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STUDY PROTOCOL

Executive Functioning Training for Reducing Cognitive Intra-Individual Variability in People Living with HIV: A Pilot Randomized, Controlled Trial Protocol

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Video Abstract

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Background and Purpose: Cognitive training programs have been attempted to improve cognition in cognitively vulnerable people living with HIV (PLWH). Some have attempted to improve episodic memory or speed of processing, while others have used an individualized cognitive domain approach targeting each person's cognitive deficits. Although effective, none of these approaches considered the influence of cognitive intra-individual variability (IIV). Cognitive IIV refers to the fluctuations in one's individual cognitive ability across cognitive domains (dispersion) or within the same test (inconsistency). Greater cognitive IIV predicts cognitive decline as well as decreased cognitive integrity and increased neuropathology. Some neuroscientists posited that poor executive functioning, known as the Executive Dyscontrol Hypothesis, increases cognitive IIV. Thus, if we can improve executive functioning, we may be able to decrease cognitive IIV and improve overall cognitive functioning. This article provides the rationale and protocol for a feasibility clinical trial examining an executive functioning training intervention in middle-aged and older PLWH.

Study Design: This study utilizes a two-arm baseline/posttest experimental design to examine the primary aim 1 (feasibility and acceptability) and the exploratory aim 1 (cognition) in 120 community-dwelling PLWH aged 40 and older. Participants will be randomized into one of the two arms: 1) 20 hours of computerized executive functioning training group, or 2) a no-contact control group. The proposed training time is 10 to 12 weeks (1 to 2 one-hour training sessions/week while working around participants' schedules). At baseline and posttest, participants will receive a 1.5 to 2-hour assessment that includes many measures including the Connor's Continuous Performance Test (Version 3), and a 50-minute self-administered computerized cognitive performance battery (BRACE+ = BrainBaseline Assessment of Cognition and Everyday Functioning).

Conclusion: This study tests an innovative intervention designed to reduce cognitive IIV; to our knowledge, no other study has targeted cognitive IIV as an intervention outcome.

Plain Language Summary: Cognitive intra-individual variability (IIV) refers to the fluctuations in one's individual cognitive ability across cognitive domains or within the same test. Greater cognitive IIV predicts cognitive decline as well as decreased cognitive integrity, increased neuropathology, and even greater mortality. We are using this concept to design cognitive interventions to help people with HIV to age successfully cognitively.

Keywords: HIV-associated neurocognitive disorder (HAND), intra-individual variation, brain fitness, cognitive reserve, cognitive training, executive functioning

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Introduction

Approximately, 44% of people living with HIV (PLWH) experience mild-to-moderate cognitive impairments known as HIV-Associated Neurocognitive Disorder (HAND), which may affect medication adherence and other instrumental activities of daily living (IADLs), mood, and quality of life.[1] However, for most PLWH with HAND, it is mild, known as asymptomatic neurocognitive impairment (ANI) which does not dramatically impair IADLs. Age-related cognitive decline is a significant concern, as 70% of PLWH in the United States will be 50 or older by 2030.[2] HIV may accentuate or accelerate the aging process, including cognitive aging.[3] In comparing the cognitive functioning of older and younger adults, both with and without HIV, generally older adults with HIV perform the worst; in fact, with increasing age with HIV, cognitive deficits can become more common and severe.[4,5] Unfortunately, pharmacological cognitive interventions have short-lived effects, if any, and can produce adverse side effects in a clinical population that is susceptible to multiple comorbidities and polypharmacy.[6]

These impairments occur across cognitive domains, although executive functioning is particularly affected. In a 2018 meta-analysis of 37 studies of PLWH, the results indicated that HIV may differentially affect executive functioning and it should be specifically targeted for intervention.[7] Executive functioning is essential for coordinating various cognitive abilities/domains, and according the Executive Dysfunction Hypothesis, enhancing executive function could improve cognitive function in PLWH. Conversely, poor executive functioning leads to disorganized and less efficient functioning in other cognitive domains, resulting in greater variability and inconsistency in cognitive performance.[7]

Recent research suggests that traditional mean-based neuropsychological assessments do not fully capture cognitive impairments in PLWH; in fact, variations in an individual's cognitive ability across cognitive domains (ie, dispersion) or across multiple trials within the same test (ie, inconsistency), known as cognitive intra-individual variability (IIV), may better reflect underlying pathology. To highlight this concept of IIV, Figure 1 shows an example of dispersion. For instance, three people (eg, Tom, Dick, and Harry) could complete a cognitive a performance battery and have the same global mean score (eg, 39), which might lead to the assumption that they are all functioning at a similar level. Albeit, if one looks at the spread of their domain scores, Tom's performance across cognitive domains was rather consistent and had little variability, while Dick's performance was more spread out, and Harry's performance fluctuated widely across the domains. Based on this underlying concept of cognitive IIV, we would expect that Harry would have more executive

