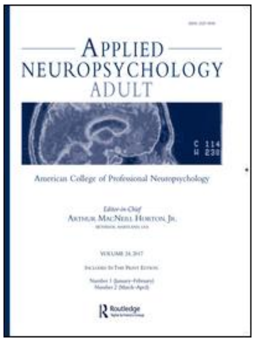

Applied Neuropsychology: Adult

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hapn21

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https://doi.org/10.1080/23279095.2021.1906678

Can individualized-targeted computerized cognitive training improve everyday functioning in adults with HIV-associated neurocognitive disorder?

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ABSTRACT

Half of people with human immunodeficiency virus (HIV) have HIV-associated neurocognitive disorder (HAND). Fortunately, cognitive training programs can improve function across cognitive domains, which may translate to everyday functioning. The Training on Purpose (TOPS) Study was designed to reverse HAND by targeting cognitive training to specific cognitive impairments that contributed to the diagnosis. A secondary aim of TOPS was to determine whether such cognitive training improved subjective and objective everyday functioning. In this two-group pre–post experimental design study, 109 adults with HAND were randomized to either: (1) a no-contact control group (no training) or (2) the Individualized-Targeted Cognitive Training group. Each participant received approximately 10 hours of cognitive training in two selected cognitive domains based on her/his individual baseline cognitive performance. Thus, 20 hours of individualized training on these two cognitive domains occurred over a course of 12 weeks in 1–2 hour sessions. Specific to the secondary aim of TOPS, measures of everyday functioning were administered before and after cognitive training to examine transfer effects. The analyses revealed that in general, speed of processing training produced benefits in everyday functioning as measured by the medication adherence visual analogue scale and the Timed Instrumental Activities of Daily Living test. Inconsistent findings were found for the other seven cognitive training protocols in either improving everyday functioning or reducing perceived everyday functioning; however, there may be other contributing factors that obscured such effects needing further research. This study demonstrated that some training protocols vary in efficacy in altering both objective and subjective everyday functioning ability.

KEYWORDS
Cognitive training; HIV; IADLs; speed of processing

In the United States in 2018, approximately 51% of people with human immunodeficiency virus (HIV) (PWH) were aged 50 and older, due both to increasing lifespan of PWH and increased rates of new infections in older people (CDC, 2020); this percentage is estimated to increase to 70% by 2030 (Wing, 2017). The population of PWH is particularly susceptible to cardiac, metabolic, and neurovascular changes associated with cognitive aging that may be accelerated by HIV (Smail & Brew, 2018). Approximately half of PWH experience cognitive symptoms that, if severe enough, result in a diagnosis of HIV-associated neurocognitive disorder (HAND) (Wei et al., 2020). Combined with nonpathological effects of aging on cognition, the prevalence and severity of HAND will likely grow along with the aging HIV population (Goodkin et al., 2017; Smail & Brew, 2018; Vance et al., 2013). Cognitive impairments in HIV are related to poorer everyday functioning on tasks such as instrumental activities of daily living (IADL) (e.g., following directions, counting change) (Vance, Fazeli, & Gakumo, 2013), driving (Vance et al., 2014), medication adherence (Caballero et al., 2019), and online shopping and banking (Woods et al., 2017). These effects on everyday function are likely to be of greater concern to PWH than how well they perform on lab-based neuropsychological tests (Kordovski et al., 2019). Given the known association between cognition and everyday functioning, if improving cognition is possible, the same may hold for improving everyday functioning. Cognitive training represents one strategy to do this.

There has been extensive publicity and research surrounding the concept of "Brain Training" or cognitive training in recent years. For a recent review of cognitive training, including a meta-analysis of such interventions and their possible impact on both healthy older adults and those experiencing mild cognitive impairment see Basak et al. (2020). This analysis examined 215 published studies and reported that cognitive training is effective in improving cognition in both healthy adults, as well as those with mild cognitive impairment (MCI), even though all 215 studies did not

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demonstrate positive effects individually. These findings are consistent with another systematic review and meta-analysis of cognitive speed of processing (SOP) training (Edwards et al., 2018), which evaluated 44 studies from 17 randomized trials using the Institute of Medicine criteria. This analysis indicated that training enhanced neural outcomes (e.g., pupil diameter, P3b amplitude), and in particular the cognitive outcomes of SOP.

In a systematic review of cognitive training programs looking specifically at PWH, Vance et al. (2019) identified 13 studies and concluded that, in general, cognitive training improved performance in the cognitive domain that was targeted (e.g., executive functioning training improved executive functioning ability). In some studies, cognitive training that targets one cognitive domain not only transferred to improvement in other cognitive domains, but also to improvements in measures of everyday functioning. For example, in a randomized sample of 46 PWH (no-contact control group or SOP training group), those in the SOP training group demonstrated improved performance on both a measure of SOP (Useful Field of View Test) and the Timed Instrumental Activities of Daily Living (TIADL) test (Vance et al., 2012).

With respect to everyday function, cognitive impairment in PWH has been shown to be associated with declines in both basic (e.g., bathing) activities of daily living (BADLs) and IADLs (e.g., medication adherence) (Johs et al., 2017). Likewise, in a sample of 162 PWH and without HIV, Vance et al. (2013) found a significant correlation between the performance-based TIADL test and several measures of SOP as well as verbal learning and memory, highlighting the importance of cognitive function on daily functioning. Similarly, significant correlations were observed between scores on the Observed Tasks of Daily Living (OTDL) test, a measure of complex everyday functioning, and neuropsychological performance measures of SOP, executive function, and verbal learning and memory. In a separate study, Morgan et al. (2014) found a significant interaction between HIV status and age for both BADLs and IADLs and for Karnofsky Performance Scale ratings. The association between cognitive impairments and BADL and IADL impairments in older PWH, coupled with evidence that cognitive training yields sustained improvement in cognitive impairments, supported exploring the possible effect of targeted cognitive training on everyday activities. Using the logic underlying targeted cognitive domain training (Vance et al., 2018), small improvements in certain cognitive domains may translate to meaningful improvement in everyday activities in which people are experiencing difficulties. Similarly, since SOP and attention are core cognitive abilities which play a role in all other cognitive domains (Fellows et al., 2014), targeted SOP or attention training might result in particularly meaningful improvement in everyday functioning.

