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ORIGINAL PAPER

Can Individualized-Targeted Computerized Cognitive Training Benefit Adults with HIV-Associated Neurocognitive Disorder? The Training on Purpose Study (TOPS)

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Abstract

Half of people with HIV (PWH) have HIV-associated neurocognitive disorder (HAND). This study examined whether cognition can be improved using a framework targeting impaired individual cognitive domains in PWH with HAND. In this two-group pre-post experimental design study, 88 adults with HAND were randomized to either: (1) a no-contact control group ($n=40$) or (2) the Individualized-Targeted Cognitive Training group ($n=48$). Baseline cognitive performance was assessed on eight cognitive domains. A theoretical framework was used to determine the two cognitive domains selected for training. With priority on speed of processing (SOP) and attention impairments, participants received SOP and/or attention training if such impairments were detected; if not, participants were assigned to cognitive training in one/two of the least impaired cognitive domains contributing to their HAND diagnosis. Global cognitive score was slightly improved following training ($p=0.256$; $d=-0.21$), but it was not significant. Significant improvements were observed on SOP following training in that domain (SOP; $d=-0.88$; $p=0.011$). SOP training also improved functioning in other cognitive domains. This individualized cognitive intervention did not change HAND status, but it did result in improved SOP, in turn yielding improvement in other cognitive domains.

Keywords Brain fitness · Cognitive reserve · Cognitive training · HIV-Associated Neurocognitive Disorder · Neuroplasticity · Speed of processing

Introduction

In 2018, nearly 51% of people with HIV (PWH) in the U.S. and dependent areas were aged 50 and older [1]; by 2030 this number is expected to increase to 70% [2].

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Combined with the effects of cognitive aging, the incidence and severity of such cognitive impairments, often referred to as HIV-associated Neurocognitive Disorder (HAND), is expected to increase as people age with HIV [3, 4]. Such cognitive impairments can impair everyday functioning (i.e., driving safely, medication adherence, financial management) and quality of life (i.e., cognitive complaints, depressive symptomatology, poor locus of control) [5]. As such, HAND can decrease autonomy and increase the need for caregiving support [6].

HIV-Associated Neurocognitive Disorder

A diagnosis of HAND is established using a neuropsychological algorithm called the Frascati criteria [7]. Developed by a team of neuroAIDS experts, these criteria require the use of norm-based (age/education) cognitive performance measures in five or more cognitive domains. HAND is diagnosed when a person performs more than 1 *SD* below his/her demographically adjusted mean in two or more cognitive

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domains (e.g., executive function, memory) [8]. (For more details regarding nuances of the HAND diagnosis see Blackstone et al. [9]). As such, it is common for PWH to meet the criteria for HAND by only a fraction of a *SD*. If there are interventions that can improve cognitive functioning by such a fraction, it is possible to reduce the incidence of the HAND diagnosis. This finding would represent a shift in the way we consider HAND, removing its stigma as a static "progressive" diagnosis to something that can be modified and treated. Indeed, studies suggest HAND has a variable course, as compared to more degenerative conditions such as Alzheimer's disease [10].

Cognitive Training

Fortunately, cognitive training programs resulting in small-to-moderate cognitive improvements, perhaps by only a fraction of a *SD,* may sufficiently improve performance in an individual's critical cognitive domain(s). In a systematic review of 13 studies on cognitive training programs in PWH, Vance and colleagues found that, in general, cognitive training successfully improved cognition in the domain that was targeted for training [11]. For example, Vance, Fazeli, Ross, Wadley, and Ball [12] randomized a sample of 46 adults living with HIV to either: (1) a no-contact control group, or (2) a speed of processing (SOP) training group. Those in the SOP training group received 10 h of computerized exercises specifically designed to improve the ability to quickly process visual stimuli. This study demonstrated that SOP training was effective as measured by the Useful Field of View test, a cognitive test of visual SOP and visual attention ($p = 0.04$, power = 0.53). In addition, the training improved everyday functioning as measured by the Timed Instrumental Activities of Daily Living (TIADL) test ($p = 0.03$, power = 0.59).

Yet, with the relatively few studies, generally underpowered due to small sample sizes, of cognitive training in PWH, the clinical utility of recommending and administering cognitive training in this clinical population remains unclear. Fortunately, studies in older adults without HIV provide additional insights. In a meta-analysis of 52 cognitive training studies using a variety of computer-based cognitive training protocols (in one or multiple cognitive domains) conducted with community-dwelling older adults aged 60–82 years old, Lampit and colleagues [13] determined that the average cognitive improvement after cognitive training was 0.22 standard deviations (*SD*). Upon closer examination, these researchers found significant cognitive improvement across various domains including SOP ($g = 0.31$), visuospatial skills ($g = 0.30$), nonverbal memory ($g = 0.24$), working memory ($g = 0.22$), and verbal memory ($g = 0.08$). Although these training gains are expressed in small-to-moderate effect sizes, based on how HAND is operationalized, such cognitive improvement after training may be enough to change this classification.

