Augmenting Cognitive Training In Older Adults

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1. Project Title

Augmenting Cognitive Training In Older Adults: The ACT Study

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3. Abstract:

The current study will investigate methods for enhancing cognitive training effects in healthy older adults by employing a combination of interventions to potentially facilitate neural plasticity and optimize 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 two-phase adaptive 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 could enhance neural plasticity when paired with a training task. We will compare changes in cognitive and brain function resulting from CT and ET combined with 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 12 months following training, and 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 possible 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 feasibly 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. **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. **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 with differing degrees of demonstrated efficacy. 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. Specifically, we will be using eight training programs from the PositScience BrainHQ suite described below.

Attention/Speed of Processing

1. *Hawk Eye*- works on visual precision, which helps the brain perceive what is seen quickly and accurately so that it can be recalled 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 participants to track several items moving around their 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 on the working memory systems.
2. *Memory Grid* - Auditory processing is one of the most important building blocks of memory. Only when participants 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. Many CT interventions fail to generate transfer to functional outcomes. 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 may potentially hold 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]

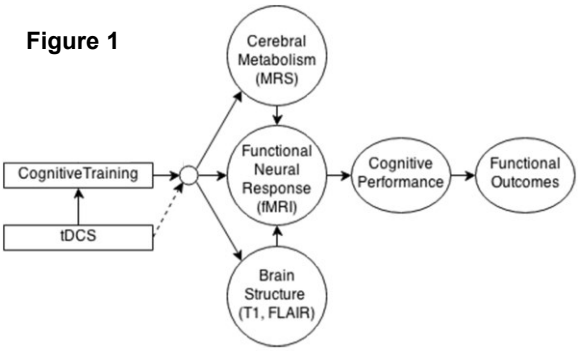
4.3.6.3. Functional neuroimaging provides a potentially powerful method for assessing healthy and abnormal brain functioning (see Cohen and Sweet, for a review[168])**.** FMRI is noninvasive, can be used in conjunction with structural MRI and MRS, and is sensitive to functional brain abnormalities.[153,157,169-179] 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).

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. [276-284]

Figure 1



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:

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 neuroplasticity and augment training effects.

- **H1.1.** CT will produce significant improvements on a composite measure of cognitive training performance on the POSIT Science BrainHQ tasks (Posit Composite Score) compared to the treatment control condition. This aim will be assessed at the end of Phase 1.
- **H1.2.** tDCS combined with CT will produce significant improvements on a composite measure of attention, working memory, processing speed, and executive function (NIH Toolbox Fluid Cognition Composite Score, NIHTB FCCS) compared to the sham treatment control condition. FCCS will serve as the study primary outcome measure.
- **H1.3.** Near and far transfer of CT and tDCS will occur, as assessed by the UM Functional Battery Composite Index and comprehensive neurocognitive assessment.

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

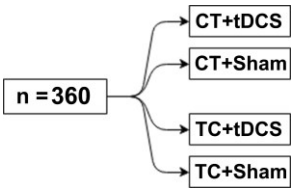
- **H2.1.** Compared to TC, CT will decrease activation in working memory and attentional brain systems (dorsolateral prefrontal cortex, medial frontal cortex, inferior parietal lobe, supplementary motor association cortex), reflecting increased neural efficiency.
- **H2.2.** Combined CT + tDCS will potentiate these effects.
- **H2.3.** Cerebral metabolite alterations will occur secondary to CT and tDCS, with long-term increases 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.

Exploratory Aim. Examine which baseline factors (e.g., clinical, demographic, neuroimaging, cognitive) best predict individual differences in neurocognitive and functional outcome.

- **HE.1.** White matter abnormalities on FLAIR MRI will predict poorer outcome.
- **HE.2.** Metabolic-vascular risk factors/disorders (e.g., diabetes) will be predictive of reduced outcome.
- **HE.3.** Alzheimer's disease risk factors (APOE4 and familial history) will predict poorer outcome.

6. Research Plan:

6.1. Experimental design. This study employs a two-phase randomized clinical trial with 360 participants total across two sites (University of Florida and University of Arizona; 240 at the University of Florida and120 at the University of Arizona). UF will be the parent site for the study. An initial cohort of 80 participants collected across the two sites will be assigned to one of four conditions as shown in Figure 2. Half of the recruited sample in Phase 1 will undergo CT; the other half will undergo training control (TC). The first interim analysis, to be performed when the first cohort of 80 completes 12-month follow-up (Phase 1), will investigate whether CT is significantly better than TC thereby enabling elimination of the TC condition. CT has previously been established with strong effects on cognitive and functional outcomes. If CT and TC are equally effective, groups will be collapsed at initiation of Phase 2 for planned assessment of adjunctive tDCS effects. If CT is more effective than TC, as previously shown, TC will be eliminated. Data from Phase 1 will also provide important mechanistic insight regarding neural mechanisms of CT vs. a well-matched education training control (TC). In Phase 2, the remaining 280 participants will be randomized to the two CT arms (i.e., eliminating the TC arms). After the remaining 280 participants have completed follow up in the CT arms (including those in Phase 1, total n=360) analyses will investigate the benefit of adjunctive administration of CT with tDCS. **Participants will be assessed at three primary time points: 1) baseline pre-training; 2) post-12 weeks of CT/TC + stimulation/sham; and 3) one year follow-up after all training (see Figure 3 for timeline).** This design will enable longitudinal analyses of CT and tDCS effects individually and in combination. We will examine CT and tDCS 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 CT, and at one-year follow-up.