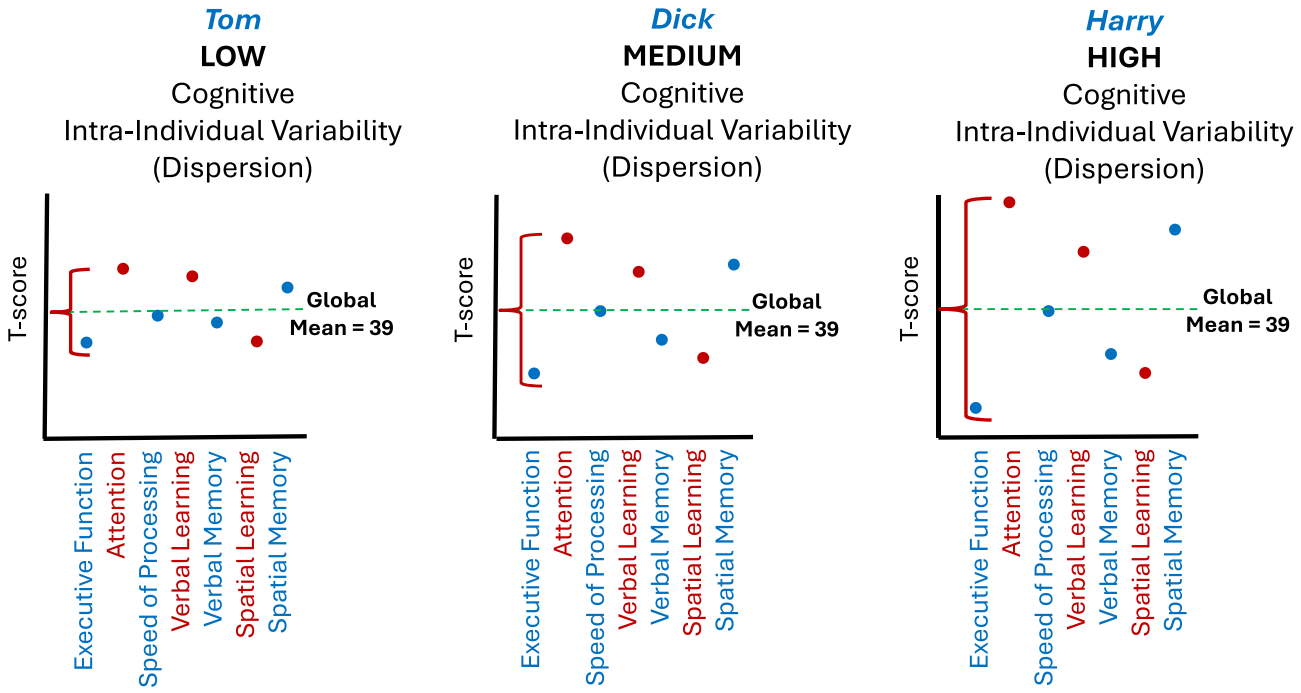

Figure 1 Example of Cognitive IIV – Dispersion.

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functioning dysfunction and that he would be more susceptible to cognitive decline than Tom and Dick; likewise, we would assume based on this spread of cognitive performance (ie, dispersion) that Dick would be more cognitively vulnerable than Tom. Similarly, as seen in Figure 2, inconsistency is measured in a similar way but within a single domain. Similarly, as seen in Figure 2, inconsistency is measured in a similar way but within a single domain. For example, in a reaction time test with multiple trials, a person's reaction time (or any response) tends to have some variability, and it would not be identical each time. In this example of seven reaction time tests measuring how quickly they responded to the correct stimulus. Tom, Dick, and Harry have the same mean-based outcome of 1.4 seconds, but, like before with dispersion, one can see that there is a lot of spread (ie, inconsistency) in their reaction times. The same interpretation applies and, that is, the greater the spread, the worse the predictive outcomes.

Greater cognitive IIV predicts cognitive decline, decreased cognitive integrity, and increased neuropathology.[8,9] One hypothesis suggests that cognitive IIV may result from "executive dyscontrol", where executive control processes are inefficient in coordinating other cognitive domains.[7,10] A meta-analysis of 37 studies found that specific domains of executive functioning are differently impacted by HIV.[7] Furthermore, an integrative review of 13 articles analyzed two types of cognitive IIV in PLWH, inconsistency and dispersion, summarizing that greater cognitive IIV in PLWH has been associated with 1) cognitive decline and poorer cognitive functioning, 2) brain atrophy in both white and gray matter volume, 3) poorer functioning in instrumental activities of daily living (IADLs, eg, medication adherence) and activities of daily living (ADLs), and 4) mortality.[11]

Cognitive training has been shown to produce changes in brain function and structure, resulting in cognitive improvements.[12] A study of working memory training by Chang et al found that approximately 10 hours of working memory training, a type of executive functioning training, was administered over 5–8 weeks to 173 participants with and without HIV.[13] At baseline, PLWH exhibited poorer cognitive functioning than the group without HIV; however, those who received the working memory training showed improvement. Compared to the group without HIV at baseline, fMRI results indicated that PLWH required greater frontal activation to perform working memory tasks, suggesting increased neural effort to compensate for their poorer cognitive functioning. After 1 to 6 months of cognitive training, both the HIV-negative group and the PLWH group showed decreased frontal brain activation, indicating improved neural efficiency. Although cognitive IIV was not examined and the training duration was not extended to 20 hours, which might have yielded stronger results, the findings suggest that executive functioning training may reduce the burden on executive control resources. Consequently, these neural resources can be redirected to other cognitive domains that need compensation. As a result, such training should reduce cognitive IIV and improve cognitive function.

