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The effect of transcranial direct current stimulation combined with cognitive training on cognitive functioning in older adults with HIV: A pilot study

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Abstract

Objective—To examine combination speed of processing (SOP) cognitive remediation therapy (CRT) and transcranial direct stimulation (tDCS) as neurorehabilitation in older HIV+ adults.

Methods—Thirty-three HIV+ adults aged 50+ completed neurocognitive testing and were randomized to either active (n=17) or sham (n=16) tDCS. Both conditions received 10 1-hour sessions of SOP CRT, with either active or sham tDCS for the first 20 minutes. Participants then completed a posttest assessment.

Results—Repeated measures analysis of variance examining Time X Condition showed small-to-medium effects in the expected direction for an executive (d=0.36), and SOP measure (d=0.49), while medium-to-large effects were observed for an executive/attention (d=0.60) and oral reading measure (d=0.75). The only statistically significant interaction was the oral reading measure. Small-to-medium and medium-to-large effects (ds=0.32, 0.58) were found for two SOP measures in the opposite direction (sham group showing greater improvements).

Conclusions—Further trials of CRT and tDCS in this population are needed, including larger samples and a non-active control and tDCS only condition, as is determination of which parameters of each technique (e.g., tDCS montage, timing of tDCS, domain targeted in CRT, number of sessions) are most effective in improving cognitive outcomes, durability of training gains, and translation to everyday functioning.

Keywords

tDCS; neuromodulation; brain stimulation; HIV/AIDS; cognitive remediation therapy

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Introduction

HIV, Aging, and Neurocognition

There has been a recent increase in the prevalence of HIV among older adults due to decreases in mortality with antiretroviral therapy (ART) (Center for Disease Control and Prevention (CDC), 2016). By 2020 it is projected that 70% of those living with HIV/AIDS in the U.S. will be aged 50 and older (*Older americans: The changing face of HIV/AIDS in America*, 2013; Smith, 2005). Recent reports by the NIH Office of AIDS Research and the U.S. Senate Special Committee on Aging emphasize the significant public health priority for research in this vulnerable and growing population (High et al., 2012; *Older americans: The changing face of HIV/AIDS in America*, 2013). In particular, research on cognitive aging with HIV is needed, given that HIV and aging have additive detrimental effects on brain structure and function (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Ernst & Chang, 2004; Jernigan et al., 2005; Nir et al., 2014; Thomas, Brier, Snyder, Vaida, & Ances, 2013) (e.g., resting state functional connectivity), and resulting additive effects on neurocognitive impairment (Hardy & Vance, 2009). HIV-associated neurocognitive disorders (HAND) are observed in as many as half of HIV-infected (HIV+) adults (Heaton et al., 2010), and older adults with HIV are at a three-fold increased risk of HAND relative to younger HIV+ adults (Valcour et al., 2004). The increased neurocognitive burden among older HIV+ individuals translates to a disproportionate risk for disruptions in real-world everyday functioning (Doyle et al., 2012; Foley et al., 2013; Morgan et al., 2013; Thames et al., 2011; Vance, Fazeli, & Gakumo, 2013; Vance, Wadley, Crowe, Raper, & Ball, 2011), representing a potential public health burden and a threat to successful cognitive aging at the individual level.

Processing Speed and Cognitive Aging with HIV

The cognitive profile of HAND among older adults reflects a pattern of frontostriatal brain dysfunction, with impairments in attention, working memory, learning, recall, executive functions, and speed of information processing (SOP) (Brew, Crowe, Landay, Cysique, & Guillemin, 2009; S. P. Woods, Moore, Weber, & Grant, 2009). Declines in SOP are particularly sensitive to the effects of both HIV and aging, with an increased vulnerability of older HIV+ individuals to SOP deficits than younger and HIV-negative counterparts (Reger, Welsh, Razani, Martin, & Boone, 2002; Vance et al., 2013; Wilkie et al., 2003). SOP decrements among older HIV+ adults demonstrate a clear translation to everyday functioning, including driving (Foley et al., 2013), medication management (Ettenhofer et al., 2009), and other instrumental activities of daily living (IADLs) (Vance et al., 2013). In the context of Salthouse's Processing Speed Theory of Cognition (Salthouse, 1996), the age and HIV-related declines in SOP (at least partly) drive poorer performance in other neurocognitive domains. Several studies support the Processing Speed Theory in aging with HIV, suggesting that a single factor (i.e., generalized slowness of performing mental operations) mediates neurocognitive declines in other domains (e.g., memory, verbal fluency) (Becker & Salthouse, 1999; Becker et al., 1997; Hardy, Hinkin, Satz, & van Gorp, 1999; Hinkin et al., 2002; Lopez, Wess, Sanchez, Dew, & Becker, 1998). Given the 1) increased vulnerability to SOP deficits, 2) influence of SOP to other cognitive domains, and

3) resulting decrements in everyday functioning in the older HIV+ population, neurorehabilitation strategies for SOP are greatly needed, including both restorative (i.e., intervention) and prophylactic (i.e., prevention) strategies.

