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Web-based cognitive training to improve working memory in persons with co-occurring HIV infection and cocaine use disorder: Outcomes from a randomized controlled trial

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Abstract

Neurocognitive impairment (NCI) remains a persistent complication of HIV disease that nearly half of persons with HIV experience, and rates are even higher in persons who use substances such as cocaine. Cognitive training is a promising intervention for HIV-associated NCI. In this randomized controlled trial, we examined the feasibility and effectiveness of a web-based cognitive training program to improve working memory in a sample of 58 persons with HIV and cocaine use disorder. Participants were randomly assigned to either the experimental working memory training arm or the attention control training arm and completed up to 48 daily sessions over 10 weeks. Overall, treatment completion (74%) and retention rates (97%) were high, and participant feedback indicated the intervention was acceptable. Our results show that the intervention successfully reduced working memory deficits in the experimental arm relative to the control arm. Our findings support both the feasibility and effectiveness of cognitive training in this population.

Keywords

HIV; cocaine; cognitive training; working memory; neurocognitive impairment

INTRODUCTION

Among the 1.1 million Americans living with HIV, prevalence estimates indicate that up to half will develop HIV-associated neurocognitive disorder (HAND) in their lifetime (1, 2). With the effectiveness of modern combination antiretroviral therapies (cART), the rates of severe HAND have declined, but milder forms remain a persistent complication of HIV disease (2-4). The neurocognitive impairment (NCI) associated with these milder forms of

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HAND can lead to concomitant impairments in real-world functioning, including driving ability, employment, and medication adherence (5-9). While effective cART regimens can reduce the effects of HIV on the central nervous system (10), behavioral interventions are needed to address the mild and moderate NCI that now predominate the clinical presentation of neuroHIV.

The abuse of illicit stimulant drugs like cocaine appears to increase the risk of HAND. Cocaine use, like other drugs of abuse, is disproportionately common among persons with HIV in the United States. In a nationally representative sample of adults, the prevalence of cocaine use in persons with HIV was 58% for lifetime and 13% for past year compared to 16% and 2%, respectively, in persons without HIV (11). Among persons with HIV, cocaine use is associated with poorer HIV clinical outcomes, including unsuppressed HIV viral load, faster disease progression, and mortality (12-15). Cocaine is also a concern due to its effect on the brain. As a powerfully addictive drug, chronic cocaine use causes persistent neurobiological changes in neural networks that control reward salience, executive control, and decision making (16-18). Behaviorally, cocaine users demonstrate prominent impairments in working memory (19-21). Case-control studies have demonstrated the additive and interactive effects of cocaine and HIV on neurocognitive functioning, particularly in the domains of executive function and working memory (22-24).

Working memory may be a key target for improving cognitive function in persons with HIV. Working memory involves the temporary storage and manipulation of information from the current environment to support complex cognitive tasks, such as comprehension, reasoning, and decision making (25). As a core executive function that supports self-regulation (26), working memory plays an important role in daily functioning. Cognitive training, which harnesses the brain’s inherent capacities for change, may be an effective intervention for improving working memory function. Cognitive training promotes or restores adaptive cognitive, socio-affective, and behavioral functioning by targeting underlying neural processes using controlled learning events, such as skills exercises that get progressively more challenging as performance improves (27, 28). While cognitive training originally emerged as a treatment for the cognitive deficits associated with schizophrenia, it has since been successfully utilized to improve cognitive functions in a multitude of other conditions, including attention deficit hyperactivity disorder, major depression, and anorexia nervosa (28-33).

Though still a relatively new area of research, a recent systematic review concluded that the studies to date examining the effects of cognitive training in adults with HIV have shown promising results in improving cognitive function (34).These studies naturally had some methodological variability and limitations, including different types of comparison groups, limited sample sizes, and brief follow-up periods, but collectively they indicate cognitive training as a viable intervention for HIV-associated NCI (34). Most studies delivered approximately 10 hours of cognitive training, which is consistent with the standard in the broader cognitive training literature; however, it is not yet clear whether an increased dosage of training would benefit HIV-associated NCI (34). Of note, in these studies, substance use was either exclusionary or was not explicitly characterized. While the potential benefits of cognitive training for substance abuse remain understudied (35), several working memory interventions across different substance use populations have yielded promising results on working memory performance and impulsive decision making (36-39). However, the potential benefit of cognitive training for improving working memory in persons with HIV who use substances has not yet been evaluated.

This study examined the feasibility and effectiveness of a web-based cognitive training intervention to improve working memory in persons living with HIV and cocaine use disorder. Participants in this randomized clinical trial were assigned to either the experimental working memory training arm or the attention control training arm. Participants completed 10 weeks of training, with assessments at baseline and post-treatment to evaluate treatment effects. We hypothesized that participants receiving the working memory training would show greater improvements in working memory performance over time relative to participants in the control arm.

METHODS

Procedures

We recruited adults with HIV aged 18–64 years old and residing independently in the community who reported a history of regular cocaine use. The key cocaine-related eligibility criteria were regular cocaine use lasting >1 year and lifetime cocaine-type stimulant use disorder. Participants also had to be on an antiretroviral (ARV) medication for >3 months at the time of enrollment. The exclusion criteria were: English non-fluency or illiteracy; ≤ 8th grade education; serious and unstable neurological or psychiatric disorders; impaired mental status; and pregnancy. To maximize generalizability, there were no exclusions related to other substance use, such as alcohol, marijuana, or other illicit drugs.

From March 2017 to November 2018, participants were recruited through flyers and brochures at infectious diseases clinics, a research contact registry, and peer referrals. Potential participants completed a brief prescreening interview to assess preliminary eligibility. Participants then attended an in-person screening to assess eligibility more comprehensively.

