References

1. Opitz A, Paulus W, Will S, Antunes A, Thielscher A. Determinants of the electric field during transcranial direct current stimulation. NeuroImage. 2015;109:140-50.
2. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011;106(3):1125-65.
3. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature reviews. 2007;8(9):700-11.
4. Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. NeuroImage. 2014;89:216-25.
5. Miranda PC, Mekonnen A, Salvador R, Ruffini G. The electric field in the cortex during transcranial current stimulation. NeuroImage. 2013;70:48-58.

PROCEEDINGS #4. AUGMENTING SAFETY LEARNING AND MEMORY WITH TRANSCRANIAL DIRECT CURRENT STIMULATION: EFFECTS OF STIMULATION TIMING ON EXTINCTION AND RECALL

Mascha van 't Wout*[1,2], Madhavi K. Reddy [1,2], Noah S. Philip [1,2], Benjamin D. Greenberg [1,2]. [1] *Department of Psychiatry and Human Behavior, Brown University, United States;* [2] *Providence VA Medical Center, United States*

1. Abstract and Introduction

Exposure-based therapy for anxiety and stress disorders such as post-traumatic stress disorder (PTSD) parallels extinction of conditioned fear [1]. Successful extinction – the generation of a novel safety memory that competes with the original fear memory – has been associated with top-down ventromedial prefrontal cortex (vmPFC) modulation [2]. Abnormalities in fear extinction and recall of extinction are core components of PTSD [1].
Facilitating endogenous vmPFC activity using transcranial direct current stimulation (tDCS) to augment extinction learning and/or the consolidation of labile safety memories paves the way for the application of tDCS during exposure-based treatments for PTSD and anxiety disorders.
In two different studies we explored whether 1) tDCS during extinction training improves subsequent extinction and extinction recall in healthy volunteers, and 2) tDCS during extinction learning versus during consolidation of extinction learning may improve extinction recall in Veterans with warzone-related PTSD.

2. Methods

Participants in both experiments completed a 2-day Pavlovian fear conditioning paradigm [3] and received one 10-minute session of 2 mA anodal tDCS over AF3, intended to target vmPFC. In Experiment 1: 26 healthy participants received tDCS during extinction of a first conditioned stimulus (CS+), and 18 healthy participants received tDCS during extinction of a second CS+. In Experiment 2: 14 Veterans with PTSD received tDCS starting simultaneously with extinction learning onset of two CS+, and 14 Veterans with PTSD received tDCS during extinction consolidation, immediately after extinction. Normalized skin conductance reactivity (SCR) was the primary outcome measure in both experiments.

3. Results

Experiment 1: Results showed a significant interaction between timing of tDCS during extinction blocks and changes in SCR over late extinction trials (p=0.03), see Fig. 1. These data indicate that tDCS was associated with accelerated late extinction learning of a second conditioned stimulus after tDCS was combined with extinction learning of a previous conditioned stimulus.

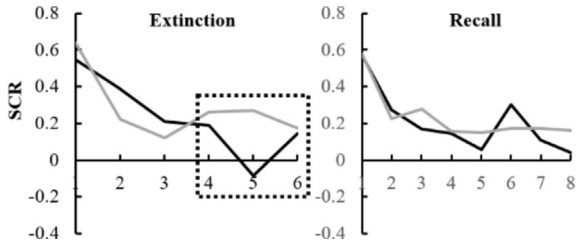

Fig. 1. SCR for tDCS during a first CS+ (black) and tDCS during a second CS+ (grey) for extinction and recall trials.

Experiment 2: Results revealed that Veterans who received tDCS during extinction consolidation showed borderline significant lower SCR (p=0.08, Cohen's d'= 0.38) to previously extinguished stimuli during early recall compared to Veterans who received tDCS during extinction training, see Fig. 2.

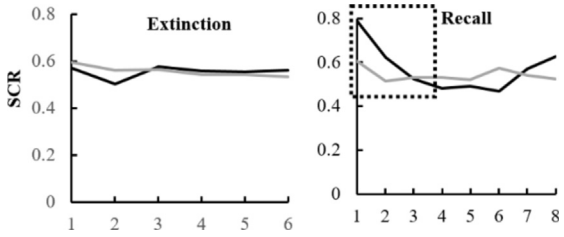

Fig. 2. SCR for tDCS during extinction of CS+ (grey) and during extinction consolidation of CS+ (black) for extinction and recall trials separately.