In a systematic review of 13 cognitive training studies in PLWH, it was found that cognitive training effectively improved the specific cognitive domain it targeted (eg, executive functioning training improved executive functioning).[14]

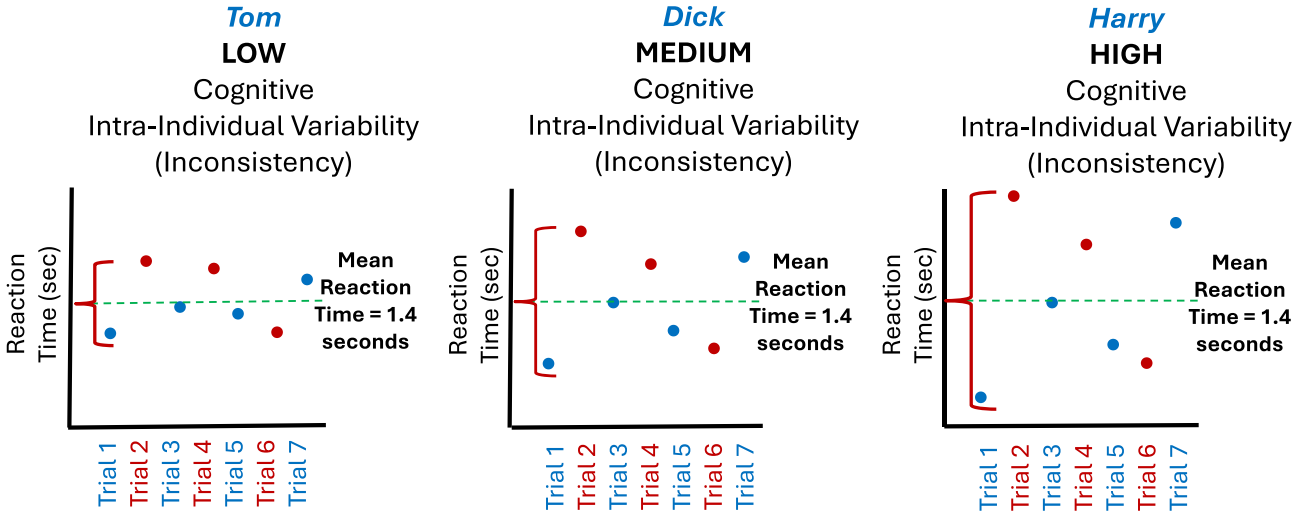

Figure 2 Example of Cognitive IIV – Inconsistency.

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Yet, none of these studies included cognitive IIV in their training protocols or outcome measures. Theoretically, enhancing executive functioning could reduce cognitive IIV and possibly reduce the prevalence and severity of cognitive impairments. It remains unclear how much executive functioning training would be tolerated as training can be fatiguing as it requires prolonged periods of staring at a computer screen and responding to stimuli and tasks. Based on a meta-analysis of cognitive training in older adults and a systematic review of cognitive training in HIV, approximately 20 hours of training is considered the upper limit for achieving optimal therapeutic benefits.[14,15]

Based on the rationale above, the purpose of this article is to provide an overview of a funded feasibility and acceptability study with the goal of reducing cognitive IIV (both dispersion and inconsistency) by administering 20 hours of executive functioning training to PLWH 40 and older and comparing their cognitive functioning, specifically their cognitive IIV scores, to a no-contact control group. This study is significant and innovative because it focuses on cognitive IIV within the context of cognitive training in PLWH. This will be the first study to use cognitive IIV as a guide to target executive functioning training to improve global cognitive ability, which may reduce the severity of cognitive impairment. It will be one of the first studies to prospectively include both types of cognitive IIV – dispersion and inconsistency – as an outcome of the study; this will allow us to examine the relationship between dispersion and inconsistency which has been greatly missed in the literature.[11]

Methods

Study Overview

This study will utilize a two-arms baseline/posttest experimental design (Figure 3) to examine the primary aim 1 (feasibility and acceptability) and the exploratory aim 1 (cognition) (Figure 4). After participants are recruited, a baseline (pretest) assessment is administered to participants during a ~1.5 to 2-hour visit at the research office. After the baseline assessment, all participants are randomized into one of the two arms: (i) an executive functioning training group with 20 hours of training or (ii) a no-contact control group. Random assignment ensures that an equal number of participants are in each arm by gender, minority status, and low vs high cognitive IIV scores (cutoff = 55 on the HRT SD (Hit Rate Standard Deviation) on the Connor's Continuous Performance Test (Version 3 (CCPT-3)). The proposed training time is 10 to 12 weeks (1 to 2 one-hour training sessions/week while working around participants' schedules). After training is completed, participants are scheduled for their posttest assessment where they are administered nearly the same assessment battery.

