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Individualized-Targeted Computerized Cognitive Training to Treat HIV-Associated Neurocognitive Disorder: An Interim Descriptive Analysis

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Nearly 50% of adults with HIV experience various degrees of HIV-associated neurocognitive disorder (HAND; Heaton et al., 2010). HAND is diagnosed using the Frascati criteria, a consensus-derived neurocognitive algorithm used in neuroAIDS research. When an individual performs more than 1 standard deviation below his/her demographically based norm (i.e., age/education adjusted) in two or more cognitive domains, then the criteria for HAND have been met (Blackstone et al., 2012). Aging often exacerbates such cognitive problems. In fact, studies clearly show that older adults with HIV perform worse on neurocognitive measures than those without HIV and younger adults with HIV (e.g., Goodkin et al., 2017). With nearly 70% of the people living with HIV in the United States projected to be 50 years of age or older by 2020, this represents a unique challenge for nurses and health care professionals (U.S. Senate Special Committee on Aging, 2013).

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Despite the need for cognitive interventions to address HAND, few approaches are available. Pharmacologic interventions such as lithium and methylphenidate have been attempted with limited, short-lived therapeutic effects, and with potential adverse side effects. Moreover, the addition of yet another prescribed medication to a clinical population facing multiple comorbidities and vulnerable to polypharmacy is not encouraged (Vance, Fazeli, Moneyham, Keltner, & Raper, 2013). Thus, behavioral interventions that promote positive neuroplasticity to protect and improve cognitive reserve are encouraged.

Computerized cognitive training programs have been shown as a safe and effective way to improve cognitive function (Lampit, Hallock, & Valenzuela, 2014). For example, in a two-group pre/post study of 46 middle-aged and older adults (40 years and older) with HIV, Vance, Fazeli, Ross, Wadley, and Ball (2012) randomized participants to either a no-contact control group or a speed-of-processing training group. Those in the speed-of-processing training group engaged in 10 hours of specially designed computer games that required participants to quickly process complex visual information. The games were adaptive such that they provided feedback on performance and also varied the speed and difficulty of the tasks so participants were always challenged near their upper threshold abilities. Compared to the control group, those who received this cognitive training improved significantly ($p = .04$) on a visual speed-of-processing measure, which translated to significant ($p = .03$) performance improvement on the Timed Instrumental Activities of Daily Living test (Owsley, Sloane, McGwin, & Ball, 2002).

Despite the limited use of cognitive training in HIV, cognitive training in HIV-uninfected community-dwelling older adults has been well researched. In a meta-analysis of 52 cognitive training studies of older adults without HIV, Lampit and colleagues (2014) found that, across cognitive domains, the average cognitive improvement following cognitive training was 0.22 standard deviations. Pooling effect sizes across these studies, significant therapeutic improvement in various domains differed widely: speed of processing ($g = 0.31$), visuospatial skills ($g = 0.30$), nonverbal memory ($g = 0.24$), working memory ($g = 0.22$), and verbal memory ($g = 0.08$). Despite some studies showing significant improvement in attention and executive functioning, pooled effect sizes were not significant for these domains.

Targeted Cognitive Training Approach

Because many cognitive training programs are known to improve performance in certain cognitive domains in as much as 1 to 1.5 standard deviations above one's demographically based (age/education) norms (Lampit et al., 2014), it is plausible that HAND diagnosis mediation may be possible. In many cases, the person may be only a fraction of a standard deviation away from being within the "normal" cognitive range for his/her age/education. Thus, targeting those cognitive domains for cognitive training may result in small to moderate improvement, perhaps enough to no longer meet the criteria of HAND, thus reversing the research diagnosis.

Purpose

Building on this information, an ongoing R21 randomized clinical trial (the Training on Purpose [TOPS] Study; proposed $N = 146$) is examining the effectiveness of this targeted cognitive training approach to reduce the prevalence of HAND in middle-aged and older adults (40 years of age and older) with HAND (Vance et al., 2018). Employing a two-group pre/post design in our case comparison study, six adults with HAND were randomized to: (a) the cognitive training group ($n = 3$), or (b) the no-contact control group ($n = 3$).