Eligible participants returned on another day to complete a baseline assessment that included a neuropsychological battery. After the baseline assessment, participants were randomly assigned to one of two arms: active cognitive training (ACT) or control training (CON). This intervention utilized Lumosity's web-based cognitive training games (Lumos Labs, Inc.; http://www.lumosity.com). Games in ACT targeted working memory, while games in CON targeted other domains, such as motor function and processing speed. For randomization, randomly-ordered blocks of 6, 8, or 10 were generated by the principal investigator using a permuted block design with a random number generator in Sealed Envelope (40). Assignments were then placed in sequentially numbered sealed envelopes that were locked in the principal investigator's office. Random assignment was completed by the training administrator (TA), who was a designated staff member responsible for monitoring participant progress during the intervention phase. The TA retrieved the next available sealed envelope and broke the seal at the time of randomization.

Participants then completed a tutorial session with the TA in which they received an overview of the web-based cognitive training program and each game they would be playing through the program. The TA ensured that the participant understood each game and was comfortable navigating the website. In addition, if the participant reported having limited or no access to a computer and/or internet at their residence, they were offered a Chromebook and hotspot device to use for the duration of the intervention.

The structure of the intervention phase was identical for the ACT and CON arms. Participants had up to 10 weeks at home to complete up to 48 cognitive training sessions. After 10 weeks, or within 1 week of completing the 48^{th} session (whichever occurred first), participants completed a post-intervention follow-up assessment to evaluate the effects of the intervention. For both the baseline and post-intervention visits, the research assistant conducting the neuropsychological testing and clinical interviews was blind to arm assignment, in order to prevent any biases during neuropsychological testing.

Participants were compensated for all study assessments, receiving $50 for the screen, $75 for the baseline, and $65 for the post-intervention visit. Participants earned $2 for every completed session, and, to encourage session completion, they earned an escalating bonus after the completion of every 6^{th} session ($5 bonus after completing 6, 12, 18, and 24 sessions; $10 after 30 and 36 sessions; and $15 after 42 and 48 sessions). Total potential earnings for completing all 48 sessions was $166. Payments for session completion were disbursed each time a bonus was earned and at the end of 10 weeks, if the participant did not complete all 48 sessions. All payments were provided using a reloadable debit card.

Procedures were approved by the institutional review board at Duke University Health System and the study was registered on ClinicalTrials.gov (Identifier: NCT02909101). Participants provided written informed consent. Figure 1 shows the flow of participants from the eligibility screening through the post-intervention follow-up. In total, 81 individuals enrolled and completed an in-depth screening. Of these, 67 (83%) were eligible and 58 (72%) completed the baseline assessment.

Screening measures

Substance use.—We administered several clinical interviews to comprehensively assess substance use history. The Addiction Severity Index-Lite (ASI-L), a semi-structured interview, assessed lifetime substance use and associated problems (41). Module E of the Structured Clinical Interview for DSM-5 (SCID-5) assessed clinical symptoms of substance use disorders (42). To measure frequency of use in the past 90 days, we utilized Timeline follow-back (TLFB) methodology to record days of use for cocaine and other substances (43, 44). A rapid urine toxicology screen that tested for cocaine, cannabis, amphetamine, methamphetamine, oxycodone, methadone, other opioids, benzodiazepines, and barbiturates was conducted to corroborate self-report of recent substance use.

Other interviews and questionnaires.—Modules A and B from the SCID-5 assessed mood and psychotic disorders. To assess literacy, participants completed the Word Reading Subtest of the Wide Range Achievement Test-4 (45). Questionnaires to assess demographic factors (such as age, race, and ethnicity) were administered using audio computer-assisted self-interview (ACASI). A urine pregnancy test was completed for persons of childbearing potential.

Finally, participants provided authorization for the release of their medical records for both current and historical care. Research staff reviewed records to ensure the absence of any exclusionary history, including unstable neurological conditions or psychiatric disorders. HIV clinical variables were also abstracted, including date of HIV diagnosis, ARV treatment, most recent CD4 count and HIV viral load, and nadir CD4 count.

Baseline measures

Substance use.—Frequency of substance use in the past 90 days was assessed via TLFB and another rapid urine toxicology screen was conducted.

Neuropsychological assessment.—Participants completed the Wechsler Test of Adult Reading (WTAR), a word reading task that includes words with atypical grapheme to phoneme translations, to estimate premorbid verbal IQ (46). Participants then completed a 60-minute battery that was designed to align with recommendations for assessing HIV-associated neurocognitive impairment (47). This battery assessed the following 7 domains of function:

1. *Working memory:* Paced Auditory Serial Addition Task-50 – number correct (48); WAIS-IV Digit Span subtest – number correct (49); WAIS-IV Letter-Number Sequencing subtest – number correct (49)
2. *Processing speed:* Trail Making Test Part A – number of seconds to completion (50); Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding subtest – total number correct (49); Stroop Color and Word Test color naming score – number of items completed (51)
3. *Learning (immediate recall):* Hopkins Verbal Learning Test – Revised (HVLT-R) – total number of words recalled on trials 1-3 (52); Brief Visuospatial Memory Test-Revised (BVMT-R) – total score for figures correctly recalled on trials 1-3 (53)
4. *Memory (delayed recall):* HVLT-R – number of words recalled on trial 4 (52); BVMT-R – total score for figures correctly recalled on trial 4 (53)
5. *Executive function:* Stroop Color and Word Test interference score – difference between actual and predicted score on the Color-Word trial (51); Trail Making Test Part B – number of seconds to completion (50); Wisconsin Card Sorting Test-64 (WCST) – total errors (54)
6. *Verbal fluency:* FAS letter fluency – number of words generated; and category fluency – number of animals generated (55)
7. *Motor skills:* Grooved Pegboard Test dominant and non-dominant hand – number of seconds to completion (56)

Raw scores for each test were converted to demographically corrected T-scores (M=50, SD=10) using published normative data (48, 49, 57). To compute severity of impairment, T scores were converted to deficit scores using a 0-5 rating, with 0 reflecting no impairment and 5 reflecting severe impairment: T ≥40 = 0, 35-39 = 1, 30-34 = 2, 25-29 = 3, 20-24 = 4, and <20 = 5. A mean domain deficit score (DDS) was then computed by averaging the deficit scores for the tests within each domain. By assigning a zero-point value to T scores within or above one standard deviation of the mean, deficit scores give less weight to performances that are within normal limits and therefore provide a more accurate characterization of impairment than simply averaging T scores. A global deficit score (GDS) was computed by averaging the DDS of the 7 domains. Overall impairment within a domain was defined as a mean DDS ≥0.5 and global impairment was defined as GDS > 0.5 (58).

