STUDY PROTOCOL

Computer Training and Transcranial Direct Current Stimulation for Cognition in HIV

Identifier: NCT03440840

National Institute on Aging grant: R21AG056256

Date: 12/2/2020

RATIONALE FOR STUDY

HIV-associated neurocognitive disorders (HAND) continue to develop in persons with HIV, even when they are otherwise effectively treated[1-3] and include deficits in attention, executive function, memory, and psychomotor speed.[4] They may have significant impacts on affected persons' ability to care for themselves, remember to take their medication, drive, and enjoy life.[5-9] **As persons with HIV age, they may also experience the same declines in cognitive functioning associated with normal aging**[10;11] While it is not clear whether the effects of HIV and aging are synergistic, it is clear that older persons with HIV experience problems in attention, psychomotor speed, and memory that have a negative impact on their lives. **Treatments for cognitive deficits in older persons with HIV thus are needed** but available treatments are limited. Computer-based cognitive training may improve function in older persons with HIV, but data from small studies suggest that effect sizes, while statistically significant, may be small.[12;13] Training software is not widely available, can be expensive, and lacks the inherent interest needed to sustain participant involvement. The uptake of these programs, even if they were inexpensive and widely available, is thus not clear.

A possible solution is to use commercial computer games for cognitive training. Commercial games, such as first person shooters (using a weapon to shoot enemies) or car racing combine the essential elements of active learning[14;15] and are fun to play. Research shows that playing games has a positive effect on cognition in older persons.[16] Although many persons assume that players are mostly young men, Pew Research **data show that 38% of women and 29% of men over 50 play computer games.**[17] Our own as well as others' studies[18;19] have shown that older persons are interested in computers and can work effectively with them when given appropriate training. Even this strategy, though, may have only limited effects on cognition in older adults.[12]

Transcranial direct current simulation (tDCS) has emerged as a safe[20] and inexpensive strategy to enhance the effects of cognitive training. Studies show substantial increases in amount and rate of learning in healthy young[21-24] as well as older persons,[25;26] and patient groups[27-29] that have included individuals with neurological disorders such as primary progressive aphasia or Parkinson's disease. tDCS may also have positive effects on depression,[30;31] and was acceptable to participants as a treatment for depression in HIV.[32] **tDCS is thus a promising technique to enhance cognitive training in older persons with HIV.**

While tDCS is an emerging treatment, it is the subject of serious investigation. Noninvasive brain stimulation technologies, including tDCS, were described as promising at a workshop at the Institute of Medicine in 2015,[33] and the NIMH Division of Translational Research will have held a workshop on tDCS by the time this application is reviewed (scheduled for 9/29-30/16).

To study tDCS and cognitive training in HIV, we completed **a pilot study** of computer game based cognitive training with and without tDCS in older persons (average age 51 years) with HIV.[34] **Results suggest a positive effect of tDCS on cognition and mood and demonstrate the potential feasibility and acceptability of the intervention.** Given the preliminary nature of the proposed study, we are seeking support under the R21 exploratory/developmental mechanism *("high risk – high reward"*) in response to the PAR 15-282, "Multidisciplinary Studies of HIV and Aging" to further explore the usefulness of cognitive training and tDCS in persons with HIV.

We will complete a randomized, single-blind treatment with blinded outcome assessments study of game-based cognitive training with and without tDCS, with an attention control group, recruiting 125 persons to ensure a total sample of 90 individuals 50 years of age and older with HIV-related mild neurocognitive disorder, to evaluate the following:

AIMS AND HYPOTHESES

AIM 1) Further explore the acceptability and feasibility of game-based cognitive training with and without tDCS in older persons with HIV infection by completing a trial that includes a control as well as groups receiving cognitive training with and without tDCS.

Hypothesis 1: *A game-based cognitive training intervention combined with tDCS will be acceptable to older persons with HIV infection.*

AIM 2) Evaluate the effects of game-based cognitive training with and without tDCS on cognition in older persons with HIV.