Methods for Changing the HAND Diagnosis

Although we may be able to improve function in specific cognitive domains via cognitive training, such training often requires 10–20 h of intense engagement per cognitive domain [13]. Many with HAND experience impairments in numerous cognitive domains [4]; thus, the time required to engage in cognitive training to improve all impaired domains could be significant (e.g., 100 h), which represents significant burden and likely would result in non-adherence. A strategy to allocate such cognitive training to a smaller number of domains may reduce such burden, facilitate adherence, and improve cognition.

To address this dilemma, such a strategy was created called the Individualized-Targeted Cognitive Training Framework [14]. This framework posits that in order to not over burden the participant, cognitive training should target the individual's impairments in SOP and attention first, if any impairments in these two domains are detected for the participant. Otherwise, cognitive training should focus on the domains that are least impaired but still contribute to the HAND diagnosis. Thus, only two cognitive domains should be targeted for training (10 h of training for each cognitive domain). This framework is based on the Diminished SOP Theory [15] and the Wickens Model of Information Processing [16], as well as evidence from the cognitive aging literature, which demonstrate that improvements in SOP and attention are core cognitive abilities that support all other cognitive domains. For example, in a sample of 186 PWH, Fellows, Byrd, and Morgello [17] observed that SOP "fully mediated the effects of age on learning, memory, and executive functioning and partially mediated the effect of major depressive disorder on learning and memory" (p. 806). Thus, improvement in these cognitive domains theoretically can transfer to improvement in other cognitive domains. (Details of the framework are described in the Methods section.)

Hypothesis

Based on this literature and the Individualized-Targeted Cognitive Training Framework just described, this study posed two aims. Aim 1 was to test the hypothesis that a person-centered cognitive training intervention targeting impaired individual cognitive domains can reduce the incidence of individuals meeting the criteria for HAND in PWH age 40 and older. Aim 2 was to explore whether targeted cognitive training would produce cognitive benefits on global and individual cognitive functioning scores.

Methods

Design Overview

The Training on Purpose Study (TOPS) examined an Individualized-Targeted Cognitive Training Framework, an algorithm to allocate domain-specific cognitive training to address each participants' unique pattern of cognitive impairment as determined during the baseline assessment. This framework was designed to decrease the severity and incidence of cognitive impairment in certain domains, and thus possibly reduce the severity and incidence of HAND. In this two-group pre/post experimental design, participants were recruited from a university HIV/AIDS clinic and were administered a comprehensive battery of cognitive and psychosocial measures at baseline. Those who met the diagnostic criteria of HAND were randomized to either: (1) a no-contact control group, or (2) an Individualized-Targeted Cognitive Training group. Participation in the no-contact control group was limited to the baseline assessment, and then the posttest assessment approximately 12 weeks later. Those in the experimental group engaged in 20 h of cognitive training programs targeting two cognitive domains, with ten hours targeting one cognitive domain and ten hours targeting another cognitive domain in which impairments were detected at baseline. Again, the framework was used to determine which specific cognitive training programs each participant received based on his/her baseline cognitive performance. After cognitive training was completed approximately 12 weeks later, these experimental participants were administered the posttest assessment. Ethical approval for this study was granted by the University of Alabama at Birmingham's Institutional Review Board.

Participants

As can be seen from the Consort Figure (Fig. 1), potential participants were recruited from flyers posted at an HIV/AIDS clinic, AIDS service organizations, local churches, and public businesses (e.g., laundromats). Those interested called a phone number listed on the flyer and were screened over the telephone to determine eligibility. Inclusion criteria included: (a) diagnosed with HIV for at least 1 year; (b) 40 years of age or older; (c) free from any severe neuromedical condition (e.g., schizophrenia, Alzheimer's disease, traumatic brain injury); (d) not currently undergoing radiation or chemotherapy; (e) able to communicate proficiently in written and spoken English; (f) adequate vision and hearing; and (g) residence within 100 miles of the research center. From this, 135 participants

