Cognitive training with and without transcranial direct current stimulation and attention and working memory in older persons with HIV

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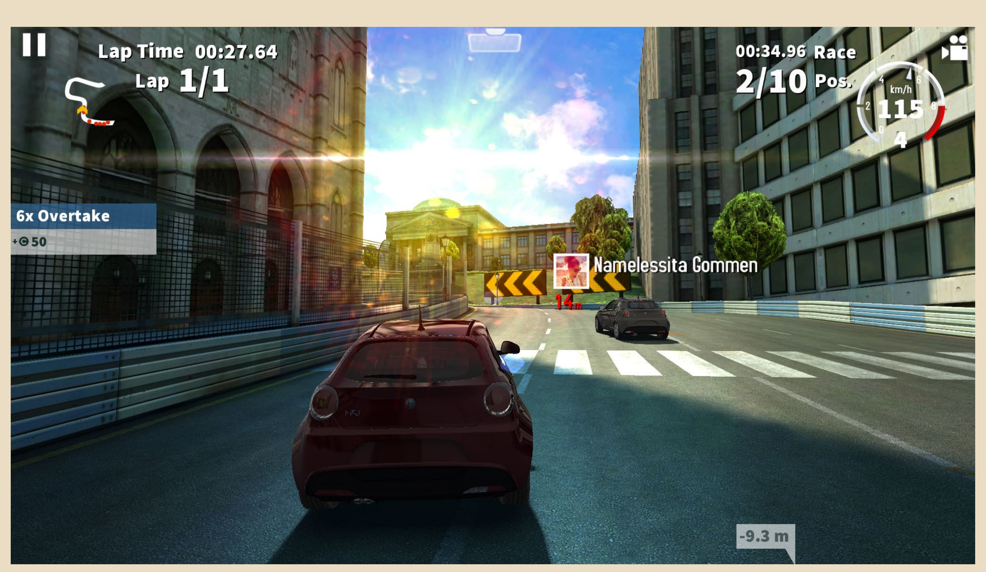
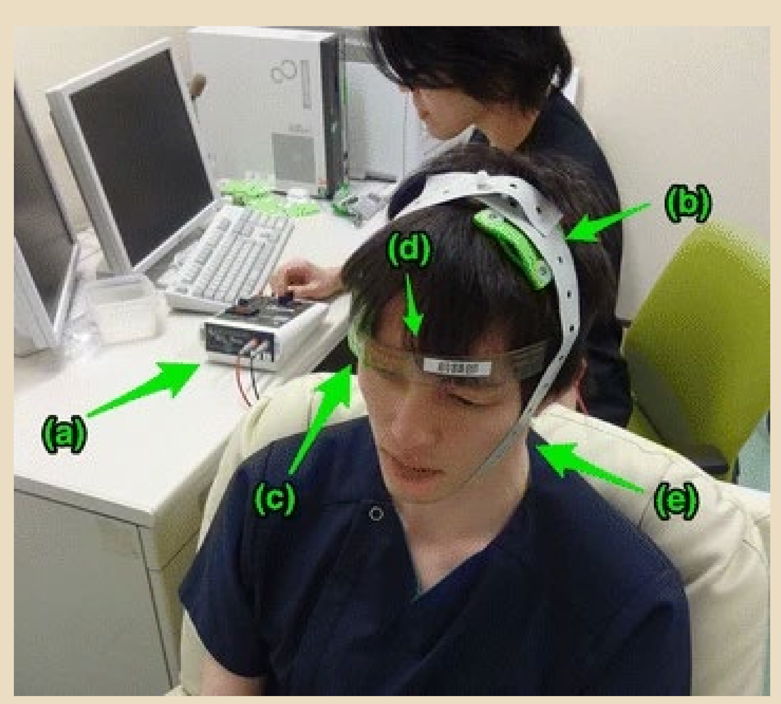
Overview

Antiretroviral therapy has resulted in reduced mortality in persons with HIV infection, however, affected individuals may experience age-related changes in cognition as well as deficits related to chronic HIV infection. To study a possible strategy to address this issue, we did a study of game-based cognitive training with and without anodal transcranial direct current stimulation (tDCS) to the left dorsolateral prefrontal cortex (F3) in 46 persons 50 years of age and older with mild neurocognitive disorder (MND by Frascati criteria). Participants completed a battery of measures, six 20-minute training sessions over two weeks, an immediate post-training assessment and a follow-up assessment 30 days later. They were assigned to (1) cognitive training + active tDCS, (2) cognitive training + sham tDCS, or (3) watching educational videos + sham tDCS (control).