Neurorehabilitation for SOP

Cognitive Remediation Therapy (CRT)—Despite the need for restorative cognitive interventions in the older HIV+ population, very few studies exist (Weber, Blackstone, & Woods, 2013) and only one targeted SOP. Vance, Fazeli, Ross, Wadley, and Ball (2012) implemented a computerized SOP CRT, grounded in the gerontological literature (Ball et al., 2002), in middle-aged and older HIV+ adults and demonstrated an improvement in SOP and on an IADL task (Vance et al., 2012). In addition to gains in SOP, in the non-pathological aging population, this SOP CRT has shown: 1) 10 year durability (Rebok et al., 2014), 2) protection against automobile crashes (Ball, Edwards, Ross, & McGwin Jr, 2010), 3) decreased depression (Wolinsky et al., 2009), 4) better quality of life (Wolinsky et al., 2006), 5) booster sessions increase cognitive gains (Ball et al., 2002), 6) efficacy in both middle-aged and older adults (Wolinsky, Vander Weg, Howren, Jones, & Dotson, 2013), and 7) generalization to improvements in executive functioning (Wolinsky et al., 2013). Both the Vance et al. (2012) and Ball et al. (2002) studies used the same training platform (Posit Science) and dose of training (i.e., approximately 10 1-hour sessions over a 2–5 week period).

Transcranial Direct Current Stimulation (tDCS)—Non-invasive brain stimulation represents a promising approach for augmenting the effects of SOP CRT in older HIV+ adults. tDCS has reemerged over the past decade for potential therapeutic effects (Bikson, Datta, & Elwassif, 2009; Cappon, Jahanshahi, & Bisiacchi, 2016; Fox, 2011; Iyer et al., 2005; Utz, Dimova, Oppenländer, & Kerkhoff, 2010). tDCS is a safe, relatively well-tolerated, and inexpensive neuromodulation technique using low-level direct electrical current to stimulate the brain, thereby subtly altering membrane potential of neurons, making them more or less likely to fire depending on stimulation parameters (Bikson et al., 2016; A. J. Woods et al., 2016). Stimulation parameters inducing a depolarizing, excitatory response are associated with an increased rate of neuronal firing are thought to facilitate neural plasticity. Several studies have shown beneficial effects of tDCS on neurocognition in clinical (Ferrucci et al., 2008; Kang, Kim, & Paik, 2012; Szymkowicz, McLaren, Suryadevara, & Woods, 2016) (e.g., stroke, Alzheimer's disease) and non-pathological populations (Clark et al., 2012; Flöel et al., 2012) (e.g., healthy aging). However, there have been mixed results, with some studies finding negative (i.e., null) effects, detrimental effects (i.e., reductions in performance), or only temporary effects (Horvath, Forte, Carter, 2015; Ferrucci et al. 2008; Sellers et al., 2015). Evidence also shows stronger effects of CRT coupled with tDCS (Fridriksson, Richardson, Baker, & Rorden, 2011; Martin et al., 2013; Park, Seo, Kim, & Ko, 2014), however again, findings are mixed (e.g., Nilsson, Lebedev, Rydström, Lövdén, 2017). Further, many studies only examine the effects of tDCS on cognitive function during tDCS (i.e., "online") or immediately following tDCS (e.g., the same day), limiting the ability to ascertain durability and clinically meaningful changes.

Combining SOP CRT and tDCS in Adults with HIV—Studies suggest that both SOP CRT and tDCS may have similar mechanisms at the neural level. Regarding SOP CRT, there is evidence that this intervention has effects on resting state functional connectivity (Takeuchi & Kawashima, 2012) as well as event-related potentials (O'Brien et al., 2013), suggesting facilitation of plasticity. Studies also suggest that tDCS causes changes in resting state functional connectivity of underlying frontostriatal circuitry (Keeser et al., 2011; Meinzer et al., 2012; Polanía, Paulus, & Nitsche, 2012). Thus, tDCS may be a particularly valuable adjunct to SOP CRT in older HIV+ adults, given the frontostriatal pattern of deficits and independent effects of age and HIV on resting state functional connectivity in this population. In other words, tDCS may heighten or modulate the effects of SOP CRT alone. Only one study has examined the effect of tDCS on cognitive function in the HIV+ population. Ownby and Acevedo (2016) examined tDCS over the DLPFC (F3) (cathode over the right supraorbital area [Fp2]) combined with six 20-minute computerized cognitive training sessions targeting psychomotor speed (i.e., a racing game) in 11 (tDCS n=6; sham n=5) older adults (age range 46–62, mean = 51.5) with HAND, and while there was no significant effect of the combined intervention the results favored tDCS for 12 of the 13 cognitive outcomes.