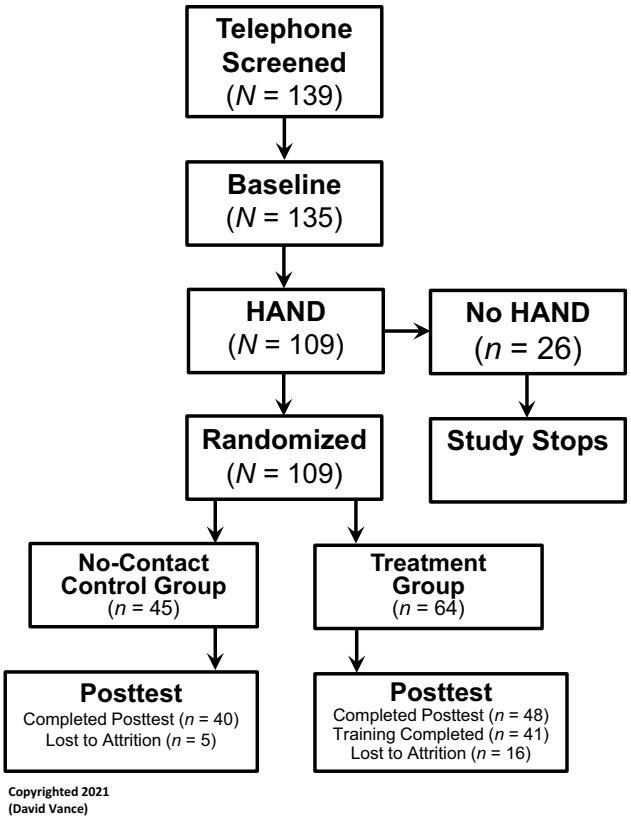

Fig. 1 TOPS consort diagram

were consented at baseline and administered a cognitive battery; based on their cognitive performance, the Frascati criteria were applied to determine whether participants met the criteria for HAND (described below). The 109 participants who met the HAND criteria were informed of this and randomized into the study. The 26 participants who did not meet the HAND criteria were also informed of this result, at which point their participation ended. Participants were compensated for the pretest/posttest assessments ($50 each) and cognitive training sessions ($15/hour of cognitive training).

Measures

Participants completed 1.5–2 h assessments at the research center at baseline/pretest and posttest. These assessments were administered by a trained cognitive tester who was supervised by the Principal Investigator to prevent drift in the cognitive assessment protocol.

Demographics

Age, gender, education, and other basic demographic information was determined by self-report at baseline.

Health Information

A health questionnaire was administered at baseline in which participants indicated prescribed medications, and alcohol (i.e., number of drinks on a typical day when drinking) and tobacco use (i.e., number of cigarettes smoked per day).

HIV Health Status

Upon entering the study, participants' medical providers were contacted for the following information: HIV-positive diagnosis confirmation, years diagnosed with HIV, current and nadir CD4+ lymphocyte count, current viral load, and HIV medication regimen.

Depression

Depression was measured using the Center for Epidemiologic Studies Depression Scale-Revised (CES-D; [18]). A score of 16 or higher reflects significant depressive symptomology.

Cognitive Domains and Frascati Criteria

Eight cognitive domains were assessed using standardized normed cognitive measures at pretest and posttest; these measures are commonly used in neuroAIDS research [9, 19]. Normed *T*-scores of the cognitive measures were used to approximate clinical ratings of cognitive functioning in each of the domains ranging from 1 (above average, if *T*-score is 55 or higher) to 9 (severe impairment, if *T*-score is 19 or below). This cognitive battery consisted of: (1) SOP (Stroop Color Naming Test, Trails A); (2) attention (Paced Auditory Serial Attention Test); (3) executive function (Stroop Interference), Trails B); (4) spatial learning and memory (Benton Visual Retention Test—Revised); (5) delayed spatial learning and memory (Benton Visual Retention Test Delayed—Revised); (6) spatial visualization (WAIS IV Block Design); (7) verbal learning and memory (Hopkins Verbal Learning Test—Revised); and (8) delayed verbal learning and memory (Hopkins Verbal Learning Test Delayed—Revised) [9, 19, 20]. Using this baseline cognitive battery, cognitive impairments were identified for training (see the Procedures/Treatment section below).

Using each participant's cognitive domains test scores combined, an algorithm was used to calculate a Global Clinical Rating score ranging from 1 (*above average*) to 9 (*severe impairment*). Specifically, scores from 5 to 9 reflected in two cognitive domains indicated HAND. Thus, using this continuum, the Global Clinical Rating score of 5 or higher was indicative of HAND [9, 19]. In making a medical diagnosis of HAND, other factors such as impairments in everyday functioning and the contribution of comorbidities to cognitive impairments are often considered. For this study, only cognitive performance was taken into consideration (e.g., meeting the criteria for the least severe category of HAND labeled as asymptomatic neurocognitive impairment [ANI]). (For more information regarding HAND and other TOPS methodological details, see Vance et al. [14]).

Procedures/Treatment Design and Rationale

Participants with HAND were randomized to the control group ($n=40$) or the cognitive training group ($n=48$). A block randomization strategy ensured a balanced assignment between women/men and Africans Americans/Caucasians. Time between baseline and posttest was approximately 85.25 ($SD=48.69$) days (control group = 84.48 ($SD=27.76$) days; cognitive training group = 85.92 ($SD=61.22$) days, t-value = 0.14(86), p-value = 0.89). Participants in the cognitive training group received ten hours of training in each of two areas of impairment detected during baseline testing. Under the supervision of a cognitive trainer, all cognitive training occurred at the research center to monitor participants' progress, assist with logging onto the computer program, provide encouragement, and maintain treatment fidelity. The cognitive trainer was taught how to administer the cognitive training and was supervised by the Principal Investigator to avoid drift in the cognitive training protocol.

Cognitive training requires intense focus and can result in fatigue. For this reason, breaks were provided to participants as needed. The training dose of ten hours in each of two cognitive domains (for a total of 20 h per participant) was selected based on the concern that training fatigue would lead to attrition as well as the U-shaped dosage-therapeutic response reported by Lampit et al. [13]. Other studies support 10 h as a sufficient training dose to improve function in a particular cognitive domain [12, 21].