The primary aim of the Training on Purpose Study (TOPS) was to examine whether targeted cognitive training can reduce the prevalence and severity of HAND in PWH 40 years of age and older, as those who are aging with HIV are more likely to develop HAND than younger PWH (Waldrop et al., 2021). Although we were not able to reduce the prevalence of HAND (Vance et al., in press), using performance-based cognitive tests representing eight cognitive domains to examine training effects, we were able to improve functioning in several cognitive domains; in particular, SOP training and executive functioning training were particularly robust. Thus, the secondary aim of TOPS, reported in this article, was to examine whether targeted cognitive training would improve subjective and objective measures of everyday activities.

Methods

Design overview

In TOPS, we examined the effectiveness of an algorithm of targeted cognitive training to decrease the severity and prevalence of HAND, as well as explore such training effects on everyday functioning (Vance et al., in press). Utilizing a two-group pre–post experimental design, participants 40 years and older were randomized to either: (1) a no-contact control group (no cognitive training at all), or (2) an Individualized-Targeted Cognitive Training group that completed 20 hours of cognitive training focused in two cognitive domains (10 hours each) that contributed the their HAND diagnosis. The University of Alabama at Birmingham's Institutional Review Board approved the ethical conduct of this study.

Participants

As seen from the Consort Diagram (Figure 1), participants were recruited from flyers posted at AIDS service organizations, an HIV/AIDS clinic, businesses in the community (e.g., laundromats), AIDS fundraising events, and local churches. Those interested called a telephone number listed on the recruitment materials and were screened over the telephone to determine basic eligibility. Inclusion criteria included: (a) ≥40 years of age; (b) diagnosed with HIV for +1 year; (c) not diagnosed with a neuromedical condition that impairs cognition (e.g., Alzheimer's disease, schizophrenia, traumatic brain injury); (d) not currently undergoing chemotherapy and/or radiation; (e) not legally blind or deaf; (f) proficient in spoken/written English; and (g) residing within 100 miles of the research center. From this, 135 participants consented at baseline and were administered a comprehensive neuropsychological battery to determine whether they met the Frascati criteria for HAND (Blackstone et al., 2012). The 109 participants who met the HAND criteria (5 or higher on the Global Clinical Rating score) were informed of this and then randomized into the study. Those 26 participants without HAND were also informed and their participation was no longer requested. Compensation for time and effort was provided for the pretest/posttest assessments ($50 each) and the cognitive training sessions ($15/hour of cognitive training).

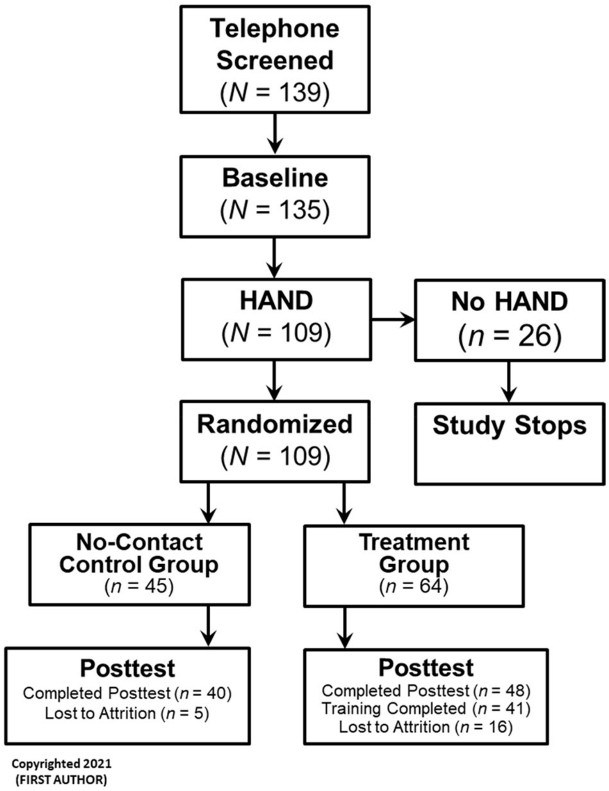

Figure 1. Training on Purpose (TOPS) consort diagram.

Measures

Participants were administered a ~1.5 hour neuropsychological and everyday functioning assessment at the research center at baseline and posttest. The measures administered during these assessments relevant to this article are listed in the following sections.

Demographics

Age, gender, years of education, and employment were indicated by self-report at baseline.

HIV health status

Each participants' medical providers provided the following information: HIV-positive diagnosis confirmation, years diagnosed with HIV, current and nadir CD4+ lymphocyte count, current quantitative HIV RNA by PRC (viral load), and types of antiretroviral HIV medication.

Health information

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

Depression

The Center for Epidemiologic Studies Depression Scale-Revised (CES-D; Radloff, 1977) was used to measure depressive symptomatology. A score of 16 or higher reflects significant depressive symptomology. Participants with significant depressive symptomatology were provide educational and referral information.

