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Augmenting cognitive training in older adults (The ACT Study): Design and Methods of a Phase III tDCS and cognitive training trial

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ABSTRACT

Background: Adults over age 65 represent the fastest growing population in the US. Decline in cognitive abilities is a hallmark of advanced age and is associated with loss of independence and dementia risk. There is a pressing need to develop effective interventions for slowing or reversing the cognitive aging process. While certain forms of cognitive training have shown promise in this area, effects only sometimes transfer to neuropsychological tests within or outside the trained domain. This paper describes a NIA-funded Phase III adaptive multisite randomized clinical trial, examining whether transcranial direct current stimulation (tDCS) of frontal cortices enhances neurocognitive outcomes achieved from cognitive training in older adults experiencing age-related cognitive decline: the Augmenting Cognitive Training in Older Adults study (ACT).
Methods: ACT will enroll 360 participants aged 65 to 89 with age-related cognitive decline, but not dementia. Participants will undergo cognitive training intervention or education training-control combined with tDCS or sham tDCS control. Cognitive training employs a suite of eight adaptive training tasks focused on attention/speed of processing and working memory from Posit Science BrainHQ. Training control involves exposure to educational nature/history videos and related content questions of the same interval/duration as the cognitive training. Participants are assessed at baseline, after training (12 weeks), and 12-month follow-up on our primary outcome measure, NIH Toolbox Fluid Cognition Composite Score, as well as a comprehensive neurocognitive, functional, clinical and multimodal neuroimaging battery.
Significance: The findings from this study have the potential to significantly enhance efforts to ameliorate cognitive aging and slow dementia.

1. Introduction

Increased life expectancy has resulted in rapid growth of the older population. The cohort of adults 65 years and older in the United States is expected to double by the year 2050 and represents one of the fastest growing age groups in many countries. Even in the absence of neurodegenerative disease, cognitive abilities can decline significantly with advanced age. Cognitive decline in later life is associated with loss of independence, decrements in financial security and quality of life, and is a predictor of dementia risk [1–8]. The increased prevalence of older adults living with cognitive difficulties has given rise to significant clinical and public health concerns.

Current cognitive training approaches have demonstrated some promise in slowing age-related cognitive decline and decreasing dementia risk [9–13]. Findings over the past decade (e.g., Advanced Cognitive Training for Independent and Vital Elderly, ACTIVE) suggest that certain cognitive training programs hold promise as an approach to ameliorate cognitive aging in healthy older adults [9,11,13–27]. Unfortunately, most training studies have shown intervention benefits mostly restricted to measures of the trained ability. Transfer to untrained cognitive and functional abilities in older adults has been found infrequently and the degree of transfer can be variable in both

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effectiveness and duration. This paucity of training generalization represents a significant barrier to overall cognitive intervention effectiveness. Methods that could potentially enhance the overall effectiveness of transfer from cognitive training are important to optimizing the overall efficacy of these programs for older adults.

Transcranial direct current stimulation (tDCS) is a non-invasive and safe electrical brain stimulation method that alters the sub-threshold membrane potential of neurons, facilitates neuroplasticity and learning, and provides a novel approach for augmenting cognitive training [28–59]. During tDCS, a weak electrical current is applied to the scalp that penetrates to stimulate underlying cortical and subcortical tissue [50,51,60–63]. tDCS applied to cortical regions has been shown to improve performance on a variety of cognitive tasks [64–67]. Bilateral tDCS to the frontal cortices improves decision-making, attention, and working memory performance in older adults [68–71]. Small pilot randomized clinical trials (RCTs) pairing cognitive training with bilateral frontal tDCS show significant and lasting improvements in older adults experiencing declining cognitive function [72–76]. Maintenance of these tDCS and cognitive training effects have been shown to last beyond one year [73,76–79]. These studies demonstrate that cognitive training combined with tDCS may lead to lasting improvement in cognitive training effectiveness for older adults. Furthermore, augmenting cognitive training with tDCS may have preventative benefits for people likely to develop dementia later in life. Our conceptual model for the effects of cognitive training and tDCS on brain function, cognitive performance, and functional outcomes is depicted in Fig. 1.

At present, large well-controlled clinical trials are needed to determine whether adjunctive tDCS and cognitive training produces clinically meaningful change in cognitive function in older adults. This paper describes the methods and design for the NIA-funded Augmenting Cognitive Training in Older Adults study (ACT). The ACT study will be the first Phase III RCT in the field of tDCS and will provide definitive insight into the adjunctive benefit of tDCS paired with cognitive training.