Methods

Overview

From the ongoing parent study, three participants from each of the treatment arms were randomly selected for description and comparison. Pre and post score comparisons are presented to show changes over time. The University of Alabama at Birmingham Institutional Review Board approved the parent study.

Participants

As part of the ongoing parent study, participants were recruited from flyers posted at clinics; eligibility was determined through a telephone screen. Eligible participants had to have been: (a) diagnosed with HIV, (b) 40 years of age or older, (c) free of any severe neuromedical condition (e.g., bipolar disorder), and (d) able to participate in written and oral activities in English. Participants were not screened for vitamin deficiencies that could contribute to cognitive impairment. Eligible participants were consented at baseline and administered a neurocognitive battery, which was used to determine whether they met the Frascati criteria for HAND; only those with HAND were randomized.

Instruments

Demographics and health.—Standard demographic data (e.g., age, gender, education) and HIV-related clinical information (e.g., CD4+T lymphocyte count, HIV viral load) were obtained at baseline. The most current clinical health information was obtained directly by a request from the participant's clinic/provider.

Frascati criteria and cognitive domains.—At baseline (pretest) and posttest, performance in eight unique cognitive domains was assessed by standardized normed measures in a neurocognitive battery: (a) attention (Paced Auditory Serial Attention Test); (b) speed of processing (Stroop Color, Trails A); (c) verbal learning and memory (Hopkins Verbal Learning Test - Revised); (d) delayed verbal learning and memory (Hopkins Verbal Learning Test/Delayed Memory–Revised); (e) executive functioning (Stroop Incongruent, Trails B); (f) spatial learning and memory (Benton Visual Memory Test–Revised); (g) delayed spatial learning and memory (Benton Visual Memory Test Delayed–Revised); and (h) spatial visualization (WAIS Block Design). It is from this baseline neurocognitive battery that cognitive deficits using the Frascati criteria are identified and targeted for cognitive training (see the Procedures/Treatment section below).

Using the Frascati criteria, those performing more than 1 standard deviation below their normed mean on any of this clinical algorithm, a global deficit score is calculated ranging from 1 (*above average*) to 9 (*severe impairment*); HAND is diagnosed with a score of 5 and higher (Blackstone et al., 2012). Similarly, each of the cognitive domains are also evaluated on the same scale. Other factors are considered when diagnosing HAND, such as performance in instrumental activities of daily living and the presence of other comorbidities; however, only cognitive performance was considered in diagnosing HAND in this study. (For additional details about HAND, see the description of the parent study in Vance et al., 2018).

Procedure/Treatment

Employing a two-group pre/post design in our case comparison study, six adults (40 years of age and older) with HAND were randomized to either: (a) the cognitive training group, or (b) the no-contact control group. Those in the cognitive training group received 20 hours of cognitive training in each of the two cognitive domains (10 hours each) in which a cognitive deficit was observed; training occurred at the research center under the supervision of a trainer who monitored their progress. In a meta-analysis of cognitive training studies, Lampit and colleagues (2014) noted that keeping the training dose at 20 hours or less could enhance the therapeutic effect size of the cognitive training; also, other cognitive studies considered 10 hours of cognitive training in a particular domain to be an acceptable therapeutic dose (e.g., Ball et al., 2002). Although a cognitive deficit could occur in multiple domains, cognitive training in several domains represents significant participant burden in time and effort spent in the laboratory. Thus, a cognitive training algorithm was developed to minimize this burden.