We hypothesized that the cognitive training + active tDCS group would show greater improvements in attention and working memory (Digit Span Forward and Backward and Letter-Number Sequencing) compared to the other groups. Mixed effects repeated measures models showed a significant interaction of group vs time for attention. Post hoc analyses showed a significant difference between the training + active tDCS and the other groups at the first follow up visit but not 30 days later. A similar but nonsignificant effect was seen for working memory. The sham group showed significant improvement in letter-number sequencing that was sustained over one month. These results suggest that cognitive training with tDCS may have positive effects on attention and working memory in older adults with HAND, but that they may not be sustained over 30 days.

Intervention





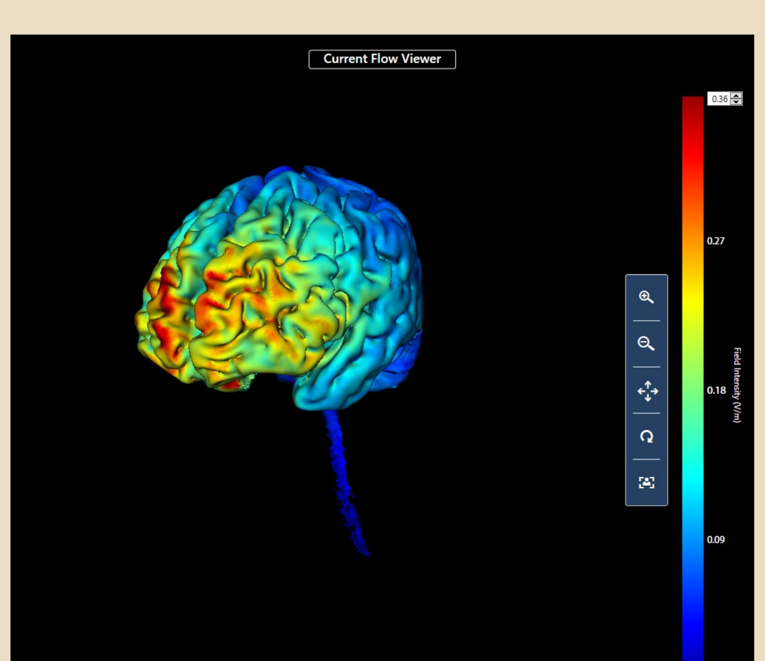


Photo credit: Yokoi, Y., Sumiyoshi, T. Application of transcranial direct current stimulation to psychiatric disorders: trends and perspectives. *Neuropsychiatr Electrophysiol* **1**, 10 (2015). https://doi.org/10.1186/s40810-015-0012-x

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Method

Procedures

Screening. Potential participants were first screened by telephone to determine whether they met study entry criteria. Inclusion criteria were age 50 years or older and complaints of cognitive difficulties. Exclusion criteria included use of medications known to affect tDCS (e.g., benzodiazepines, serotonin reuptake inhibitors, dopaminergic agents), seizure disorder, personal or family history of bipolar disorders, and left handedness. Persons meeting entry criteria were scheduled for an in-person eligibility assessment.

Eligibility. Persons completed a neuropsychological assessment to determine whether they met Frascati criteria for mild neurocognitive disorder, i.e., cognitive difficulties, intact functional status, and functioning at least one standard deviation below population norms in at least two cognitive domains. Persons who met these criteria then provided written informed consent for their participation under a protocol approved by the NSU IRB.

Baseline Assessment. Baseline assessments included a neuropsychological battery that included the Digit Span subtest of the Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV). This subtest includes three attention-related tasks: (1) digit span forward, (2) digit span backward, and (3) a task that includes numbers and letters.

