobia, metal implants that are contraindicated for MRI). 7) Physical impairment precluding motor response or lying still for 1 hr and inability to walk two blocks without stopping.8) Certain prescription medications may possibly reduce effects otherwise induced by the tDCS stimulation protocol, and are listed on a Drug Exclusion List attached to the Appendices in Miscellaneous attachments of this study. 9) Hearing or vision deficits that will not allow for standardized cognitive training stimulation; ie colorblindness, inability to hear through headphones (with or without hearing aids), macular degeration or other significant diseases that cause severe loss of vision. If vision is corrected with lenses to appropriate levels, then participant will be eligible. 10) Left handedness, as those with left-handedness have a higher percentage rate of atypical functional lateralization for brain functions, which would significantly interfere with interpretability of brain data.

Rationale: (1) neurological diseases affecting the brain create obvious confounds that would obscure the study’s findings or increase risk from non-invasive brain stimulation (i.e., seizures). (2) The NACC UDS will be used to exclude people meeting criteria for severe dementia, as this study is focused on more mild cognitive deficits; (3) past opportunistic brain infection, and (4) a history of severe psychiatric illness

(schizophrenia, chronic intractable unipolar or bipolar depression) also would directly affect neurocognitive test performance and thus would confound study findings. (5) Unstable (e.g., cancer) and certain chronic medical conditions (e.g., severe obesity) may also confound findings and increase study attrition; (6) Given that this study requires MRI imaging to address all aims, factors that make MRI imaging unsafe or infeasible for particular study candidates will serve as a basis for exclusion; and (7) Physical limitations are a basis for exclusion based on inability to participate in all study procedures. Excluding people who cannot walk or sit for an hour will reduce problems in the scanner that could confound study findings.

Protection against Risk.

*Protection against Risk of confidentiality***.** Information pertaining to research subjects will be obtained from (1) interviews with subjects and (2) procedures described in the "research design and methods" section. All data will be considered confidential according to HIPPA guidelines for personal health information. All participants will sign a combined consent to participate in research and HIPPA compliant confidentiality document approved by the IRB overseeing the clinical recruitment setting (i.e. the University of Florida IRB, and the Florida Department of Health IRB).

Precautions will be taken to ensure that all research materials are inaccessible to anyone other than the investigators, and by ensuring that only qualified and trained individuals conduct the study research procedures. Prior to study initiation, procedures for protecting the confidential nature of participant data collected will be reviewed and all questions or concerns will be clarified at this time. These procedures will be reviewed throughout the study. Staff will be trained and certified in handling human subject information to maintain privacy and confidentiality. Procedures for allowing access to investigators to use this information for research will be under the authority of the PI and will follow HIPPA compliant guidelines for the release of PHI.

Contact information for study participants will be kept in separate files and databases from the research data. This information will be used by the research assistants to send reminders about follow-up times and appointments via phone, email or mail correspondence. The information will only be kept on computers or devices that are both password protected and encrypted. Any written forms will be kept in locked file cabinets or locked briefcases. None of the research data in the central data base will have participant identity information. No results will ever be reported in a personally identifiable manner. All research data will be entered directly into a web-based survey that is maintained by the University of Florida CTSI (REDCap), and the data are encrypted as soon as they are sent in a wireless format. The data will be transferred and stored on secure servers at the University of Florida, with no identifying information.

No survey data will be labeled with the participant’s name or other identifying information, but will instead be labeled with a study ID number. Documents linking study ID numbers to identifying information (e.g., name, address, etc) will be stored electronically in a password-protected file. All paper-data with identifying information will be stored in locked file drawers, separate from coded data. Documents linking study ID

numbers to identifying information will be destroyed at the end of the study. Documents containing data collected on un-consented individuals (i.e., screening logs used to avoid approaching the same individual for study enrollment twice) will be shredded daily. All electronic data will be secured and encrypted. Identifying information will not be reported.