As mentioned, participants may have impairments in up to all eight cognitive domains; however, it is not feasible to target 80 h of cognitive training (i.e., 10 h of training/domain × 8 cognitive domains). For this reason, a cognitive training algorithm was developed to target the cognitive domains that would be most likely to reverse the HAND diagnosis for each individual participant, and in which the participant might have the greatest amount of cognitive reserve. The Individualized-Targeted Cognitive Training Framework was designed specifically for this study with three steps [14]. In step one, participants with impairments in either SOP ($n=22$) or attention ($n=13$) were automatically assigned cognitive training in one or both of those domains; as alluded to previously, these are considered core cognitive abilities that support the functioning of other cognitive domains. In step two, participants without impairments in either SOP or attention (or with impairments in only one) were assigned to cognitive training in their least

compromised (but still impaired) cognitive domain(s) (i.e., closest to cutoff of 1 *SD* below the demographically-adjusted mean). The rationale for this was that participants may have more cognitive reserve in relatively preserved domains and may obtain greater benefit from training in these domains than in more compromised domains. This approach purposely manipulates the criteria by which HAND is diagnosed by targeting the cognitive domain needing the least improvement to no longer meet the HAND criteria.

In step three, participants were assigned to play computerized modules that were selected specifically to improve their abilities in the targeted cognitive domains. The modules used for each cognitive domain were as follows: (a) SOP (Double Decision; Hawkeye; Visual Sweeps); (b) attention (Divided Attention; Target Tracker); (c) executive function (Mind Bender; Mixed Signals); (d) spatial learning and memory (Mental Maps; True North); (e) delayed spatial learning and memory (Mental Maps; True North); (f) spatial visualization (Mental Maps; True North); (g) verbal learning and memory (Memory Grid; Syllable Stacks); and (h) delayed verbal learning and memory (Memory Grid; Syllable Stacks). More information about these cognitive training modules can be found at www.brainhq.com.

A treatment adherence checklist was used to review with participants the amount of time that they had engaged in cognitive training. The software also monitors the amount of time participants spend engaged in each exercise. The correlation between the checklist and the software on time engaged in cognitive training was very high $r = 0.935$; $p = 0.001$). For the convenience of the participants, they could do two hours of training at a time to reduce the number of visits to the research center, but in general, most participants spread out their cognitive training sessions. Participants completed cognitive training in an average of approximately 12 weeks (averaging 1.66 h/week of cognitive training). Lampit and colleagues found optimal therapeutic effects occurred when training sessions are administered 1–3 times per week—dosage parameters incorporated in the TOPS protocol [13]. Furthermore, similar to the seminal ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) Study ($N = 2802$), participants were considered to be trained in each cognitive domain when they successfully completed 7–10 h of training in each domain [21].

Data Analysis

To produce fair comparisons between study groups across cognitive domains, based on their baseline cognitive assessment, the same cognitive training assignment algorithm was applied to participants in the control group to determine the training they would have received had they been randomized to the individualized-training group [22]. Thus, outcomes from the trained group in a specific domain were compared to those from participants in the control group who were their matches in the sense that they would have received that specific training. From this, two sets of analyses were conducted, a completers-only analysis ($n = 41$ trained vs. $n = 40$ in the control group) and an intention to treat (ITT) analysis including $n = 7$ participants who did not complete training ($n = 48$ in the training group vs. $n = 40$ in the control group). The ITT results are presented in this report. A completers-only analysis may be informative when examining the actual potential of the cognitive training, and results are available as supplemental materials (Supplemental tables 1, 2 and 3). The main conclusions did not differ across the two sets of analyses, although there was some variability in the estimates, as expected from changes in small samples. The sample size considerations for the study were based on feasibility and, as with any pilot project [23], the study was not powered for formal statistical inference. Therefore, interpretation is based on in-sample measures of effect size and results are considered exploratory. Analysis began by examining balance between study groups with respect to baseline characteristics (e.g., age, gender, race, HIV markers, etc.) using measures of effect size, such as Cohen's *d* (small ~ 0.2, medium ~ 0.5, large ~ 0.8) and Cramer's *V* (small ~ 0.1, medium ~ 0.3, large ~ 0.5, for cross-tabulations comparing two groups) [24]. Next, for each of the eight cognitive domain scores, descriptive statistics were tabulated at the pre- and post-intervention time-points by study group (matched by assigned training and hypothetical assigned training). Linear mixed-effects models with a random effect for subject were used to estimate the between-group difference in change from pre- to post-intervention, using a time-by-group interaction coefficient. The variance components from each model were used to estimate a pooled *SD* for each domain score, which was then used to standardize the interaction coefficient and provide a measure of effect size (Cohen's *d*). The Satterthwaite approximation to degrees of freedom was used for significance tests of the interaction effect. Analyses were conducted using R software version 3.6 [25].