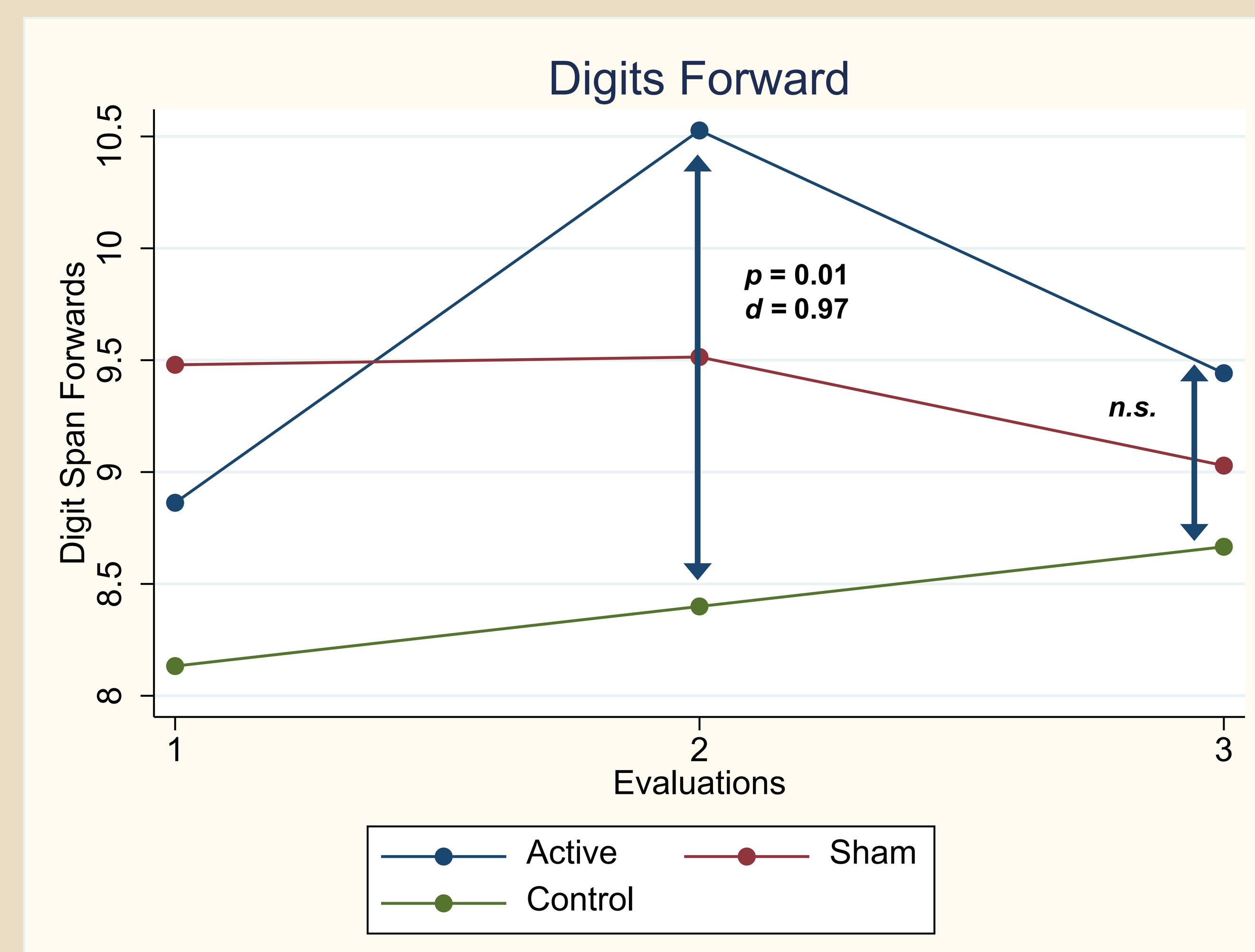
Intervention. Participants were randomly assigned to one of three conditions: (1) Active tDCS (1.5 mA for 20 minutes, anode at F3 and cathode at Fp2) together with active cognitive training using a car racing game; (2) Sham tDCS (ramping to 1.5 mA over 30 seconds, then ramping down for the remainder of the 20 minute session) with active cognitive training, and (3) Control condition that included sham tDCS and watching an educational video for 20 minutes. All participants completed six 20-minute sessions over two weeks.

First follow-up. Participants completed the neuropsychological battery after completing the sixth training visit, usually within 1-2 days.

Second follow-up. Participants returned after approximately 30 days for a second follow-up that again included the neuropsychological battery.

Analyses

Planned analyses were based on study hypotheses that the combination of active tDCS with cognitive training would result in greater improvement in reaction time, attention, and psychomotor speed compared to cognitive training alone which in turn would be related with greater improvement than seen in the control condition. Attention was operationalized as participants' performance on the WAIS-IV Digit Span subtest. Participants' performances over the course of the study were assessed using mixed effects models using SAS PROC MIXED with age, gender, race, education, and log viral load as covariates and each task in the Digit Span subtest as outcomes.