Protections of risks related to study questionnaires. To minimize any risks related to emotional responses to questionnaires, persons will be informed about the types of questions included in the surveys, which are similar to the types of questions persons might be asked by their doctor in a clinical setting.

Protection of risks related to tDCS. To minimize risk associated with tDCS, participants will be monitored throughout stimulation sessions and asked to report any discomfort. If scalp sensation is uncomfortable, stimulation levels will be decreased to a comfortable level or will be stopped. In the event of a headache, stimulation will be decreased to a comfortable level (where the headache or nausea is no longer present) or will be stopped. All tDCS sessions will be administered and continually supervise by a trained experimenter. The above symptoms have only been reported when participants are actively being stimulated. However, to assess for any symptoms occurring during the 24 hour interval between stimulation sessions, we will administer a brief symptom screening questionnaire at the beginning (symptoms in the past 24 hours) and end of each session (symptoms during stimulation). tDCS has not been shown to cause seizures nor lower the seizure threshold in animals. There are no reports of seizure induced by tDCS in human participants in the literature. However, this may not be true for epilepsy patients, whose seizure threshold rates are likely abnormal. Prior history of neurological disorders is an exclusionary criterion for our study and thus no participants will have a history of seizure.

Protection against risks associated with neuroimaging. MRI is widely regarded as a safe, noninvasive procedure for visualization of brain tissue in both adults and children. Prior fMRI studies by our group and by other groups document the innocuous nature of these procedures. Prior to study participation, all participants will be informed of the MRI procedure during the informed consent/assent process. The proposed study will be performed on an FDA approved Phillips 3 Tesla scanner located at the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) research facility at UF. There are no known long-term effects of MRI procedures on the body. The FDA Information Sheets, Food and Drug Administration, October 1995, p. 79, lists as a non-significant risk device, “Magnetic Resonance Imaging (MRI) Devices within FDA-specified parameters.” This study satisfies those parameters. The 3.0 tesla MR scanners meets FDA parameters for field strength, gradient switching, and RF power deposition for all FDA-approved acquisition schemes including echo-planar imaging. In addition, this research protocol involves the use of an FDA-approved acquisition scheme, or the power deposition of experimental acquisition scheme proposed meets FDA parameters as verified on a phantom using the power monitoring system installed on the MR scanner. Both Dr. Woods and trained MRI staff will check for exclusion criteria. The main MRI-related risks include: (a) sensitivity to the loudness of the MRI machine - all subjects will be given and must wear ear plugs; a squeeze-ball and microphone will be

provided so that they may stop the testing if they become uncomfortable or anxious at any time; (b) claustrophobia - subjects will have the opportunity to practice in a simulator and to become as familiar and comfortable as possible before commencing the experiment. In addition, they will be given the opportunity to examine the scanner before the tasks starts. The study will be ended early if the space is a problem for them; no medications (e.g., benzodiazepines or tranquilizers) will be offered to them; (c) lightheadedness when sitting up after lying in the MRI machine - this feeling sometimes occurs but has always gone away in a few minutes. Participants will thus be assisted in getting up to make sure they do not fall; (d) risks associated with having an MRI in pregnant women - while risks to pregnant women have not been conclusively documented, reports of potential risk to unborn fetuses have prompted the exclusion of these individuals from research. Given the age range of our sample, the probability that one of our female subjects will be pregnant is relatively low. Nevertheless, as a standard procedure, all female participants will undergo a test to determine pregnancy prior to entering the MRI. In sum, the MRI neuroimaging procedures pose no radiological or medical risk, given that participants with metal implants susceptible to magnetic heating will be excluded based on standard scanner policies. A small number of people may become anxious in the small space of the scanner. These individuals will have the opportunity to terminate the scan session. Furthermore, all recruits will be screened for phobias prior to enrollment. FMRI procedures will be supervised by Dr. Woods, a close collaborator with Dr. Song Lai, the MR physicist in charge of the facility. There is a medical technologist at the imaging site at all times to insure scanner safety, and neuroradiologists on call as needed. If an abnormality is noted on the structural MRIs by study staff, the PI will provide the participant with a copy of the scan and encourage them to follow up with a neurologist.