Results

Participant Characteristics

Table 1 shows baseline characteristics of the $N = 88$ participants included in the ITT analysis. On average, participants were 54.2 ($SD = 7$) years old, about two thirds were male ($n = 60$, 68.2%), and the majority were African American ($n = 75$, 85.2%). Participants had an average of 12.4 ($SD = 2.2$) years of education and reported an average income of approximately $17,600 ($SD = $14,600). In terms of selected HIV characteristics, on average participants had

Table 1 Participant characteristics at baseline by group assignment

Variable	No-contact control group ($n=40$)		Individualized-targeted cognitive training ($n=48$)		*Effect size*
	n (%)	Mean (*SD*)	*n* (%)	Mean (*SD*)	
Age		54.23 (7.42)		54.19 (6.65)	d = 0.01
Gender					V = 0.11
Male	25 (62.5%)		35 (72.92%)		
Female	15 (37.5%)		13 (27.08%)		
Race/Ethnicity					V = 0.14
African America	36 (90%)		39 (81.25%)		
Caucasian	4 (10%)		8 (16.67%)		
Other	0 (0%)		1 (2.08%)		
Education (years)		12.5 (2.11)		12.4 (2.36)	d = 0.05
Household income ($10 K)		1.75 (1.35)		1.77 (1.56)	d = 0.01
Years diagnosed with HIV		16.45 (8.52)		17.54 (7.73)	d = 0.13
Current CD4+ T lymphocyte count/mm^3		762.13 (444)		630.13 (423.87)	d = 0.3
Nadir CD4+ T lymphocyte count/mm^3		401.31 (379.68)		324.26 (328.67)	d = 0.22
Number of prescribed medications		5.23 (4.41)		5 (4.11)	d = 0.05
Prescribed ART	29 (72.5%)		40 (83.33%)		V = 0.13
CES-Depression		16.08 (9.13)		18.69 (11.85)	d = 0.24
Alcohol use* (no. of drinks)		1.83 (0.81)		1.81 (1.02)	d = 0.01
Tobacco use (cigarettes/day)		4.4 (6.76)		3.15 (4.16)	d = 0.23

d Cohen's d, *V* Cramer's V, *ART* antiretroviral therapy, *CES-Depression* Center for Epidemiological Studies Depression Scale, *SD* standard deviation, *$10 K* ten thousand dollars

*Alcohol Use ranges from 1 (not applicable/don't drink), 2 (one to two drinks), 3 (three to four drinks), 4 (five to six drinks), 5 (seven to nine drinks), and 6 (ten or more drinks)

been living with HIV for 17 years ($SD=8.1$), had current CD4+ T lymphocyte count/mm^3 of 691.5 ($SD=435.8$), lowest recorded count/mm^3 of 359.6 (SD = 352.9), and the majority were on ART ($n=69$, 78.4%). The mean CESD score was 17.5 ($SD=10.7$), with $n=51$ (58%) reporting CESD ≥ 16, indicating severe depressive symptomatology. Measures of effect size did not suggest any major imbalance between the study groups, however, a moderate difference in mean current CD4+ T lymphocyte count/mm^3 scores was observed, with a higher value in the control group. On further inspection, it was found that the difference came from the right tail of the distribution with a few participants having relatively high CD4+ T lymphocyte counts. After a log transformation of CD4+ T lymphocyte counts, the between-group standardized difference was reduced to $d=0.2$ (a small effect size).

Effects of Training on Cognitive Domains

Table 2 presents descriptive statistics and measures of training effect overall and by each specific cognitive domain. The between-group comparisons for specific domains include only participants trained in that domain vs. matched control participants (i.e., control participants who would have received training in that domain had they been randomized to the training group). A small beneficial intervention effect ($d=-0.21$) was observed for the Global Clinical Rating. Large beneficial effects were observed for the SOP ($d=-0.88$), Executive Function ($d=-0.89$), and Spatial Learning and Memory ($d=-0.71$)) domains. Medium to moderate beneficial effects were observed for Attention ($d=-0.45$) and Delayed Spatial Memory ($d=-0.32$)). A moderate detrimental effect was observed for the Delayed Verbal Memory ($d=0.35$) domain.

Table 3 presents measures of training effect on all cognitive domains, comparing participants trained in a specific domain vs. their respective matched control participants. Herein, due to the number of comparisons, we focused on the medium to large effects ($d \geq 0.5$), ignoring trivial and small effects. Compared to their control counterparts, participants who received SOP training showed medium to large improvements on Attention, Verbal Learning and Memory, Delayed Verbal Memory, and Executive Functioning (d ranging from − 0.7 to − 0.63). Participants who received Attention training showed a medium to large improvement on Executive Functioning and Delayed Verbal Memory. Participants who received Delayed Verbal Memory training showed medium to large

Table 2 Intent to treat analysis comparing cognitive outcomes between groups with the same training assignment