4. Discussion and Conclusion

The results of these two studies provide initial data that tDCS may influence extinction learning and memory processes in healthy volunteers as well as Veterans with PTSD. Additionally, tDCS appears to have a time-dependent effect in relation to extinction and recall. Namely, tDCS during initial extinction learning may influence subsequent extinction, but tDCS during extinction consolidation, i.e. after extinction learning, may enhance memory for extinction. This is relevant for designing clinical tDCS applications aimed to reduce anxiety and stress-based symptomatology.

References

[1] VanElzakker MB, Dahlgren MK, Davis FC, Dubois S, Shin LM. From Pavlov to PTSD: The extinction of conditioned fear in rodents, humans, and anxiety disorders. Neurobiol Learn Mem 2014;113:3-18
[2] Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 2007;62:446-54
[3] Milad MR, Orr SP, Pitman RK, Rauch SL. Context modulation of memory for fear extinction in humans. Psychophysiology 2005;42:456-64.

PROCEEDINGS #5. A PILOT STUDY OF COGNITIVE TRAINING WITH OR WITHOUT TDCS FOR COGNITIVE DEFICITS IN OLDER PERSONS WITH HIV

Raymond L. Ownby*[1], Janny Rivera [1], Erick Mejia [1], Amarilis Acevedo [2]. [1] *Department of Psychiatry and Behavioral Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA;* [2] *College of Psychology, Nova Southeastern University, Fort Lauderdale, FL, USA*

1. Abstract

Background: HIV infection is associated with cognitive impairments even when otherwise effectively treated. This study explored the usefulness of cognitive training with and without transcranial direct current stimulation (tDCS) in older persons with HIV.

Method: Eleven individuals with HIV-related mild neurocognitive disorder were randomly assigned to receive computer-based cognitive training with or without anodal tDCS at 1.5 mA X 20 minutes to the left dorsolateral prefrontal cortex. Those not receiving active tDCS received sham treatment. Participants completed a battery of cognitive tests and self-report measures before and after training.
Results: Cognitive test data suggest that persons receiving tDCS improved on measures of learning and working memory to a greater extent that those who did not. Those receiving tDCS reported improved mood and fewer cognitive problems after training. Participants stated that they enjoyed training.
Conclusion: Cognitive training with tDCS may be useful in addressing HIV-related cognitive dysfunction.

2. Introduction

In spite of advances in treatment that make it a manageable chronic condition, HIV infection is associated with the development of cognitive deficits [1]. These deficits in cognition are associated with problems in self-care skills and reduced quality of life [2]. Further, these problems may combine with age-related changes in cognitive function as individuals with HIV age [3].
Computer-delivered cognitive training and transcranial direct current stimulation (tDCS) have both shown promise in enhancing cognition [4, 5]. While training with programs specifically developed to target cognitive deficits in older persons has shown promise in persons with HIV infection, the long-term viability of this approach is unclear given the limited availability of the software and its low level of inherent interest. Others have suggested that widely available computer games may be effective in improving cognition in older persons [6]. Popular computer games have high levels of inherent interest and thus may be more likely to engage users.
No readily identifiable study has investigated the effectiveness of computer games to address cognition in persons with HIV, nor has any study investigated the effects of tDCS combined with cognitive training in HIV. The purpose of this study was thus to investigate the feasibility and potential effectiveness of cognitive training with and without tDCS in persons with HIV-related cognitive deficits.

3. Methods

We recruited 14 individuals meeting criteria for HIV-related mild neurocognitive disorder (report of cognitive difficulties and below average performance on cognitive testing in two domains). Individuals were excluded if they were left handed or were taking medications that might affect tDCS, such as psychotropics [7]. After eligibility determination, participants completed a battery of neuropsychological measures and self-reports of cognitive function and mood. They then completed six 20-minute cognitive training sessions over two weeks after random assignment to treatment condition, active tDCS (1.5 mA X 20 minutes over the left dorsolateral prefrontal cortex) or sham (1.5 mA ramping up for 30s and then discontinued). Training consisted of a car racing game that emphasized attention and cognitive speed. After training, participants completed the same assessment battery. tDCS was provided in a single-blind approach, with baseline and follow-up evaluations and interviews completed by an assessor blind to assignment.

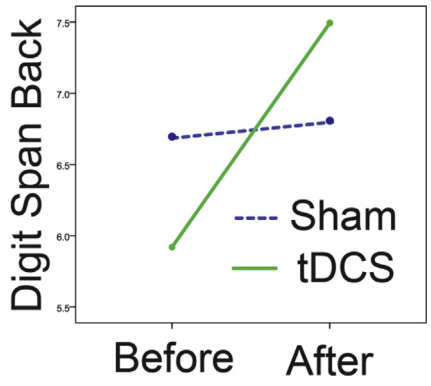

Fig. 1. Working memory.