Human Subjects/Ethical Approval

Human subject use/ethical approval for this study was approved by the University of Alabama at Birmingham Institutional Review Board on January 3, 2022 (#FWA0000596) and remains in compliance. The study was registered with Clinical.Trials.gov (NCT05598047) prior to enrollment. Participants are explained the study over the phone and if they are eligible and agree to participate, they are mailed a consent form and a date for their baseline visit to the center is arranged. When they come to their baseline visit, a trained staff member explains the consent form to them again in person, reviewing all the specific elements of the consent process (ie, confidentiality, right to discontinue, etc). Participants are then given a brief true/false test to see if they understand the consent form; if they fail the test, the consent form is explained to them again, and the participant is given the test again. If they fail the test again, they are not allowed to participate in the study. If they pass the test indicating that they understand the consent form and what the study is about and about what rights they have, then they are allowed to sign the consent form and proceed with the study activities. In this study, the guidelines outlined in the Declaration of Helsinki are followed.

Rationale and Background of Study Aims

In this two-arm baseline/posttest experimental design, the overall aim of this study is to assess the feasibility and acceptability of the executive functioning training intervention on PLWH as examined through the baseline and posttest assessment. This will harness feedback for future implementation of the executive functioning training in PLWH. One primary study aim and one exploratory aim are examined. The primary aim is to determine the feasibility and

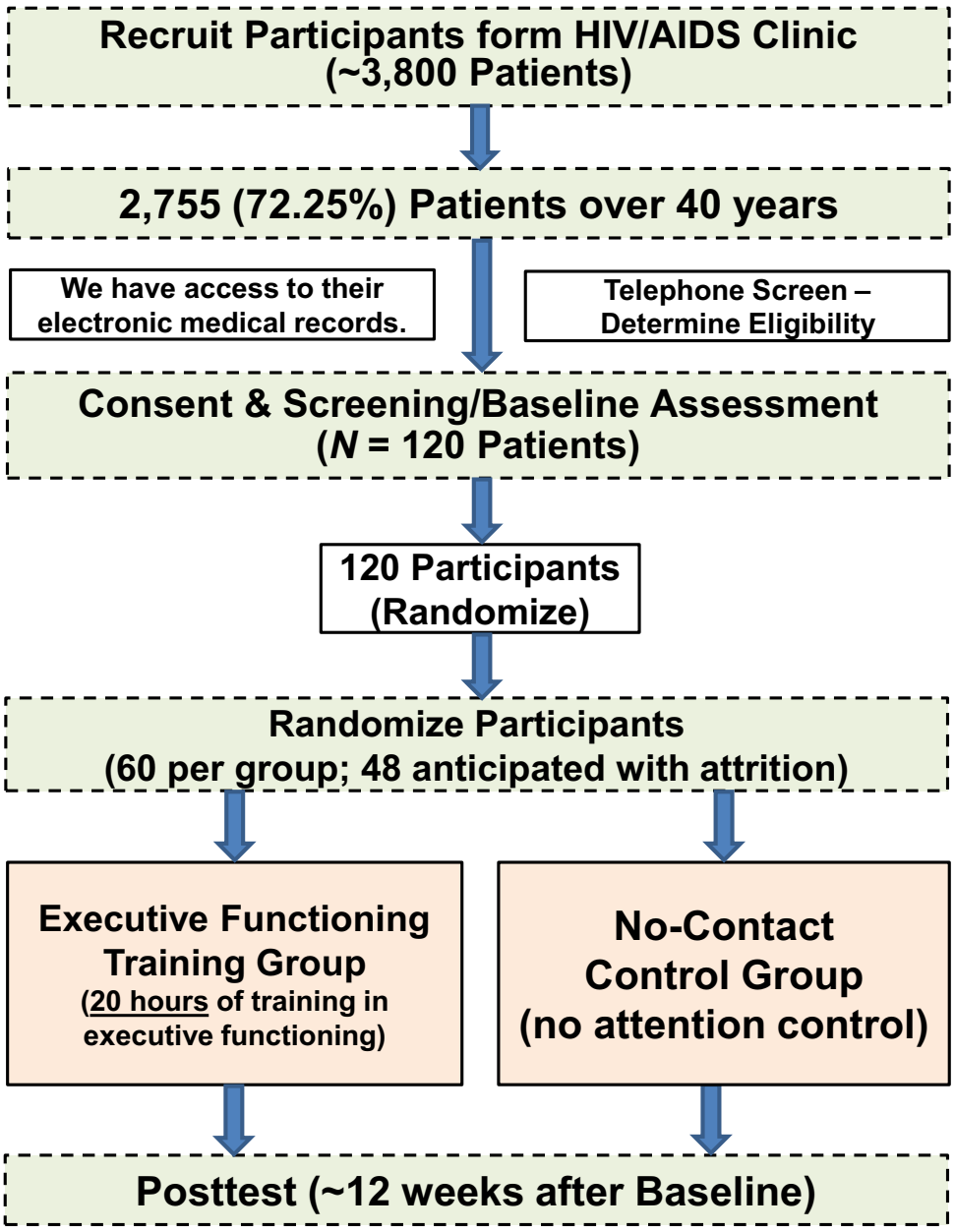

Figure 3 Study Design and Flowchart.