Protection against risks associated with neurocognitive tests. The neurocognitive assessments have minimal risk associated with them. Some participants experience stress associated with being tested, though this tends to be quite limited. Breaks will be given in those cases. Research staff that collect data have been trained in the conduct of all cognitive function tests by other senior staff members. Research staff members will be certified in the conduct of the cognitive function tests before they work with study participants.

Data and Safety Monitoring Plan:

A data and safety monitoring plan (DSMP) will be implemented to ensure the safety of all participants involved in the study and to ensure the validity and integrity of the data. The PI will be responsible for coordinating activities of the DSMP, including: arranging meetings and communications, and identifying and reviewing relevant participant materials. The data and safety information obtained on each study participant will be reviewed at weekly meetings. The primary goal of the DSMP will be to monitor the progress of the study and safety of participants and if necessary, recommend modifying the study or terminating the study as appropriate.

Concerns that might dictate modification or termination of the study include:

- Participant safety
- Outcome data
- Data quality
- Integrity
- Intervention efficacy
- Recruitment
- Performance

Both the PI and the study staff will review the study weekly and examine reports of adverse incidents and reports of study participant recruitment and follow-up. Throughout the course of the study, information regarding issues deemed critical to the study or to the safety of research participants will be provided to the PI and primary mentors. As a result of receiving this critical information, a meeting to discuss this information may be convened. Information deemed critical would include:

- Serious and non-serious adverse events that may occur
- Suspicion of scientific fraud or misconduct
- Any other issues which may warrant protocol changes or modifications.

Because this is an exploratory study with minimal risk associated with the proposed intervention and limited financial resources, there will not be an external data safety and monitoring board for this study. The research team, however, will follow the procedures for data safety and monitoring as required by the Institutional Review Board at the University of Florida (UF IRB).

The research team will monitor participants for any potential adverse events, and all reported events will be forwarded by the PI to the UF IRB.

Procedure for collection and storage of data. A number of quality control procedures will be used to ensure the validity and integrity of the data and the safety of all participants involved in the study. Relevant data and safety information obtained on each study participant will be verified against the original source documents by the primary study coordinator and any identified discrepancies will be reviewed at these weekly meetings. The primary goal of these meetings will be to monitor the progress of the study and safety of participants and if necessary, recommend modifying the study or terminating the study as appropriate.

All identifying information will be archived in Dr. Woods' neuroimaging laboratory within the Center for Cognitive Aging and Memory at UF. Imaging data will undergo several levels of processing, and all raw and processed data will be archived on a password-protected server in password-protected folders and files. Only study staff will have access to these files. The self-report data will be double entered using the SPSS Data Entry system. This system signals the user when an out-of-range value is entered. All data entry is then verified via double-entry, with the program signaling mismatches with the original entry. Next, computer-generated reports of variable frequencies and subject lists will be reviewed, leading to possible corrections to coding or entry. After checking for accuracy of data within a given group, data will be stored in the password-protected folders along with the imaging data.

Location and logistics of data collection. All procedures involving human subjects will be performed at facilities of the UF Health Care System. Neurocognitive testing and training will be performed at either the Clinical and Translational Research Institute or the AMRIS/MBI UF facility. Several clinical research examination rooms are equipped and dedicated to neurocognitive and functional assessment, and contain all necessary computers and test materials. Blood for serum biomarker analysis will also be collected at this site. The Clinical and Translational Research Institute (CTSI) which contains laboratories, freezers, and main frame computers. Storage of neuroimaging data backup will occur there. Neuroimaging will take place at the AMRIS facility of the McKnight Brain Institute.