Intervention arms

Games for each arm were selected based on the designated domain of function identified by Lumosity. Games selected for ACT specifically designated working memory as the focal brain attribute for the game, whereas games selected for CON specifically did not designate working memory or other aspects of memory function. Games increased in difficulty as the participant played. For example, the number of items a participant needed to remember or the speed of stimulus presentation increased across trials. Details about each game are presented in Appendix 1. Participants could complete one session per day and each session lasted 20-30 minutes. Each session included a random selection of 4 of the possible games, and each game was played twice back-to-back. After completing each game twice, participants had the option to play the same game an unlimited number of additional times or move on to the next game, until they cycled through all 4 games for that session.

The TA received daily data reports from Lumosity to monitor participant progress. The reports detailed which games were completed, when they were completed, and the scores for each game. Participants received a check-in call whenever they went more than 2 days without completing a session. During check-ins, the TA answered any participant questions and assisted in troubleshooting technical issues as needed. Participants also received a call after completing every 6th session. During this call, participants were encouraged to continue completing sessions and they were also informed that a payment for that block of sessions, including the bonus, would be loaded onto their debit card.

Intervention engagement metrics.—For each participant, we computed the overall number of sessions completed to evaluate feasibility. Treatment completion was defined as ≥75% of sessions (36 out of 48). However, because some participants may not have been actively engaged with the game content while completing sessions, we examined game scores to check whether participants improved over time, as proxy of engagement. We computed the overall number of games where scores improved over time (ranging from 0 to 8). Improved performance on a game over time was defined as the average of the final six scores on a game being greater than the average of the first six scores on that game. If a participant completed a game fewer than 12 times during the intervention period, change over time could not be evaluated and that participant’s performance for that game was therefore categorized as not improved.

Follow-up procedures

The post-intervention evaluation repeated the full baseline assessment as well as a follow-up version of the ASI-L. Participants also completed an intervention process assessment (IPA) at this visit to evaluate their experiences with the intervention, including perceived benefits of sessions, barriers to doing sessions, and feedback about the frequency, length, and number of sessions. Participants read statements about the intervention and rated their level of agreement with each statement on a 5-point scale. Participants provided ratings for their general satisfaction with sessions (1 = Very dissatisfied, 2 = Somewhat dissatisfied, 3 = Neutral, 4 = Somewhat satisfied, 5 = Very satisfied) and how helpful they found sessions overall (1 = Very unhelpful, 2 = Somewhat unhelpful, 3 = Neutral, 4 = Somewhat helpful, 5 = Very helpful). Acceptability was defined as ratings of >3.5 on the 5-point scales for satisfaction and helpfulness. To encourage participants to provide both positive and critical feedback, the IPA was administered using ACASI.

Data analysis plan

Analyses were conducted using SPSS 26.0.0.0. To characterize the sample and test for potential failures of randomization, we utilized chi-square tests, Fisher's exact tests, independent samples t-tests, and Mann-Whitney U tests to compare the ACT and CON arms. To examine feasibility and acceptability of the intervention, chi-square and independent samples t-tests were used to examine group differences on session completion metrics and the IPA questionnaire responses. Using an intent-to-treat analysis, we examined the differential effects of treatment arm on the primary outcome of working memory (domain deficit score) by conducting a 2 (Arm: ACT vs. CON) × 2 (Time: Baseline vs. Follow-up) mixed-model general linear model analysis. Time was the within-subjects factor defined by baseline versus follow-up, and study arm was the between-subjects factor. Age, estimated premorbid IQ (WTAR standard score), and number of games improved (a proxy of intervention engagement) were included as covariates in the model. To examine the specificity of the cognitive training intervention, we used the same models to test for differences on performance in other cognitive domains. Statistical significance was defined as p-value of <0.05.

RESULTS

Sample characteristics

In the final sample of 58 adults, 29 participants were randomized to each arm. Participants were 48.62 (*SD* = 9.15) years old with 11.97 (*SD* = 2.37) years of education on average. The majority of participants were male (72%) and African American (86%). All participants were currently engaged in HIV care. The mean number of years since HIV diagnosis was 15.90 (*SD* = 7.53), and the most recent HIV viral load was suppressed at <50 copies/mL for 83% of participants. The median most recent CD4 cell count was 633.50 (*IQR* = 395.00) and the median nadir CD4 was 158.00 (*IQR* = 346.00). Table 1 compares the study arms on key characteristics. There were no significant differences on any demographic, HIV, or substance use characteristics, indicating that randomization was effective. The majority of participants (62%) in both arms had GDS scores indicating impairment [$\chi^2(1) = 0.29$, $p = 0.59$]. The only difference between arms on baseline neuropsychological testing was that participants in CON had higher impairment scores in the motor skills domain relative to participants in ACT.

Feasibility and acceptability

A total of 43 (74%) participants were loaned computer equipment for the trial, with 42 (72%) using a Chromebook and 28 (48%) utilizing a hotspot, and there was no difference on equipment usage by arm [$\chi^2(1) = 0.81$, $p = 0.37$], Session completion metrics are summarized in Figure 1. Participants completed 37.33 (*SD* = 18.53) of the 48 possible sessions on average [$t(56) = -1.35$, $p = 0.18$]. The majority of participants (59%) completed all 48 sessions, 16% completed 36-47 sessions, 16% completed 2-35 sessions, and 10% completed only one session [$\chi^2(3) = 2.25$, $p = 0.52$]. There was no difference in treatment completion by arm for any metric.

Ratings from the process assessment are presented in Table 2. Participants agreed that they completed sessions because they believed the sessions would be helpful to them (*M* = 4.20, *SD* = 0.64). However, while participants in ACT were generally neutral about payment as a motivator for completing sessions, participants in CON were significantly more likely to agree that they completed sessions because they knew they would be paid. Objectively, participants in CON had a greater number of games with improved scores over time relative to ACT participants [*M* = 6.59, *SD* = 2.68 and *M* = 4.79, *SD* = 2.97, respectively; $t(56) = -2.41$, $p = 0.02$]. In terms of participants' own perceptions, though, participants in ACT agreed more strongly than CON participants that their performance improved over time.