In our Individualized-Targeted Cognitive Training Framework (Vance et al., 2018) and based on a baseline neurocognitive assessment, if participants experienced a deficit in either attention or speed of processing or both, those domains were automatically targeted for training based on cognitive theory (i.e., Wickens Model of Information Processing and Diminished Speed of Processing Theory) and evidence from the cognitive literature that improving these cognitive abilities may fundamentally support cognitive function in other cognitive domains. Otherwise, specific cognitive domain training was targeted to the cognitive domains closest to the threshold of 1 standard deviation below the patient's demographically adjusted norm. Cognitive training modules that were designed to improve cognitive abilities in each of these cognitive domains were used. The following modules were used to address cognitive deficits observed in each of the eight cognitive domains: (a) attention (Divided Attention & Target Tracker), (b) speed of processing (Double Decision, Hawkeye, & Visual Sweeps), (c) verbal learning and memory (Memory Grid & Syllable Stacks), (d) delayed verbal memory (Memory Grid & Syllable Stacks), (e) executive function (Mind Bender), (f) spatial learning and memory (Mental Maps & True North), (g) delayed spatial learning and memory (Mental Maps & True North), and (h) spatial visualization (Mental Maps & True North). For more information about cognitive training modules, please see www.brainhq.com. Participants received all 20 hours of cognitive training. Meanwhile, those in the no-contact control group received only pretest and posttest

assessments. On average, the time between pretest and posttest for those in the cognitive training group and the no-contact control group was 62.67 days and 64.33 days, respectively.

Data Analysis

To observe changes in the HAND diagnosis and changes in the targeted cognitive domains, a simple pre-post comparison of these cases was conducted. Side-by-side comparisons in the cognitive changes were provided to show exactly where cognitive changes occurred between the three cases in each group.

Results

As seen in Table 1, cases were 56 to 65 years old and mostly African American men with a similar education level. Not shown, the average CD4+ T lymphocyte count was 873.83 cells/mm³ (range = 232–1,574 cells/mm³), and HIV viral load was undetectable for everyone. Incidentally, all participants were on combination antiretroviral therapy. Participants had been diagnosed with HIV for 18.3 years on average, ranging from 4 to 25 years.

In the cognitive training group, Case A experienced the most therapeutic change, as exhibited by a reduction in the global deficit score of 2 points, from 9 at pretest to 7 at posttest. Using the Individualized-Targeted Cognitive Training Framework, although Case A displayed cognitive deficits in all eight of the cognitive domains, this person received training in speed of processing and attention based on the underlying theoretical framework discussed earlier. Following training in these areas, beneficial cognitive changes were observed in speed of processing and attention as well as in verbal learning and memory, delayed verbal learning and memory, executive function, spatial learning and memory, and delayed spatial learning and memory. For Cases B and C, no improvement on the global deficit score was observed. Furthermore, cognitive training in the respective deficit area improved function in only one domain (Case C, spatial learning and memory).

In the no-contact control group, Case F also experienced a change in global deficit score of 2 points, from 8 at pretest to 6 at posttest, as well as beneficial cognitive changes in verbal learning and memory, spatial learning and memory, and delayed spatial learning and memory. Meanwhile, Cases D and E displayed a pattern of poorer cognitive performance from pretest to posttest.

In Table 1, by tallying the beneficial and detrimental cognitive changes across the eight cognitive domains, the cognitive training group improved by 16 points, while the no-contact group declined by 15 points. This represented a 31-point difference between the groups, favoring cognitive improvement in the cognitive training group.

Discussion

Our interim descriptive study reflects an emerging pattern of cognitive improvement and maintenance in those who received cognitive training. Unfortunately, the hope of reversing the diagnosis of HAND was not observed in these three cases, although some improvement

was noted, especially for Case A, who received the targeted speed of processing and attention training. Perhaps targeting these cognitive domains regardless of other cognitive domain deficits could produce the most beneficial cognitive outcomes. Indeed, studies have shown that speed of processing may be the most amenable domain to change (Ball et al., 2002), and also may translate to other cognitive domains (Vance et al., 2018). Further, in a similar descriptive case study, Hossain and colleagues (2017) randomized three older adults with HAND to receive either 10 hours of speed-of-processing training, 20 hours of speed-of-processing training, or 10 hours of a sham computer training. The participant who received 20 hours of speed-of-processing no longer met the Frascati criteria for HAND; this is the first and only study to show an intervention that might reverse the HAND diagnosis.

