Title
Cognitive Rehabilitation for Cocaine Use Disorder

Author
Kalapatapu, Rajkumar Kiran

Publication Date
2020

Peer reviewed|Thesis/dissertation

Cognitive Rehabilitation for Cocaine Use Disorder

by
Rajkumar Kalapatapu

DISSERTATION
Submitted in partial satisfaction of the requirements for degree of
DOCTOR OF PHILOSOPHY

in

Epidemiology and Translational Science

in the

GRADUATE DIVISION
of the
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Approved:

DocuSigned by:
Kevin L. Delucchi — Kevin L. Delucchi
03A04C3B7702462...
Chair

DocuSigned by:
Deborah Barnes — Deborah Barnes
DocuSigned by:
Kevin L. Delucchi — Kevin L. Delucchi
DocuSigned by:
Valerie Gruber — Valerie Gruber
DocuSigned by:
Hahn, Judith — Hahn, Judith
FEC9CE9B26AC446...
Committee Members

Dedication and Acknowledgements

Thank you to the following people for their mentorship (alphabetical order):

Deborah E. Barnes, PhD, MPH (UCSF)

Steven L. Batki, MD (UCSF)

Kevin L. Delucchi, PhD (UCSF)

Gordon M. Giles, PhD, OTR/L, FAOTA (Samuel Merritt University, Oakland, CA)

M. Maria Glymour, ScD, MS (UCSF)

Valerie A. Gruber, PhD (UCSF)

Judith A. Hahn, PhD (UCSF)

Thank you to all of my previous mentors at the Indiana University School of Medicine, the Icahn School of Medicine at Mount Sinai, and Columbia University.

Thank you to the National Institute on Drug Abuse
for helping to fund my clinical research ideas and my graduate school education.

Thank you to my late parents:

Umamaheswara Rao Kalapatapu, MD

SithaGita Rajyalakshmi Mukkamala Kalapatapu, MD, DGO

Thank you to my late maternal grandmother:

Rajkumari Mukkamala, MA, MSc

Cognitive Rehabilitation for Cocaine Use Disorder

Rajkumar Kiran Kalapatapu

Abstract

Brief Statement of the Problem: Effectively treating cognitive impairment as part of a comprehensive treatment plan for adults with cocaine use disorder (CUD) could potentially improve important clinical outcomes, such as abstinence, quality of life, and treatment completion. Because existing models of cognitive rehabilitation have yielded small to medium effect sizes in improving cognition in CUD, newer models of cognitive rehabilitation are needed to improve cognition more effectively in CUD.

Description of the Methods and Procedures Used to Gather Data: This dissertation describes a pilot 12-week, randomized, parallel group outpatient study of treatment-seeking adults with CUD (age 18-65) who were mild-to-moderately cognitively impaired and dissatisfied with their quality of life. Participants were randomized to a “Cog-Rehab” arm (drug counseling + occupational therapy-based cognitive rehabilitation), or to a “Control” arm (drug counseling + psychoeducation/computer exercises).

Condensed Summary of the Findings: Study participants had a mean age of 57.5 years (SD 5.8), 30 (96.8%) were male, 19 (61.3%) were Black, 12 (38.7%) were White, 6 (19.4%) were Latino, 15 (48.4%) were single, and had a mean education of 12.8 years (SD 1.4). Some significant between-group effect sizes were found for certain neurocognitive measures (favoring Cog-Rehab arm: attentional bias 1.0 attention 0.7, visual memory 0.8, executive function 1.0) and one functional assessment (favoring Cog-Rehab arm: Drug User Quality of Life Score 0.8). This study was feasible, acceptable, and provides preliminary evidence for efficacy based on effect sizes. MET-R performance was significantly associated only with the overall impulsivity neurocognitive domain (adjusted coefficient 0.8, 95% CI 0.2 to 1.3) on a neurocognitive battery. The MET-R may be uniquely measuring the domain of impulsivity that is not captured by traditional neurocognitive testing.