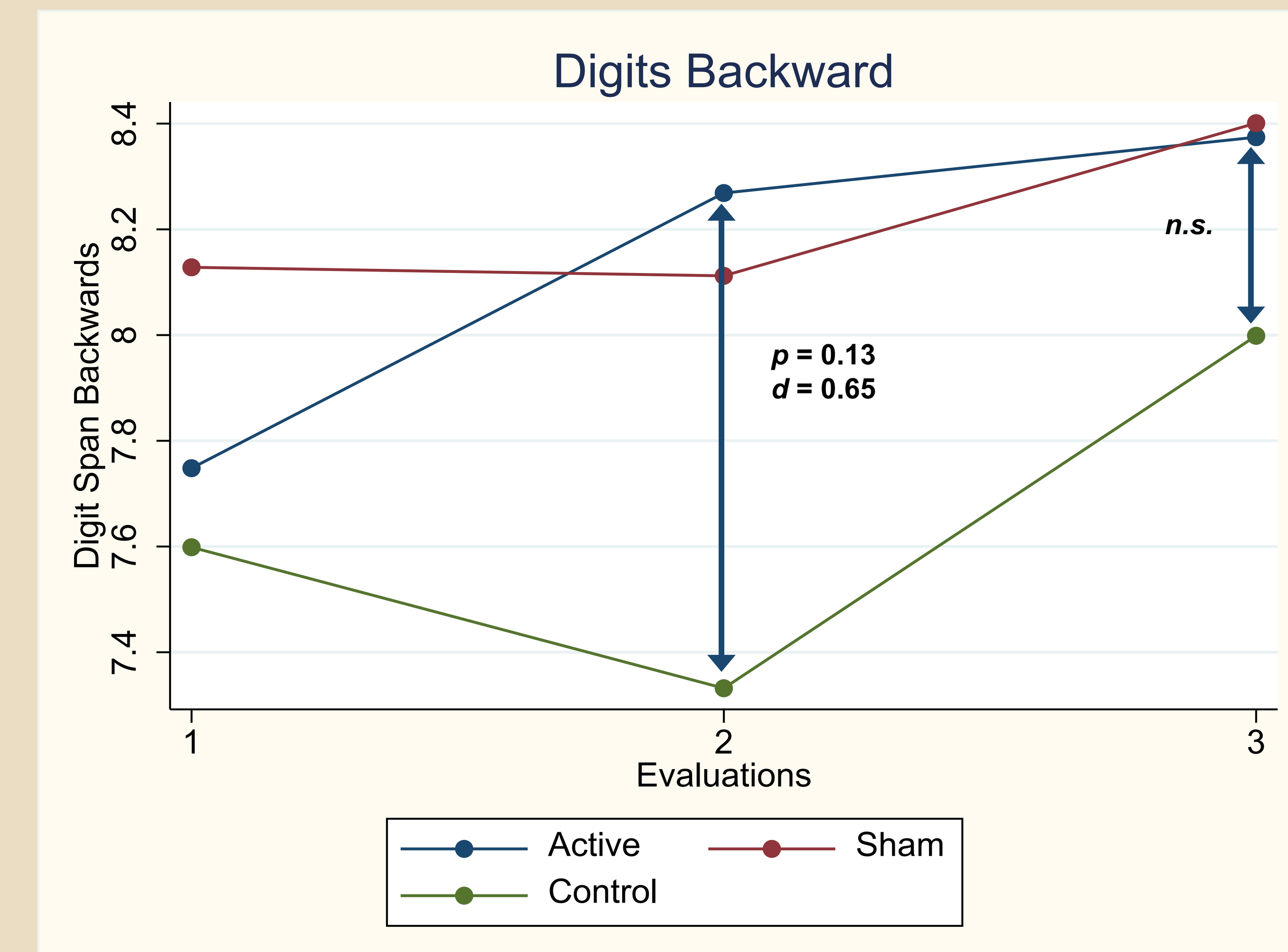
Results

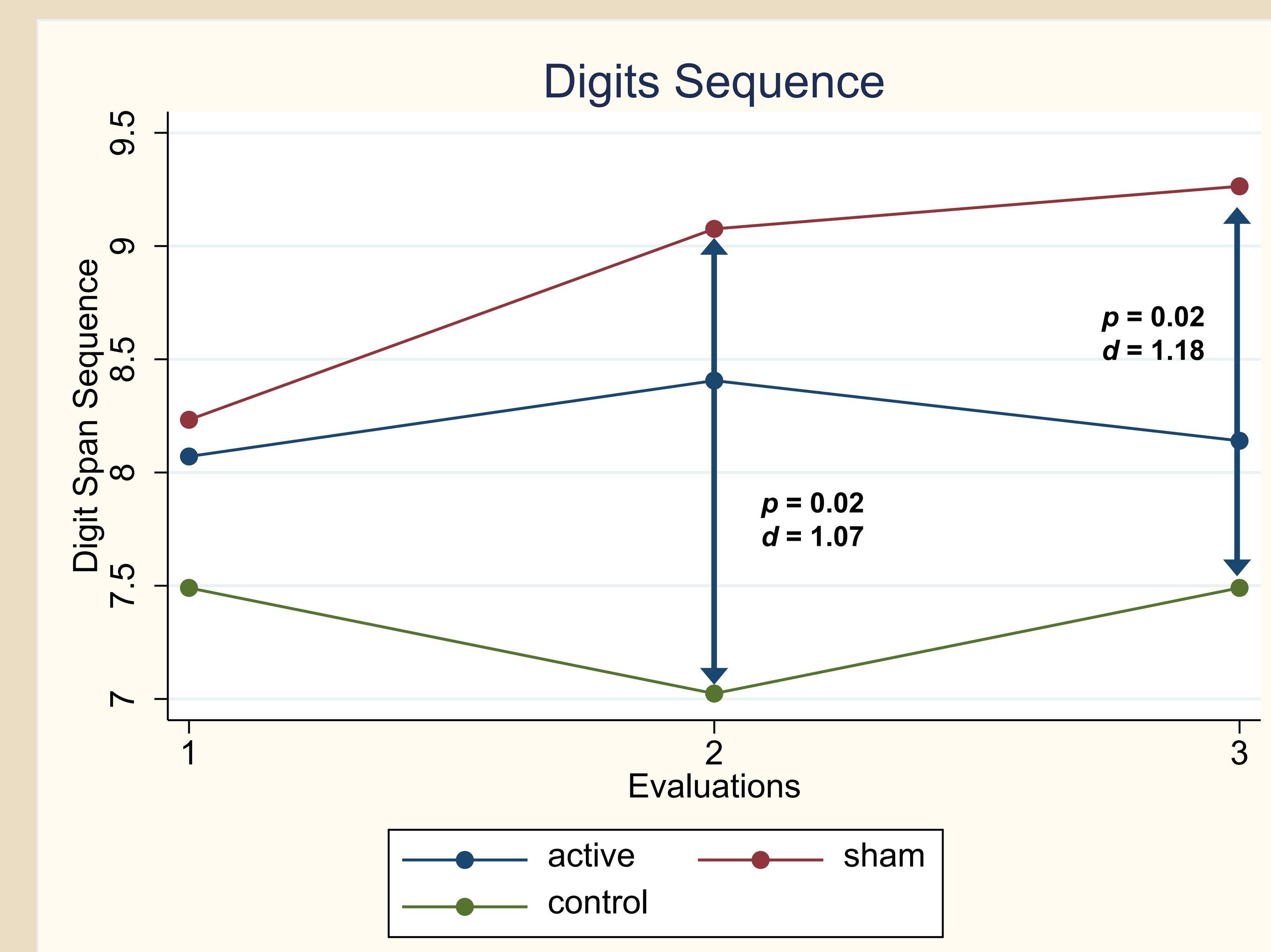
Our sample included 46 participants, of whom 43 completed all study procedures. The group included 37 men and 9 women, with 17 whites and 29 blacks. Their average age was 58.9 years (range 50 to 73) and had an average educational experience of 13.1 years (range 6 to 20 years).

Analyses showed that the training effect for **digit span forward** was significant (F [4, 27.8] = 2.77, p = 0.047. Post hoc tests (Sidak corrected for multiple comparisons) showed a significant difference between active and control groups at the first follow up (evaluation 2; t [28.93] = 2.61, p = 0.01, d = 0.97) but that this difference was no longer significant at the second follow-up (evaluation 3; t [29.45] = 1.05, p = 0.30, d = 0.39).

Training effects for **digit span backward** were not significant; examination of a simple pre-post model for the active compared to the control group (not including the second follow-up (evaluation 3) showed that the difference between active and control groups approached statistical significance (F [1, 27.8] = 2.66, p = 0.11. Post hoc comparison approached significance and were consistent with a moderately large effect size (t [23.58] = 1.58, p = 0.13, d = 0.65).

The effect for **digit sequencing** was significant for the sham treatment group but not the active treatment group (t [16.9] = 2.43, p = 0.03, D = 1.18), with the difference significant for the immediate follow-up (evaluation 2; t [22.31] = 2.52; p = 0.02, d = 1.07).





Conclusions

These results show that the cognitive training may have a positive impact on attention and working memory in persons with HIV-related cognitive deficits. At least for digits forward, tDCS appears to have had an augmenting effect on cognitive training. The different pattern of response on digits forward and backward and letter-number sequencing suggests the possibility that tDCS may have a differential impact on outcomes based on the cognitive skills required. On digits forward and backward we found no evidence of sustained improvement over 30 days, although the sham group continued to be significantly better than control on letter-number sequencing over that period. Ongoing cognitive training and tDCS may be required to produce a sustained effect on these persons' cognitive function.