Purpose and Specific Aims

With the increased longevity of HIV+ individuals, and the combined effect of HIV and aging on cognitive and everyday functioning, there remains a significant need for first-line intervention approaches to reduce the burden of HAND. Non-pharmacological approaches are particularly needed, given the high pill burden and resulting adverse side effects in the HIV population. The goal of this pilot study was to explore the feasibility and acceptability of tDCS combined with SOP CRT in older HIV+ adults (i.e., ≥ 50 years old) in a pre-post design randomized controlled trial and to evaluate whether tDCS would augment the effects of SOP CRT on cognitive outcomes after approximately one week. Given the small sample size in this pilot study, analyses focus primarily on effect size estimation rather than parametric hypothesis testing. The first hypothesis was that the SOP CRT + tDCS condition would show larger gains (i.e., effect sizes) than the SOP CRT + sham tDCS condition on the primary cognitive domain (i.e., SOP measures). Second it was hypothesized that the tDCS condition would also demonstrate generalization to secondary neurocognitive domains (particularly executive/attention measures given the montage used) compared to the sham tDCS condition (i.e., larger effect sizes for non SOP measures). While many studies combining tDCS and CRT to improve cognitive outcomes have used variations of prefrontal anode electrode placement (e.g., bilateral [i.e., right and left] dorsolateral prefrontal cortex (DLPFC) with anodes on F3 and F4 and cathodes on the non-dominant arm [study used two stimulators] (Park et al., 2014); left DLPFC with anode over F3 and cathode on right deltoid muscle (Martin et al., 2013)), we chose to adopt the broader montage used by Clark and colleagues (2012) with frontal anode electrode placement with shoulder return electrode (cathode) (i.e., anode over F10 [right inferior frontal cortex] and cathode over contralateral upper arm). Given the large effect sizes yielded in that study and given that this was a pilot study with the goal of detecting a "signal" of whether combined tDCS and CRT is effective in this population this broad stimulation montage was preferred.

Method

Participants and Procedure

This study received Institutional Review Board approval from the University of Alabama at Birmingham. Older (aged 50 and older) HIV+ participants were recruited with flyers at a university HIV/AIDS Clinic in Birmingham, Alabama. Interested participants called our study center and were administered a telephone screen to determine eligibility. The eligibility requirements included that participants self-reported to: 1) be HIV+ and a patient at the university clinic (for later extraction of clinic data), 2) be 50 years or older, 3) not be homeless, 4) be able to speak and understand English, 5) not be mentally impaired (i.e., no Alzheimer's, dementia, mental retardation), 6) not be legally blind or deaf, 7) not currently undergoing chemotherapy or radiation therapy, 8) not have history of brain trauma with loss of consciousness greater than 30 minutes, 9) not have neurological problems (i.e., schizophrenia, migraines, bipolar disorder, history of stroke, epilepsy, or seizures), 10) not have untreated hypertension, 11) be right handed (in order to reduce the potential confounding effect of lateralization of brain functions on cognitive performance and tDCS effects), 12) not have intracranial metal plates or other such implants, or biomedical device (e.g., pacemaker). For eligibility requirements 1, 2, 5, and 9, we were able to confirm this self-report data with clinic data. As some medications may impact the effect of tDCS, we gathered a medication list from each subject at baseline and coded those that were sodium channel blockers, calcium channel blockers, and selective serotonin reuptake inhibitors. There was no significant difference between conditions on sodium (tDCS n=1, sham n=0, p=0.32) or calcium channel blocker (tDCS n=4, sham n=1, p=0.17) use, while there was a difference on selective serotonin reuptake inhibitor use (tDCS n=5, sham n=0, p=0.02). However, we examined these variables as potential covariates on subsequent models and they did not change the pattern of results.

Eligible participants were scheduled for their baseline visit, which consisted of providing written informed consent, cognitive testing and questionnaires (see Measures below). After baseline testing participants were randomized using a stratified randomization algorithm that matched the tDCS and sham groups on age, gender, race, education level, and baseline SOP (i.e., UFOV Risk Category—explained further in Measures below). Forty-two subjects were randomized, however 3 subjects were lost to follow-up and 6 subjects were deemed ineligible (1 with history of both stroke and schizophrenia, 1 with history of stroke, 2 with schizophrenia diagnosis, and 2 with fistula for dialysis on electrode return site—upper left arm). Note that these 9 subjects were equally distributed between treatment arms (n=4 in tDCS and n=5 in sham; $\chi^2(1, N=42) = 0.14$, $p = 0.71$). The final sample included 33 participants (17 in tDCS and 16 in sham; see Figure 1 for a study flow chart). All but one participant were currently taking ART (who was in the tDCS condition). See Table 1 for participant characteristics. This study was registered in ClinicalTrials.gov (NCT02391311).

After randomization participants completed the intervention component in-lab under the supervision of trained research assistants. In each condition, participants completed 10 1-hour computerized CRT sessions using Posit Science (BrainHQ.com) over the course of approximately 2 weeks, in which they alternated between two games targeting to improve