Cognitive domains and Frascati criteria

Using standardized normed cognitive performance tests at baseline (pretest) and posttest, eight cognitive domains were assessed. These cognitive performance tests are routinely utilized in the neuroAIDS research (Blackstone et al., 2012; Woods et al., 2008). *T*-scores of the cognitive tests approximate clinical ratings of objective cognitive functioning for each of the eight 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 (Trails A, Stroop Color Naming Test); (2) attention (Paced Auditory Serial Attention Test); (3) executive function (Stroop Interference, Lezak 1995), 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). From the baseline assessment, impairments in cognitive functioning were identified for training purposes (see the Procedures/ Treatment section).

Using each participant's neuropsychological test scores, an algorithm was used to calculate a Global Clinical Rating score ranging from 1 (*above average*) to 9 (*severe impairment*). If two domains were in the impaired range (5–9), then the Global Clinical Rating score reflected the more severe level of impairment identified. In this continuum, a global impairment score of 5 or higher was indicative of HAND (Blackstone et al., 2012). Technically, other factors such as impairments in everyday functioning and the contribution of comorbidities to cognitive impairments are taken into consideration when diagnosing HAND. For our study, only cognitive performance was used in making this diagnosis. (For more information regarding HAND and other TOPS protocol procedures, see Vance et al., 2018). Therefore, our study required participants to meet at least the minimum criteria for HAND, which is the mild cognitive impairment criterion for ANI (deficits that are 1 *SD* below the mean in 2 cognitive domains).

Medication adherence visual analogue scale (VAS)

This measure of medication adherence provides a visual analogue scale/line from 0% to 50% to 100% and asks participants to mark an X on that line that corresponds to "What percent of your HIV medications did you take?" during the past month. The percentage is the value used in analyses (Giordano et al., 2004).

Simplified medication adherence questionnaire

This questionnaire asks three key questions about taking one's medication as prescribed and in a timely manner; higher scores indicate better adherence. Two items are on a 6-point scale and one item on a 5-point scale; this last item was transformed mathematically to be on a 6-point scale and then summed with the other two items. Higher scores indicate better medication adherence. This measure is validated with virological outcomes and has good internal consistency ($\alpha = 0.75$) and inter-observer agreement (88.2%) (Knobel et al., 2002).

Timed Instrumental Activities of Daily Living (TIADL) test

This performance-based test measures the accuracy and time it takes to perform five IADLs used in everyday functioning including finding a number in a phone book, counting change, reading ingredients from food cans, locating food items on a shelf, and reading directions from a medication bottle. A scoring algorithm accounts for the time and accuracy, generating a score with lower scores indicating better functioning. Test–retest reliability is 0.64. (Goverover et al., 2007; Owsley et al., 2002).

Modified Lawton and Brody Activities of Daily Living (ADL) questionnaire

This self-reported questionnaire consists of 16 ADL domains that measure a participant's self-perceived functional status, specifically their decline from prior functioning and need for assistance. Scores include a total BADL complaints (e.g., dressing) continuous score as well as a total IADL complaints (e.g., laundry) continuous score, with higher scores reflecting more impaired activity domains. An IADL Dependence categorical variable was also generated, such that if current functioning level was lower than the highest level of functioning for at least two domains, this resulted in a classification of IADL Dependent (Fazeli et al., 2014; Lawton & Brody, 1969).

Procedures/treatment design and rationale

Participants with HAND were randomized in a 1:1.4 ratio to the control group or the cognitive training group to slightly favor more participants being assigned the experimental treatment as this was the focus of the study with limited resources. We employed a block randomization strategy to safeguard balanced assignment between Africans Americans/Caucasians and men/women. We did not randomize according to HAND severity; however, baseline global cognitive score between the two groups were similar and not significantly different (no-contact control group = 7.18 ($SD = 1.52$) & the treatment group = 7.48, $p = 0.26$). Time between baseline and posttest was on average 85.25 ($SD = 48.69$) days (no-contact control group = 84.48 ($SD = 27.76$) days; treatment group = 85.92 ($SD = 61.22$) days, $p = 0.89$). In the no-contact control group, participants received no cognitive training (or any type of intervention or sham-intervention) and did not have contact with the researchers between the baseline and posttest assessments; these participants only received the baseline and posttest assessments. After posttest, the control group did not receive the cognitive training. In the treatment group, participants engaged in ten hours of training for two cognitive domains (20 hours total) for which impairments were detected at baseline. All cognitive training occurred at the research center under the supervision of a neuropsychological trainer to monitor participants' progress, assist with any computer issues, offer reassurance and reinforcement, prevent drift in the protocol, and ensure treatment fidelity.

Based on the concerns of cognitive training fatigue leading to attrition as well as the diminishing therapeutic return of over training (i.e., U-shaped dosage-therapeutic response reported by Lampit et al., 2014), we selected a training dose of ten hours in each of two cognitive domains. In the cognitive training literature, a therapeutic dose of 10 hours is appropriate to increase function in a targeted cognitive domain (Ball et al., 2002; Vance et al., 2012); but to reemphasize, participants in the treatment group received 10 hours of training for each of the two cognitive domains in which they received training for a total of 20 hours of cognitive training altogether.

A problem associated with applying cognitive training to address HAND is that participants may have impairments in all eight cognitive domains. Training in more than two domains represents significant participant burden as such training can be fatiguing, resulting in non-adherence. Thus, we created a cognitive training algorithm to target the cognitive domains that hypothetically could best reduce the prevalence of HAND for each individual participant. The Individualized-Targeted Cognitive Training Framework (Vance et al., 2018) was developed explicitly for this study. In step one, participants with cognitive impairments in either SOP or attention were assigned cognitive training targeting their least compromised (but still impaired) cognitive domain (i.e., closest to a cut-off of 1 *SD* below the demographically adjusted mean); this was done specifically so participants would no longer meet the clinical criteria of HAND. Based on the Diminished SOP Theory (Salthouse, 1996) and the Wickens Model of Information Processing (Wickens et al., 2013), SOP and attention are considered core cognitive abilities upon which other cognitive domains depend. Theoretically, improvements in these cognitive domains may transfer to improvements in other cognitive domains, and possibly improvements in everyday functioning. For instance, in a sample of 186 PWH, Fellows et al. (2014) found 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). Participants' performance on the everyday functioning measures and self-reported cognitive complaints were not used in making any determination of the cognitive domain chosen for training.