Mean ratings for overall satisfaction (*M* = 4.09, *SD* = 1.21) and perceived helpfulness (*M* = 4.09, *SD* = 1.08) of the intervention were both above the 3.5 cut-off, indicating that acceptability was high. Participants across both arms agreed that the games were fun (*M* = 4.00, *SD* = 0.95) and challenging (*M* = 4.07, *SD* = 0.78). Participants also disagreed that the games were too difficult (*M* = 2.43, *SD* = 1.02), though there was trend for ACT participants to feel more neutral about this statement.

There were no differences by arm in evaluating the structure of the intervention. Participants found playing games twice back-to-back was helpful (*M* = 3.88, *SD* = 1.01). They felt the length of each session (*M* = 3.05, *SD* = 0.59) and the number of sessions overall (*M* = 2.91, *SD* = 0.79) were "just right." They also disagreed that it was difficult to complete 5-6 sessions per week (*M* = 2.25, *SD* = 1.15) or to complete sessions for 10 weeks (*M* = 2.21, *SD* = 1.16).

Post-intervention outcomes

Retention in the trial was high, with 97% completing the post-intervention follow-up, and there were no differences by arm in attrition [Fisher's test, $p = 1.000$]. One participant from each arm was lost to follow-up (one moved out of state and the other went to a long-term residential treatment program).

In the 2 (Arm) × 2 (Time) mixed-model general linear model, there was a significant group-by-time interaction for the working memory DDS with a medium effect size [$F(1, 51) = 4.47$, $p = 0.04$, $\eta_p^2 = 0.08$], such that ACT had greater improvements relative to CON

(Figure 2). From baseline to follow-up, ACT working memory DDS decreased from 0.29 [standard error (*SE*) = 0.09] to 0.14 (*SE* = 0.07), whereas CON scores increased from 0.21 (*SE* = 0.09) to 0.26 (*SE* = 0.07). There were no significant main effects for time or arm-by-time interaction effects for other cognitive domains with all $p > 0.05$. There were main effects for group on both motor [$F(1, 51) = 8.25$, $p = 0.01$, $\eta_p^2 = 0.14$] and fluency DDS [$F(1, 51) = 4.96$, $p = 0.03$, $\eta_p^2 = 0.09$]. Consistent with baseline scores, DDS was lower in ACT relative to CON for motor (ACT $M = 0.26$, $SE = 0.17$; CON $M = 0.98$, $SE = 0.17$) and fluency (ACT $M = 0.10$, $SE = 0.08$; CON $M = 0.38$, $SE = 0.08$). Overall, these results suggest that the intervention effect was specific to working memory.

DISCUSSION

This randomized controlled trial supports the acceptability and preliminary effectiveness of a web-based cognitive training program to improve working memory in persons with HIV who use cocaine. Participants' ratings for both satisfaction and helpfulness were high, and the large majority completed at least 36 sessions over 10 weeks. In support of our hypothesis, the intent-to-treat analyses revealed differential effects by study arm on working memory over time, with deficit scores decreasing in ACT but increasing in CON. Moreover, the intervention effects were specific to working memory. Given that the training sessions are fully computerized and administered by participants at home on their own schedule, this promising intervention could be easily integrated into HIV services.

A key finding of our study is that web-based cognitive training was feasible to implement in this sample of persons with HIV, most of whom were actively using cocaine. Participants across both arms indicated that the number of sessions and the duration of the intervention overall were acceptable, and their general response to the web-based program and its content was positive. However, given limited financial resources, many of our participants did not have internet and computer access. As such, providing Chromebooks and mobile hotspots was key to facilitating engagement. Additionally, because many participants required basic computer instruction and assistance during the trial, the tutorial session and the availability of a staff member for technical troubleshooting throughout the intervention were important for ensuring treatment completion.

Our results suggest that participants in the ACT arm developed internal motivation to complete the sessions. On the process measure, participants in CON agreed that payment motivated their session completion, whereas ACT participants were neutral to this statement. This finding is intriguing, given that CON participants had a greater number of games with improved scores compared to ACT participants, which suggests that they were engaged while completing sessions. Ultimately, these differences may be related to the difficulty of the games in ACT relative to those in CON. Because the ACT arm targeted working memory, those games likely required more cognitive effort and objectively were more difficult than the CON games, which required only simple set-shifting or processing speed. Indeed, participants' perceptions support this idea. All participants felt the games were challenging, but ACT participants perceived the games to be more difficult than their CON counterparts.

Building upon on the growing literature on the efficacy of cognitive training in persons living with HIV (34), our study provides the first examination of cognitive training in persons with HIV who use substances, a group that is at particularly high risk for NCI. A major strength of this trial was the attention-matched comparison group, in which participants completed an equivalent number and intensity of games that differed only in the cognitive skills that were targeted. In addition, our experimental design utilized a comprehensive neuropsychological battery that included multiple tests for each domain of function, and our retention rates for the post-intervention follow-up were excellent. Our study does has several limitations that should be noted. First, our follow-up occurred right after the intervention was completed. Therefore, our findings represent only the short-term effects of the intervention. A longer follow-up period would be necessary to determine the long-term durability of effects. Second, our assessment did not include an evaluation of functional impairment, which would be important in examining the real-world impact of the intervention. Future studies should include a detailed evaluation of functional impairment pre- and post-treatment. Finally, due to the experimental design of the two arms, the intervention had to be delivered on a computer. As the intervention is rolled out for implementation on a smartphone or tablet, whose portability would allow more flexibility in both timing and location of completing sessions, engagement in the sessions may be further enhanced. A recent study supports the acceptability of mHealth interventions among people with HIV who use cocaine (59).