Table of Contents

List of Figures

List of Tables

Chapter 1 Abstract

Background: As cognitive impairment moderates clinical outcomes in adults with cocaine use disorder (CUD), effectively treating cognitive impairment as part of a comprehensive treatment plan for CUD could potentially improve important clinical outcomes, such as abstinence, quality of life, and treatment completion. Because existing models of cognitive rehabilitation have yielded small to medium effect sizes in improving cognition in CUD, newer models of cognitive rehabilitation are needed to improve cognition more effectively in CUD.

Aims: Practitioners in the occupational therapy (OT) field work on improving the function of various cognitively impaired populations (e.g., stroke, traumatic brain injury, schizophrenia) by using cognitive-adaptation techniques to enhance cognition in daily quality of life/function. OT can address the cognitive and problem-solving deficits that lead to a breakdown in daily life skills. A model of OT-based cognitive rehabilitation in CUD may strongly improve cognition, ultimately improving important clinical outcomes. The overall project aims were to examine the improvement in cognition, examine the improvement in cocaine abstinence, and examine the improvement in daily quality of life/function from a novel model of OT-based cognitive rehabilitation.

Methods: This paper describes the protocol for a pilot 12-week, randomized, parallel group outpatient study of treatment-seeking adults with CUD (age 18-65) who were mild-to-moderately cognitively impaired and dissatisfied with their quality of life. Participants were randomized to a "Cog-Rehab" arm (drug counseling + OT-based cognitive rehabilitation), or to a "Control" arm (drug counseling + psychoeducation/computer exercises). Because this study was a pilot trial, the initial goals were to assess feasibility of enrollment and acceptability of all study procedures by participants.

Discussion: This manuscript describes the protocol for a pilot study that will assess the feasibility and acceptability of a novel approach for improving cognition in adults with CUD and cognitive impairment. CUD remains a significant public health problem in the U.S., and cognitive

impairment moderates clinical outcomes in CUD. Integrating OT-based cognitive rehabilitation in a comprehensive treatment plan for CUD could have a direct and significant positive impact on the public health burden of this population.

Chapter 1 Main Body

INTRODUCTION

Cocaine use disorders (CUDs) remain a significant U.S. public health problem [1, 2]; in 2014, there were an estimated 1.5 million current (past-month) cocaine users aged 12 or older, and data from the 2011 Drug Abuse Warning Network report show that one in three drug misuse or abuse-related emergency department visits (40 percent) involved cocaine. Having a diagnosis of CUD is associated with cognitive impairment [3-8] (medium to large effect sizes [9]) in the domains of psychomotor speed [10-12], memory [10, 13-18] (up to 47% of patients with CUD [19]), attention/concentration [13, 20-25], and executive function [26-30]. One study showed that 30% of those with CUD and even 12% of recreational cocaine users exhibited clinically relevant global cognitive impairment [31, 32]. Cognitive impairment in those with substance use disorders (SUDs) [33-37] is associated with relapse [38, 39], lower likelihood of treatment completion [40-44], lower motivation [45], and worse quality of life [46, 47]. As cognitive impairment moderates clinical outcomes in CUD [42, 43], effectively treating cognitive impairment as part of a comprehensive treatment plan for CUD could potentially improve important clinical outcomes, such as abstinence, quality of life, and treatment completion.

Pharmacologic interventions are being studied to treat cognitive impairment in CUD [48-52]. However, pharmacotherapy has limitations. Many treatment-seeking individuals with CUD take medications for comorbid disorders [53-55] (e.g., major depression [56], bipolar disorder [57], schizophrenia [58]), active cocaine use interacts with prescribed medications and other active drug use [59, 60], and abuse of many classes of prescribed medications is a current public health problem [61-64]. These limitations can lead to problems with medication adherence, medication-drug toxicity, and treatment dropout. Non-pharmacologic cognitive rehabilitation interventions can play an important role in the treatment of CUD by avoiding potential adverse effects from drug interactions.

Non-pharmacologic cognitive rehabilitation interventions have been added to substance use disorder treatment in those with cognitive impairment, some computerized [65-97] and others not [85, 98-107]. Because existing models of cognitive rehabilitation have yielded small to medium effect sizes in improving cognition in CUD [68, 69, 76, 77], newer models of cognitive rehabilitation are needed to enhance existing models and to improve cognition more effectively.