acceptability of the intervention by specifically assessing feedback, acceptability, and attrition (Table 1). The exploratory aim will examine baseline/posttest differences in measures of IIV (ie, dispersion and inconsistency) as well as several cognitive indices (Table 1). More specifically, we hypothesize that i) executive functioning training will improve executive functioning, ii) executive functioning training will reduce the prevalence/severity of cognitive impairments globally and across cognitive domains (eg, executive functioning, attention, verbal learning, verbal memory), and iii) executive functioning training will reduce cognitive IIV (ie, dispersion and inconsistency).

Recruitment

Participants will be recruited from an HIV/AIDS clinic using flyers and other recruitment materials. These recruitment materials describe the study purpose and protocol as well as state the compensation that will be provided for participating. Those interested in cognitive training or have concerns about their own cognitive health are encouraged to call.

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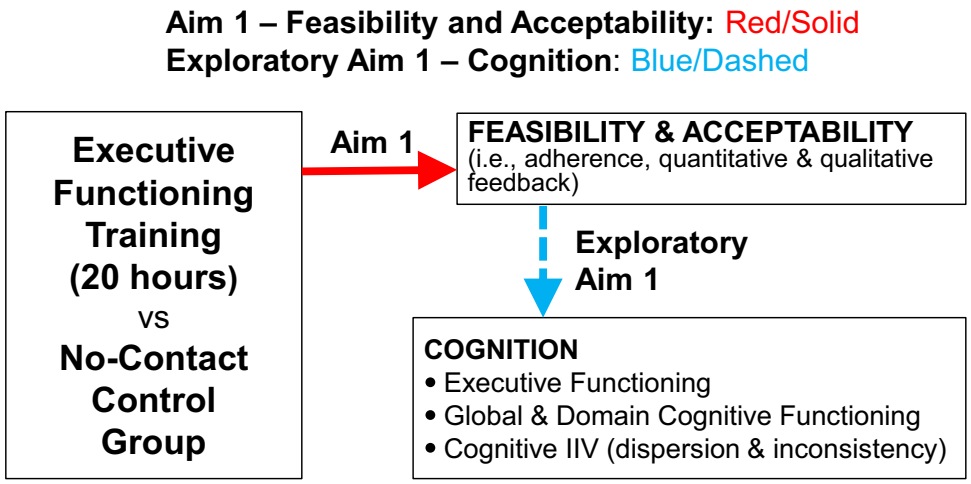

Figure 4 Conceptual Framework with Study Aims.

Participants are instructed to call the research office for further information, and during this time, the research assistant screens them over the phone to determine if they meet the basic eligibility criteria. Only those who meet these criteria are invited into the study, otherwise they are thanked but excused from further participation. In addition, participants are also recruited via a participant contact list provided by the HIV/AIDS clinic in which participants indicated a priori that they wanted to be contacted for studies. As with recruitment by flyers, participants were administered a screen over the phone to determine their eligibility.

The eligibility criteria consisted of the following. Participants must be 40 or older, English-speaking, and diagnosed with HIV for at least 1 year. Since participation requires ~12 weeks and in-person visits, participants living beyond 60 miles away from the center will be excluded. Participants living in unstable housing (eg, halfway house) or with significant neuromedical comorbidities (eg, schizophrenia) will be excluded. Other physical or neurological conditions (eg, legally blind/deaf, currently undergoing radiation or chemotherapy, history of significant brain trauma, or diagnosed with COVID-19 over the past 3 months) that could impact cognitive functioning or testing also necessitate exclusion. These criteria are typical of neuroHIV studies.[16,17] As cognitive training effects can be robust two years after training is completed, those who have received cognitive training within the past three years will be excluded.

Table 1 Study Measures Corresponding to Study Aims

Demographic, Background, and Covariate Measures	Aim 1: Feasibility and Acceptability	Exploratory Aim 1: Cognition
• Demographic Questionnaire • Wide Range Achievement Test-3 (WRAT-3) • Addiction Severity Index (ASI) • HIV History/Status • Centers for Epidemiological Studies – Depression (CES-D) • Medical Outcomes Scale Form-35 (MOS-35) • Medication Adherence Visual Analog Scale (VAS) • Electronic Medical Records (EMR)	• Baseline Assessment of Cognitive Training Questionnaire • Cognitive Training Satisfaction Questionnaire (after 10 hours of training completed and posttest only) • Perception of Their Need of Cognitive Training • Exit Survey • Attrition & Adherence Rates (after study data collection)	**Inconsistency** – Connor's Continuous Performance Test-3 (CCPT-3) **Dispersion** – BrainBaseline Assessment of Cognition and Everyday Functioning (BRACE+) • Executive Functioning Test • Attention Test • Speed of Processing Test • Immediate & Delayed Verbal Learning/Memory Test • Spatial Memory Test • Global Composite – formed by combining the above BRACE+ tests

Retention

To encourage retention, we utilize several strategies. First, we provide snacks and beverages to participants while they visit the center. Second, we offer free parking, which is conveniently located on a level lot immediately outside of our building. Third, we provide Medical UBER transportation, free of charge, if participants request it. Fourth, we compensate participants $50 USD for completing the baseline assessment, $75 USD for completing the posttest assessment, and $15 per hour of cognitive training completed.