In conclusion, our study demonstrates the acceptability, feasibility, and effectiveness of web-based cognitive training for improving working memory in persons with co-occurring HIV infection and cocaine use disorder. Cognitive training is an exciting avenue to pursue in HIV care because it is relatively low cost and scalable in resource-limited settings with few mental health specialists. A larger trial with a longer duration of training and targeting more domains is needed to test the durability of effects and improvement in daily living.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010–2016. HIV Surveillance Supplemental Report. 2019;24(No. 1).
2. Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, et al. HIV-associated neurocognitive disorder - pathogenesis and prospects for treatment. Nat Rev Neurol. 2016;12(5):309. [PubMed: 27080521]
3. Gates TM, Cysique LA. The chronicity of HIV infection should drive the research strategy of neuroHIV treatment studies: a critical review. CNS Drugs. 2016;30(1):53–69. [PubMed: 26749584]

4. Heaton RK, Clifford DB, Franklin DR Jr., Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010;75(23):2087–96. [PubMed: 21135382]
5. Thames AD, Arentoft A, Rivera-Mindt M, Hinkin CH. Functional disability in medication management and driving among individuals with HIV: a 1-year follow-up study. J Clin Exp Neuropsychol. 2013;35(1):49–58. [PubMed: 23237014]
6. Cattie JE, Doyle K, Weber E, Grant I, Woods SP. Planning deficits in HIV-associated neurocognitive disorders: component processes, cognitive correlates, and implications for everyday functioning. J Clin Exp Neuropsychol. 2012;34(9):906–18. [PubMed: 22731608]
7. Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsychol Soc. 2004; 10(3):317–31. [PubMed: 15147590]
8. Rabkin JG, McElhiney M, Fernando SJ, Van Gorp W, Lin SH. Predictors of employment of men with HIV/AIDS: A longitudinal study. Psychosom Med. 2004;66(1):72–8. [PubMed: 14747640]
9. Laverick R, Haddow L, Daskalopoulou M, Lampe F, Gilson R, Speakman A, et al. Self-reported decline in everyday function, cognitive symptoms, and cognitive function in people with HIV. J Acquir Immune Defic Syndr. 2017;76(3):e74–e83. [PubMed: 29016449]
10. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. Lancet Infect Dis. 2013;13(11):976–86. [PubMed: 24156898]
11. Shiau S, Arpadi SM, Yin MT, Martins SS. Patterns of drug use and HIV infection among adults in a nationally representative sample. Addictive behaviors. 2017;68:39–44. [PubMed: 28088742]
12. Cook JA, Burke-Miller JK, Cohen MH, Cook RL, Vlahov D, Wilson TE, et al. Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women. AIDS. 2008;22(11):1355–63. [PubMed: 18580615]
13. Campa A, Martinez SS, Sherman KE, Greer JP, Li Y, Garcia S, et al. Cocaine use and liver disease are associated with all-cause mortality in the Miami Adult Studies in HIV (MASH) cohort. J Drug Abuse. 2016;2(4).
14. Rasbach DA, Desruisseau AJ, Kipp AM, Stinnette S, Kheshti A, Shepherd BE, et al. Active cocaine use is associated with lack of HIV-1 virologic suppression independent of nonadherence to antiretroviral therapy: use of a rapid screening tool during routine clinic visits. AIDS Care. 2013;25(1):109–17. [PubMed: 22670566]
15. Tolson C, Richey LE, Zhao Y, Korte JE, Brady K, Haynes L, et al. Association of substance use with hospitalization and virologic suppression in a southern academic HIV clinic. Am J Med Sci. 2018;355(6):553–8. [PubMed: 29891038]
16. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. Am Journal Psychiatry. 2002; 159(10):1642–52. [PubMed: 12359667]
17. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. 2011;12(11):652–69. [PubMed: 22011681]
18. Feil J, Sheppard D, Fitzgerald PB, Yucel M, Lubman DI, Bradshaw JL. Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control. Neurosci Biobehav Rev. 2010;35(2):248–75. [PubMed: 20223263]
19. Potvin S, Stavro K, Rizkallah E, Pelletier J. Cocaine and cognition: A systematic quantitative review. J Addict Med. 2014;8(5):368–76. [PubMed: 25187977]
20. Albein-Urios N, Martinez-Gonzalez JM, Lozano O, Clark L, Verdejo-Garcia A. Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: Implications for cocaine-induced neurotoxicity. Drug Alcohol Depend. 2012;126(1-2):1–6. [PubMed: 22475814]
21. Lopes BM, Goncalves PD, Ometto M, Dos Santos B, Cavallet M, Chaim-Avancini TM, et al. Distinct cognitive performance and patterns of drug use among early and late onset cocaine users. Addictive behaviors. 2017;73:41–7. [PubMed: 28475942]
22. Meade CS, Towe SL, Skalski LM, Robertson KR. Independent effects of HIV infection and cocaine dependence on neurocognitive impairment in a community sample living in the southern United States. Drug Alcohol Depend. 2015;149:128–35. [PubMed: 25697913]

23. Meade CS, Conn NA, Skalski LM, Safren SA. Neurocognitive impairment and medication adherence in HIV patients with and without cocaine dependence. J Behav Med. 2011;34(2):128–38. [PubMed: 20857187]

24. Dash S, Balasubramaniam M, Villalta F, Dash C, Pandhare J. Impact of cocaine abuse on HIV pathogenesis. Front Microbiol. 2015;6:1111. [PubMed: 26539167]

25. Baddeley AD. Working memory. Oxford, England: Oxford University Press; 1986.

26. Hofmann W, Schmeichel BJ, Baddeley AD. Executive functions and self-regulation. Trends Cogn Sci. 2012;16(3):174–80. [PubMed: 22336729]

27. Keshavan MS, Vinogradov S, Rumsey J, Sherrill J, Wagner A. Cognitive training in mental disorders: Update and future directions. Am Journal Psychiatry. 2014;171(5):510–22. [PubMed: 24700194]

28. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. Am Journal Psychiatry. 2007;164(12):1791–802. [PubMed: 18056233]

29. Krabbendam L, Aleman A. Cognitive rehabilitation in schizophrenia: A quantitative analysis of controlled studies. Psychopharmacology. 2003;169(3-4):376–82. [PubMed: 12545330]