In step two, if participants did not have impairments in either SOP or attention, they were assigned cognitive training targeting their least compromised (but still impaired) cognitive domain (i.e., closest to a cut-off of 1 *SD* below the demographically-adjusted mean); this was done specifically so participants would no longer meet the clinical criteria of HAND. In step three, participants were assigned to play computerized modules that were selected specifically to improve performance in their individually selected targeted cognitive domains. We worked with participants to schedule convenient times for them to complete their individual training sessions at the research center. More information about the cognitive training modules for each domain, can be found at www.brainhq.com and in our protocol article (Vance et al., 2018).

Using a treatment adherence checklist, the neuropsychological testers monitored the amount of time participants engaged in cognitive training for both targeted cognitive domains. Also, the cognitive training software automatically monitors the amount of time participants spend engaged in each exercise. The correlation between the checklist and the software on time engaged in training was very high ($r = 0.935$; $p = 0.001$). To reduce participant burden, participants could engage in two hours of training at a time to reduce the number of visits to the research center. Cognitive training was conducted around 12 weeks, averaging 1.66 hours/week of cognitive training. In their meta-analysis of 52 cognitive training studies, Lampit et al. (2014) observed optimal therapeutic effects occurred when training sessions are administered 1–3 times per week – dosage parameters observed in the TOPS Study. In regards to dosage, we considered participants to be fully trained in each domain when they successfully completed 7 out of 10 hours of cognitive training, an approach similar to the seminal ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) Study ($N = 2,802$) (Ball et al., 2002). When examining the actual potential of the cognitive training, such a completers-only analysis ($n = 41$) is considered appropriate. We had participants ($n = 7$) who did not complete training; their data were included in an intent-to-treat analysis.

Data analysis

The sample size considerations for the study were based on feasibility and, as any pilot project (Leon et al., 2011), 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. To produce fair comparisons between study groups across domains of cognitive training, the same cognitive training assignment algorithm was applied to participants in the control group to determine the training they would have received if they had been randomized to the individualized-training group and hypothetically assigned training (Imbens & Ruvin, 2015). 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) (Cohen, 1988). Data from all randomized participants were included in the group comparisons, regardless of their level of participation in the study. Baseline characteristics were also examined for association with attrition from the study. Next, for each of the Everyday Functioning measures, descriptive statistics were tabulated at the pre- and post-intervention time-points by study group, and 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. Following an Intention-to-Treat approach, the models used all available data at each time-point, and conceptually relevant baseline characteristics associated with attrition were used as controlling covariates (age, years of education, and alcohol use) in order to address bias resulting from missing data (Groenwold et al., 2012). The variance components from each model were used to estimate a pooled standard deviation for each everyday functioning measure, 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. Using baseline data of all individuals screened for the study ($N = 135$), Pearson correlations between everyday functioning measures and cognitive domain scores were estimated and interpreted (small ~0.1, medium ~0.3, large ~0.5) (Cohen, 1988). Analyses were conducted using R software version 4.0.3 (R Core Team, 2019).

Results

Demographics

Table 1 shows baseline characteristics of the $N = 109$ randomized participants. On average, participants were 53.26 ($SD = 6.7$) years old, about two thirds were male ($n = 76$, 69.7%), and the majority were African American ($n = 92$, 84.4%). Participants had an average of 12.2 ($SD = 2.3$) years of education, and they reported an average household income of approximately \$17,100 (SD = \$13,600). In terms of selected HIV characteristics, on average participants had been living with HIV for 16.6 ($SD = 8.1$) years, had current CD4+ T lymphocyte count/mm^3 of 670.6 ($SD = 414.2.8$), lowest recorded count/mm^3 of 360.7 ($SD = 340.3$), and the majority were prescribed antiretroviral therapy (ART; $n = 87$, 79.8%). Participants had an average of 5 ($SD = 4.1$) prescribed medications, reported currently consuming an average of 1.7 ($SD = 0.9$) alcoholic drinks/day ($n = 56$, 51.4%, reported not consuming any alcohol), and smoking 4.1 ($SD = 5.6$) cigarettes/day ($n = 55$, 50.5% reported not smoking). Participants' Center for Epidemiologic Studies Depression Scale (CESD) scores had an average of 18.1 ($SD = 10.6$), with 65 (59.6%) reporting CESD scores ≥16 indicative of 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

Table 1. Participant characteristics.

	No-contact control group ($n = 45$)		Individualized-targeted cognitive training ($n = 64$)		
Variable	*n* (%)	Mean (*SD*)	*n* (%)	Mean (*SD*)	Effect size
Age		53.78 (7.17)		53.42 (6.42)	$d = 0.05$
Gender					$V = 0.06$
Male	30 (66.67%)		46 (71.88%)		
Female	15 (33.33%)		18 (28.13%)		
Race/Ethnicity					$V = 0.09$
African America	39 (86.67%)		53 (82.81%)		
Caucasian	6 (13.33%)		10 (15.63%)		
Other	0 (0%)		1 (1.56%)		
Education (years)		12.4 (2.3)		12.13 (2.39)	$d = 0.12$
Household income ($10 K)		1.71 (1.31)		1.7 (1.4)	$d = 0.01$
Years diagnosed with HIV		16.33 (8.36)		16.81 (7.95)	$d = 0.06$
Current CD4+ T lymphocyte count/mm^3		752.98 (430.88)		610.82 (394.38)	$d = 0.35$
Nadir CD4+ T lymphocyte count/mm^3		400.34 (378.1)		332.52 (310.87)	$d = 0.2$
Number of prescribed medications		5.02 (4.25)		4.97 (3.97)	$d = 0.01$
Prescribed ART	33 (73.33%)		54 (84.38%)		$V = 0.13$
CES-Depression		17.24 (10.36)		18.73 (10.71)	$d = 0.14$
Alcohol Use* (no. of drinks)		1.73 (0.81)		1.7 (0.95)	$d = 0.03$
Tobacco Use (cigarettes/day)		4.02 (6.49)		4.08 (5)	$d = 0.01$

Notes. 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).