Storage of collected data. All electronic data are stored in password protected, secured computer systems. All paper data will be stored in a locked file cabinet. Data will only be removed when coded, entered, or audited. Only the participant's study identification number will appear on any data forms. Only the PI, the Co-Is, and the RAs will have access to the completed data forms and electronically stored data. All data are considered part of the participant's confidential record. Data collected from research participants will be stored in a secured, password protected computer file that is separate from network systems. All paper data (e.g., subject contact information, consent forms, etc.) will be placed in a locked file cabinet within 24 hours of their acquisition as designated by the study's RA . All data will remain confidential. A file will be maintained that associates the participant's name with that participant's study identification number. This file will be kept in a locked cabinet separate from the study data

Data entry requirements. The data entry system will require a login identification and password in order to gain access to the data. Where appropriate, validation and range rules will be applied to the actual entry fields. Only the PI and Co-Is will be able to view the data in its raw state.

Audit/verification of entered data. All data designated as primary outcome data will be subject to a 100% cross-referencing between electronic and paper forms. This audit must have an error rate less than 1%. If the verification fails the audit, all data will be re-entered, the original computer files discarded, and the newly re-entered data audited. This process will continue until the audit no longer exceeds the maximum allowable error rate. All audits will be supervised and documented by the PI.

Data management and analysis. Our research team has substantial experience in the design and implementation of data management procedures that provide accurate recording and storage of data, participant confidentiality, and timely analysis. Based on our past experience, we believe that our major data management and analysis needs for the proposed project can be met by using a high-end PC, equipped with the latest version of SPSS for Windows and appropriate spreadsheet programs. All data files are automatically backed-up daily.

Data quality control. All staff involved in data collection will be trained and certified to ensure their competence, and re-certified periodically throughout the study as we have done in similar trials. Data will be collected and numerically coded using pre-tested electronic entry forms. At the time of collection, there will be initial clerical review of all

data for accuracy and completeness. Every effort will be made to ensure that missing data are kept to a minimum. Data entry programs with range checking and response validation will be used for all data entered. Under supervision from the PI, the data manager will conduct error checking procedures and preliminary analyses on all data to ensure their accuracy. The RAs will be trained to avoid omissions in data entry and computer entry protocols will be programmed to avoid accidental skipping of question items. We believe that the quality control system to be used will ensure a complete and accurate database, and maximize the likelihood that the intervention will be delivered correctly and efficiently. As we have done in prior studies, a manual of procedures will be developed during the initial study start-up period that explicitly describes the specific procedures related to intervention delivery, data collection, and quality assurance.

Frequency of data review. Relevant data and safety information obtained on each study participant will be verified against the original source documents by the primary study coordinator on a bi-weekly basis. As noted above, any identified discrepancies will be discussed with the Principal Investigator and reviewed at weekly meetings.

Measurement and reporting of participant accrual and adherence to eligibility criteria. Review of the rate of participant accrual, adherence to inclusion/exclusion criteria will occur weekly during the recruitment phase and then every month to assure that participants meet eligibility criteria and ethnic diversity goals outlined in the grant proposal.

Designation of an independent monitoring committee. The Independent Monitoring Committee for this study will consist of an established board which has reviewed all studies conducted within the CAM-CTRP during bi-annual conference calls for the past six years.

Safety Review Plan Study progress and safety will be reviewed monthly (and more frequently if needed) by the principal investigator. Progress reports, including participant recruitment, retention/attrition, and AEs will be provided the IoA Independent Monitoring committee for bi-annual reviews. An annual report will be compiled and will include a list and summary of AEs. In addition, the annual report will address (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The annual report will be signed by the chair of the Independent Monitoring Committee and may be forwarded to the IRB, NIH, & CTSI. The IRB and other applicable recipients will review progress of this study annually.

Final storage of paper data. All paper data (e.g., consent forms) will be housed at a facility that specializes in the storage of medical/ research information. The destruction date of these files will be at least 7 years from the termination of the study and will be authorized by the Principal Investigator of the research study.

Access to cleaned computer data. Once the study is complete, and all data have been collected, entered and passed the audit process, the data will be available to the Principal Investigator and his designates for analysis. Only the Principal Investigator can

give permission for the release of aggregated study data. No confidential information may be released without the express written consent of the study participants. Only copies of the finalized data will be released. The original data file will remain in its pristine state.