Hypothesis 2: *Action game based cognitive training will be superior to attention control, while action game training with tDCS will be superior to cognitive training alone (**control + sham** < **training + sham** < **training + tDCS**) on measures of reaction time, attention, and psychomotor speed.*

A. SIGNIFICANCE

Cognitive deficits persist in HIV even with viral suppression. Even though advances in treatment of HIV infection have made it a manageable disease, affected individuals continue to develop HIV-associated neurocognitive disorders (HAND).[1;2] Cognitive deficits have been found across a range of domains, but commonly include executive functions, attention, memory, and psychomotor speed.[4;35-38]

Cognitive deficits have significant impacts on patients' self-care, medication adherence, driving, and quality of life. Studies have linked HAND to functional status in persons with HIV infection.[9;39] Verbal memory, for example, has been linked to medication adherence.[40] The ability to plan and execute complex sequences of actions is essential to complex adaptive behaviors, and has been linked to executive dysfunction and cognitive slowing in individuals with HAND.[38] Similarly, the ability to multitask, required to complete many instrumental activities of daily living (IADLs), was linked to IADL performance.[41]

HAND may be compounded by age-related cognitive changes. As persons with HIV infection become older, they can develop the same age-related cognitive changes as do uninfected older persons.[11] Older persons with HIV infection are also susceptible to the same comorbidities that affect cognition in uninfected older persons as well, such as cardiovascular disease and diabetes.[42-45] Although it is not clear whether the relation of HAND and cognitive aging is additive or synergistic,[46;47] both are sources of cognitive problems for older persons with HIV.

Effective treatments for HAND are needed. Researchers have studied various strategies to improve HAND. One study showed that methylphenidate could improve cognitive slowing.[48] Other studies have evaluated a number of medications but have found little or no effect on cognition in HAND.[49-51] Recently, though, Sacktor et al. reported an effect on cognition for the antidepressant paroxetine.[52]

Computer-based cognitive training may be useful in treating cognitive deficits in older persons with HIV. Vance and colleagues have explored the usefulness of computer-based cognitive training to address HAND.[53;54] Using commercially available software they showed improvements not only in the task trained (Useful Field of View) but also in IADLs (Timed Instrumental Activities of Daily Living). Others have evaluated the effects of cognitive training programs to improve cognition in healthy older adults. They found significant but modest effects on memory.[12;13] One important study, the ACTIVE trial,[55] showed positive effects of psychomotor speed training that were significant after 5 years.[56] The expense and lack of inherent interest in training software,[57] which may be out of reach of indigent patients, are drawbacks. **Cost, availability, and lack of inherent interest thus may limit the use of cognitive training interventions.**

Commercial computer games are effective in cognitive training and address these limitations. Gaming has positive effects on cognition.[15] Action video games in particular may be effective in developing attention and psychomotor speed[14] while being readily available and often free. Wu and Spence showed that game playing improved visual search via improved ability to inhibit distractors.[58;59] First person shooters (games that involve targeting enemies with a simulated weapon) improve attention and visual processing.[60] An extensive meta-analysis on cognitive training of spatial skills showed that the benefits of training persist and transfer to other non-game spatial tasks.[61] As summarized by Merzenich in *Nature Reviews Neuroscience:*

"Video games are controlled training regimens delivered in highly motivating behavioral contexts. The documented gains in processing speed, attentional control, memory, and cognitive and social control that result from playing specific games are expected. Because behavioral changes arise from brain changes, it is also no surprise that performance improvements are paralleled by enduring physical and functional neurological remodeling."[14]

What about older persons? Action video games also improve cognition in older (age 50+) persons.[16] Anguera et al., for example, in a paper in *Nature,* showed that a car racing game improved attention and working memory in older adults.[62] Basak et al.[63] (in *Psychology and Aging*) suggest that training across multiple contexts in games promotes transfer of training to other tasks, and report positive effects of game play on executive functions and working memory. The ability of computer game playing to improve psychomotor speed is particularly relevant to older adults, as training in this domain has a positive effect on IADLs,[64;65] driving,[66] and even the risk for dementia.[67] **Data thus support the usefulness of computer gaming to improve cognitive function in older persons in ways that have meaningful effects beyond laboratory measures of cognition.**