SOP (i.e., Double Decision and Target Tracker). Both conditions were also applied tDCS during the first 20 minutes of each 1-hour session, using the F10 (anode) and contralateral upper arm (cathode) montage using the Soterix conventional 1X1 device, using a 5×7 cm saline soaked sponge (4mL per side). The 10–20 international system for electrode placement was used. Devices in both conditions were set to 2.0mA; however in the sham condition, the device ramped up to 2.0mA for 30 seconds and then immediately ramped down to 0.00mA, and after 20 minutes the device shut off. This shamming procedure is typical of that used in other studies (e.g., Nilsson et al., 2017; Ownby & Acevedo, 2016). For the tDCS condition, the device ramped up to 2.0mA and stayed at that level for 20 minutes and then shut off. In both conditions the tDCS application (cranial measurement and electrode placement) occurred prior to the start of CRT, then the 20 minutes of tDCS began at the start of the 1 hour of CRT and participants continued to engage in the CRT after the 20 minutes of tDCS ended until the end of the 1-hour session. Participants were monitored by a research assistant for the entirety of each session. After the 10 sessions were complete, participants were scheduled for an immediate posttest identical to their baseline assessment as close as possible (ideally within 1 week) to their last CRT session (sample Median (IQR) days = 2 (1 – 4)). Overall we attempted to have subjects begin the intervention within one week of the baseline, and on average the duration of training was 21 days for the sample, and on average the posttest occurred 2 days after the last training session. Thus the typical timeline of the study from start to finish was 4–5 weeks. Note that the tDCS administrator was not blinded to condition, while the posttest assessor was blinded (and the baseline assessor was blinded by design as randomization occurred after baseline testing). Participants were paid $50 each for the baseline and posttest assessments, and $10 per each 1-hour session ($100), for a total compensation of $200.

Measures

Participants completed a demographic and health questionnaire that queried them on basic demographics such as their age, race/ethnicity, income, as well as presence of several comorbidities (e.g., diabetes, hypertension, heart attack). Participants were queried on their self-reported HIV characteristics, including length of diagnosis and current CD4 count and viral load. This information was confirmed with clinic records. Depressive symptoms were measured using the Beck Inventory-II (BDI-II (Beck, Steer, & Brown, 1996)). A cognitive battery was administered that covered most major cognitive domains, and included a greater number of SOP measures relative to other cognitive domains given the nature of the intervention. These measures included: the Useful Field of View Test (UFOV (Ball, Edwards, & Ross, 2007)) (computerized visual attention and SOP measure with three subtests (each subtest score reflects display duration of the stimuli in milliseconds in which 75% accuracy was achieved): subtest 1 (SOP), subtest 2 (divided attention), subtest 3 (selective attention), a total score (sum of subtests 1–3), and a Risk Category ranging from 1-Very Low Risk to 5-High Risk which is a function of the 3 subtests scores with scores of 2 or higher indicative of at least some SOP decrement; for all UFOV scores higher scores reflect worse functioning); the Letter and Pattern Comparison Task (Salthouse, 1991) (SOP) (scores reflect number of correct responses and higher scores indicate better functioning); Digit Symbol Substitution Task (Wechsler, 1997) (SOP) (scores reflect number of correct responses and higher scores indicate better functioning); and the NIH Toolbox Cognition

Battery (NIHTB-CB (Gershon et al., 2013)). The NIHTB-CB is a brief (~30 minutes) and comprehensive computerized cognitive assessment administered on a PC. The tests include measures of executive function (Flanker, Dimensional Card Change Sorting), attention (Flanker), episodic memory (Picture Sequence Memory Test), language (Picture Vocabulary Test, Oral Reading Recognition Test), processing speed (Pattern Comparison Test), and working memory (List Sorting Test). NIHTB-CB yields raw, computed, and uncorrected scaled scores (details in NIHTB-CB manual; nihtoolbox.org). For the current study we utilized scores recommended by NIHTB-CB administrators to examine raw change (which may be obscured with normed scores) and take into account computer adaptive testing on some of the measures: computed scores for Flanker, Dimensional Card Change Sorting, Picture Sequence Memory Test, Picture Vocabulary Test, and Oral Reading Recognition Test; and raw scores (i.e., total correct) for the List Sorting Test and Pattern Comparison Test. We also used normative (corrected for age, education, gender, and ethnicity) total T-scores (average across all measures) to characterize global impairment in the sample for descriptive purposes (i.e., T < 40 = impaired). For all tests, higher scores indicate better functioning.

Finally, questionnaires were administered pertaining to the intervention component. Specifically, the tDCS Sensation Questionnaire (Clark et al., 2012) was administered during each of the 10 training sessions, in which participants were asked to rate their sensation at 5 and 10 minutes into the tDCS protocol, using the following scale: “0) no sensation, 1) cold, 2) some tingling, 3) warm, 4) lots of tingling/some itching, 5) very warm, 6) lots of itching, 7) burning (like a sunburn), 8) burning (like scalding water), 9) ‘hurts a lot’”. Participants then completed the Exit/Training Survey (Vance et al., 2012) at the posttest assessment in which they were asked questions regarding their experience in the intervention, including how uncomfortable they felt the device was (1 = not at all to 5 = extremely) and whether or not they believed they were in the “sham” or “real” group.