Cognitive domain for the cognitive training conducted	No-contact control group ($n=40$)			Individualized-targeted cognitive training ($n=48$)			Difference in change		
	n	Baseline Mean (*SD*)	Posttest Mean (*SD*)	*n*	Baseline Mean (*SD*)	Posttest Mean (*SD*)	*Effect size, Cohen's d*	*Test statistic, t(df)*	*p*-value
Global Cognitive Score*	40	7.18 (1.52)	6.65 (1.86)	48	7.48 (1.38)	6.62 (1.39)	− 0.21	− 1.14(86)	0.2567
Speed of processing*	19	5.89 (1.1)	5.63 (1.21)	22	6.55 (1.3)	5.18 (1.37)	− 0.88	− 2.65(39)	0.0117
Attention*	17	5.59 (0.62)	4.24 (1.52)	16	5.25 (0.58)	3.38 (1.54)	− 0.45	− 1.06(31)	0.296
Verbal learning and memory*	9	5.44 (0.73)	4.89 (2.09)	15	6.07 (0.88)	5.67 (1.88)	0.1	0.19(22)	0.8482
Delayed verbal memory*	10	5.6 (0.97)	5.2 (2.3)	13	6 (1.35)	6.23 (2.28)	0.35	0.71(21)	0.4833
Executive function*	5	5.2 (0.45)	4.4 (1.82)	4	5.25 (0.5)	3.25 (1.89)	− 0.89	− 0.99(7)	0.3546
Spatial learning and memory*	8	6.25 (1.58)	5.12 (2.17)	8	5.88 (1.96)	3.38 (2)	− 0.71	− 1.54(14)	0.1468
Delayed spatial memory*	5	5 (0)	3.8 (2.17)	8	6.75 (1.49)	5 (2.14)	− 0.32	− 0.48(11)	0.6401
Spatial visualization*	7	5.57 (0.79)	4.57 (1.51)	10	5.8 (1.14)	4.7 (2.36)	− 0.06	− 0.11(15)	0.9102

*Lower scores indicate better functioning. Cognitive ratings range from: 1 = above average; 2 = average; 3 = low average; 4 = borderline; 5 = definite mild impairment; 6 = mild-to-moderate impairment; 7 = moderate impairment; 8 = moderate-to-severe impairment; 9 = severe impairment. For comparison purposes, controls in this analysis were compared to treatment group as if they were assigned a similar hypothetical assignment

improvements on SOP and Executive Functioning. Participants who received Executive Functioning training showed medium to large improvements on SOP, Attention, and Delayed Verbal Memory. Participants who received Spatial Learning and Memory training showed medium to large improvements on SOP, Delayed Verbal Memory, and Executive Functioning. Participants who received Delayed Spatial Memory training showed medium to large improvements on SOP and Attention. Participants who received Spatial Visualization training showed a large detrimental effect on Executive Functioning.

Attrition

For the purpose of providing information on potential characteristics of participants at risk of attrition from future cognitive training studies, measures of effect size were used to compare the $n=21$ participants who were lost to follow-up vs. the $n=88$ who provided a post-test assessment, on sociodemographic characteristics and baseline cognitive scores. In terms of the relevant differences found, participants who dropped from the study were more likely to be assigned to cognitive training ($n=16$, 76.2% vs. $n=48$, 54.5%, V = 0.17); tended to be older (M[SD] = 54.2[6.97] vs. 50.9[4.7], $d=0.5$)); tended to have more years of education ($M[SD]=12.4[2.2]$ vs. 11.4[2.6], $d=0.46$); tended to have slightly lower depression symptoms (CESD: $M[SD]=17.54[10.7]$ vs. 20.7[9.6], $d=0.31$); and tended to consume more alcohol (no. daily drinks: $M[SD]=1.8$ [0.9] vs. 1.3[0.6], $d=0.61$).

Discussion

Aim 1 of this study was to examine whether a person-centered cognitive training intervention targeting impaired individual cognitive domains would reduce the incidence of HAND diagnoses. An early interim descriptive study ($n=6$) comparing experimental and control participants of TOPS showed observable cognitive improvement in those who received cognitive training, but no change in HAND diagnosis [26]. Completion of the TOPS study revealed similar findings; global clinical rating improved, but not to the point in which a HAND diagnosis could be changed (i.e., at post-test 6 (15%) control and 3 (6.25%) experimental participants no longer met the criteria for HAND). Therefore, the intervention was not effective in changing the diagnosis; however, additional analyses on individual domains suggested the intervention exerted therapeutic cognitive benefits.

Aim 2 of this study was to examine, overall, whether cognitive training could produce cognitive changes, even if not effective in reducing the incidence of HAND. As observed in our analyses, SOP was improved. Furthermore, some support for the Salthouse Diminished SOP Theory was found in that improved SOP transferred to improvement in other cognitive domains (i.e., attention, verbal learning and memory, delayed verbal learning and memory, executive functioning); this suggests that SOP as a cognitive domain supports the functioning of other domains. Our finding also corresponds to the meta-analysis by Lampit and colleagues which found SOP training to be the most robust cognitive training approach [13]. Of interest, cognitive training in domains other than SOP also transferred to improvements

Table 3 Intent to treat analysis of domain specific training effects on other cognitive domains