Table 2. Cognitive baseline and posttest scores for everyday functioning ($N = 109$).

	No-Contact Control Group			Individualized-Targeted Cognitive Training			Difference in Change		
Everyday Functioning Measures	Baseline ($n = 45$) Mean (*SD*)	Posttest ($n = 40$) Mean (*SD*)	Change Estimate (*SE*)[a]	Baseline ($n = 63$) Mean (*SD*)	Posttest ($n = 48$) Mean (*SD*)	Change Estimate (*SE*)[a]	Estimate (*SE*)[b]	*p*-value	Effect Size, Cohen's *d*
Medication VAS	89.66 (15.62)	90.98 (13.24)	1.21 (3.12)	90.92 (19.05)	90.85 (16.87)	−0.16 (2.73)	−1.45 (4.13)	0.726	−0.09
Simplified Medication Adherence Questionnaire	15.96 (2.63)	15.77 (2.98)	−0.09 (0.46)	15.85 (3.15)	16.22 (2.61)	0.39 (0.41)	0.48 (0.61)	0.431	0.17
Timed Instrumental Activities of Daily Living[c]	0.07 (0.76)	0.02 (0.78)	−0.06 (0.08)	0.15 (0.66)	−0.02 (0.61)	−0.19 (0.07)	−0.13 (0.11)	0.227	−0.2
Lawton & Brody – BADL Complaints[c]	0.27 (0.72)	0.22 (0.66)	−0.04 (0.08)	0.11 (0.36)	0.1 (0.37)	0.02 (0.07)	0.07 (0.11)	0.555	0.12
Lawton & Brody – IADL Complaints[c]	2.07 (2.86)	1.65 (2.54)	−0.37 (0.48)	2 (2.68)	1.67 (2.21)	−0.31 (0.43)	0.06 (0.64)	0.925	0.02

Notes. VAS = visual analogue scale; BADL = basic activities of daily living; IADL = instrumental activities of daily living. [a]Linear contrasts from linear mixed-efefct models adjusted for baseline age, alcohol use, and education. [b]Group by time interaction coefficient in linear mixed-effect models adjusted for baseline age, alcohol use, and education. [c]Higher scores indicate more everyday functioning impairment.

participants having relatively large CD4+ T lymphocyte counts. After a log transformation of CD4+ T lymphocyte counts, the between-group standardized difference was reduced to $d = 0.26$ (a small effect size).

Effects of training on everyday functioning

Using the ITT approach with posttest completers, Table 2 presents descriptive statistics and measures of training effect on everyday functioning measures regardless of training received (or hypothetically assigned for control participants). A small beneficial effect was observed for the TIADL test ($d = -0.2$) and the Simplified Medication Adherence Questionnaire ($d = 0.17$). Effects for other measures ranged from no effect to trivial magnitude.

Table 3 presents measures of training effect on everyday functioning measures, comparing participants trained in a specific domain vs. their respective matched control participants. For the sake of parsimony, due to the number of comparisons, trivial or small effect findings were not discussed, only small-to medium effects or larger are noteworthy. Compared to their control counterparts, participants who received SOP training showed small improvements on the Medication VAS ($d = 0.22$) and the TIADL test ($d = -0.17$) (Table 3).

Compared to their control counterparts, participants who received attention training showed small to medium improvements on the Lawton & Brody—BADL Complaints (i.e., reduced complaints) ($d = -0.38$) and the Lawton & Brody – IADL Complaints ($d = -0.27$) (Table 3).

Compared to their control counterparts, participants who received verbal learning and memory training showed small to medium beneficial effects on the Simplified Medication Adherence Questionnaire ($d = 0.3$) and the TIADL test ($d = -0.28$); however, they showed detrimental effects of small to medium magnitude on the Medication VAS ($d = -0.29$), the Lawton & Brody – BADL Complaints ($d = 0.51$), and the Lawton & Brody – IADL Complaints ($d = 0.22$) (Table 3).

Table 3. Training effect on everyday functioning measures.

	Cognitive Training							
	SOP	Attention	Verbal Learning and Memory	Delayed Verbal Memory	Executive Functioning	Spatial Learning and Memory	Delayed Spatial Memory	Spatial Visualization
N Training at baseline	29	21	21	17	5	11	11	13
N Training at posttest	22	16	15	13	4	8	8	10
N Control at baseline	20	18	11	13	6	9	5	8
N Control at posttest	19	17	9	10	5	8	5	7
Everyday Functioning Measures	Cohen's *d* (*p*-value)	Cohen's *d* (*p*-value)	Cohen's *d* (*p*-value)	Cohen's *d* (*p*-value)	Cohen's *d* (*p*-value)	Cohen's *d* (*p*-value)	Cohen's *d* (*p*-value)	Cohen's *d* (*p*-value)
Medication VAS	0.22 (0.524)	0.08 (0.833)	−0.29 (0.468)	−0.12 (0.83)	0.51 (0.548)	−0.11 (0.835)	−1.06 (0.108)	−0.17 (0.767)
Simplified Medication Adherence Questionnaire	−0.15 (0.63)	0.12 (0.706)	0.3 (0.426)	0.22 (0.648)	0.68 (0.439)	−0.17 (0.63)	−0.39 (0.383)	0.91 (0.116)
Timed Instrumental Activities of Daily Living	−0.17 (0.503)	−0.08 (0.719)	−0.28 (0.28)	0.04 (0.919)	−1.18 (0.216)	0.06 (0.91)	−0.28 (0.67)	−0.62 (0.164)
Lawton & Brody – BADL Complaints	0.01 (0.968)	−0.38 (0.36)	0.51 (0.375)	0.8 (0.163)	0.6 (0.521)	0 (1)	0.02 (0.963)	0.41 (0.074)
Lawton & Brody – IADL Complaints	−0.05 (0.891)	−0.27 (0.511)	0.22 (0.694)	0.13 (0.766)	0.81 (0.387)	0.13 (0.792)	−0.14 (0.836)	0.38 (0.51)