Will older persons, and especially older women, play computer games? Data on this question show that older persons, including older women, are already playing computer games – in fact, according to Pew Research more women (38%) than men (29%) over age 50 play computer games.[17] While there are differences among games played by men and women (e.g., shooters by men and puzzle solving by women), data show that older persons play computer games, and that older women play games with substantial

frequency. Belchior et al.[68] showed that a commercial game engaged older persons more than a cognitive training program, and qualitative studies of older gamers show that they enjoy gaming and believe that it helps them maintain cognitive function.[69-71]

Sex as a biological variable. The importance of understanding the impact of cognitive training interventions in older women with HIV is highlighted by data suggesting that neurocognitive function in women may be affected more severely by HIV-1 infection than in men.[72-75]

Transcranial direct current stimulation (tDCS) shows promise in enhancing the effects of cognitive training. Although gaming-based training is promising due to its ability to engage older persons, as with other cognitive training strategies its effect may be statistically significant but small. **tDCS** involves the application of a small current (1-2 mA) on the scalp, inducing a current in parts of the brain involved in cognition.[76] Training studies show that tDCS is associated with significant enhancement of cognitive training,[21;23;77] is safe,[20] and has mild side effects such as redness and a burning or tingling sensation.[78;79] An extensive review of safety data shows that older persons are not at increased risk for adverse effects,[20] and it was acceptable to participants in an open-label trial of depression in older persons (mean age 53 years) with HIV.[32]

Several authors argue that tDCS could be useful in maintaining and improving cognitive function in older adults.[80;81] A study that combined functional magnetic resonance imaging (fMRI) and tDCS in older adults performing a semantic word generation task showed that a single session of tDCS temporarily improved their performance to the same level as younger controls.[82] Another study showed that tDCS combined with working memory training increased the persistence of training effects.[83] Yet another study showed that tDCS with working memory training also improved function on ecologically-relevant tasks.[84] Two meta-analyses on the use of tDCS in older adults supported its effectiveness. The first included 25 studies with 448 participants,[25] while the other included 14 studies with 331 participants.[26] A substantial body of research thus the supports the utility of tDCS combined with cognitive training in older adults.

Does tDCS work, and if so, how? It may appear implausible that a small electrical current applied to the scalp, inducing an even tinier current in the brain, could have an impact on cognition and mood. An extensive body of research, though, shows that tDCS can have positive effects on cognition in healthy young persons,[21;23;23;77] in older persons,[25] and in persons with neuropsychiatric disorders.[85] Behavioral observations are supported by neuroscience research showing that DC stimulation enhances long term potentiation (LTP, a central mechanism of learning and memory[86]) in rat hippocampus.[87;88] tDCS has also been associated with increased release of brain-derived neurotrophic growth factor (BDNF) in rat hippocampus.[88;89] As BDNF is critical in learning and memory[90;91] and also is a potential mechanism of antidepressant medication action,[92;93] this finding supports not only the observed cognitive effects of tDCS but also its antidepressant effects.[31]

The underlying neural mechanisms of tDCS action have also been explored with respect to its effects on neurotransmitter and neuromodulator pharmacology. Amphetamine, for example, enhances the effects of tDCS,[94] while dopamine receptor blockade abolishes it.[95] At a broader level, magnetic resonance spectroscopy (MRS) shows chemical changes in the brain during tDCS.[96] Meinzer and colleagues showed that tDCS over the left inferior frontal gyrus enhanced performance on a semantic retrieval task while improving connectivity with other language areas on fMRI.[97] Research on the mechanisms of tDCS thus has shown that it has effects at the cellular, cortical, and network levels.

tDCS is safe and inexpensive. Safety data on tDCS were recently summarized.[20] Over 33,200 sessions and 1,000 participants, no severe adverse events have been reported. Common side effects of tDCS include redness and mild irritation at the site of stimulation; these resolve after stimulation is discontinued. tDCS, if effective when combined with cognitive training, will be cost-effective. Many tDCS studies have used readily available iontophoresis (medication delivery) devices that cost $300 to $500. Powered by nine-volt batteries, these simple devices are rugged and can be used by multiple persons over many training sessions. Even a short series of treatments can have persistent effects,[23;82] and the utility of booster sessions has yet to be systematically explored. It may also be possible to train patients to use tDCS at home.[98]