30. Twamley EW, Jeste DV, Bellack AS. A review of cognitive training in schizophrenia. Schizophr Bull. 2003;29(2):359–82. [PubMed: 14552510]

31. O'Connell RG, Bellgrove MA, Dockree PM, Robertson IH. Cognitive remediation in ADHD: effects of periodic non-contingent alerts on sustained attention to response. Neuropsychol Rehabil. 2006;16(6):653–65. [PubMed: 17127571]

32. Elgamal S, McKinnon MC, Ramakrishnan K, Joffe RT, MacQueen G. Successful computer-assisted cognitive remediation therapy in patients with unipolar depression: a proof of principle study. Psychol Med. 2007;37(09):1229–38. [PubMed: 17610766]

33. Tchanturia K, Davies H, Campbell I. Cognitive remediation therapy for patients with anorexia nervosa: preliminary findings. Ann Gen Psychiatry. 2007;6(1):14. [PubMed: 17550611]

34. Vance DE, Fazeli PL, Cheatwood J, Nicholson WC, Morrison SA, Moneyham LD. Computerized cognitive training for the neurocognitive complications of HIV infection: A systematic review. J Assoc Nurses AIDS Care. 2019;30(1):51–72. [PubMed: 30586083]

35. Verdejo-Garcia A Cognitive training for substance use disorders: Neuroscientific mechanisms. Neuroscience & Biobehavioral Reviews. 2016;68:270–81. [PubMed: 27236041]

36. Bickel WK, Yi R, Landes RD, Hill PF, Baxter C. Remember the future: Working memory training decreases delay discounting among stimulant addicts. Biol Psychiat. 2011;69(3):260–5. [PubMed: 20965498]

37. Brooks SJ, Wiemerslage L, Burch KH, Maiorana SA, Cocolas E, Schioth HB, et al. The impact of cognitive training in substance use disorder: The effect of working memory training on impulse control in methamphetamine users. Psychopharmacology. 2017;234(12):1911–21. [PubMed: 28324119]

38. Rass O, Schacht RL, Buckheit K, Johnson MW, Strain EC, Mintzer MZ. A randomized controlled trial of the effects of working memory training in methadone maintenance patients. Drug Alcohol Depend. 2015;156:38–46. [PubMed: 26404954]

39. Houben K, Wiers RW, Jansen A. Getting a grip on drinking behavior: training working memory to reduce alcohol abuse. Psychol Sci. 2011;22(7):968–75. [PubMed: 21685380]

40. Sealed Envelope Ltd. Create a blocked randomisation list2017; (3/3/2017). Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists.

41. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The fifth edition of the Addiction Severity Index. J Subst Abuse Treat. 1992;9(3):199–213. [PubMed: 1334156]

42. First MB, Williams JBW, Karg RS, Spitzer RL. Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV). Arlington, VA: American Psychiatric Association; 2015.

43. Robinson SM, Sobell LC, Sobell MB, Leo GI. Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. Psychol Addict Behav. 2014;28(1):154–62. [PubMed: 23276315]

44. Sobell LC, Sobell MB. Timeline Follow-back User's Guide: A Calendar Method for Assessing Alcohol and Drug Use. Toronto: Addiction Research Foundation; 1996.

45. Wilkinson GS, Robertson GJ. Wide Range Achievement Test–4 (WRAT-4). Lutz, FL: Psychological Assessment Resources; 2006.
46. Wechsler D. Wechsler Test of Adult Reading (WTAR) Manual. San Antonio, TX: Harcourt Assessment; 2001.
47. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69(18):1789–99. [PubMed: 17914061]
48. Diehr MC, Cherner M, Wolfson TJ, Miller SW, Grant I, Heaton RK. The 50 and 100-item short forms of the Paced Auditory Serial Addition Task (PASAT): Demographically corrected norms and comparisons with the full PASAT in normal and clinical samples. J Clin Exp Neuropsychol. 2003;25(4):571–85. [PubMed: 12911108]
49. Wechsler D. Wechsler Adult Intelligence Scale--Fourth Edition: Administration and Scoring Manual. Bloomington, MN: Pearson; 2008 2008.
50. Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation 2nd ed. Tucson, AZ: Neuropsycholgy Press 1993.
51. Golden CJ. Stroop Color and Word Test. Chicago, IL: Stoelting; 1978.
52. Brandt J, Benedict RHB. Hopkins Verbal Learning Test -- Revised professional manual. Lutz, FL: Psychological Assessment Resources, Inc; 2001.
53. Benedict RHB. Brief Visuospatial Memory Test-Revised Professional Manual. Odessa F, editor. Odessa, FL: Psychological Assessment Resources, Inc.; 1997.
54. Kongs SK, Thompson LL, Iverson GL, Heaton RK. Wisconsin Card Sorting Test-64 Computerized Version. Odessa, FL: Psychological Assessment Resources; 2000.
55. Benton A, Hamsher K, Sivan A. Multilingual Aphasia Examination (3rd ed.). Iowa City, IA: AJA Associates; 1983.
56. Klove H. Grooved Pegboard. Lafayette, IN: Lafayette Instruments; 1963.
57. Heaton RK, Miller SW, Taylor MJ, Grant I. Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Lutz, FL: Psychological Assessment Resources, Inc; 2004.
58. Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol. 2004;26(3):307–19. [PubMed: 15512922]
59. Brown SE, Krishnan A, Ranjit YS, Marcus R, Altice FL. Assessing mobile health feasibility and acceptability among HIV-infected cocaine users and their healthcare providers: Guidance for implementing an intervention. mHealth. 2020;6:4. [PubMed: 32190615]