Notes. VAS = visual analogue scale; BADL = basic activities of daily living; IADL = instrumental activities of daily living.

Table 4. Association between everyday functioning measures and cognitive domain scores.

	Baseline Cognitive Domains								
Everyday Functioning Measures	Global Clinical Rating Score r (*p*-value)	SOP r (*p*-value)	Attention r (*p*-value)	Verbal Learning and Memory r (*p*-value)	Delayed Verbal Memory r (*p*-value)	Executive Functioning r (*p*-value)	Spatial Learning and Memory r (*p*-value)	Delayed Spatial Memory r (*p*-value)	Spatial Visualization r (*p*-value)
Medication VAS	0.08 (0.389)	0.12 (0.168)	0.08 (0.367)	0.11 (0.224)	0.12 (0.189)	0.16 (0.063)	0 (0.993)	0.01 (0.888)	0 (0.961)
Simplified Medication Adherence Questionnaire	0.08 (0.338)	0.08 (0.362)	0.06 (0.467)	0.09 (0.328)	0.09 (0.301)	0.1 (0.277)	0.04 (0.682)	0.05 (0.557)	−0.06 (0.529)
Timed Instrumental Activities of Daily Living	0.49 (<0.001)	0.47 (<0.001)	0.51 (<0.001)	0.43 (<0.001)	0.41 (<0.001)	0.27 (00.002)	0.38 (<0.001)	0.34 (<0.001)	0.33 (<0.001)
Lawton & Brody – BADL Complaints	0.14 (0.108)	0.15 (0.097)	0.13 (0.152)	0.04 (0.614)	0.1 (0.249)	0.02 (0.862)	0.1 (0.256)	0.14 (0.115)	0.19 (0.027)
Lawton & Brody – IADL Complaints	0.04 (0.679)	0.12 (0.18)	0.02 (0.793)	−0.03 (0.695)	0.09 (0.292)	−0.09 (0.313)	0.03 (0.739)	0.06 (0.476)	0.04 (0.622)

Notes. VAS = visual analogue scale; BADL = basic activities of daily living; IADL = instrumental activities of daily living.

Compared to their control counterparts, participants who received delayed verbal memory training showed a large detrimental effect on the Lawton & Brody—BADL Complaints ($d = 0.8$) (Table 3).

Compared to their control counterparts, participants who received executive functioning training showed medium to large improvements on the Medication VAS, the Simplified Medication Adherence Questionnaire, and the TIADL test ($|d|$ ranging from 0.51 to 1.18); however, they also showed medium to large detrimental effects on the Lawton & Brody—BADL Complaints ($d = 0.6$) and the Lawton & Brody – IADL Complaints ($d = 0.81$) (Table 3).

Compared to their control counterparts, participants who received delayed spatial memory training showed a small to medium improvement on the TIADL test ($d = -0.28$) and medium to large detrimental effects on the Medication VAS ($d = -1.06$) and the Simplified Medication Adherence Questionnaire ($d = -0.39$) (Table 3).

Compared to their control counterparts, participants who received spatial visualization training showed medium to large improvements on the Simplified Medication Adherence Questionnaire ($d = 0.91$) and the TIADL test ($d = -0.62$); however, they showed small to medium detrimental effects on the Medication VAS, the Lawton & Brody—BADL Complaints, and the Lawton & Brody – IADL Complaints ($|d|$ ranging from 0.17 to 0.41) (Table 3).

Association between everyday functioning measures and cognitive domains

Table 4 presents correlations between everyday functioning measures and the cognitive domain scores using data from the $N = 135$ screened for the study. The TIADL test was the only functioning measure showing relevant association with all cognitive domains (r ranging from 0.27 to 0.51).

Table 5. Examination of attrition between groups.

Variable	Stayed to posttest ($n = 88$) n (%)	Stayed to posttest ($n = 88$) Mean (SD)	Dropped out ($n = 21$) n (%)	Dropped out ($n = 21$) Mean (SD)	Effect size
Group Assignment					$V = 0.17$
Cognitive training	48 (54.55%)		16 (76.19%)		
Control	40 (45.45%)		5 (23.81%)		
Age		50.9 (4.72)		54.2 (6.97)	$d = 0.5$
Gender					$V = 0.07$
Male	16 (76.19%)		60 (68.18%)		
Female	5 (23.81%)		28 (31.82%)		
Race/Ethnicity					$V = 0.08$
African America	17 (80.95%)		75 (85.23%)		
Caucasian	4 (19.05%)		12 (13.64%)		
Other	0 (0%)		1 (1.14%)		
Education (years)		11.38 (2.64)		12.44 (2.24)	$d = 0.46$
Household income ($10 K)		1.48 (0.75)		1.76 (1.46)	$d = 0.21$
Years diagnosed with HIV		14.86 (8.07)		17.03 (8.08)	$d = 0.27$
Current CD4+ T lymphocyte count/mm^3		584.95 (303.77)		691.52 (435.84)	$d = 0.26$
Nadir CD4+ T lymphocyte count/mm^3		364.95 (291.2)		359.61 (352.95)	$d = 0.02$
Number of prescribed medications		4.52 (3.4)		5.1 (4.22)	$d = 0.14$
Prescribed ART	18 (85.71%)		69 (78.41%)		$V = 0.07$
CES-Depression		20.71 (9.59)		17.5 (10.72)	$d = 0.31$
Global Cognitive Score[a]		7.34 (1.45)		7.19 (1.47)	$d = 0.1$
Alcohol Use[b] (no. of drinks)		1.29 (0.56)		1.82 (0.93)	$d = 0.61$
Tobacco Use (cigarettes/day)		5.48 (6.11)		3.72 (5.5)	$d = 0.31$