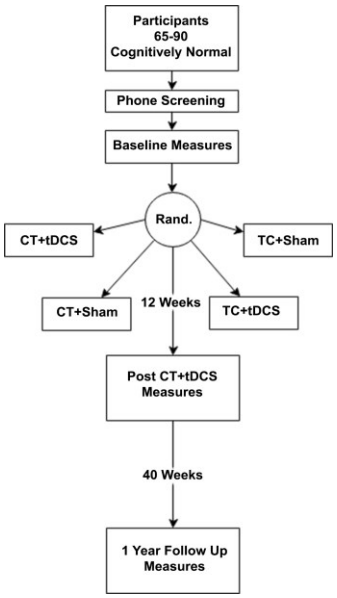


6.2. Study participants and randomization procedure. We will recruit 240 older adults (women = 120; age: 65-89 years) at UF. Study participants will consist of healthy individuals who have expressed an interest in taking part in an intervention aimed at optimizing and possibly preserving cognitive functioning and brain health. Web-based permuted block randomization (with block size 8) will be used. In phase 1, each block will have two participants for each arm. In phase 2, each block will have four participants for each remaining arm. We will enroll people with evidence of age-related cognitive decline as defined by performance below the 80th percentile on the Cognitive Training assessment. People with pre-existing dementia, neurological brain disease, or who meet criteria for a diagnosis of mild cognitive impairment (MCI) will be excluded.

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), 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.

Functional outcome. Since important clinical questions remain with

respect to the extent to which CT generalizes to other cognitive abilities and everyday functioning, a set of functional and ecologically derived outcome measures will be used that were developed and used by Czaja (consultant) and her colleagues. Like the NIH Toolbox, this battery is computerized, well standardized with good norms on accuracy and response time from older adults. It taps into important everyday functions such as using an ATM machine and refilling a prescription. See Appendix 2 for detailed manual.

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 a single ROI (frontal) 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.

6.3. Procedural sequence. The sequence and flow of the assessments to be conducted at baseline and each subsequent assessment is shown in Subject Timeline.

Single Subject Timeline	Month														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Phone Screening															
Consent Form															
Screening															
Baseline Measurements															
Cognitive Training/tDCS															
Post-CT Measurements															
1 Year Follow-Up Measurements															

Study Timeline	Year 1				Year 2				Year 3				Year 4				Year 5			
	3	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12	3	6	9	12
Project Start-Up																				
Recruitment/Screening			C1*					C2												
Baseline Measurements			C1					C2												
Cognitive Training/tDCS				C1					C2											
Post-CT Measurements					C1							C2								
1 Year Follow-Up Measurements								C1								C2				
Interim Analysis (IA)								IA												
Final Data Analysis																				

* Notes: 1) Number of participants in Cohort 1 and 2 are 80 and 280, respectively. The allocation ratio for the last cohort depends on results from IA. Measurements = MRI/Neurocog/Functional Outcomes

Screening Visit

Task	Estimated Time
Informed Consent	45
Full medical History/rx drugs	15
MRI screening form	5
NACC UDS	45

WTAR	5
BDI	5
Computer use questionnaire	5
Vision/color vision/hearing	10
AD-8	3
Cognitive Training assessment	20

Assessment Visits

Task	Estimated Time
MRI scan	60
MRI scan practice	20
MRI safety questionnaire	5
NIH toolbox	45
Computerized functional task	40
HVLT	20
Stroop	10
PASAT	10
COWA & Animals	5
Digit Span	10
Symbol Digit Coding	5
Letter-Number Sequencing	5
Trails A&B	5
BVMT-R	20
BDI	5
STAI	5
PSQI (sleep)	5
SF-36	5
Apathy scale	2
PROMIS	2
AUDIT-10	8
DAST-10	5
UCLA loneliness	3
Social Network Scale	5
CALCAP	8
IADL Questionnaire	5
Expectancy Questionnaire	5
Driving Questionnaire	10
10 meter walk test	5
Abbreviated Medical History/rx drugs	10
Cognitive Training Assessment	20

We will inform potential participants about the study, and facilitate the informed consent process using the IRB approved ICF. We will then screen for inclusion/exclusion criteria and schedule them for baseline evaluation. All assessments are identical otherwise. Assessment visits will be split over a two-day period, to reduce participant burden and ensure quality data collection.

6.4 Cognitive Training. CT will involve sixty sessions over 12-weeks (40 hours total); this includes ten daily sessions combined with stimulation for two weeks, then one weekly session combined with stimulation for the remaining ten weeks. The remaining 40 sessions will be performed by participants at their home on days they do not receive stimulation. *Training platform.* CT employs an eight component, PositScience BrainHQ suite via its researcher portal (described in section 4.3.3). These tasks are web-based and multi-platform (i.e., Windows, Mac). Participants will be required to have minimum screen sizes and specific viewing distances. The interface masks performance feedback to reduce frustration in the control condition. Study interventionists will provide weekly 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. Participants will have computers supplied, with training and orientation sessions and 24/7 support.

Training control. The TC condition will serve as a control for the CT condition. TC will involve sixty sessions over 12-weeks (40 hours total); this includes ten daily sessions combined with stimulation for two weeks, then one weekly session combined with stimulation for the remaining ten weeks. The remaining 40 sessions will be performed by participants at their home on days they do not receive stimulation. The duration and frequency of TC will match that of CT. TC involves watching educational videos produced by the National Geographic Channel, which cover a range of topics such as history, nature, and wildlife. Participants will be asked to complete questions on the content of the videos to ensure sustained attention.