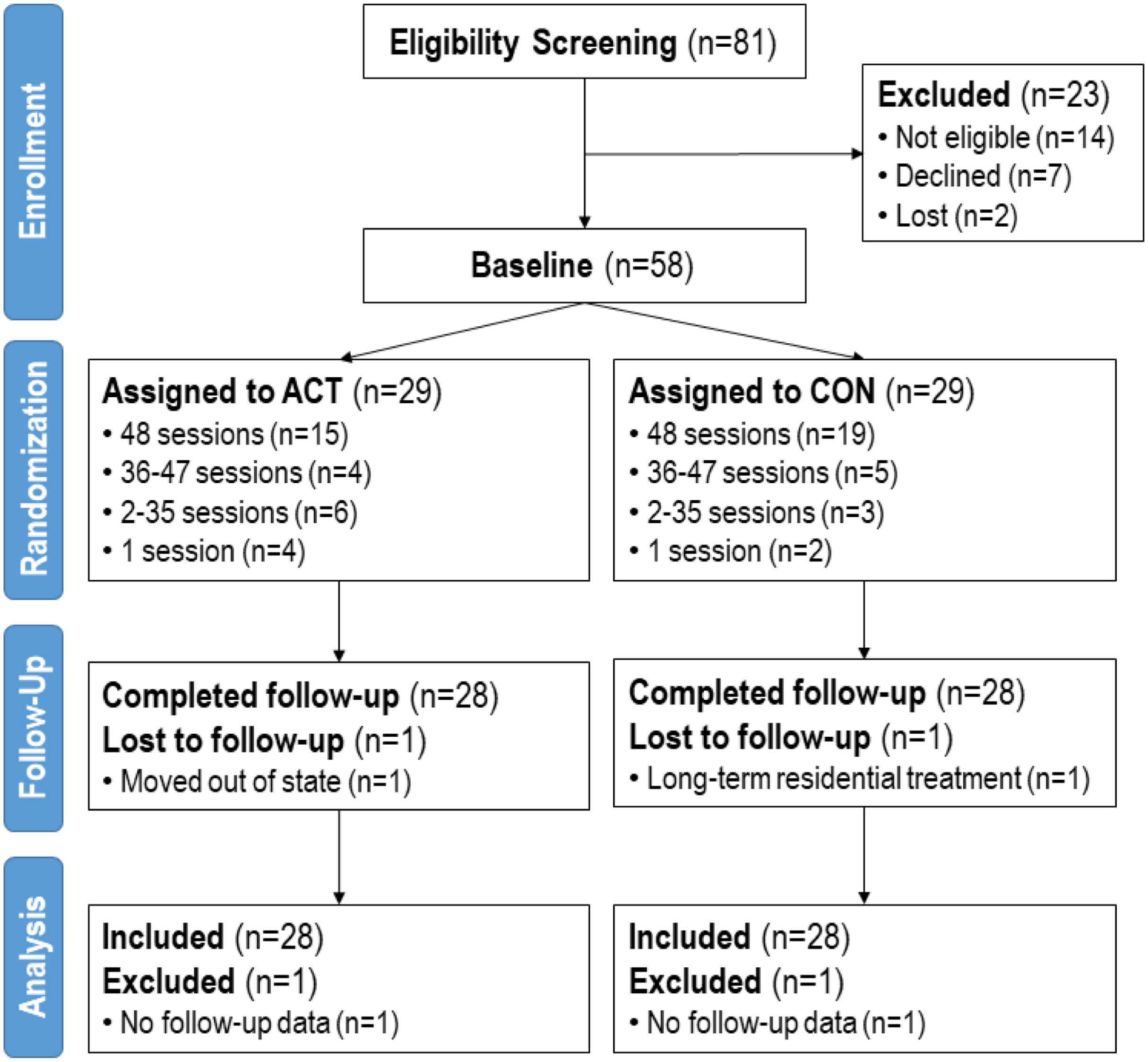

Figure 1.

Flow diagram of participant recruitment, enrollment and retention.

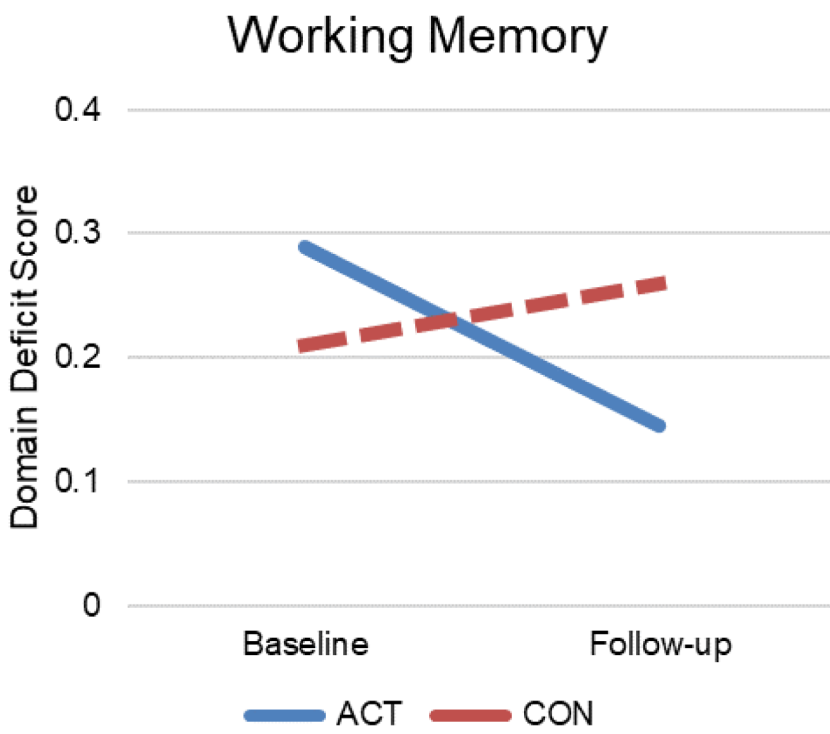

Figure 2.
Intent-to-treat analysis on working memory. Estimated marginal means are shown.

Table 1.