Historically, cognitive rehabilitation has been divided into models of remediation & adaptation [108-111]. Remediation focuses on restoring cognition; potential mechanisms of restoring cognition include neuroplastic changes through prefrontal–temporal–parietal systems and improving brain activation in prefrontal and thalamic regions, though the mechanisms for remediation have not been fully elucidated [112-114]. Both non-computer-cognitive-remediation programs [98-107] and computer-cognitive-remediation programs [65, 66, 73-84], such as PSSCogRehab [67-71], NeurXercise [72], and Cogmed [75, 81, 82, 88] have been tested in those with SUDs (primarily in those with alcohol use disorder [AUD]). Non-computer-cognitive-remediation programs have included repetitive paper-pencil puzzle-like tasks, cognitive tasks using workbooks and manuals, and card sorting tasks. Computer-cognitive-remediation programs have been developed by software companies across the world and have focused on various cognitive domains, such as working memory, attention, executive function, and problem-solving. Only a few studies have included CUD [67-69, 76, 77]. These studies have generally yielded small to medium effect sizes in improving cognition in CUD (e.g., R^2 = 0.08 at follow-up month 5 and R^2 = 0.07 at follow-up month 6 [67]; Cohen's d = 0.37 [68]; Generalized eta-squared η_G^2 = 0.069 [69]), though they may have still meaningful secondary effects, such as higher treatment engagement and higher treatment commitment [68].

Adaptation focuses on compensating for cognitive impairment. Cognitive-adaptation strategies include time pressure management [115] & compensatory rules [116] for attention deficits, memory diaries [117] & mnemonics [118] for memory deficits, and problem solving training [119] & goal management training [120] for executive function deficits. Various studies

[120-128] suggest that cognitive-adaptation can improve cognition, functional capacity, and subjective quality of life in various types of cognitively impaired patients, such as traumatic brain injury patients [129] and psychotic patients [130, 131]. A 12-visit cognitive-adaptation individual manual used in the study of psychotic patients [130] contained fundamental cognitive-adaptation strategies, such as vigilance exercises, memory aids, mnemonics, rhyming, chunking, and problem-solving.

There are limited data of cognitive-adaptation in those with SUDs. In 16 participants with psychiatric/substance use disorders and cognitive deficits [132], cognitive-adaptation strategies (time management, calendars, appointment books) improved punctuality for appointments. A 3-week study in those with AUDs found younger participants to improve more on memory tests than older participants [133]. An 8-week study in those with AUDs found an improvement on the Boston Remote Memory Recognition subtest [134]. Given the literature of cognitive-adaptation in various populations [120-129, 131], research is warranted on the effectiveness of cognitive-adaptation in treating cognitive impairment in CUD and whether results from other populations generalize to CUD.

A strong non-pharmacologic option is to integrate concepts from the field of Occupational Therapy (OT) into the cognitive rehabilitation of CUD. OT improves the function of various cognitively impaired patients (e.g., stroke, traumatic brain injury, schizophrenia) by using cognitive-adaptation/compensation to enhance cognition in daily quality of life/function [120-129, 131], and OT can address the cognitive and problem solving deficits that lead to a breakdown in daily life skills [135]. The effectiveness of OT-based cognitive rehabilitation in treating cognitive impairment in CUD has not been examined through research. A model of OT-based cognitive rehabilitation in CUD may strongly improve cognition, ultimately improving important clinical outcomes such as abstinence and quality of life.

One neuroscience theory underlying adaptation is that adaptation may capitalize on the strength of habit learning to help individuals form new habits in thinking [131]. Because habit

learning is intact among individuals abusing substances [136, 137], OT-based cognitive adaptation may teach healthier habits to those with CUD that could not be achieved from remediation alone. Thus, we hypothesize that adding adaptation to remediation will lead to an improvement in clinical outcomes. This hypothesis is not tested in the present study, but rather could be tested in subsequent studies. As the CUD literature to date has primarily focused on cognitive-remediation in CUD, combining cognitive-remediation and OT-based cognitive-adaptation represents a newer model of cognitive rehabilitation to improve cognition more effectively in CUD. Most prior studies use a single approach to improving cognition; this study will use a combined approach, hypothesizing that using two approaches to improving cognition could result in greater benefits than a single approach alone.