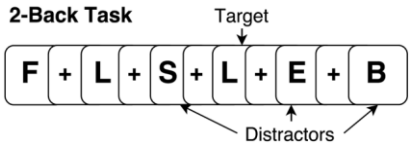
Cognitive Training assessment. An assessment of performance on the 8 cognitive training tasks will be given at the screening and assessment visits. The assessment consists of ten levels (comprised of the games described in section 4.3.3.) designed to challenge working memory, attention, executive function, and speed of processing. The assessment takes approximately twenty minutes to complete.

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) 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-I/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. Quality Control: We will take a brief set of pictures of the participant's head after the electrodes are placed to make sure that the electrodes are in the correct location. These photos 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.

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

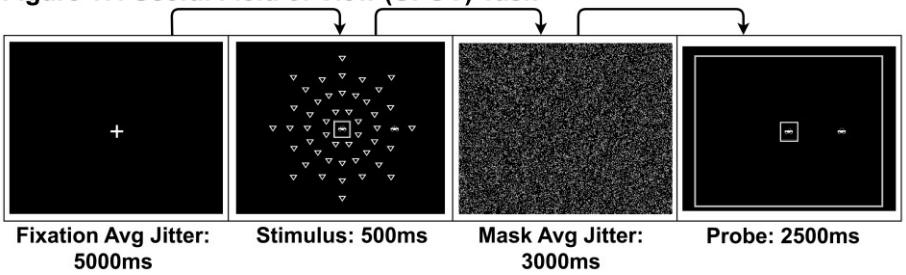
6.6.1. FMRI paradigms. We will present the two FMRI tasks (2-Back, UFOV) using E-Prime 2 software (Psychology Software Tools, Inc., Pittsburgh, PA), with the video signal on a screen behind the participant's head. The screen is viewed through a double-mirror attached to the head coil. An MR-compatible 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 briefly with a small rest period between each. 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.



Useful Field of View. *This task will measure brain changes due to alterations in attention and decision-making processes due to BrainHQ Double Decision and Freeze Frame training.* We will assess attentional and decision-making processes on a scanner adapted event related UFOV task that requires participants to simultaneously apprehend the identification of a centrally located target (car or truck) and the location of a target (car) among a parametrically manipulated array of distractors (0-47 distractors). Following a visual mask, participants then make a two-alternative forced choice (correct or incorrect) decision based on whether both the central target and distal target (without distractors) are identical to what was seen in the prior display (Figure 17).Two five-minute blocks of 56 trials are presented. Accuracy and reaction times are recorded. Jitter prior to stimulus presentation and response probe allows contrasts assessing unique activation associated with attentional and decision-making brain regions, providing mechanistic insight into cognitive training effects.

Figure 17. Useful Field of View (UFOV) Task



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 Magnetic Resonance Spectroscopy (MRS): GABA-edited spectra will be acquired using the MEGA-PRESS experiment, from a 3x3x3 cm3 voxels (medial frontal). Spectra will be analyzed using Gannet and LCModel to assess cerebral metabolites and neurotransmitter concentrations.[295]. [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 localization. Analyses: Volumetric indices will be obtained for total gray and white matter, FreeSurfer ROIs[296-298], and a priori ROIs (MRS, FMRI).

6.7. Neurocognitive Assessment: Assessments will include a neurocognitive battery (see Table 7). The battery consists of standardized, well-established neurocognitive measures with strong reliability and validity [304]. For cognitive measures with functions assessed see Table 7 below. Our goal is to assess global cognitive ability (NIH-Toolbox: cognitive module), and specifically attention-executive functions, working memory, processing speed, and memory. These are domains affected by aging[24,31,146,305-314] and will also tap the domains assessed by FMRI (Aim 2).

Table 7. Neurocognitive Assessment	
HVLT	Verbal Learning/Memory
Stroop	Attention/Executive
Trail Making A & B	Executive
COWA & Animals	Verbal Fluency
BVMT	Visual Memory
Symbol Digit Coding	Processing Speed
Letter Number Sequencing	Working Memory
PASAT	Working Memory
Digit Span	Working Memory
NIH Toolbox Subtests:	
* Dimensional Card Sort	Executive
* Flanker	Attention/Executive
* Picture Sequence	Episodic Memory
* Picture Vocabulary	Language
* Oral Reading	Language
* Pattern Comparison	Processing Speed
* List Sorting	Working Memory

6.7.1. Functional Outcomes. A touchscreen computer-based functional assessment tool will be used to measure tasks like medication management, ATM banking, prescription refill via voice menu. Task difficulty can be varied and real-time efficiency and accuracy data are collected; the measure is highly correlated with component cognitive abilities targeted in this study[315,316]. See Appendix 2 for a detailed manual.

6.7.2. QOL and 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 two measures will serve as important assessments of interventions influence on everyday life.

6.8. Alcohol and Drug Use Questionnaires. We will administer the Alcohol Use Disorders Test (AUDIT-10) and Drug Abuse Screening Test (DAST-10). These measures will provide

valuable information about how drug and alcohol use may alter the overall efficacy to tDCS, cognitive training and education training.

6.9. Driving Record Assessment. Driving records will be requested following the completion of the intervention; records will be requested at 5 years post intervention and at 10 years post intervention. These records will allow us to examine real world driving outcomes. The driving record assessment is optional (the participant choses to consent to this portion or not at screening). Participants who do not consent to the driving record assessment can still participate in the study.

6.10. Walking assessment. We will administer a 10-meter walk test. This test measures the time it takes participants to walk ten meters in a line. Participants are instructed to walk at their normal pace, as if they were walking down the street. Participants are instructed to use any walking aids they normally use (e.g. cane).