Notes. 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. [a]Lower scores indicate better functioning; [b]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).

Attrition

In terms of relevant differences found between participants who dropped from the study ($n = 21$) and participants who provided a posttest assessment (Table 5), those 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], $d = 0.61$). The characteristics with the largest magnitude of association with dropout (age, years of education, and alcohol use) were used as adjusting covariates in models estimating results shown on Tables 2 and 3.

Discussion

Overall, those who were assigned cognitive training experienced a small improvement on a speed-based everyday functioning task, the TIADL test, and the Simplified Medication Adherence Questionnaire compared to those who had no training. Yet, when examining specific types of cognitive domain training, some findings were consistent with those from previous studies, while others were inconsistent. As such it is important to dissect and compare these findings closely to the literature and results from the TOPS first aim article (Vance, et al., in press). Based upon Wickens Model of Information Processing and the Diminished SOP Theory discussed earlier, both SOP training and attention training were expected to exert the greatest cognitive benefits and translation to everyday functioning improvements; indeed we found that both domain training protocols produced such positive results. SOP training was associated with improvements in the performance-based TIADL test and a self-assessment of medication adherence (i.e., Medication Adherence VAS). These findings are consistent with previous SOP training studies. Small improvement was observed for the TIADL performance test in prior studies (Edwards et al., 2005; Vance, Fazeli et al., 2012; Brien et al., 2013), while the small-to-medium improvement on medication adherence is a new finding, but not inconsistent with the pattern of improved efficiency in everyday functioning. Similarly, for attention training, small-medium improvement was observed on self-ratings of BADL and IADL complaints. Prior electrophysiological studies suggest that after such cognitive training, adults experience increased N200, N2c, and P3b amplitudes (O'Brien et al., 2013; Zendel et al., 2016). It is thought that both SOP and attention training uniquely reduce dependence on prefrontal regions (an area commonly susceptible to dysregulation in HIV; Melrose et al., 2008), therefore strengthening functional connectivity in executive function and visual attention in seronegative older adults (Ross et al., 2019) and reallocating such response to posterior brain regions. This reallocation of processing is thought to potentially reduce the need for top-down cognitive control that can improve both attention and SOP in older adults and translate to everyday functional improvements (O'Brien et al., 2013).

When examining the other cognitive training protocols, the results are mixed as detrimental effects were found for some everyday functioning outcomes. For example, detrimental effects, varying in magnitude, were repeatedly found for subjective outcomes such as medication adherence and ADL outcomes across the other training protocols. Cautious interpretation is warranted for cognitive training protocols as sample size was profoundly smaller than the SOP and attention training, especially for executive function training.

To make sense of these findings, it is important to consider two germane points. First, the implicit hypothesis underlying these cognitive training programs is that, cognitive training will improve cognitive ability in that domain which will then translate to improved everyday functioning. However, if there was a minimal amount of improvement in the cognitive domain after training, then those findings between cognitive training and everyday functioning outcomes should be censored, or at least interpreted with caution. In our parent study article, 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 ($d = -0.32$). Trivial intervention effects were observed for verbal learning and memory ($d = 0.1$) and spatial visualization ($d = -0.06$). A moderate detrimental effect was observed for the delayed verbal memory ($d = 0.35$). Thus, by using a cutoff of $d = -0.45$ or higher effect size, only findings on SOP, attention, executive functioning, and spatial learning and memory training results on everyday functioning should be considered clinically meaningful.

Second, only one of the measures of everyday functioning was performance-based (i.e., TIADL test) while all the others were self-reported, subjective measures of everyday functioning. Perhaps these cognitive training protocols made people more sensitive or observant of how they were not performing their everyday activities well. In that regard, some of these changes in perceptions of everyday functioning may be a result of the cognitive training, and the study itself focused on everyday functioning (i.e., Hawthorne effect), increasing the cognitive ability to be self-aware and overly or under sensitive of how they are negotiating their self-care and their environment, which might explain the various findings on subjective everyday functioning.

Implications for practice

Combined with the neuroAIDS and cognitive aging literatures, several implications for practice emerge. First, as many PWH age and experience cognitive impairments that can restrict their everyday functioning, growing evidence demonstrates that certain types of cognitive training, such as SOP training and executive training can improve functioning in TIADLs as well as in driving and perhaps medication adherence (Vance, Fazeli, Cheatwood, et al., 2019). A caveat of this is that not all training protocols are the same. Some cognitive training produces more cognitive benefits than others, so the benefits may not be the same across all types of cognitive training (Vance et al., in press). Therefore, clinician recommendations to patients to engage in such cognitive training should be measured, clearly stating the advantages over some versions of cognitive training versus others.