Measures

A comprehensive battery of measures (Table 1) will be administered at the baseline and posttest (approximately 12 weeks later) assessments. This battery assesses 1) demographic and participant characteristic measures (ie, Demographic Questionnaire), educational quality (ie, Wide Range Achievement Test-3), substance use (ie, Addiction Severity Index (ASI)), depressive symptoms (ie, Centers Epidemiological Studies – Depression Questionnaire (CES-D)), quality of life (ie, Medical Outcomes Scale – 35), medication adherence for HIV (ie, Medication Adherence Visual Analog Scales – a percentage measure of how consistently one takes their HIV medication); 2) Aim 1 measures, specifically feasibility and acceptability measures; and 3) Exploratory Aim 1 measure, specifically cognitive functioning performance measures. Several study-developed questionnaires are also included, such as a Baseline Assessment of Cognitive Training Questionnaire, Cognitive Training Satisfaction Questionnaire, Perception of Their Need of Cognitive Training, and Exit Survey. Reaction time will be computer administered using the Connor's Continuous Performance Test – Version 3 (CCPT-3; from which inconsistency will be calculated; similar to Figure 2) and a computer-tablet administered cognitive functioning performance battery (ie, BRACE+; from which dispersion will be calculated; similar to Figure 1) will also be administered at baseline and posttest. These measures of feasibility and adherence as well as cognitive functioning tests are described further below.

Feasibility and Acceptability Measures of Aim 1

Baseline Assessment of Cognitive Training Questionnaire

Using this experimenter-generated measure, at baseline only, participants will be asked questions about computer use, knowledge about cognitive training, their perceptions about whether they need cognitive training, knowledge about HIV and cognition, etc. Both quantitative and qualitative (ie, open-ended responses) data will be collected.

Cognitive Training Satisfaction Questionnaire

Using this experimenter-generated measure, participants will be asked questions at posttest to assess likes/dislikes of the intervention; both quantitative questions and qualitative (ie, open-ended responses) data are gathered as has been used in our previous cognitive intervention studies to evaluate feasibility and acceptability.

Perception of Their Need of Cognitive Training

Using this experimenter-generated measure, participants will be asked questions at baseline and posttest to answer question related to how much they think or believe that they need cognitive training and how much they think it will improve their abilities. Some studies suggest that expectations of the benefits of cognitive training influence adherence and cognitive benefits.[18–20] Baseline and posttest differences will be examined to determine if participating in this intervention changed such perceptions.

Exit Survey

If a participant withdraws, they will be administered a brief quantitative and qualitative (ie, open-ended responses) survey to assess what he/she liked/disliked about the training, how to improve it, and why he/she is withdrawing from the study. We also ask if they have received any other cognitive intervention during this time.

Attrition/Adherence Rates

As the study will keep track of the number of visits to the research office for baseline and posttest appointments (attrition) and how much computer training is completed on the computer (adherence), the overall study attrition rate and adherence rate of the participants will be calculated, similar to our other cognitive training studies.[5,21]

Cognition Measures of Exploratory Aim 1

Inconsistency – Connors' Continuous Performance Test, Version 3 (CCPT-3)

The Connors' Continuous Performance Test (CCPT-3) is used to measure IIV inconsistency, which refers to the variability in a single person's performance on a single task (ie, within a task) across multiple instances or trials, such as the variability observed across a person's distribution of reaction times (RT) on a cognitive task. Two common formulas to calculate this variability are the intra-individual standard deviation (iSD) and the coefficient of variation (CoV).[22] These measures are assessed and will be calculated at both baseline and posttest as an outcome variable to evaluate the overall improvements in cognitive function. The CCPT-3 is a widely accepted test for evaluating sustained and selective attention and impulsivity. It is the most frequently used test in cognitive IIV research to determine IIV inconsistency coefficients.[11,23]

Dispersion – BrainBaseline Assessment of Cognition and Everyday Functioning (BRACE+)

The BrainBaseline Assessment of Cognition and Everyday Functioning (BRACE+) is a HIPAA compliant tablet-based cognitive assessment platform, supported by NIMH R42099964 and Digital Artefacts/UCSD. It is designed to be self-administered without requiring literacy (ie, automated audio/video instructions). BRACE+ uses validated cognitive tests that are sensitive to mild-to-moderate cognitive impairments and have demonstrated good validity relative to a comprehensive standard cognitive performance test battery and test–retest reliability. During its development, BRACE+ generated T-scores (mean = 50, SD = 10) using a normative-based regression approach, adjusted for age, sex, race/ethnicity, and education. The data came from the Women's Interagency HIV Study (WIHS, all women) and the Multicenter AIDS Cohort Study (MACS, all men).