6.11. Quality Control. We will record (with audio and/or video) study procedures for the purpose of ensuring quality data collection. Participants will consent (via a checkbox on the informed consent form) to this recording. Recording will only be done on participants who provide written consent.

6.12. Theft Prevention. This study will be loaning out university computers and other supplies. All university equipment must be returned when the participant completes or withdraws from the study. In the event university equipment is stolen we will be required to file a police report with local authorities. We will make copies of the participant's driver's license when they are provided university equipment. Having a copy of the driver's license provides us with needed information in the event of lost or stolen university property. This procedure is described in the informed consent form. As a driver's license is protected health information it will be kept separate from any de-identified data.

6.13. Transportation. Certain potential participants may lack reliable transportation to the study sites. When possible study staff may transport willing participants to the study sites using a vehicle owned by the Department of Clinical and Health Psychology. All study staff will follow the procedures and regulations for operating University owned vehicles as described by UF Environmental Health and Safety at: http://www.ehs.ufl.edu/programs/insurance/automobile/

To facilitate transportation to and from the study site Uber Health may be used if the participants desire to have transportation provided. All costs associated with Uber Health will be covered by the study; the participant will not have any cost associated with the Uber Health travel. The option to have travel provided will be offered to all potential study participants within a 40 mile radius of the study site as costs outside of a 40 mile radius will not be feasible with the current travel budget.

Uber Health offers a HIPAA compliant service designed specifically with enhanced ease and privacy in mind for those using the service. Participants will not need to have any account associated with Uber and study staff will coordinate the whole process. The Uber driver will send the participant a text when they are about to arrive at their location, however, the participants personal phone number will not be revealed and instead a covert masking of numbers is provided by Uber to allow the driver and passenger to communicate without revealing their personal phone numbers. If participants do not have or use mobile phones the study coordinator can help coordinate the pickup.

6.14. Payment. Participants will receive $75 in gift cards at the end of each of the three MRI sessions to compensate them for their time and effort.

If participants are traveling from more than 20 miles away (one-way) to the study location they will receive an additional $10 compensation per study visit. If they attend all study visits they will receive an additional $270 in compensation for travel. If participants live less than 20 miles away they will receive no additional compensation for travel. If participants are utilizing Uber Health for transportation they will not receive the additional $10 per visit compensation.

6.15. Notification of Participants for Cognitive Findings Leading to Study Exclusion. The Montreal Cognitive Assessment (MoCA) serves as a brief global dementia screening tool commonly implemented in clinical practice. Any participant falling below the 1.5 SD norms (adjusted for age and education) would screen fail in the ACT study, as per current criteria. If this occurs, the participant will first be contacted via phone call by the study physician (Dr. DeKosky) and then provided with a letter from the study team describing their reason for screen fail and encouraging them to follow up with their primary care physician (the letter and phone call template are submitted in miscellaneous attachments in the myIRB system). The procedure for implementation will be built into our RedCap data system such that any person meeting this criterion will trigger an email to the site PI and site physician alerting the team to follow up with the participant and to provide the phone call by the study physician and a letter notifying the participant.

6.16. COVID-19 Adjunctive Study

6.16.1 Background

In early 2020 the COVID-19 pandemic reached the United States, and has been subsequently spreading rapidly throughout the state of Florida. The pandemic has brought about an exceptional number of public health ramifications. The most striking public response has been to push for a quarantining of exposed, or likely exposed, citizens and a general practice of ‘social distancing’ for the masses. Additionally, public places frequented by older adults, such as churches and community centers, have been closed leaving an unprecedented number of older adults shuttered in. It has been almost unanimously found that social isolation is a major health problem for older adult populations living in the general community (Nicholson 2012). There currently is a unique opportunity to investigate an enforced social isolation that affects older adults of all demographics. In this study we will record and investigate the outcomes of social isolation for older adults as well as analyze the individual factors that contribute to certain outcomes.

We have a unique set of circumstances where older adults are being forced to remain in their home and away from people indiscriminately. This relative uniformity in social isolation in response to a significant, state-wide crisis allows us to observe the effects of the pandemic on the wellbeing and daily life of older adults, even in adults who might otherwise not experience social isolation in their lifetimes. With such a wide array of people affected we can investigate individual responses to the crisis by looking at a variety of factors as well as track the responses over time.

6.16.2 Specific Aims

The following aims will be accomplished using cognitive tests and psychosocial questionnaires in an older population during the immediate COVID-19 pandemic and aftermath:

Aim 1—Assess the current consequences of the COVID-19 social isolation in comparison to pre- COVID 19.

H.1.1 Social isolation resulting from the COVID-19 pandemic will result in an alteration in cognition, daily living, mental health, and wellbeing in an older adult population.

Aim 2—Monitor and record changes in the older adult population throughout and following the COVID-19 pandemic and social isolation.

H.2.1. There will be distinct variations in individual responses to social isolation resulting from the COVID-19 pandemic and there will be observable characteristics that contribute to the differences in response.

16.6.2 Research Plan

Study timetable and logistics. Due to the rapidly evolving situation our aim is to administer the study measures as soon as possible pending IRB approval. All adjunctive administrations will be completed with no in person contact via online surveys and telephone calls. At the final COVID-19 assessment time point participants will be asked to complete an in person visit where MRI and blood draw will be done.