Participant characteristics by study arm (*N*=58)

	ACT (n = 29)	CON (n = 29)	Statistic	p value
Demographic and other characteristics				
Male sex, n (%)	24 (83%)	18 (62%)	$\chi^2(1) = 3.11$	0.08
Age in years, M (SD)	48.97 (10.09)	48.28 (8.28)	$t(56) = 0.28$	0.78
African American race, n (%)	26 (90%)	24 (83%)	Fisher's test	0.71
Education in years, M (SD)	12.07 (2.67)	11.86 (2.07)	$t(56) = 0.33$	0.74
WTAR Standard Score, M (SD)	81.97 (14.47)	83.14 (13.75)	$t(56) = -0.32$	0.75
Current depression (SCID Module A)	3 (10%)	6 (21%)	Fisher's test	0.47
HIV characteristics				
Years since HIV diagnosis	15.66 (6.91)	16.14 (8.22)	$t(56) = -0.24$	0.81
Nadir CD4+ T cells/mm^3, *Mdn (IQR)*	100.00 (24.50, 314.50)	225.00 (61.50, 416.00)	U=311.00	0.09
Current CD4+ T cells/mm^3, *Mdn (IQR)*	574.00 (287.50, 826.00)	670.00 (489.50, 857.50)	U=328.50	0.15
Suppressed viral load, n (%)	23 (79%)	25 (86%)	Fisher's test	0.73
Cocaine use characteristics				
Days of cocaine use in past 90 days, M (SD)	22.45 (26.81)	21.17 (21.33)	$t(56) = 0.20$	0.84
Primary route of administration, n (%)			$\chi^2(1) = 0.08$	0.77
Inhalation	21 (72%)	20 (69%)		
Intranasal	8 (28%)	9 (31%)		
Current cocaine use disorder, n (%)	25 (86%)	23 (79%)	Fisher's test	0.73
Years of regular cocaine use, M (SD)	19.38 (11.33)	16.07 (9.96)	$t(56) = 1.18$	0.24
Other substance use in oast 90 days				
Any alcohol use, n (%)	27 (93%)	25 (86%)	Fisher's test	0.67
Any marijuana use, n (%)	16 (55%)	19 (66%)	$\chi^2(1) = 0.65$	0.42
Any opiate use, n (%)	4 (14%)	9 (31%)	Fisher's test	0.21
Baseline neuropsychological functioning				
GDS, M (SD)	0.67 (0.50)	0.76 (0.61)	$t(56) = -0.57$	0.57
Working memory DDS, M (SD)	0.29 (0.55)	0.21 (0.40)	$t(56) = 0.63$	0.53
Processing speed DDS, M (SD)	0.53 (0.57)	0.29 (0.49)	$t(56) = 1.74$	0.09
Learning DDS, M (SD)	1.59 (1.36)	1.50 (1.36)	$t(56) = 0.24$	0.81

	ACT (*n* = 29)	**CON (*n* = 29)**	**Statistic**	***p* value**
Memory DDS, *M* (*SD*)	1.38 (1.27)	1.41 (1.42)	$t(56) = -0.10$	0.92
Executive function DDS, *M* (*SD*)	0.49 (0.58)	0.64 (0.64)	$t(56) = -0.93$	0.36
Verbal fluency DDS, *M* (*SD*)	0.12 (0.34)	0.34 (0.63)	$t(56) = -1.68$	0.10
Motor skills DDS, *M* (*SD*)	0.33 (0.52)	0.91 (1.32)	$t(56) = -2.22$	0.03

Note. M = Mean; SD = Standard deviation; Mdn = Median; IQR = interquartile range.

Table 2.

Participant ratings of the intervention (*N*=56)

	ACT (*n* = 29)	CON (*n* = 29)	Statistic	*p* value
Overall satisfaction (1 = Very dissatisfied, 2=Somewhat dissatisfied, 3 = Neutral, 4 = Somewhat satisfied, 5 = Very satisfied)	4.04 (1.32)	4.14 (1.11)	$t(54) = -0.33$	0.74
Overall helpfulness* (1 = Very unhelpful, 2=Somewhat unhelpful, 3 = Neutral, 4 = Somewhat helpful, 5 = Very helpful)	4.14 (1.15)	4.04 (1.02)	$t(53) = 0.36$	0.72
I got better at playing the games over time	4.39 (0.69)	3.89 (0.92)	$t(54) = 2.31$	0.02
The training sessions were fun	4.07 (0.94)	3.93 (0.98)	$t(54) = 0.56$	0.58
The training sessions were challenging	4.11 (0.74)	4.04 (0.84)	$t(54) = 0.34$	0.74
I thought some of the games were too difficult	2.68 (1.09)	2.18 (0.90)	$t(54) = 1.87$	0.07
I completed sessions because I thought they would be helpful to me	4.14 (0.76)	4.25 (0.52)	$t(54) = -0.62$	0.54
I completed sessions because I knew I would be paid for my time	3.04 (1.10)	3.61 (0.88)	$t(54) = -2.15$	0.04
I liked the website that was used for the sessions	4.07 (0.98)	4.04 (0.96)	$t(54) = 0.14$	0.89
Playing games twice back-to-back in each session was helpful	3.71 (1.21)	4.04 (0.74)	$t(54) = -1.20$	0.24
It was difficult to complete 5 or 6 sessions per week	2.29 (1.27)	2.21 (1.03)	$t(54) = 0.23$	0.82
It was difficult to complete sessions for 10 weeks	2.18 (1.22)	2.25 (1.11)	$t(54) = -0.23$	0.82
What did you think about the length of each session? (1 = Too short, 2=Somewhat short , 3 = Just right, 4 = Somewhat long, 5 = Too long)	3.07 (0.38)	3.04 (0.74)	$t(54) = 0.23$	0.82
What did you think about the number of sessions overall? (1 = Definitely not enough, 2=Maybe not enough , 3 = Just right, 4 = Maybe too many, 5 = Definitely too many)	2.89 (0.83)	2.93 (0.77)	$t(54) = -0.17$	0.87
How often… (1 = None of the time, 2=Only a few times or rarely, 3 = Some of the time, 4 = Most of the time, 5 = All of the time)				
Were you able to complete all 8 games in a single sitting?	4.21 (0.83)	4.14 (1.01)	$t(54) = 0.29$	0.77
Did you complete training sessions after getting high or buzzed?	1.96 (1.04)	2.25 (1.27)	$t(54) = -0.92$	0.36

[*] One participant skipped this item.

Note. Standard deviations are presented in parentheses after the mean. Participants rated each item on a 5-point agreement scale (1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree) unless otherwise noted.