2. Study design and methods

2.1. Overall design

This National Institute on Aging (NIA) funded study employs a two-phase randomized clinical trial with a planned 360 participants total across three sites (University of Florida, University of Miami, and University of Arizona; 120 at each site). The trial is registered at clinicaltrials.gov as NCT028511. A unique feature of the trial is the study design, which is intended to increase the efficiency of the trial. In Phase 1, an initial cohort of 80 participants collected across all three sites will be assigned to one of four conditions as shown in Fig. 2a. Half of the recruited sample in Phase 1 will undergo cognitive training; the other half will undergo education training, which is serving as a control. The first interim analysis, to be performed when the initial cohort of 80 participants completes a 3-month follow-up (Phase 1), will investigate whether cognitive training is significantly better than training control on a composite measure of cognitive training performance on the Posit Science BrainHQ tasks (Posit Composite Score). This will then determine whether we can eliminate the training control condition. Cognitive training in older adults has previously been established to improve proximal cognitive training outcomes in hundreds of published studies (for reviews, see [80–83]). In addition, our pilot data supported proximal transfer to cognitive training outcomes in the cognitive training condition versus the education control condition. These data are consistent with decades of cognitive training literature. No additional participants will be assigned to the training control groups if 1) cognitive training is found to be significantly superior to training control on proximal training outcome measures or 2) conditional power is calculated to be $< 80\%$ even if sample size were increased by 80 participants. If conditional power from interim analyses is calculated to be $> 80\%$, 40 or 80 participants (the smaller sample size that provides at least 80% conditional power) will be assigned to the four arms. Data from Phase 1 will also provide important mechanistic insight regarding neural mechanisms of cognitive training vs. a well-matched education training control, facilitating overall interpretation of Phase 2 data. Neural mechanisms to be compared between those who did and did not receive training (i.e., education control) will include change in: (a) functional connectivity between regions of interest (ROIs) attributed to training, (b) GABA concentrations in frontal cortices, (c) gray matter surface area and cortical thickness in training related ROIs, d) white matter volume in training-related ROIs, e) white matter hyperintensity load within training-related ROIs. In Phase 2, the remaining 280 participants will be randomized to the two cognitive training arms (i.e., eliminating the training control arms; cognitive training with tDCS and cognitive training with the sham, Fig. 2b). After the remaining 280 participants have completed follow up in the cognitive training arms (including those in Phase 1, total n = 360) analyses will investigate the benefit of adjunctive administration of cognitive training with tDCS on the primary outcome measure: NIH Toolbox Fluid Cognition Composite Score. Participants will be assessed at three primary time points: 1) baseline pre-training; 2) post-12 weeks of cognitive training/training control + stimulation/sham; and 3) one year follow-up after all training (see Fig. 3 for timeline). This design will enable longitudinal analyses of cognitive training and tDCS effects individually and in combination. We will examine cognitive training and tDCS effects on secondary measures of cognitive performance, functional and metabolic

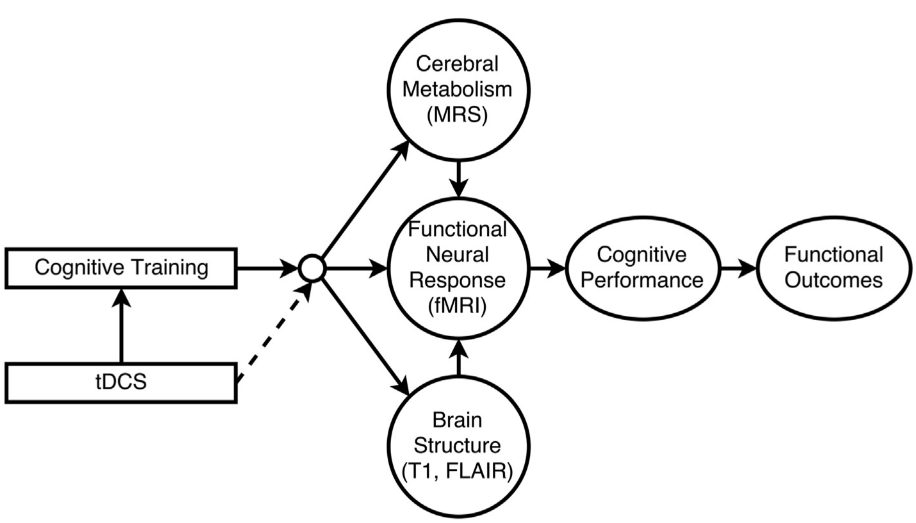

Fig. 1. ACT Conceptual Model. Cognitive training holds promise for reducing the adverse effects of cognitive aging, enhancing neuroplasticity, cognitive efficiency, functional capacity, and quality of life. In theory, coupling cognitive training with an intervention that increases neuroplasticity (e.g., tDCS) could augment training outcomes. We hypothesize that CT leads to improvements in neuroplasticity (GABA MRS) and functional brain response (FMRI). In turn this can lead to improved cerebral metabolic health and structural brain preservation. Coupling cognitive training with tDCS will increase neuroplasticity in brain areas important for working memory, focused attention/executive attention, and processing speed, improve effectiveness of cognitive training, and ultimately cognitive health and functional abilities.

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