Monitoring physical health and safety**.** All assessment visits will be conducted at a central location and all testing sessions will be conducted and supervised by a trained and certified research staff that will monitor potential adverse experiences and symptoms. At each visit, participants will be asked to report any adverse events they have experienced since their last visit. Immediate medical treatment will be provided for any illness or injury resulting from this study. Trained nursing staff members are present in the research center at all times, and a physician will also be available to evaluate the participant if needed.

In addition to the assessments conducted at in-person study visits, participants will be contacted by phone on a weekly basis between the end of training and the 12-week follow-up visit and will be asked to report any adverse events that have occurred since their previous phone contact or study visit. Specifically, they will be asked about any adverse events, including itching, pain, nausea, headache, etc. they have had. Participants will also be asked about their mood, including depressive symptomatology, and other health related activities (i.e., physical activity), as well as general health status. Based on reported symptoms, participants may be asked to come in for an additional follow-up assessment visit with one of the healthcare professionals on the study team (i.e., physician or psychologist) for further evaluation of their symptoms. Based on information obtained at this visit, participants will then be referred for follow-up assessment and/or treatment with the appropriate healthcare provider.

Monitoring mental health and safety. At each assessment visit, participants will complete the BDI to assess for depressive symptom severity. Any participant who endorses clinical levels of any psychiatric disorder or who endorses suicidality will be referred to Dr. Cohen, study psychologist, for further follow-up assessment. The psychologist will then provide a recommendation regarding the appropriate course of follow-up and also advise on whether it is safe for the participant to continue in the study. If a participant is found to be actively suicidal with a plan and/or intent, they will be escorted immediately to the emergency room at the Shands Hospital at the University of Florida. If safety is an issue, UF security or local authorities will be called for assistance. If a participant endorses suicidal thoughts or significant psychopathology, participants will be referred for further by evaluation with Dr. Whitehead (Licensed psychologist and co-investigator). Based on this evaluation, she will recommend follow-up assessment and treatment appropriate to the situation including treatment at the Psychology and/or Psychiatry Clinics within Shands Hospital at the University of Florida.

Adverse Event Reporting. An **adverse event (AE)** is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the intervention irrespective of whether it is considered related to the intervention.

Non serious adverse events. Defined as conditions that may be unpleasant and bothersome to the participant that does not require discontinuing the study.

Serious adverse events (SAEs). Defined as events that may be harmful to the participant and/or may be serious enough to warrant either temporary or permanent discontinuation of the study intervention, either because they are intolerable or because they are judged to be potentially harmful. All serious adverse events require immediate reporting and an assessment of the implications for the continuation of the study and/or modification of the consent form. The following are considered serious events:

It is acute or life threatening;
It results in prolonged, permanent or severe disability;
It is another severe illness including worsening of a pre-existing condition, injury or accidents;
It is an inpatient hospitalization or surgical procedure, or a treatment to prevent a serious event;
It results in death;
It is a clinically significant abnormal laboratory or diagnostic test.

Table 3. Adverse Event (AE) Classification

Adverse Event (AE) Classification	
Definite.	Temporal pattern + known or expected AE response pattern + confirmed by stopping the intervention + reappearance of AE on re-challenge
Probable.	Temporal pattern + known or expected AE response pattern + confirmed by stopping the intervention + could not be explained by participant's clinical state
Possible.	Temporal pattern + known or expected AE response pattern + could have been produced by a number of other factors
Unknown.	Relationship for which no evaluation can be made
Not related.	AE for which sufficient information exists to indicate that the cause is unrelated to the study intervention

Classification of AE severity. The principal investigator will evaluate adverse events for seriousness, expectedness, severity, and relationship to study intervention at each study visit. The primary mechanism for ensuring participant safety will be clinical observation of symptoms. The study will be conducted and supervised by trained study staff that are certified in CPR and will monitor potential adverse experiences and symptoms. During each visit, participants will log any health-related problems or symptoms they are experiencing. These sheets will be reviewed by study staff before allowing the participant to continue. Community health services will be contacted immediately if warranted by the participants' symptoms.