The overall project aims were to examine the improvement in cognition, examine the improvement in cocaine abstinence, and examine the improvement in daily quality of life/function from a novel model of OT-based cognitive rehabilitation. This paper describes the protocol for a pilot 12-week, randomized, parallel-group outpatient study of treatment-seeking adults with CUD who were mild-to-moderately cognitively impaired and dissatisfied with their quality of life. Participants were randomized to a “Cog-Rehab” arm (drug counseling + OT-based cognitive rehabilitation), or to a “Control” arm (drug counseling + psychoeducation/computer literacy). In the “Cog-Rehab” arm, OT-based cognitive rehabilitation consisted of adaptation strategies taught by a therapist and remediation techniques practiced on a computer. To control for therapist interaction and computer interaction in the “Cog-Rehab” arm, the “Control” arm tasks consisted of psychoeducation taught by a therapist and computer literacy exercises; no cognitive rehabilitation occurred in the “Control” arm. To increase generalizability to daily function [138-142], a part of each OT-based cognitive rehabilitation session occurred in various settings around the Veterans Affairs hospital where the study took place (e.g., cafeteria, store, coffee cart, etc.).

As cognitive impairment moderates clinical outcomes in CUD, effectively treating cognitive impairment as part of a comprehensive treatment plan for CUD could potentially improve important clinical outcomes. This research has the potential to improve the future clinical care of individuals with CUD by integrating OT-based cognitive rehabilitation as part of a comprehensive treatment plan for CUD.

METHODS

Overall Study Design

This study was a randomized, parallel-group outpatient study of treatment-seeking adults with CUD. Potential participants were initially screened over the telephone. If the potential participant met criteria based on a telephone interview, the participant was then scheduled for an in-person screening visit (Figure 1.1).

Study Setting

This study was conducted at the San Francisco Veterans Affairs Health Care System (SFVAHCS) between 7/1/2014 and 6/30/2019. The principal investigator's office was physically located in the opioid treatment program (OTP) outpatient clinic at the SFVAHCS. This study was registered on clinicaltrials.gov (NCT01684293). This study was approved by both the University of California, San Francisco (UCSF) Institutional Review Board (IRB) and the SFVAHCS Clinical Research Workgroup. All participants were paid in cash (US dollars) for their study participation.

Study Population

Word-of-mouth and flyers around the SFVAHCS were used to recruit potential participants for treatment-seeking adults with CUD. Because the principal investigator's office was located in the OTP clinic, most participants came through word-of-mouth from the OTP clinic. Because flyers were also posted around the SFVAHCS, participants from outside the OTP clinic were eligible to participate. Sampling would be characterized as convenience, because one key study requirement was to be a veteran at the SFVAHCS (Table 1.1).

Verbal consent was used to conduct the screening telephone interview. If the potential participant met criteria based on the telephone interview, the individual was then scheduled for the first screening visit. During the first screening visit, the screening consent form for the screening process was reviewed by the principal investigator, any questions answered, and the written screening consent form was signed by the individual after the individual passed a screening consent quiz. The screening consent form included a Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization contact form to speak with his/her primary care physician for collateral medical history. A waiver of consent to obtain family history, per 45CFR46.116(c), was obtained from the IRB. For participants who passed the first and second screening visits, a third screening visit was scheduled. During the third screening visit, after reviewing all screening data, the written study consent form was signed by the participant after the participant passed a study consent quiz (Figure 1.1).

The inclusion and exclusion criteria are listed in Table 1.1. Overall, adult veterans at the SFVAHCS with a primary cocaine use disorder, cognitive impairment, and stable concurrent medical/psychiatric illnesses (if present) were targeted for recruitment. Regarding the inclusion criteria, based on two previous iterations of this pilot study where the study team had difficulty recruiting and retaining participants with active cocaine use, the decision was made to recruit relatively more stable participants with at least three months of remission from cocaine use. However, no penalty would be enforced if a participant relapsed during the study. The 1.5 standard deviation impairment criterion on two performance-based neurocognitive measures was based on consensus after reviewing the literature and discussion with neuropsychologists. Instead of using a generic quality of life scale, the Drug User Quality of Life Scale was used to assess quality of life areas relevant to individuals with substance use disorders [143, 144].