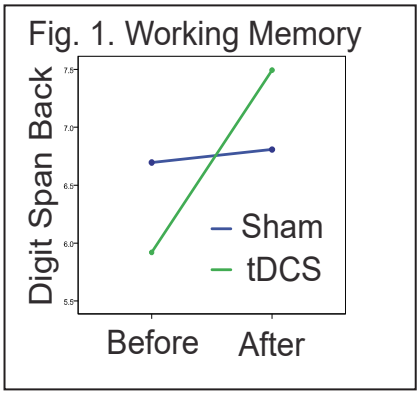
B. INNOVATION

The proposed study is innovative in its use of a computer-based game for cognitive training in HIV and its combination of cognitive training with tDCS. No readily identifiable study has examined gaming or tDCS to improve cognition in persons with HIV infection; this study will allow an evaluation of an action game requiring quick reactions, sustained attention and psychomotor speed, and the combination of an action game with tDCS as well as provide a contrast with computer-based learning (attention control). Other researchers have examined each of these strategies in healthy older adults and in some patient groups, but this study would be innovative in allowing an assessment of the effects of cognitive training with and without tDCS in HAND.

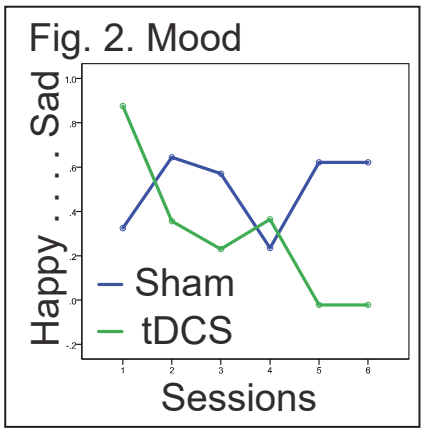
C. APPROACH

PRELIMINARY STUDIES

Pilot study of game-based cognitive training with and without tDCS.[34] Participants were 11 individuals treated for HIV infection who reported cognitive difficulties and evidenced objective cognitive impairment in two neuropsychological domains, meeting Frascati criteria for mild neurocognitive disorder (MND).[99] They were randomly assigned to training with or without tDCS. We used an off-the-shelf computer game that is inexpensive (free to download on Windows™), was of an appropriate level of difficulty, and is widely popular thus likely to be acceptable to our users. *GT Racing 2* (Gameloft SE: Paris, France) requires that individuals steer a simulated car over courses that include city streets and racetracks. Each course requires that the user achieve a basic level of proficiency before moving on to the next. The initial difficulty allows all players to be successful while the game becomes increasingly difficult. We chose a car racing game because of previous demonstrations of the effects of a similar game on cognition in older persons[62] and our judgment that a car racing game would be more acceptable to women than a first person shooting game. Participants were trained to use an Xbox game controller (a popular console game device) connected via USB to a laptop computer, with the computer displaying the game on a 23-inch screen. Each race lasted from 1 ½ to 2 ½ minutes, with the investigator in control of the computer and starting the next trial immediately after completing the previous one.

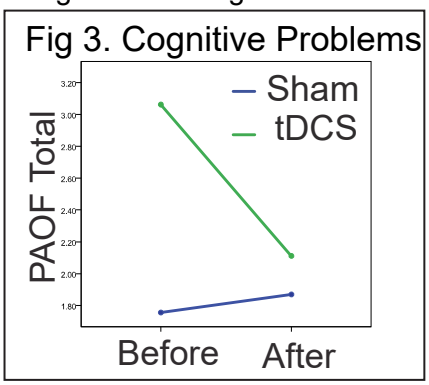


Before and after six 20-minute training sessions over two weeks with either active or sham tDCS, participants completed a battery of cognitive measures (attention and working memory; verbal learning and memory; psychomotor speed) as well as self-report measures of cognitive difficulties and mood. All assessments were completed by an evaluator blind to treatment assignment or via automated computer-assisted self-interview (ACASI) on a touch screen computer with the investigators out of the room.