Statistical Analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., 2016), except the Holm-Bonferroni procedure which was conducted in Microsoft Excel. First the tDCS and sham groups were compared on demographic, health, and HIV disease variables using either t-test or chi-square when appropriate. In order to examine the effect of treatment (i.e., the Condition X Time interaction), we conducted a series of repeated measures analysis of variance (ANOVAs) for all cognitive outcome variables (i.e., UFOV subtests 1–3 scores, UFOV total score, UFOV Risk Category, Letter and Patter Comparison total correct, Digit Symbol Substitution total correct, NIHTB-CB [Flanker, Picture Sequence Memory, List Sorting, Pattern Comparison, Dimensional Card Change Sorting, Oral Reading Recognition, Picture Vocabulary]). Given the small sample size in this pilot study, we were most interested in exploring effect sizes. Then several exploratory post-hoc analyses were conducted. First we examined separate paired-samples t-tests within the tDCS and sham groups for all cognitive outcome variables. Paired samples t-tests were also conducted for the overall sample to examine the overall cognitive training effect from pre to post. For all t-tests we employed the Holm-Bonferroni multiple comparison correction procedure (Holm, 1979), which is advantageous over the

Bonferroni method for alpha inflation as it is conservative and more powerful relative to the Bonferroni method (Aickin & Gensler, 1996; Seaman, Levin, & Serlin, 1991).

Results

Demographic and Trial Characteristics

Note that no adverse events occurred in the current study. Overall, 33 subjects were included in analyses (n=17 tDCS and n=16 sham). Groups were well matched on demographic, health, and HIV variables, with the exception of a difference for lower current CD4 counts in the sham group that approached significance ($p<0.10$). The groups also did not differ significantly on most parameters of the intervention (e.g., overall duration of training). There was a significant difference in average reported sensation at 5 minutes into the stimulation across the 10 sessions and a difference that approached significance ($p<0.10$) in the reported sensation at 10 minutes such that the tDCS group reported greater sensation than the sham group at both time points (Means and SDs: 5 minutes: tDCS=2.97 (1.08), sham=2.26 (0.66), $p=0.03$; 10 minutes: tDCS=2.86 (0.86), sham=2.34 (0.65), $p=0.06$). However, there was no significant difference between groups at posttest on which condition they believed they received ($p=0.21$; tDCS: 12% sham, 41% real, 47% don't know; sham: 12% sham, 69% real, 19% don't know) and how uncomfortable they felt the device was ($p=0.23$; tDCS=2.24 (1.20), sham=1.75 (1.06)). See Table 1 for full sample descriptives. Note that all cognitive measures did not differ between groups at baseline, with the exception of a difference that approached significance ($p<0.10$) between tDCS and sham conditions on baseline Flanker ($p=0.05$).

tDCS Effects

Table 2 compares baseline and posttest means and mean differences by condition and *p*-values for the interaction of Condition X Time yielded on the repeated measures ANOVAs. We also conducted exploratory effect sizes analyses on this interaction due to the lack of power. Small to medium effects in the expected direction (i.e., such that the tDCS group had a larger effect) were found for Dimensional Card Change Sorting, and Letter and Pattern Comparison, while a medium to large effect was found for Flanker and Oral Reading Recognition. Little to no effect was found for Picture Sequence Memory, Picture Vocabulary, List Sorting, UFOV subtest 2 and 3, UFOV total, UFOV Risk Category, and Digit Symbol Substitution. Note that for Oral Reading Recognition the medium to large effect size was driven largely by the sham group's performance declining from baseline to posttest. For UFOV subtest 1 and Pattern Comparison (i.e., NIHTB-CB), there were a small to medium and medium to large effects (respectively) in the opposite direction such that there was a stronger effect in the sham group. The interaction of Condition X Time was only statistically significantly different for Oral Reading Recognition, which again was driven by the reduction in the sham group. In order to examine whether any outliers may have been driving this Oral Reading Recognition reduction in the sham group, we examined Z scores for the baseline to posttest difference scores, and no influential outliers were found (i.e., no individual difference scores were greater than or equal to 3 standard deviations above or below the mean).

Exploratory Posthoc Analyses

T-tests within each condition showed that for the tDCS group, the following measures improved significantly at $p<0.05$ (see Table 3) from pre to post after correction using Holm's procedure: UFOV subtest 3, UFOV total, and Digit Symbol Substitution. For the sham group only UFOV subtest 3 improved significantly at $p<0.05$ from pre to post after correction using Holm's procedure. When collapsing both the tDCS and sham groups to examine the overall effect of CRT, we found that after correction using Holm's procedure there was a significant ($p<0.05$, see Table 3) improvement in performance from pre to post on the following measures: UFOV subtest 3, UFOV total, Digit Symbol Substitution, Letter and Pattern Comparison, and Picture Sequence Memory.