Second, as PWH develop cognitive impairments including HAND, this can create a concern and anxiety. In TOPS, we informed participants of their HAND diagnosis and later qualitatively assessed at posttest their reaction to this information (Vance, Jensen, et al., 2019). This qualitative analysis revealed several themes including S*adness*, *Anxiety*, *Unexpected*, *Concerned*, *Not Concerned/No Reaction*; interestingly other themes emerged including *Confirmation* (self-revelation of having cognitive impairment), *Knowledge Seeking*, and *Desire to Improve*. Participants expressed fear about HAND but also wanted to know more about how to prevent or treat it; cognitive training may be an additional tool, in combination with other positive health behaviors such as physical exercise, to help address those concerns and fears. Nevertheless, cognitive training may help PWH assuage concerns about their cognitive and everyday functioning.

Implications for research

From this study, several implications and future directions for research are posited. First, additional studies on the effects of cognitive training on everyday functioning should incorporate more measures of objective, performance-based everyday functioning such as the UCSD Performance-Based Skills Assessment Brief (UPSA-B (Moore et al., 2017), especially measures that have more technology-related everyday tasks (i.e., internet used, computer skills) would be of value to modernize and extend the science (Vance et al., 2009). For example, although the TIADL test is a performance-based instrument and has been shown to be sensitive to cognitive training in some studies, some of the items in it may not be reflective of changes in modern everyday functioning. On the TIADL test task of looking up a phone number in a phone book, with proliferation of smart phones and other handheld devices and widespread internet connectivity, phonebooks are obsolete. In a study of 93 participants with PWH (43 with HAND) and 42 neurocognitive normal people without HIV, Woods et al. (2017) examined performance on internet-based household IADLs such as internet shopping and banking. These researchers found that those with HAND experienced lower internet-based task scores and that such scores correlated with poorer motor skills, executive function, numeracy, and episodic memory.

Second, in addition to cognitive training to improve everyday functioning, training in everyday functioning skills may also be a more direct way of doing this for PWH. For example, in a sample of community-dwelling older adults, Czaja et al. (2020) used both SOP training (i.e., UFOV® training) and a computer-based functional skills assessment training (CFSAT) program in older adults with and without cognitive impairments. Participants were assigned to either: (1) CFSAT alone or (2) CFSAT plus SOP training. Technological tasks were the focus of CFSAT which included ATM banking, online shopping, ticket kiosk, interacting with a pharmacy website, and internet IADLs. Using this training, researchers were able to improve everyday functioning in both groups; however, 29% in the CFSAT group achieved "mastery" while 32% those in the combined intervention achieved "mastery." Interesting CFSAT also assesses such everyday functioning tasks and could be incorporated into other studies. Incidentally, by learning such everyday skills, this in turn may improve cognitive abilities as it has also been observed in other studies that show that those who learn new skill (i.e., photography) experience improvements in memory and other cognitive domains (Vance et al., 2009).

Third, this study provided unique insights suggesting that different cognitive training protocols may produce different therapeutic benefits on everyday functioning. In fact, a combination of various cognitive training protocols may yield the best therapeutic outcomes. In the TOPS study, 20 individualized combinations of training protocols were delivered; regrettably, with such a small sample size, it prevents a meaningful comparison between training protocols. Future studies could incorporate a multiphase optimization strategy (MOST) design to determine which combination of training provides the most therapeutic benefit (Collins, 2018). The TOPS study provided a precursor to this approach, demonstrating that two cognitive training protocols can be administered simultaneously. By using the MOST design, this approach could be conducted more systematically to examine this.

Strengths and limitations

All studies have methodological strengths and limitation; this study is without exception. Four study strengths were noted. First, standardized norm-based neuropsychological measures were used to assess cognition and determine HAND, which assists with generalizing the findings across the literature. Second, a block randomization procedure was utilized to control for race and gender. Third, standardized cognitive training modules were employed. This ensured that participants received the exact training within the cognitive domain they were assigned. And, fourth, five measures of subjective and/or objective everyday functioning were used.

These strengths are related to some of the limitations observed in this study. First, although by no means exhaustive, the measures of everyday functioning represent a range in which to examine the impact of cognitive training on everyday functioning; there are clearly other more real world and current measures of everyday functioning that were not taken into consideration. Second, despite using standardized neuropsychological measures, no true cognitive domain tests exist. Although cognitive domain tests are carefully designed to minimized reliance on other cognitive domains to complete a test, even some minor cognitive function in other domains is recruited such that a cognitive measure is actually measuring some aspect of other cognitive abilities (i.e., spillover effect). Third, and similarly, just as there is spillover with cognitive tests, there is spillover with cognitive training in that there is no "pure" cognitive domain training. In fact, with the design of this study, the training effects are inter-related between particular cognitive domains depending on which cognitive domains were trained in conjunction by each individual. Fourth, this was not a longitudinal study. Some of the changes from cognitive training may take months to emerge. Fifth, other variables of interest could have also impacted the cognitive training effect such as years with HIV (long-term survival), cognitive reserve, sleep hygiene, and past/current substance use; these were not accounted for in analyses. Finally, our sample expressed a high degree of depressive symptomatology which could have had an individual effect on each cognitive training protocol; unfortunately, with the small sample size, it was not feasible to look at the effect of this variable on each of the nine training conditions.

Conclusion

In summary, this study was the first to administer a combination of cognitive training protocols in an individualized manner tailored to the participants' cognitive performance with the goal of improving everyday functioning and reducing HAND. Once the cognitive effect size of each sub-study was considered, it appears that some performance-based and subjective measures of everyday functioning were improved. Observing cognitive training effects in SOP, attention, and executive functioning specifically, a future cognitive protocol incorporating all three components may prove to be the most optimal combination to improve subjective and objective everyday functioning; in fact, the MOST protocol may be a novel way to investigate moving this science forward. Albeit, more research and consensus is needed to determine how to effectively measure everyday functioning, as current objective and subjective measures come with their own strengths and limitations that directly impact clinical practice and effectiveness.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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