Individuals receiving ***active tDCS*** received 1.5 mA stimulation for 20 minutes during training with the anode (positive electrode) located over the left dorsolateral prefrontal cortex (DLPFC) and the cathode (negative electrode) in the right supraorbital area. The left DLPFC was chosen as stimulation site because of its use in other studies that showed effects on attention,[100] working memory,[101-104] executive functions,[24;85] and psychomotor speed,[105] and the role of the DLPFC in motor learning.[106] ***Sham participants*** experienced the same procedures but the tDCS device was only turned on for the first 30 seconds, allowing the current to ramp up, and then it was turned off. Six sessions on every other day were chosen to represent a plausible training protocol that would be acceptable while providing an estimate of training effects.[26]

After each session, participants responded to three questions via ACASI that asked how they would rate their thinking, mood, and discomfort during training. After all training sessions and follow-up testing, the blinded evaluator completed a final interview during which participants were asked to which group they had been assigned, whether the intervention was helpful, and whether they would participate in a study of tDCS and cognitive training in the future.



Results. The average age of participants was 51.2 years (SD = 4.71); they had completed 6 to 15 years of education (mean 11.18, SD = 2.27). Two women, and two whites were participants; the majority were thus African-American men. As correlations of age, gender, education, race, and immune status (viral load and CD4 count) with cognitive variables were substantial and judged to be potentially meaningful, we included them in analysis of covariance (ANCOVA) models assessing differences in performance before and after training with or without tDCS.

As we were primarily interested in exploration of preliminary results via graphing and effect sizes, analyses focused on the extent to which the interactions between time and treatment condition might represent an effect of tDCS on outcomes. Examples of covariate corrected baseline and follow-up changes for each group are presented in Figures 1 to 3. **Figure 1** (higher scores reflect better performance)

presents results for Digit Span Backward (working memory) performance, suggesting that persons in the tDCS group may have improved relatively more over the baseline assessment than did those in the sham group (effect size, or ES = 1.74). **Figure 2** (lower scores reflect better mood) shows mood ratings completed immediately after six training sessions. Participants in the active group rated their mood as better over time (ES = 1.07). **Figure 3** (lower scores indicate fewer problems) shows changes in the Patient Assessment of Own Function (PAOF) total[107] over assessments. This rating reflects participants' reports of a range of cognitive difficulties, with the active group reporting fewer problems with thinking and memory after training (ES = 1.50).

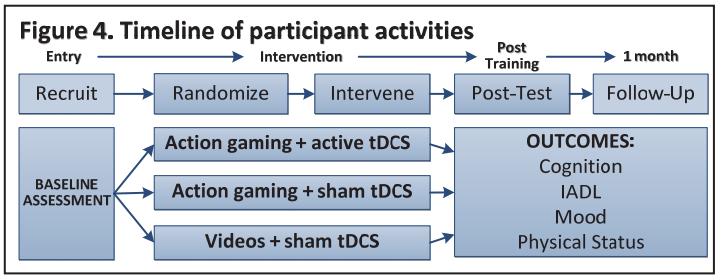
Effect sizes for treatment by time for all outcome measures are presented in **Table 1,** for the Wechsler Adult Intelligence Scale—IV[108] Digit Span subtest (attention and working memory), the Hopkins Verbal Learning Test—Revised[109] (verbal learning and memory), the Trail Making Test Parts A and B,[110] and the Grooved Pegboard[111] (psychomotor speed)**.** The effect size for Trail Making Test Part A was in the reverse direction in favor of the sham treatment group. When analyses included change in depressive symptoms on the Center for Epidemiological Studies—Depression[112] scale before and after training, the effect size for PAOF was smaller (0.83) while that for Digit Span Backward became much larger (greater than 10, $p = 0.011$). As suggested by Cohen,[113] effect sizes in the range of 0.5 to 0.8 are "medium," while 0.8 and greater are "large." **Results thus suggest that training + tDCS has positive effects both on objective measures of attention and psychomotor speed and self-report of cognitive problems and mood.**