Experimental design. Participants will complete the same set of tasks several times starting with acute administration 1, followed by monthly repeats for 6 months, with a final assessment at 9 months following the first. A total of 8 assessments will be completed. Participants will be asked to complete one in person visit at the final COVID-19 time point. At this visit MRI will be conducted to examine possible neurological consequences of social isolation from the ongoing pandemic. Only resting state functional and structural scans will be done as to not impact functional measures of the main study. The MRI will last around 1 hour (see measures section below for additional details regarding the MRI). At this final time point we will also draw a small amount of blood with the aim of conducting COVID-19 antibody testing. COVID-19 antibody testing will allow better classification of previous COVID-19 positive participants. Blood will be collected by a trained phlebotomist in a biosafety level 2 lab at the McKnight Brain Institute and processed in a biosafety level 3 lab. Upon request participants will be provided with their COVID-19 antibody results.

Participants. A strength of this proposed adjunctive study is that baseline (pre-COVID-19) data has already been collected on the ACT study sample. This adjunct will allow us to collect additional information in willing participants without interfering with the main study aims. Participation is completely voluntary and in no way affects participation in the main ACT study.

Recruitment. Participants who have enrolled in the ACT study will be contacted by phone to assess interest in this adjunctive study. Due to the timing of current events,

we aim to contact all current participants within 30 days of revision approval. However, we will continue to recruit those who we have been unable to make contact with until the PI deems that it is no longer fruitful. Only participants who have been enrolled in the main study prior to March 16, 2020 will be asked to participate in the COVID 19 adjunct. To supplement phone recruitment we will mail letters to eligible participants.

Inclusion/Exclusion Criteria. Only participants who have previously provided written informed consent to participate in the ACT study will be contacted. The only additional inclusion criteria is a willingness to participate in the adjunctive measures.

Measures. Adjunctive measures will be conducted via a combination of telephone and REDCap online survey responses. Self-Report questionnaire measures will be completed by the participants using REDCap. An email will be sent to participants with the link to the REDCap survey for them to complete. Cognitive assessments will be completed via telephone and entered by research staff into REDCap. For participants without internet or computer access an option will be provided to complete all measures via telephone. In total each assessment will last around 1 hour. See the table below for an estimate of the time each measure will take. All measures have been previously approved to be completed in the main ACT study with the exception of newly created COVID-19 specific questionnaires. We will be conducting an additional MRI at the 9-month COVID-19 time point.

MoCA*:* A version of the MoCA without visual elements will be completed over the phone. The MoCA is a cognitive screening measure. We will use all three versions of the MoCA in a counterbalanced order over the 8 assessments to limit test-retest effects.

UDS Number Span: This measure assesses working memory by asking participants to remember a series of digits and to repeat them in forward and backward order.

Alcohol Use Disorder Identification Test (AUDIT)*:* This measure is a widely used self-report questionnaire designed to assess alcohol use. Alcohol use is common in adult populations and this measure will allow us to quantify use, potential impacts of use, and relate it to stress, individual differences in stress and response to the COVID-19 pandemic.

Beck Depression Inventory (BDI)*:* Symptoms of depression may be a relevant factor in response to uncertainty and social unrest.

Pittsburgh Sleep Quality Index (PSQI)*:* Sleep problems are common. This can impact emotional status and cognition, including sustained attention. Thus, we have selected a measure that assesses sleep quality.

State-Trait Anxiety inventory (STAI)*:* Subjects may experience increased anxiety as a result of the turbulent circumstances surrounding the pandemic.

UCLA Loneliness Scale*:* Designed to measure one's subjective feelings of loneliness as well as feelings of social isolation.

PROMIS Cognitive Scale*:* Assesses a person's perception of cognitive function in areas such as concentration, memory, and mental acuity. Cognitive functions have been known to diminish in periods of extreme stress, which could be aroused as a response to the COVID-19 pandemic.

PROMIS Physical Function Scale: Assesses a person's perception of their ability to perform daily activities of living such as chores around the house or carrying groceries.

Social Network Scale*: Assesses participants' social networks, such as the frequency, time, and number of people they communicate with on a regular basis.*

Medical Outcomes Study Short Form-36*: Self report questionnaire that assesses a variety of functional health outcomes.*

Apathy Scale*: Measures self-reported feelings of apathy.*

COVID-19 Questionnaire: Self report questionnaire that assesses the impact of COVID -19 in areas such as a participant's health behaviors, psychological wellbeing, and employment.

Pet Questionnaire: Assesses the influence of animal companions during self-isolation.

Medical Changes Questionnaire: Assesses any change in medical conditions, such as the worsening or appearance of new health problems.

MRI: We will collect structural T1 images, FLAIR (white matter hyper-intensities), resting state fMRI, diffusion-weighted imaging (white matter integrity) and magnetic resonance spectroscopy (cerebral metabolism). With emerging concerns that COVID attacks the central nervous system, these data will be important for understanding the impact of COVID on brain health in older adults. When compared to each participants most recent ACT MRI, these data will be invaluable for quantifying the impact of COVID-19 on brain health.

Estimated time of Online/Phone assessments

Task	Estimated Time (Minutes)
MoCA	10
UDS Number Span	10

AUDIT	8
BDI	5
PSQI	5
STAI	5
UCLA Loneliness Scale	3
PROMIS Cognitive Scale	2
PROMIS Physical Function Scale	2
Social Network Scale	5
SF-36	5
Apathy Scale	2
COVID-19 Questionnaire	10
Pet Questionnaire	5
Medical Changes Questionnaire	5
Total	**82**

6.16.3 **Safety Monitoring.** The current pandemic is likely to result in increased mental health problems among the general population. If participants indicate suicidality on the BDI the study psychologist (Dr. Ron Cohen) will immediately contact them for evaluation and referral for treatment.

6.16.5 Adjunctive Study Payment. Participants willing to complete the adjunctive study will receive a $20 payment for their time for each assessment timepoint. This payment is in addition to any other payment they may receive for the main study. An additional $30 will be paid for the final visit MRI and blood draw.