Success of the blinding procedure was evaluated at study conclusion. We also interviewed participants about their reactions to the training, including their perception of its efficacy and whether they would participate in a similar study in the future.
All participants provided written informed consent for their participation. This study was registered at ClinicalTrials.gov (NCT02647645).

4. Results

Eleven participants completed all study procedures; their mean age was 51.5 years, two were women and two were white, with the other African American. Two participants withdrew prior to randomization as they believed our training site was too distant from their home after they completed eligibility determination. The other participant withdrew because of hospitalization for a health condition not related to study participation. All participants stated that they believed that they had been assigned to the active tDCS condition.
Results were evaluated in analysis of covariance models (ANCOVA) models controlling for age, gender, education, and immune status, examining effect sizes and direction for the interaction of assessment occasion (before and after training) by group. Because of our small sample size and low statistical power, evaluation focused on effect sizes rather than tests of significance. Of 14 effects evaluated, 13 were positive in suggesting an effect of tDCS, with sizes ranging from moderate to large by conventional interpretive guidelines [8], from 0.73 to 2.66 (Table 1). Results for a measure of working memory (Digit Span Backwards) are presented in Fig. 1. Inspection of the Figure suggests that persons receiving active tDCS improved on this measure relatively more at the second testing compared to individuals receiving sham. Participants' mood and report of cognitive difficulties also improved (effect sizes in Table 1).
Nine participants indicated they believed the training with tDCS was valuable; the two participants who did not had been assigned to the sham condition. All indicated they would participate in a similar study in the future and many spontaneously expressed that they enjoyed the training. Several asked about how they could obtain the game.

5. Discussion and Conclusion

While limited by our small sample size, participants' interviews suggest that game-based cognitive training with or without tDCS was acceptable and even enjoyable to older persons with HIV infection. Results of cognitive testing before and after training suggest that tDCS may enhance the effects of cognitive training in this population, similar to findings in other populations. They also provide preliminary estimates of effect size for use in future research. Objective results were mirrored in participants' self-report of cognitive difficulties, and their self-report of mood also suggested improvement over training sessions.
Participants reported enjoying the intervention drawing on a car racing game, and all stated that they would participate in a similar study in the future. This pilot study thus shows that game-based cognitive training may be useful in addressing HIV-related cognitive deficits. Given the importance of cognitive deficits in individuals with HIV and the lack of effective

Table 1
Effect sizes for the interaction of group by pre- and post-test results. Results expressed as eta-squared and Cohen's *d*.

	η^2	*d*
DS Forward	0.116	0.73
DS Backward	0.431	1.74
Sequencing	0.552	2.22
Learning	0.163	0.88
Memory	0.824	2.58
Trails A	0.638	*-2.66*[b]
Trails B	0.151	0.84
Pegs Dom	0.122	0.75
PAOF	0.361	1.50
CESD	0.221	1.07

[a]DS Forward = Digit Span Forward; DS Back = Digit Span Backwards; Sequencing = Digit Span Sequencing; Learning = Hopkins Verbal Learning Test—Revised total recall; Memory = Hopkins Verbal Learning Test—Revised delayed recall; Recognition = Hopkins Verbal Learning Test—Revised recognition memory; Trails A, Trails B = Trail Making Test, Parts A and B; Pegs Dom = Grooved Pegboard, Dominant Hand Time; PAOF = Patient Assessment of Own Functioning total; CESD = Center for Epidemiological Studies Depression Scale.
[b] Effect size is in the opposite direction to all others, suggesting better performance in the control condition.

treatments for them, results of this pilot suggest that further study is warranted.

References

[1] Heaton RK, Clifford DB, Franklin DR, Jr. et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010;75:2087-2096.
[2] Gorman AA, Foley JM, Ettenhofer ML, Hinkin CH, van Gorp WG. Functional consequences of HIV-associated neuropsychological impairment. Neuropsychol Rev 2009;19:186-203.
[3] Wendelken LA, Valcour V. Impact of HIV and aging on neuropsychological function. J Neurovirol 2012;18:256-263.
[4] Smith GE, Housen P, Yaffe K et al. A cognitive training program based on principles of brain plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. J Amer Geriatr Soc 2009;57:594-603.
[5] Coffman BA, Clark VP, Parasuraman R. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. Neuroimage 2014;85 Pt 3:895-908.
[6] Zelinski EM, Reyes R. Cognitive benefits of computer games for older adults. Gerontechnology 2009;8:220-235.
[7] Medeiros LF, de Souza IC, Vidor LP et al. Neurobio-logical effects of transcranial direct current stimulation. Front Psychiatry 2012: 3;110.
[8] Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.). New York: Routledge, 1988.