Cognitive training	n trained	n trained	Cognitive domains							
			Speed of processing	Attention	Verbal learning and memory	Delayed verbal memory	Executive functioning	Spatial learning and memory	Delayed spatial memory	Spatial visualization
			d [t(df), p-value]	*d [t(df), p-value]*	*d [t(df), p-value]*	*d [t(df), p-value]*	*d [t(df), p-value]*	*d [t(df), p-value]*	*d [t(df), p-value]*	*d [t(df), p-value]*
Speed of processing	22	19	**−0.88 [−2.65(39), 0.01]**	−0.67 [−2.63(39), 0.01]	−0.63 [−2.29(39), 0.03]	−0.62 [−2.29(39), 0.03]	−0.7 [−2.63(39), 0.01]	−0.2 [−0.71(39), 0.48]	−0.31 [−1.05(39), 0.30]	−0.17 [−0.71(39), 0.48]
Attention	16	17	−0.43 [−1.66(31), 0.11]	**−0.45 [−1.06(31), 0.30]**	−0.37 [−1.72(31), 0.10]	−0.51 [−2.05(31), 0.05]	−0.76 [−2.38(31), 0.02]	−0.24 [−0.65(31), 0.52]	−0.45 [−1.38(31), 0.18]	−0.06 [−0.22(31), 0.83]
Verbal learning and memory	15	9	0.28 [1.02(22), 0.32]	0.29 [0.67(22), 0.51]	**0.1 [0.19(22), 0.85]**	0.26 [0.55(22), 0.59]	0.12 [0.24(22), 0.81]	−0.03 [−0.09(22), 0.93]	−0.04 [−0.11(22), 0.91]	−0.16 [−0.47(22), 0.64]
Delayed verbal memory	13	10	−0.74 [−1.77(21), 0.09]	−0.16 [−0.56(21), 0.58]	0.27 [0.45(42), 0.66]	**0.35 [0.71(21), 0.48]**	−0.67 [−1.66(21), 0.11]	0.18 [0.6(21), 0.56]	−0.1 [−0.38(21), 0.71]	−0.12 [−0.29(21), 0.78]
Executive Function	4	5	−0.56 [−2.63(7), 0.03]	−1.24 [−1.97(7), 0.09]	−0.12 [−0.13(7), 0.90]	−1.06 [−1.11(14), 0.28]	**−0.89 [−0.99(7), 0.35]**	−0.4 [−0.53(7), 0.61]	−0.46 [−0.8(7), 0.45]	−0.17 [−0.47(7), 0.65]
Spatial learning and memory	8	8	−0.94 [−2.31(14), 0.04]	0.17 [0.28(14), 0.79]	0.14 [0.45(14), 0.66]	−0.5 [−1.26(14), 0.23]	−0.95 [−1.5(14), 0.16]	**−0.71 [−1.54(14), 0.15]**	0.14 [0.42(14), 0.68]	−0.06 [−0.13(14), 0.90]
Delayed spatial memory	8	5	−0.56 [−1.57(11), 0.14]	−0.76 [−2.93(11), 0.01]	−0.09 [−0.19(11), 0.85]	0.29 [0.74(11), 0.47]	−0.27 [−0.47(11), 0.65]	0.21 [0.3(11), 0.77]	**−0.32 [−0.48(11), 0.64]**	0.1 [0.29(11), 0.78]
Spatial visualization	10	7	−0.28 [−1.22(15), 0.24]	−0.25 [−0.52(15), 0.61]	−0.23 [−0.56(15), 0.58]	−0.34 [−0.71(15), 0.49]	0.72 [1.64(15), 0.12]	−0.25 [−0.57(15), 0.58]	0.27 [0.7(15), 0.50]	**−0.06 [−0.11(15), 0.91]**

Training effects of participants in the intervention group were compared pretest and posttest to participants at baseline that also had the same cognitive domain deficit. Effect size d=Cohen's d. For comparison purposes, controls in this analysis were compared to treatment group as if they were assigned a similar hypothetical assignment

in non-trained domains, particularly SOP and executive functioning. This suggests wide-spread neural activation reflective of positive neuroplasticity [27].

Implications for Practice

Several important considerations for clinical practice follow from this study. First, of the 135 participants at baseline, 109 (81%) met the cognitive definition of HAND. Such a high incidence of HAND suggests that monitoring and screening for cognitive health is an essential component of a routine visit. Second, coupled with the existing literature, this study provides partial support for the use of cognitive training to remediate or protect cognition, especially in the domains of SOP and executive function [12]. In fact, in the ACTIVE study, older participants who received SOP training also experienced other therapeutic benefits including reduced incidence of depression and dementia over time [28],and also improved in the areas of locus of control, self-rated health, health-related quality of life, driving safety and mobility, and everyday functioning as measured by the TIADL test [29, 30]. As mentioned earlier, in a separate study of 46 PWH randomized to SOP training or a no-contact control group, Vance and colleagues also observed improved performance in everyday functioning as measured by the TIADL after cognitive training [12]. Currently there are no consensus guidelines for the treatment of HAND and HIV-related cognitive impairment; however, it is likely that cognitive training will be one of the recommendations moving forward, along with encouraging healthy lifestyle behaviors (i.e., ↑ physical exercise, ↓ stress). Third, a diagnosis of HAND can generate much angst and confusion. In fact, in this TOPS study, we informed participants of their HAND diagnosis and at posttest qualitatively assessed their reaction to receiving this news from us [31]. The themes that emerged were *Sadness*, *Anxiety*, *Unexpected*, *Concerned*, *Not Concerned/No Reaction*, but surprisingly other themes included *Confirmation* (that they knew they were experiencing cognitive issues), *Knowledge Seeking*, and *Desire to Improve*. Particularly noteworthy, participants wanted to know more about how to treat HAND and improve and protect their cognitive abilities, thus assuaging their fears and improving their quality of life. Engaging in cognitive training can be part of that approach.