6.17 Safety procedures for resumption of in person research (June 2020)

Additional COVID precautions for assessment/study visits at the MBI. All surfaces in the lab space will be disinfected before and after each participant. Keyboards, mice, ipad screens, etc. will be disinfected before and after each session. 6 foot distancing will be observed in all sessions. PPE will be worn by the participant and the study staff at all times. AMRIS COVID guidelines will be followed for all MRI procedures (MRI compatible PPE, no additional visitors or personnel in the MRI suite, etc.). All study activities occur within the MBI. The MBI has positioned PPE and sanitization stations throughout the ground floor. Participants will be met outside the building by study staff, provided with PPE, if they do not arrive with PPE, and escorted directly to the study location on the ground floor.

Additional COVID precautions for tDCS. For the tDCS intervention, we are required to apply electrodes on the scalp of the participant. As is already our standard, only disposable electrodes are used for each visit to prevent any potential cross participant contact and electrodes are disposed of in biowaste containers after each session. All study staff wear non-latex exam gloves for all study procedures and gloves are disposed of in bio-waste containers after each session. Headstraps to affix electrodes to the scalp will be disinfected

with Clorox after each use. Measurement of electrode locations requires placement of small marks using either a sharpie or wax pencil to determine the precise location for the electrode on the scalp. Thus, the tip of the pen/pencil makes contact with the scalp. Each participant will be assigned a single sharpie/pencil and it will only be used on that participant (labeled with participant ID). Once the participant has completed all intervention sessions, the pen will be disposed of in biowaste. After each session, the pen tip will be wiped with Clorox for disinfection.

Additional COVID precautions for Cognitive Training. Participants are provided a laptop for completion of cognitive training. The laptop surfaces will be disinfected before being provided to the participant. For in lab training sessions, the laptop surfaces will be disinfected before and after each session

6.18 Mechanisms, response heterogeneity and dosing from MRI-derived electric field models in tDCS augmented cognitive training

We will leverage existing multimodal neuroimaging and behavioral outcomes data from the ACT trial to 1) **elucidate mechanism of action** underlying response to tDCS treatment with CT**,** 2) **address heterogeneity of response** in tDCS augmented CT by determining how individual variation in the dose of electrical current delivered to the brain interacts with individual brain anatomical and lesion characteristics; and 3) **refine the intervention strategy** of tDCS paired with CT by evaluating computational methods for estimating precision delivery of targeted dosing characteristics to facilitate tDCS augmented outcomes. We will employ state of the art MRI-derived computational modeling and machine learning (ML) applied to existing data to 1) create precision individualized computational models of electrical current in the brain from tDCS for all 360 participants in ACT (based in T1 weighted images), 2) determine the characteristics of electrical current calculated from electric current models associated with trial outcomes, and 3) evaluate a computational method for calculating possible precision dosing of tDCS parameters for optimizing trial outcomes in older adults.

To date, all prior trials of tDCS have applied a fixed dosing strategy (e.g., 2mA for 20 min with electrodes at F3/F4 [10-20 measurement system]) in attempts to enhance CT – including ACT. However, prior research demonstrates that individual variability in head and brain anatomy (e.g., degree of atrophy, skull thickness, etc.) significantly alters the spread and intensity of direct electrical current delivered to the brain person to person. The impact of individual variation in electrical current delivered to the brain for clinical outcomes has rarely been examined, and methods aimed at increasing stimulation effectiveness and optimizing readiness to learn are only now beginning to be explored. We will use advanced MRI-derived computational modeling of electrical current from existing MRIs to provide a means for accurately estimating individual differences in tDCS current delivery to the brain in the largest existing sample of participants undergoing tDCS (i.e., ACT) with multimodal neuroimaging data. When combined with state-of-the-art machine learning approaches and behavioral outcome data (only unblinded once ACT has completed all follow-up visits), precision models of tDCS current will be derived to identify critical stimulation dosing characteristics (e.g., current intensity, direction/path of current) in specific brain regions associated with response vs. non-response to tDCS and CT intervention. These data will not only provide much needed information for determining how individual participant characteristics impact tDCS efficacy, but will also serve as a foundation for future precision medicine applications of tDCS and CT to remediate cognitive decline in older adults and potentially prevent or alter the trajectory towards Alzheimer's disease.

Aim 1. Determine inter-individual variability in tDCS current distribution using MRI-derived finite element modeling.

H1.1. Variability in neuroanatomy (e.g. increased atrophy, sulcus depth, skull thickness, etc.) will significantly decrease current intensity and alter the pathway/direction of electrical current flow induced by tDCS in the brain.

H1.2. White matter lesions, as measured by white matter hyper-intensities on FLAIR imaging, will significantly decrease current intensity and significantly alter the direction of electrical current flow induced by tDCS.

Aim 2. Determine critical tDCS current properties and specific brain regions associated with responder vs. non-responder to tDCS and CT intervention using machine learning.

H2.1. Current intensity and direction will significantly predict response vs. non-response to tDCS and CT intervention on the NIH Toolbox Fluid Cognition Composite Score (ACT primary outcome).

H2.2. Current intensity and direction within bilateral rostral middle frontal, right superior frontal and frontal pole, and left pars orbitalis regions will most strongly predict response vs. non-response to tDCS and CT intervention.

H2.3. Current intensity and direction will outperform clinical/demographic characteristics alone (e.g., age, sex, comorbidities, mental health, Alzheimer's disease risk, cognition, etc.) in predicting tDCS response.

Exploratory Aim. Evaluate computational methods for achieving precision delivery of dosing characteristics in tDCS.