Table 1. Effect sizes	*d*
Digit Span Forward	0.73
Digit Span Backward	3.63
Digit Span Sequencing	2.22
HVLT-R Total	0.88
HVLT-R Delayed	2.58
Trail Making Test, Part A	*2.66*
Trail Making Test, Part B	0.84
Grooved Pegboard	0.75
PAOF Total	1.50
CESD	1.07
Average	**1.58**

Success of the blind and participant reactions. We asked participants to tell us which treatment group they had been assigned to; all stated that they had received active tDCS. Nine of the 11 participants believed the intervention had been helpful to them (including several assigned to sham) while two participants stated they were not sure or believed it had not been helpful--they were assigned to sham. **Several participants commented:** *"I got better every visit"* (active tDCS), *"I think it helped my memory"* (sham tDCS), *"I feel like it helped with concentration and focusing"* (active), *"Helped out a little – to put more thinking about things before I act"* (active), and *"Now I can think longer on more stuff and my memory is somewhat better"* (active). All stated they would participate in a similar study in the future. Both men and women indicated that they enjoyed the car racing game.

PLANNED STUDY

Overview. This will be a randomized, single-blind trial with blinded outcome assessments evaluating the effects of computer game based cognitive training with or without tDCS compared to an attention control, watching educational videos on a computer (Figure 4). We will enroll 120 participants to obtain a final n of 90 (allowing for attrition) who will be randomly assigned in equal numbers to (1) attention control (educational videos + sham tDCS), (2) cognitive training with an action (car racing) game + sham tDCS, or (3) cognitive training with an action game + active tDCS. The study will thus implement the training protocol from the pilot study (which participants found enjoyable and subjectively helpful) but will now include an attention control group to help evaluate nonspecific effects of computer use. This study will also expand the assessment battery to include measures of functional status, motor function, frailty, driving, and medication adherence. We will ask participants to return for a follow-up one month after the final visit to determine if training effects are maintained, laying the groundwork for a larger study that could explore strategies to maintain treatment effects if they are obtained.



Inclusion. Participants will be treated for HIV infection, on a stable regimen of antiretroviral medications for at least one month, aged 50 years or older, and meet Frascati criteria[99] for mild neurocognitive disorder based on report of cognitive difficulties and cognitive deficits in two domains as determined by neuropsychological testing. **Exclusion.** Participants will be excluded if they have conditions that might affect their safety when receiving tDCS (e.g., seizure disorder), or on medications that can affect tDCS (psychotropic medications can affect how tDCS works) or are severely cognitive impaired.

Recruitment. We have been successful in recruiting for previous studies through contacts with Broward House, the largest HIV service provider in Broward County (Fort Lauderdale) Florida. We have also worked with Care Resource, a non-profit providing HIV medical care in both Broward and Miami-Dade counties, and the HIV clinic at Broward Health, the largest health care provider in Broward County. We will address the need to make a special outreach to women by using a female recruiter and specifically addressing potential concerns by emphasizing that training and support will be available throughout the study. We will also be able to recruit participants in a study completed by Dr. Acevedo (co-investigator) with Hispanics with HIV infection over 50 which included a number of women. In a previous study,[114] we recruited 124 participants with HIV infection over 18 months and retained 120 over 8 weeks.

Procedures

Single blind treatment. The rationale for a single- rather double-blind design stems from the nature of currently-available tDCS devices. Those that are FDA approved for use with humans have been developed as iontophoresis drug delivery devices and do not have the capacity to mask active stimulation from the operator. Our design, as discussed above, will employ single-blind stimulation but all assessments will be completed by an evaluator who is blind to treatment assignment or via ACASI with the investigator not in the room. As reported above, this procedure was successful in our pilot study, and others have reported similar success.[30] In fact, in one moderately large study Brunoni et al. found that blinding their patients to tDCS assignment was effective, while blinding them to active vs. placebo medication was not.[30]

Eligibility determination. The same questionnaire and neuropsychological measures of attention, working memory, verbal learning and memory, and psychomotor speed used in the pilot study (described above) will be used to determine eligibility. As part of eligibility determination participants will provide copies of recent laboratory values including HIV-1 RNA (viral load) and CD4 count.