PROCEEDINGS #6. RELATION OF PERCEIVED DISCOMFORT TO TREATMENT EFFECT IN A BLINDED STUDY OF TDCS IN OLDER ADULTS WITH HIV

Raymond L. Ownby*[1], Janny Rivera[1], Erick Mejia[1], Amarilis Acevedo[2]. [1] *Department of Psychiatry and Behavioral Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA;* [2] *College of Psychology, Nova Southeastern University, Fort Lauderdale, FL, USA*

1. Abstract

Background: Development of appropriate control conditions for tDCS is essential to evaluate the effect of tDCS as distinct from other factors that affect outcomes in clinical studies, such as attention or perception of active treatment. In this pilot study, we assessed the effect of subjective discomfort on treatment effect size in a study of tDCS in older individuals with HIV to determine whether it was a factor in treatment effect even when participants could not predict the treatment they received.
Method: We asked participants in a blinded study of cognitive training with (n = 6) and without (n = 5) active tDCS to report their level of discomfort after each of six 20-minute training session completed over two weeks. At study conclusion, a blinded interviewer asked participants their impression of treatment group assignment. All participants believed they had received active treatment. We then assessed the impact of participants' report of subjective discomfort during training on size of treatment effect.
Results: On 13 of 14 measures, tDCS showed a positive effect size on cognitive and self-report measures, with effect sizes ranging from 0.73 to -2.66. Group differences in rating of discomfort were found in analyses that took age, gender, education, and immune status into account. When statistical models included average discomfort over sessions, five effect sizes increased in magnitude, six decreased, and one stayed the same.
Conclusion: In this small study, subjective experience of discomfort in an otherwise successfully blinded study had a little impact on treatment effect size. Subjective discomfort may not have an important effect on study outcomes when participants' perceptions of treatment assignment are successfully blinded.

2. Introduction

Although advances in antiretroviral treatment strategies have made HIV a manageable disease, infection with HIV continues to be associated with the development of cognitive deficits in areas such as psychomotor speed and memory [1]. Cognitive deficits are important because of their effects individuals' ability to care for themselves, remember to take medications and cope with a complex medical condition [2]. These deficits may have even greater impact on older individuals who may experience both HIV- and aging-related cognitive decline [3].
Treatment strategies for HIV and aging-related cognitive deficits are limited. Researchers have suggested that computer-based cognitive training may be helpful in aging-related cognitive decline [4], while multiple studies have shown that transcranial direct current stimulation (tDCS) may enhance the effect of cognitive training in healthy individuals as well as those with neurological disorders. We are engaged in continuing study of the effectiveness of cognitive training with and without active tDCS to address cognitive deficits in older individuals with HIV infection.
A key problem in assessing the effectiveness of tDCS has been how best to control for the possibly confounding effects of extraneous factors in clinical studies. Factors such as patient and research expectations of effect, attention paid to participants, and the experience of discomfort or side effects can influence participant perceptions of intervention effectiveness and objective study outcomes. The purpose of the analyses presented here was to evaluate the impact of subjective discomfort on treatment effect size in participants who all stated that they believed they had received active tDCS. As the sample is small, we have evaluated possible treatment effects based on estimated of effect size. In these analyses, we assessed the impact of subjective discomfort on treatment effect size to assess its impact on observed treatment effects.

3. Methods

Fourteen individuals meeting criteria for HIV-related mild neurocognitive disorder, including subjective cognitive complaints and neuropsychological test results at least one standard deviation below the mean in two domains, were recruited for this study. Exclusion criteria included left-handedness and presence of another neurological or psychiatric disorder that might be affected by tDCS. Individuals using psychotropic medications whose function might affect tDCS were also included. Eleven participants completed all study procedures and provided data for the analyses presented here.
After their eligibility was established, participants completed a battery of neuropsychological tests as well as two self-report measures focused on cognitive difficulties and depressive symptoms. They were then randomly assigned to receive computer-based cognitive training with active or sham tDCS. Persons in the active group received anodal tDCS to the left dorsolateral prefrontal cortex at 1.5 mA for 20 minutes during training, while those receiving sham received a 30 s ramp-up after which the tDCS device was turned off and the current ramped down over a similar interval.