HE.1. Adjusting tDCS current intensity input into computational models will achieve precision delivery of targeted dosing characteristics.

HE.2. Adjusting electrode locations input into computational models will achieve precision delivery of targeted dosing characteristics.

No new data will be collected from participants to achieve these aims. Only existing data collected with consent from participants in the course of the primary ACT study will be used. These data will be analyzed using advanced analytic methods (computational modeling and machine learning) to achieve all three aims specified in section 6.18.

Aim 1. *Dependent measures.* The primary dependent measure in Aim 1 is current density computed in individual head models from existing MRIs. Current components will be further quantified as current intensity and direction. *Rationale*. Computed current density will provide an estimate of tDCS current dose within brain regions unique to each person's neuroanatomy. *Outcome analyses.* **H1.1.** The regression analysis between current density (dependent variable) and anatomical measures (independent variable) e.g., brain volume ratio, sulcus depth, bone thickness will test the hypothesis that unique current density distribution in each person is significantly affected by individual characteristics in neuroanatomy. **H1.2.** Current characteristics generated from models will be compared between inclusion and exclusion of white matter lesions. A false discovery rate (FDR)-corrected voxel-wise within participants analysis will test the hypothesis that inclusion of white matter lesions in computational models significantly alters current characteristic predictions.

Aim 2. *Dependent measures.* The primary dependent measure in Aim 2 is balanced accuracy. This measure provides an overall index of the performance to differentiate responders from non-responders. *Rationale*. By using this measure, we provide a single performance indicator upon which the **heterogeneity of response** in tDCS augmented CT can be revealed. Much of our preliminary data is based on analyses using this measure. *Outcome analyses.* All analyses will be conducted with the intent to optimize prediction of tDCS outcome. McNemar test at one-tailed 0.05 significance level will be conducted to determine whether current intensity and direction will outperform clinical and demographic characteristics alone in predicting tDCS response.

Exploratory Aim. *Dependent measures.* The primary dependent measure in the Exploratory Aim is log-likelihood distance measure. Adjustments of electric current intensity and electrodes placement in computational models will be used to minimize the log-likelihood distance measure to the Gaussian Mixture Model of the responders' current distribution.

Timeline. Construction of the MRI-derived finite element computational models as described in aim 1 is estimated to begin in January 2021. We estimate approximately 24 months will be required to complete this process. By Q3 2022 the ACT study is anticipated to be completed and access to the currently blinded randomization conditions will be available to complete aim 2 and the exploratory aim.

The additional analyses described in section 6.18 will not impact study participation in any way. The analyses will only use data collected under currently approved study procedures.

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 participants will be monitored during the entire MRI scan in case any problems occur. The risks of MRI are:

- The MRI scanner contains a very strong magnet. Therefore, participants may not be able to have the MRI if they have any type of metal implanted in their body, for example, any pacing device (such as a heart pacer), any metal in their eyes, or certain types of heart valves or brain aneurysm clips. A MRI technologist will question participants about any contraindications before they enter the scanner.
- There is not much room inside the MRI scanner. Participants may be uncomfortable if they do not like to be in close spaces ("claustrophobia"). During the procedure, participants will be able to talk with the MRI staff through a speaker system, and, in the event of an emergency, participants 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 participants. Participants will be given earplugs to reduce this risk, and headphones for added protection.
- If an obvious abnormality is discovered during the participant's MRI scan, they will be informed about it by the research team, and will be provided with a copy of the MRI scan and we will encourage them to see their primary care physician. MRI will only be done for research purposes in this study.
- Participants will be monitored very carefully while in the scanner, and repeatedly checked to ensure comfort.

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.

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 an initial study visit. Participants will also have access to a 24-hour help line should they have trouble working with the training computer.

Educational training. There is a risk participants may find ET to be challenging, fatiguing, and/or boring. Research staff will be present to address any concerns. Participants are free to skip any content they find objectionable and refrain from answering any questions that they find uncomfortable. All material presented has been judged appropriate for an educational setting.

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

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

Participants will be asked questions about previous and current alcohol and drug use with two questionnaire measures (AUDIT-10 and DAST-10). These questions are of a particularly sensitive nature. There is a risk that participants may feel uncomfortable about answering such questions. Like any other part of the study, participants are free to decline to answer anything that they are uncomfortable with.

Other possible risks to participants may include fatigue due to the testing. Should this occur, participants can take a rest-break at any time or may discontinue the testing at any time.

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

Researchers will take appropriate steps to protect any information they collect about participants. However, there is a slight risk that information about participants could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass participants, or possibly affect their insurability or employability.

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 participants. If participants are currently participating in another study using transcranial direct current stimulation or transcranial magnetic stimulation, they will not be enrolled in this study until all external studies are completed.

If participants consent to the COVID-19 ancillary blood draw risks associated with phlebotomy apply. These include discomfort at the site of puncture, possible bruising and swelling around the puncture site, rarely an infection, and uncommonly faintness from the procedure.

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, advertisements such as

newspaper, magazine, and bus ads, 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. Contact information will also be obtained through the UF Health Consent2Share registry to identify potential participants. If Consent2Share contacts are interested in hearing more about the study, they will be administered the phone screening. If we are unable to reach potential participants we will leave a phone message (see phone message script) to let them know the reason for our call. If they are interested in hearing more about the study they will be directed to call us back and then administered the approved phone screening after confirming initial interest and addressing any questions they may have. The contact information will be securely stored during the event and immediately stored in the Woods Lab after the event 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. Age 65 to 89 years; this age group was selected because it is at high risk of age-related cognitive decline and have a sufficiently long life expectancy[319] to participate in the study;
2. Evidence of age-related cognitive decline in the Cognitive Training assessment defined by performance below the 80th percentile.
3. Ability to participate in the intervention and attend training sessions; willingness to be randomized to either treatment group.