All adverse events (AEs) will also be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled either definitely, probably, possibly or unrelated to the study intervention. The classification of potential relationship to the intervention is shown in Table 3.

Effective screening will exclude individuals who would be at increased medical risk as a result of participation in this research. FMRI contraindications, such as claustrophobia or some metal implants will be assessed by telephone screening and again on the day of the scan. Dr. Woods, who has completed MRI safety training and

has over 4 years experience screening FMRI participants, will supervise these procedures. The RA who will conduct neuroimaging analyses will be trained in UF AMRIS safety procedures and will also be responsible insuring for participant safety. Adverse events, although unlikely, may occur as a result of neuroimaging.. Such events will immediately be reported by Dr. Woods (PI) to the local IRB, with serious adverse events reported to both the IRB and NIH.

SAE reporting. Serious adverse events (SAEs) that are unanticipated, serious, and possibly related to the study intervention will be reported within 24 hours of study's knowledge of the SAE to the Independent Monitor, IRB, and CTSA in accordance with the regulatory requirements. Anticipated SAEs or those unrelated to the study intervention will be reported to the same individuals/entities in accordance with regulatory requirements.

Minor events will be reported to the IRB at the time of annual review, as well as to the oversight committee on a bi-annual basis. Both the principal investigator and the study staff will review the study weekly and examine reports of adverse incidents and reports of study participant recruitment and follow-up. Throughout the course of the study, information regarding issues deemed critical to the study or to the safety of research participants will be provided to the principal investigator and other study investigators as needed. As a result of receiving this critical information, a meeting to discuss this information may be convened. Information deemed critical would include:

- serious and non-serious adverse events that may occur;
- suspicion of scientific fraud or misconduct;
- any other issues which may warrant protocol changes or modifications.

Adverse event (AE) and serious adverse event (SAE) determination and monitoring will be achieved via administration of structured questionnaires. Standardized forms for referring and treating study participants who experience adverse events will be in place.

Documentation of Training on Protection of Human Participants. All key personnel on the study have successfully completed and obtained certification from their respective institutions for Mandatory Education in Human Research Subjects Protection. The Mandatory Education is described as follows:

On August 23, 2000, an institutional policy was enacted requiring all clinical investigators and their key personnel to undergo mandatory education in human research subject protection. The program was initiated on September 1, 2000 and includes all clinical researchers regardless of source of research funding. At the core of the self-directed training program is the tutorial manual entitled, "Protecting Study Volunteers in Research" by Dunn and Chadwick. Each researcher receives a copy of the manual and, in a timely fashion, completes the test included in the manual. Each researcher must obtain a score of ≥86 to complete the certification requirements to conduct clinical research at this institution. In all cases, no researcher will be allowed to conduct clinical research without proof of human research subject protection education after September 30, 2001.

Additional and continuing education opportunities for clinical researchers include the Office of Research Administration newsletter that is circulated to approximately 900 recipients every 6 weeks. Relevant information concerning research review is available on the UF ORA web page. In addition to standard institutional research information, the web page contains links to other sites such as CenterWatch, NIH.

8. Possible Benefits:

There are well-documented benefits for older adults who participate in cognitive training, including improvement in working memory, attention, and executive functions. Deficits in these cognitive abilities significantly impact quality of life, financial capacity, medication adherence, and mortality in older adults. All participants undergoing CT may benefit from these effects. Those participants randomly assigned to the active tDCS+CT treatment group may experience further benefit beyond that of cognitive training alone. Benefits to society will include the contribution of novel data regarding the efficacy of neuromodulation methods for enhancing cognitive training effects in older adults. This may help inform treatment protocols in a growing segment of the US population (i.e., those 65 years and older). Data collected from this study will serve as a foundation for larger clinical studies that examine optimized methods for treating aging-related cognitive decline using cognitive training and tDCS. Some participants may not benefit from the study at all.

9. Conflict of Interest:

None

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