The BRACE+ also demonstrated good discriminant validity by effectively differentiating between PLWH with and without HAND, using a T-score cutoff of less than 40 on the gold standard cognitive tests. Designed for repeat administration, BRACE+ randomizes trials from all experimental conditions within each test administration, creating an unlimited number of "versions" of each test and ensuring that no two test administrations are alike, avoiding practice effects that plague many current cognitive assessments.

The BRACE+ measures various cognitive domains including 1) executive functioning, 2) attention, 3) speed of processing, 4) verbal learning, 5) verbal memory, and 6) spatial memory. Using the IIV formula for dispersion, a dispersion coefficient can be generated by measuring the fluctuation in one's individual cognitive variability across cognitive domain, as it typically conducted with cognitive batteries such as these.

Randomized Two Arm

Executive Functioning Training Arm

Participants in the Executive Functioning Training Arm will perform various exercises (eg, Mind Bender) that necessitate set shifting, which involves maintaining at least two sets of rules and determining the appropriate one for a given response (see Table 2). Participants will be engaged in 1 to 2 hours of training at a time where they sit in front of a computer, the research assistant logs them on to their account, and the training program will present the various training exercises (around 15 minutes in each) and then it rotates to other similar cognitive training exercises. By rotating to other types of related executive functioning training exercises, this is purposely done to avoid repetition and boredom and encourage engagement and interest.

The Training On Purpose Study (TOPS) included 88 PLWH and a subset of those participants (n=9) engaged in 10 hours of executive functioning training, which found that the use of these cognitive training exercises yielded a significant effect size (d=−0.89). Yet, other studies suggest a dosage of 20 hours of training is considered as the upper limit required to achieve an optimal therapeutic effect.[14,15,22] Thus, 20 hours is the target dosage for this study.

No-Contact Control Arm

This arm will not receive any intervention. Due to this study's pilot nature and feasibility constraints, we do not have the resources to include a contact control group. Notably, previous research has demonstrated no significant difference between no-contact control groups and contact control (sham) groups, and both served as an excellent comparison for cognitive intervention.[24]

Table 2 Executive Functioning Training Exercises

Cognitive Training Domain	Cognitive Training Exercises Matching the Cognitive Domain (see POSIT Science Inc (Brain HQ) at www.brainhq.com for Details)
Executive Functioning – These exercises require one to set shift; that is, to maintain at least two sets of rules and decide which one is appropriate for the response. In a prior cognitive training study in PLWH, the effect size for executive functioning training in our last study was $d = -0.89$.[22]	**Mind Binder –** This exercise is a "set shifting" exercise where one is presented with two rules, but one must choose the correct answer based upon the rules provided in this exercise. **Mixed Signals –** This exercise requires one to listen to a number, letter, or other information while looking at a similar set of information, similar to the Stroop test. **Card Shark –** This exercise is an extension of a visual n-back paradigm using an aspect of executive functioning (ie, working memory). **Freeze Frame –** This exercise is an extension of the go/no go paradigm using an aspect of executive functioning (ie, working memory).

Power Analysis

The sample size for this study is based on three considerations: 1) the exploratory rather than confirmatory nature of the project which focuses on feasibility and effect size estimation rather than null hypothesis significance testing (as there have not been cognitive training studies on cognitive IIV for HIV); 2) the effect size obtained in our Training on Purpose Study (TOPS) on PLWH for global cognitive score of |d|=0.21; and 3) an expected attrition rate of 19.2% based on TOPS. An effective sample size of 48 per group (after attrition; n per group = 60 enrolled; total N=120) is sufficient for estimating reasonable upper and lower bounds for an effect size, assuming random sampling from the target population. We conducted 5000 computer simulations of an experiment with a true effect size of 0.22 comparing two groups with n = 48, intra-subject correlation of 0.5, and data distributed following a Student's t (df = 48) distribution. Tabulation of the 16th and 84th percentiles (ie, 68% of the distribution centered at the mean) of the 5000 observed effect sizes resulted in the interval 0.02–0.42, which provided reasonable lower and upper bounds for the expected effect size in a larger sample. If formal testing is conducted at a traditional level of 0.05, and again assuming intra-subject correlation of 0.5, a sample of 48 per group provides 80% power to detect an effect of 0.57 (a medium effect size).

Data Analysis

For the primary aim, feasibility and acceptability of the adherence rate of the protocols and attrition rate will be calculated. Measures of bivariate association will be used to explore predictors of attrition and adherence. We will tabulate training satisfaction responses and apply qualitative techniques to examine open-ended responses to feedback about training. We will have multiple sources of data (ie, see Table 1) in which we can triangulate data to examine barriers and strengths to the acceptability and feasibility of this intervention in this clinical population.