Implications for Research

Although cognitive training was somewhat effective in improving some cognitive domains, the algorithm used to select training domains may not be the most therapeutic for two reasons. First, as we selected the least impaired cognitive domains for training (unless SOP or attention impairments were detected), participants may not have had to improve much in order to rise above the criterion for HAND. Second, it is possible that targeting the most impaired domains, instead of the least impaired, may produce the greatest overall cognitive improvement by reducing intra-individual variability (i.e., dispersion) in cognitive functioning [32, 33]. Studies suggest that greater variability in performance across cognitive domains (e.g., very poor executive function and SOP, but superior verbal memory) predicts progressive cognitive decline. In fact, intra-individual variability is related to cognitive decline in older adults [34], structural atrophy in hippocampal and entorhinal areas in normal older adults and adults with Mild Cognitive Impairment (MCI) [33], and everyday functioning deficits in older PWH [32]. Thus, targeting those out of range, most impaired, cognitive domains for cognitive training may be a better therapeutic approach than the algorithm tested in the TOPS study. So instead of training to the diagnostic criteria of HAND, cognitive training targeting the most impaired cognitive domain may be more clinically relevant. Yet this approach assumes that one has enough cognitive reserve within that domain to benefit from the cognitive training [11, 35].

Strengths and Limitations

All studies have limitation and strengths; this study is no exception. Notable study limitations are below. First, although standardized cognitive measures were used, no true test of each cognitive domain exists. All domain-specific cognitive tests minimize, but never eliminate completely (i.e., spillover effect) the contribution of other cognitive domains to task performance. Second and similarly, although cognitive training is directed toward strengthening function in one specific cognitive domain, such benefits also spillover to other domains. Third, it is not clear whether the training effects observed are robust over time as this was not a longitudinal study. Fourth, due to financial limitations of this pilot study, a no-contact control group was employed; in future studies, a social and computer contact control group would have provided a more matched, meaningful comparison [36]. In fact, in a cognitive training study that used both a no-contact control group and social/computer-contact groups, the effect sizes between the two control groups were very similar, which demonstrates that they are both effective control groups [37]. Fifth, some attrition bias may have occurred, with those being assigned to the experimental group being slightly more likely to drop out of the study, possibly due to the demands of the cognitive training. Sixth, although we used a randomization procedure to control for race and gender, other criteria were not considered due to the small sample size. Seventh, as in any intervention study, there is the possibility of attention bias in that participants may perceive their cognition is improving by engaging in the cognitive intervention, regardless of

whether there is any therapeutic efficacy to the intervention. And finally, some self-report items were used (i.e., depressive symptomatology).

Likewise, three study strengths were noted. First, we used accepted procedures and norm-based standardized cognitive performance measures to diagnosis HAND. Second, we employed a block randomization procedure to control for race and gender. And third, we used commercially available, standardized cognitive training modules; this ensured that the participants received the exact training within each of the distinct cognitive domains being targeted.

Conclusion

In summary, this study is innovative in delivering a combination of cognitive training protocols in an individualized manner tailored to the participants' cognitive performance level. Although the overall approach was not effective in reducing the incidence of HAND, cognitive improvement was observed following some cognitive training protocols, especially SOP. Future research may consider other algorithms in which computerized cognitive domain training can be combined with other cognitive strategies (e.g., reducing intra-individual variability to produce better cognitive stability), and possibly paired with other therapies (e.g., transcranial direct current stimulation, nootropics) to improve and protect cognition as PWH age.

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Declarations

Conflict of interest *Financial interests*—Karlene Ball owns stock in the Visual Awareness Research Group (formerly Visual Awareness, Inc.), and Posit Science, Inc., the companies that market the Useful Field of View Test and speed of processing training software. Posit Science acquired Visual Awareness, and Dr. Ball continues to collaborate on the design and testing of these Assessment and training programs as a member of the Posit Science Scientific Advisory Board. *Non-financial interests*—David E. Vance, Pariya L. Fazeli, Andres Azuero, Virginia Wadley, and James L. Raper report no real or perceived vested interest that relate to this article that could be construed as a conflict of interest.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent to Publish Participants consented that their data would be used in aggregate form for publication purposes.

Research Involving Human Participants and/or Animals This study was approved by the ethics committee of the University of Alabama at Birmingham's Institutional Review Board (IRB) titled "Individualized-Target Cognitive Training in Older Adults with HIV (Training On Purpose Study) TOPS))", with the following Registration Number – IRB00000726. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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