Discussion

The goal of this study was to determine whether combination tDCS and CRT would show greater cognitive benefits than CRT and sham tDCS in a sample of older adults with HIV. While results did not show an overall significant effect of this combined intervention approach, examination of effect sizes showed that there were medium to large effects and small to medium effects in the expected direction for executive and attention measures (Flanker and Dimensional Card Change Sorting) and one SOP measure (Letter and Pattern Comparison). This finding is consistent with the fact that we used a frontal anode tDCS electrode montage in the current study. Thus, it was not surprising that we failed to find improvements in other cognitive domains, such as memory. However, the only statistically significant Condition X Time interaction was on an oral reading recognition measure, which yielded a medium to large effect. There were also small to medium and medium to large effects in the unexpected direction for two SOP tests (UFOV subtest 1 and Pattern Comparison NIHTB-CB measure) such that the sham group showed the greatest improvement. We speculate that this anomalous finding was simply a random outcome, as results from our study and the literature largely favor tDCS for cognitive outcomes. Again, while the repeated measures ANOVAs did not show an overall significant interaction of Condition X Time, these effect sizes suggest greater SOP improvements in the tDCS condition as well as translation to other cognitive domains. While lack of significant findings may be due to power, another explanation may be that the tDCS effects were temporary and not durable to our posttest assessment. While our results are generally consistent with the Ownby and Acevedo (2016) study that also examined combined cognitive training and tDCS in adults with HIV, in that we found some promising effect sizes favoring tDCS, there were some methodological differences that may have explained why that study found larger effect sizes across a greater number of measures. First, their study did not use a shoulder return electrode (cathode) as we did, and as such applied a more focal stimulation which may have resulted in a greater effect. Further, their cognitive training was a racing game, and not necessarily a cognitive remediation therapy program as we used, thus our effect sizes may have been obscured due to our sham group receiving an active intervention.

Exploratory posthoc paired samples t-tests within each of the treatment arms showed that after adjustment for multiple comparison, the tDCS condition significantly improved on three SOP/visual attention outcome measures, while the sham group only improved on one.

When collapsing both conditions and examining pre to post changes, significant improvements were found on five measures. While this latter finding may suggest an overall effect of CRT, unfortunately, the lack of a non-active (i.e., no-contact) control group or a tDCS only condition prevented further investigation to determine differences between our two treatment arms and those with no CRT or tDCS or tDCS only. Thus results of those analyses should be interpreted with caution. Further, the lack of a true control group limited the ability to look at true effect sizes—as the current study examined effect size differences between two groups who received interventions (i.e., we expected improvements in both conditions as they both received CRT).

Possible explanation into the unexpected finding regarding the oral reading task may have largely been driven by the reduced performance by the sham group at posttest. A follow-up analysis showed that this effect was not driven by any influential outlier(s). Yet, the improvements in the tDCS group may have been an indication of true tDCS effects. While not the expected domain that would be the most amenable to change, there are several studies in the literature showing significant effects of tDCS on reading abilities. For example, Turkeltaub et al. (2012) found in a sample of below average female readers (mean age 26.7) that tDCS of the left posterior temporal cortex resulted in improvements in word reading efficiency.

There are several limitations of the current study that may have contributed to the findings. First, the sample size was small, yet it is consistent with other tDCS training studies in the literature and we believe it was reasonable for a preliminary pilot study. Second, as mentioned, the current study design lacked a no-control/non-active group that experienced neither CRT nor tDCS, as well as a tDCS only condition, and triple-blinding. Specifically, while our study was technically double-blind, in that the assessors and subjects were blind to condition, the PI (who was also the tDCS administrator and statistical analyst) was not, which could have introduced bias to the results. While we do acknowledge the possibility of practice effects in the short time frame of our study, we believe the fact that both the tDCS and sham conditions had the same exposure and timing accounted for this. Further, while we attempted to enroll a representative sample of HIV-positive older adults, the sample was overwhelmingly African American male, which may not generalize to the national and global HIV demographic, but is reflective of the current HIV demographic of Birmingham, Alabama (STD Prevention and Control, 2015). Related, HIV-positive older adults are a very heterogeneous population, and while we attempted to gather data on potential confounding variables to treatment effect (e.g., comorbidities, HIV characteristics), there may have been other unexamined variables that may have influenced the efficacy of tDCS (such as skull thickness, CSF space/atrophy, structural brain differences, etc.). Another hypothesis for the results may have been the tDCS montage chosen (i.e., F10 anode and contralateral upper arm cathode). While the goal of this pilot study was to administer a relatively broad range of stimulation to determine whether there would be a signal of an effect, it may be that a more focal montage using high definition tDCS may be needed for stronger and more specific effects (e.g., F3/F4). Another limitation is that our cognitive battery, while comprehensive, did not include all cognitive domains (e.g., visuospatial functioning). Lastly, while treatment arms were balanced on SOP performance at baseline, the current study did not require participants have SOP deficits per se (or cognitive impairment in general), thus ceiling

effects may have resulted in less room for improvement. While we did examine the effect of treatment among those with the poorest baseline SOP as well as those with baseline cognitive impairment, no consistent patterns emerged, which was likely due to the fact that there were very few participants in these analyses causing reduced power to draw conclusions. Following up the 33 subjects in this study in the future will allow examination of the potential prophylactic (i.e., preventative) effect of this intervention approach in those who do not necessarily have frank impairment at baseline. In other words, did those in the tDCS condition maintain better cognitive functioning over time as compared to the sham condition?

In summary, the results of this pilot study suggest that it may be too early to evaluate any meaningful effect or to recommend combination tDCS and CRT clinically for this population. Thus, results support the need for additional randomized controlled trials of this combined technique in larger samples including a no-contact or non-active (e.g., internet control) control group as well as a tDCS only condition for more accurate approximation of effect sizes. Future studies will need to determine what parameters of each technique (e.g., montage and amperage of tDCS, timing of tDCS, domain targeted in CRT, number of sessions) are most effective in improving cognitive outcomes. Furthermore, future work is needed to examine the long term durability of such training gains and whether these gains have meaningful translation to everyday functioning outcomes, such as IADLs. For example, a study in healthy older adults showed that combination tDCS and working memory training resulted in far transfer gains in everyday function outcomes one month later (Stephens & Berryhill, 2016). If future studies show promising results, the next step will be to determine the most practical, safe, and ethical avenue and venue for treating patients with this approach. Recent reports have begun to examine the feasibility and efficacy of at-home employment of tDCS protocols (Andre, et al., 2016; Charvet et al., 2017).