For the exploratory aim, cognitive performance will be assessed post-intervention. Between-group differences in proportions will be converted into effect size using the method by Chinn,[25] and confidence intervals will be estimated. For each cognitive outcome measure (Global Score, IIV Dispersion, IIV Inconsistency), longitudinal models will be fitted with a group assignment indicator, time-point indicator, and group by time-point interaction. A random effect for participants will be fitted to account for non-independence among the repeated measures on the same individuals. Linear contrasts will be used to estimate and compare the groups' mean outcome change. The between-group difference in change will be transformed into an effect size with respective confidence intervals. If necessary, the models will be adjusted for baseline covariates imbalanced at baseline or associated with attrition. Interpretation will be based on the magnitude of the estimated effect sizes and the resulting width of the respective confidence intervals.

Discussion

As PLWH age, concerns mount that HIV and the factors surrounding HIV (ie, inflammation, stigma) may accelerate or accentuate the cognitive aging process.[3] These impairments occur across cognitive domains although executive

functioning is particularly affected.[26] In a 2018 meta-analysis of 37 studies of PLWH, executive dysfunction may be more pronounced and should be specifically targeted for intervention.[7] Age-related changes in the frontal lobe are associated with reduced executive functions (ie, working memory, set-shifting, inhibitory control), and white matter hyperintensities in the frontal lobe may specifically contribute to the decline in executive function observed with aging.[27] Computerized cognitive training interventions have shown significant improvements in executive functioning, as well as in processing speed, episodic memory, working memory, and overall cognitive performance.[28]

Improving executive functioning ability/resources can improve functioning in other cognitive domains. In prior work with the TOPS Study involving PLWH with HAND, executive functioning training not only improved executive functioning (n=9; d=−0.89) but improvements were also observed in the speed of processing (d=−0.56), attention (d=−1.24), and delayed verbal learning and memory (d=−0.40).[22] By training executive functioning, we expect to reduce cognitive IIV (indicating improvement in executive coordination), which may subsequently improve global cognition and decrease the prevalence and severity of cognitive impairment.

This is the first study to use IIV as a guide for focusing solely on executive functioning training to improve global cognitive ability, which may reduce the severity and prevalence of cognitive impairment. This study will be the first to prospectively include both types of cognitive IIV – dispersion and inconsistency; this will allow us to examine the relationship between dispersion and inconsistency in cognitive IIV, which is a concept relatively unexplored in the cognitive training and cognitive rehabilitation literature.

The initial step is to validate the clinical effectiveness of executive functioning training in reducing cognitive impairment and improving cognitive functioning. After this proof of concept, further studies should examine: 1) changes in neurological structures/pathways using fMRI and 2) the extent to which this cognitive training approach in PLWH improves everyday functioning and quality of life. Future research could also focus on improving specific cognitive domains other than executive function to determine if the strain on executive functioning is reduced and cognitive impairment symptoms alleviated. Although we initially considered this broader approach, we concluded that focusing on reducing cognitive IIV by improving executive functioning is a necessary first step.

Nursing Implications

The study highlights the significant implications of executive functioning training for reducing cognitive impairment and enhancing cognitive functioning in nursing practice. First, as a part of holistic care, nurses may consider incorporating executive function assessments into routine patient evaluations, especially for PLWH, and should be trained to accurately administer assessments and interpret results to identify patients who may benefit from targeted cognitive training interventions. Second, nurses can educate PLWH about possible executive dysfunction and ways to improve this cognitive ability. Lastly, nurses should emphasize the importance of interdisciplinary collaboration that can contribute to the overall well-being and quality of life of PLWH with cognitive challenges.

Strengths/Limitations

All studies have strengths and limitations, and this study is without exception. Notable strengths include the following. First, this study is the first to examine whether cognitive IIV can be modified by cognitive training. Second, it incorporates both types of cognitive IIV, dispersion and inconsistency. Third, it utilizes computerized cognitive testing, which should potentially minimize tester error. Notable limitations include the following. First, this study is minimally powered to explore global cognitive differences, but not across various cognitive domains (ie, verbal learning, processing speed). Second, this study occurs in a city in the Southern United States; regional differences may prevent the findings from being generalizable. And third, this study lacks follow-up beyond 12 weeks, so it is unclear whether the training effect would be robust over time (ie, 6 months, 12 months, 24 months).

Conclusions

In conclusion, as PLWH age, they will be more at-risk for cognitive impairment; as such nurses and other healthcare professionals will require therapeutic strategies to mitigate the risk of such cognitive decline and neurological dysfunction. Prior research has suggested that cognitive training approaches can be minimally to moderately effective in

improving cognitive function, at least in the short term and only with specific cognitive domains. Fortunately, the protocol presented here suggests that perhaps EFT can improve this cognitive ability and in turn improve cognitive IIV. This is important because cognitive IIV may be a more important predictor of developing cognitive impairments in PLWH than mean-based cognitive measures. Thus, it is the expectation of this study that targeting the reduction of cognitive IIV, including the underlying neurological sequelae, the trajectory of such detrimental outcomes can be altered. At the juxtaposition of neuroscience and nursing care, cognitive IIV is an innovation in exploring the neurocognitive issues of HIV.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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