Although these preliminary findings are intriguing, obviously more research is needed, such as how long the benefit of cognitive training lasts, whether it be weeks, months, or even years. A recent study by Edwards and colleagues (2017) found that, in a large sample of community-dwelling older adults without HIV, 10 hours of speed-of-processing training reduced the prevalence of dementia as much as 29% over a 10-year period compared to controls. Clearly, these were astounding long-term benefits for cognitive training; unfortunately, our TOPS Study does not have the longevity to determine how long the cognitive benefits from training will last.

As the parent study (TOPS Study) continues, larger samples will be available to determine whether this Individualized-Targeted Training Framework is effective in reducing not only the prevalence of HAND, but the severity of it, as was observed in Case A. Furthermore, given the relationship between cognition and quality of life, depression, and everyday functioning, even minor improvements in these cognitive domains may produce therapeutic noncognitive benefits.

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Table 1.

Demographic Characteristics and Pre/Posttest Cognitive Performance Scores

Variable	Targeted Cognitive Training Group			No-Contact Control Group			Between-Group Observations
	Case A	Case B	Case C	Case D	Case E	Case F	
Age, years	65	60	58	56	56	62	Participants are demographically similar
Sex	Male	Male	Male	Male	Male	Female	
Race	AA	Caucasian	AA	AA	AA	AA	
Education (years)	12	12	12	12	13	8	
Global deficit score							
Pretest *	9	5	8	8	8	8	
Posttest *	7	5	8	9	8	6	Similar changes observed in both groups.
Change	-2	0	0	+1	0	-2	
Speed of processing	Trained						
Pretest	8	3	4	5	7	5	
Posttest	6	3	2	4	6	5	Changes favor the training group by 2 points.
Change	-2	0	-2	-1	-1	0	
Verbal learning and memory	Trained						
Pretest	8	6	8	8	6	7	
Posttest	5	6	7	8	5	6	Changes favor the training group by 2 points.
Change	-3	0	-1	0	-1	-1	
Delayed verbal learning and memory	Trained						
Pretest	7	5	7	6	8	6	
Posttest	7	6	9	9	9	6	Similar changes observed in both groups.
Change	0	+1	+2	+3	+1	0	
Executive function							
Pretest	5	1	7	5	5	1	
Posttest	3	2	2	6	6	2	Changes favor the training group by 11 points.

Variable	Case A	Case B	Targeted Cognitive Training Group			No-Contact Control Group			Case F	Between-Group Observations
Change	-2	+1	-5	+1	+1		+1	+1		
Attention	Trained									
Pretest	5	1	1	6	6		6	1		Changes favor the training group by 3 points.
Posttest	2	1	1	6	6		6	1		
Change	-3	0	0	0	0		0	0		
Spatial learning and memory			Trained							
Pretest	9	2	6	3	4		4	8		Changes favor the training group by 11 points.
Posttest	8	2	2	9	6		6	6		
Change	-1	0	-4	+6	+2		+2	-2		
Delayed spatial learning and memory										
Pretest	8	1	3	2	6		6	7		Changes favor the training group by 8 points.
Posttest	6	2	2	9	6		6	6		
Change	-2	+1	-1	+7	0		0	-1		
Spatial visualization										
Pretest	5	1	1	1	3		3	3		Changes favor the control group by 5 points.
Posttest	8	2	2	2	2		2	3		
Change	+3	+1	+1	+1	-1		-1	0		
Within-person observations	Case A improved by 2 global points. Targeted training was effective.	No global improvement. Targeted training was not effective.	No global improvement. Targeted training effects were mixed.	No global improvement.	No global improvement.			Case F improved by 2 global points.		

Note. AA = African American; Education (year) = 12 (high school graduate or equivalency). Trained = participant received 10 hours of training in this domain due to cognitive deficit in this domain

* = A score of 5 or higher is indicative of HIV-Associated Neurocognitive Disorder (HAND); 1 = detrimental cognitive change; - = beneficial cognitive change.

As a caveat, investigators were not blinded to treatment assignment.