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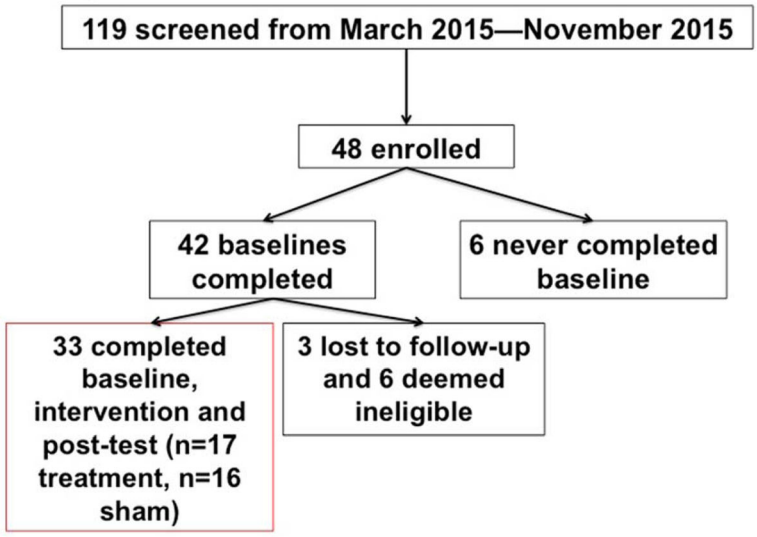

Figure 1.
Study Flow Chart

Table 1

Sample Demographic and Health Characteristics

	tDCS Condition (n=17)		Sham Condition (n=16)		
Variable	**M(SD) or %**	**Range**	**M(SD) or %**	**Range**	**p-value**
Age	56.00 (3.24)	52 – 63	55.63 (5.38)	51 – 71	0.81
Age Categories					0.17
50–55	53%	75%			
56–60	35%	6%			
61–65	12%	13%			
>65 *	0%	6%			
Gender (% Male)	65%	--	69%	--	0.81
Race (% AA)	82%	--	88%	--	0.68
Income		--			
0–10K	41%		44%	--	0.86
10–20K	47%		50%		
20–30K	12%		6%		
Education	12.53 (1.77)	9 – 16	12.63 (2.00)	10 – 18	0.89
HIV Length (Years)	16.18 (7.53)	2 – 29	14.38 (8.28)	5 – 34	0.52
Current CD4 Self Report[a]	832.93(358.67)	347 – 1800	624.33 (225.54)	169 – 900	0.09
Most Recent Prior Lab CD4	758.00 (316.94)	241 – 1353	578.94 (271.69)	165 – 1122	0.09
Most Recent Lab CD4 Days Prior	120.00 (92.27)	2 – 289	114.31 (112.35)	6 – 357	0.87
Nadir CD4 Lab	184.29 (235.18)	2 – 781	174.94 (199.18)	2 – 550	0.90
Most Recent Prior Lab Viral Load (% UD) **	94%		94%		0.96
Most Recent Lab Viral Load Days Prior	59.71 (40.88)	2 – 124	79.31 (77.91)	6 – 283	0.37

	tDCS Condition (n=17)		Sham Condition (n=16)		
Variable	**M(SD) or %**	**Range**	**M(SD) or %**	**Range**	**p-value**
Hypertension (% Yes)	53%	--	69%	--	0.35
Diabetes (% Yes)	12%	--	6%	--	0.58
Dyslipidemia (% Yes)	47%	--	25%	--	0.19
Beck Depression Inventory-II	11.50 (12.03)	0 – 34	9.56 (6.60)	3 – 27	0.58
Total Days Trained	9.64 (1.22)	5 – 10	9.81 (0.54)	8 – 10	0.62
Training Duration (days)	21.41 (4.60)	14 – 30	22.44 (7.33)	13 – 36	0.63
Total Minutes Trained	581.77 (57.91)	360 – 600	590.38 (30.05)	480 – 600	0.60
Days Post Test Occurred After Training	2.24 (1.60)	0 – 5	4.25 (4.06)	1 – 14	0.07
Baseline UFOV Risk Category					
1-Very Low Risk	53%		56%		0.99
2-Low Risk	18%		19%		
3-Low to Moderate Risk	12%		6%		
4-Moderate to High Risk	12%		13%		
5-High Risk	6%		6%		
Baseline Cognitive Impairment (%)	59%		53%		0.75

Notes.

[a]=4 in sham and 2 in tDCS condition missing data;

[*]Only 1 subject over 65 in sham condition;

[**]100% concordance with current self-report viral load. All but one subject was on ART, who was in the tDCS condition.