Baseline assessments. Eligible participants will then complete a more extensive assessment that includes measures of premorbid functioning, reaction time, verbal and visuospatial learning, attention and working memory, and executive functioning. A detailed assessment protocol is included as an appendix to this submission. Assessments will also measure elements of frailty,[115] as it may occur even in middle-aged adults with HIV infection[116] and is an independent predictor of multimorbidity in HIV.[117] The acceptability of the intervention to participants will be evaluated with a questionnaire we used previous projects[114;118] based on the Technology Acceptance Model.[119] We will evaluate participants' satisfaction with the intervention and perception of side effects with a questionnaire based on the Treatment Satisfaction Questionnaire for Medication (TSQM)[120;121] but modified to make it relevant to cognitive training and tDCS.

In light of the importance of evaluating the practical significance of training effects as well as their impact on laboratory cognitive measures, the battery includes a measure of health-related quality of life (SF-36) and a self-report measure of instrumental activities of daily living. We will ask participants about their adherence to medication and other treatments using a previously validated strategy.[122] Given the potential relation of psychomotor speed to driving,[66] we also include a self-report measure of driving habits[123] sensitive to mild cognitive impairment.[124]

Training. All participants will complete six 20-minute training sessions in our computer lab. Sponge electrodes (25cm^2) will be placed over the left dorsolateral prefrontal cortex (anode) and the right supraorbital area (cathode). In the **active tDCS** condition, participants will receive 1.5 mA stimulation for 20 minutes while they will play the car racing game. In the two **sham conditions**, the tDCS will be turned on and current allowed to ramp up over 30 s to 1.5 mA after which the device will be switched off. The racing + sham tDCS will then play the car racing game for 20 minutes, and the attention control group will watch a 20-minute educational video with sham tDCS and respond briefly to questions about its content as used in other studies[12;13] and our own unpublished study. Immediately after each session, participants will respond to rating questions about cognitive function, mood, and discomfort.

Post-test and Follow-up. After completing six training sessions, participants will complete the same assessment battery as at baseline, and again one month later (see Appendix and Figure 4).

POSSIBLE ISSUES

Age. While it is true that the age for our participants may be somewhat younger (50 or older) than most studies of the elderly, we believe that this range is common in individuals with HIV infection and will include persons with age-related cognitive changes. The mean age in a study showing that frailty was associated with multimorbidity for example, was 46 years.[117]

Game-based cognitive training includes many elements – how to determine what is the active ingredient? It is true that action games require a wide range of cognitive skills across a variety of contexts with

repetition in multiple situations. Bavelier et al.[129] argue that it is precisely this aspect of game playing that promotes transfer of training from the game to other activities, unlike other cognitive training programs.

Single blind. Especially given the importance of rigor and reproducibility in NIH-sponsored research, the use of a single blind design may raise concerns. This concern is balanced with the need to use devices FDA-approved for use with humans and the previous success of the single blind strategy in other trials[30] as well as the pilot study.

Depression vs cognition. Results of the pilot study as well as other studies show that tDCS may improve both cognition and mood. Our pilot study reflects changes in both. Including change in depression in analyses reduced the effect size of treatment on self-report of cognitive difficulties, but increased the effect size for cognitive measures. We thus will explore the extent to which change in mood affects cognition by examining it as a covariate and, if warranted, in a mediation analysis.

Multiple covariates with small sample. In analyses for the preliminary study, it was judged important to include multiple potential covariates (age, gender, race, immune status) to evaluate treatment effects, even with a small but heterogeneous sample. Given larger samples in most studies this may seem inappropriate, but we note that the in his first presentation of analysis of covariance (ANCOVA) in 1934, Fisher used four measurements on four entities (tea producing plots in Ceylon) to demonstrate the technique's utility.[130]

Future studies will examine the impact of ongoing training over a longer period and the usefulness of booster sessions. If this study suggests an impact on functional status, a future study might evaluate the impact of the intervention on biological markers of illness and actual performance of the activities of daily living.

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