Rationale: (1) The age range is selected to include a higher proportion of persons with cognitive deficits. (2) Participants will need to show some form of impairment to be included in the study in order to avoid biasing the study with extremely high functioning individuals. (3) Participants must be willing to perform study activities.

Exclusion criteria*:* 1) Neurological disorders (e.g., dementia, stroke, seizures, traumatic brain injury). 2) Evidence of cognitive impairment (as defined by NACC UDS performance below 1.5 standard deviations on age/sex/education normative data in at least one cognitive domain). 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., claustrophobia, metal implants). 7) Physical impairment precluding motor response or lying still for 1 hr and inability to walk two blocks without stopping. 8) Currently on GABA-ergic or glutamatergic medications, or on sodium channel blockers. 9) Left-handedness.

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-moderate cognitive impairment; (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. (8) GABA-ergic, glutamatergic, or sodium channel blocking medications may alter or block the ability of tDCS to facilitate tissue excitability. (9) Left-handedness complicates the interpretation of FMRI 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 HIPAA guidelines for personal health information. All participants will sign a combined consent to participate in research and HIPAA 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 HIPAA 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 depending on the participant's preference. Research assistants may contact study participants via phone, email, or mail to provide directions to the study site or answer general questions or concerns about the study. In order to avoid participants who are lost to follow up, we will contact study participants periodically between their 3 month post intervention visit and their one year follow up visit at approximately 3 month intervals. We will send a letter and/or email to participants who we are unable to contact via phone to see if their contact information has changed. 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 database 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. Only de-identified data will be entered into the REDCap database across all sites. A data confidentiality agreement will be signed and filed with the UF IRB before any data are collected at any site.

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 will be stopped. In the event of a headache, stimulation 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 h 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 Siemens 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; 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. 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:

The research team 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.

A data and safety monitoring plan (DSMP) has been implemented to ensure the safety of all participants involved in the study and to ensure the validity and integrity of the data. 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.

- The PI's will be responsible for coordinating activities of the DSMP, including:
    - Lab Meetings twice per month, to discuss participant involvement in the study, and any issues that have developed or need revision
    - Safety concerns
    - Data Storage and safety
    - Participant safety
    - Outcome data
    - Data quality
    - Integrity
    - Intervention efficacy
    - Recruitment
    - Performance

Both the PI and the study staff will review and examine reports of adverse incidents immediately, and make reports to the IRB as necessary for any and all of the following situations:

- 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.

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 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. Cohen's and Woods neuroimaging laboratory within the Center for Cognitive Aging and Memory. Imaging data will undergo several levels of processing, and all raw and processed data will be archived on a University 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 RedCap Data 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 the clinical research unit of the Center for Cognitive Aging and Memory with an ancillary location at the Village at Gainesville. Several clinical research examination rooms are equipped and dedicated to neurocognitive and functional assessment, and contain all necessary computers and test materials. Storage of neuroimaging data backup will occur at the CAM Neuroimaging Laboratory. Neuroimaging will take place at the AMRIS facility of the McKnight Brain Institute.

Sharing of data from collaborating sites. Due to the multi-center design of the study, data will be shared with the University of Florida from a collaborating site, the University of Arizona. The collaborating site will send fully de-identified data. Data transfer will take place using the secured infrastructure of the University of Florida RedCap system for questionnaire data. De-identified raw neuroimaging data will be transferred to UF using the Secure File Transfer Protocol (SFTP) onto UF Dropbox servers. A data confidentiality agreement will be signed and filed with the UF IRB before any data are collected at any site.

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. 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.

Safety Review Plan Study progress and safety will be reviewed twice per month (and more frequently if needed) by the principal investigator. 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 IRB and other applicable recipients will review progress of this study annually.

Final storage of paper data. All paper data (e.g., consent forms) may be scanned, and will finally 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.

Description of plan for safety monitoring. Protection of participants from risks related to the study is of paramount concern.

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 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. 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.

Data and Safety Monitoring Board (DSMB):

A **Data Safety Monitoring Board (DSMB)** is established, with responsibility to monitor all aspects of the study, including those that require access to any masked data. The DSMB and its chair are named and approved by the NIA. It is planned that the DSMB meets by conference call as determined by the DSMB and the NIA. The DSMB has access to all deidentified study data, documents and progress. The Intervention and Safety Committee**, comprised of safety personnel from each site, the Chair, and a representative of the DMAQC** reports to the DSMB for issues related to participant safety.

The DSMB has the following charges:

- Review the study protocol.
- Review data (including masked data) over the course of the trial.
- Identify problems relating to safety over the course of the study.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety and endpoints.
- Make recommendations regarding recruitment, treatment effects, retention, compliance, safety issues and continuation of the study.

- At any time, the DSMB may recommend discontinuation of any component/treatment group of the study

Finally, the NIA makes the final decision on whether or not to accept the DSMB's recommendation about discontinuation of any component of the study. Any serious adverse event that might be due to the study intervention are reported to the DSMB, the IRBs, and to the NIA Project Office. The exact timeline for reporting serious adverse events is determined by the DSMB, IRBs, and NIA.

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. Those participants randomly assigned to the CT groups may benefit from these effects. Participants assigned to the Education Training Control group may obtain better knowledge about educational facts from the videos, but are unlikely to have the same benefits as those in the CT group. Those participants randomly assigned to the 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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