UFOV = Useful Field of View test.

Table 2

Baseline and Posttest Means and Mean Differences by Condition and Effect Sizes and p-values for Interaction of Condition by Time

	tDCS Condition (n=17) M(SD)			Sham Condition (n=16) M(SD)					
	Baseline	**Posttest**	**Difference**	**Baseline**	**Posttest**	**Difference**	**p-value**	**Cohens D**	**η^2**
Picture Vocabulary Computed (Verbal)	1576.00 (294.70)	1594.88 (305.90)	18.88 (149.39)	1505.88 (194.96)	1516.00 (213.37)	10.13 (159.77)	0.87	0.06	0.001
Flanker Computed (Executive/Attention)	7.05 (1.19)	7.52 (0.97)	0.47 (0.66)	7.81 (0.87)	7.92 (0.92)	0.11 (0.56)	0.10	0.60	0.083
Picture Sequence Memory Computed (Memory)	408.91 (55.55)	439.17 (73.58)	30.26 (61.94)	376.83 (56.41)	413.46 (65.93)	37.05 (64.27)	0.76	−0.11	−0.003
List Sorting Raw (Working Memory)	13.47 (3.04)	14.06 (2.49)	0.59 (2.74)	14.31 (4.61)	14.69 (3.74)	0.38 (2.60)	0.82	0.09	0.002
Pattern Comparison Raw (SOP)	42.18 (10.01)	43.47 (7.95)	1.29 (7.16)	44.56 (11.29)	49.88 (13.10)	5.31 (7.12)	0.12	−0.58	−0.078
Oral Reading Recognition Computed (Verbal)	1780.59 (403.02)	1806.29 (455.75)	25.71 (130.88)	1880.25 (310.15)	1818.13 (325.65)	−62.13 (107.80)	0.04	0.75	0.124
Dimensional Card Change Sorting Computed (Executive)	5.59 (1.48)	6.26 (0.89)	0.67 (0.99)	6.22 (1.37)	6.52 (0.93)	0.30 (1.11)	0.32	0.36	0.032
UFOV 1	42.99 (57.94)	42.16 (52.84)	−0.82 (32.86)	35.22 (41.34)	23.34 (14.36)	−11.88 (38.75)	0.38	−0.32	−0.025
UFOV 2	131.68 (132.57)	77.32 (115.91)	−54.35 (81.79)	124.64 (131.24)	89.87 (101.03)	−34.78 (138.45)	0.62	0.18	0.008
UFOV 3	253.01 (115.76)	176.34 (122.27)	−76.67 (55.53)	267.54 (107.62)	180.86 (121.72)	−86.68 (80.47)	0.68	−0.16	−0.006
UFOV Risk	2.00 (1.32)	1.71 (1.40)	−0.29 (0.68)	1.94 (1.34)	1.50 (0.73)	−0.44 (0.96)	0.62	−0.18	−0.008
UFOV Total	427.68 (278.58)	295.83 (281.58)	−131.85 (140.06)	427.40 (221.59)	294.07 (218.76)	−133.33 (175.00)	0.98	0.00	0.000
Letter and Pattern Comparison (SOP)	67.06 (16.41)	73.12 (17.02)	6.06 (8.50)	70.06 (13.43)	72.69 (13.63)	2.63 (5.46)	0.18	0.49	0.057
Digit Symbol Substitution (SOP)	39.00 (11.88)	43.06 (13.12)	4.06 (4.62)	42.19 (13.93)	46.31 (12.28)	4.13 (5.43)	0.97	0.00	0.000

Note. SOP = Speed of Processing; UFOV = Useful Field of View test.

Table 3

p-values from paired samples t-tests for cognitive training effects within condition and with conditions combined

	p-value from pre to post tDCS	p-value from pre to post sham	p-value from pre to post conditions combined
Picture Vocabulary Computed (Verbal)	0.61	0.80	0.58
Flanker Computed (Executive/Attention)	0.0095	0.44	0.01
Picture Sequence Memory Computed (Memory)	0.0611	0.0424	**0.0047**
List Sorting Raw (Working Memory)	0.39	0.57	0.30
Pattern Comparison Raw (SOP)	0.47	0.0093	0.0159
Oral Reading Recognition Computed (Verbal)	0.43	0.0359	0.45
Dimensional Card Change Sorting Computed (Executive)	0.0139	0.30	0.0123
UFOV 1 (SOP)	0.92	0.24	0.33
UFOV 2 (SOP—divided attention)	0.0145	0.33	0.0274
UFOV 3 (SOP—selective attention)	**<0.0001**	**0.0006**	**<0.0001**
UFOV Risk (SOP)	0.0962	0.0895	0.0161
UFOV Total (SOP)	**0.0013**	0.0081	**<0.0001**
Letter and Pattern Comparison (SOP)	0.0096	0.0738	**0.0015**
Digit Symbol Substitution (SOP)	**0.0023**	0.0083	**<0.0001**

Note. Significant p-values ($p<0.05$) that remained after correcting for multiple comparisons using the Holm's correction procedure are BOLDED. Oral reading significant p-value is due to a decline in control group. SOP = Speed of Processing; UFOV = Useful Field of View test.