Regarding the exclusion criteria, because the study was conducted at the SFVAHCS, the presence of concurrent psychiatric and medical disorders was expected, and the study team aimed to recruit participants with stable concurrent disorders. The cut-off for the Beck

Depression Inventory-II score [145] was chosen to exclude participants with severe depression. The cut-offs for the Wechsler Test of Adult Reading standard score [146] and Mini-Mental State Examination score [147] were chosen to exclude participants who would not be able to understand the reading material provided during the study due to an intellectual disability and severe cognitive impairment, respectively. Having an active legal issue (e.g., current charges, parole, or probation) was chosen as an exclusion criterion for administrative reasons to avoid study involvement with the court system during the study.

Study Randomization

Participants were randomized to the Active "Cog-Rehab" arm or the Control arm (Table 1.2). Simple randomization was completed using the Research Randomizer website [148].

Study Intervention

Because the intervention in this study was a new intervention that had not been tested previously in a clinical setting, the IRB wanted to ensure that participants in both arms were receiving some form of substance use disorder treatment. As a result, weekly individual or group drug counseling (choice was up to each participant) was required for study participation.

The active "Cog-Rehab" arm consisted of 36 hours of training (24 hours computer-based, 12 hours therapist-based) over a 12-week study period (Table 1.2). The online software PSSCogRehab [149] was used for the 24 hours of computer-cognitive-remediation (4 modules [Attention, Memory, Executive, Problem Solving]). All participants came to the SFVAHCS OTP outpatient clinic to do the computer training, which was supervised by the principal investigator and research assistants. All participants progressed through the same fixed sequence of modules. Each module adapted to the individual's performance, and each module required participants to remain with a given exercise until sufficient mastery was achieved. No penalty would be enforced if a participant did not master all modules within 24 hours of training, and the participant would stop wherever they were in the sequence of modules; alternatively, we would not expect a participant to finish modules before 24 hours due to the sheer number of exercises

and increasing level of difficulty in each module. PSSCogRehab has been tested as an adjunct to standard of care SUD treatment in various substance use disorder [68, 69] and non-substance use disorder populations [95, 150-157]. The 12-visit cognitive-adaptation individual manual by Twamley et al [130, 131] was used for the 12 hours of therapist-based training. The principal investigator and/or research assistants conducted the therapist trainings. Each visit began with teaching OT-based cognitive-adaptation strategies, and a homework assignment was given. Other cognitive topics such as scheduling and sleep hygiene were discussed. Strategies were then practiced in various settings around the SFVAHCS (e.g., cafeteria, store, coffee cart, pharmacy, hoptel [on-site lodging at the SFVAHCS], etc.) to link the cognitive strategy to a setting outside of the office and increase the generalizability to daily function; every 1-hour visit included 45 minutes of learning in the SFVAHCS OTP outpatient clinic and 15 minutes of practicing around the SFVAHCS. A higher dose of 24 hours for the computer-cognitive-remediation was selected, as a stronger dose of computer-cognitive-remediation training may result in stronger cognitive effects [158-161]; the dose of therapist training was kept as 12 hours, as the cognitive-adaptation manual was designed for 12 hours of therapist-based training.

The control arm also consisted of 36 hours of training (24 hours computer-based, 12 hours therapist-based) over a 12-week study period (Table 1.2). The software Typing Master [162] and computer literacy topics (e.g., Microsoft Word, Excel, PowerPoint, etc.) were used for 24 hours of computer typing exercises. All participants came to the SFVAHCS OTP outpatient clinic to do the computer training, which was supervised by the principal investigator and research assistants. Typing has been used a control arm in previous studies of cognitive rehabilitation for substance use disorders [67, 68]. Psychoeducation was used for the 12 hours of therapist-based training. The principal investigator and/or research assistants conducted the therapist trainings. Each visit began with teaching the psychoeducation topic, and a homework assignment was given. Topics were then practiced in various settings around the SFVAHCS

(e.g., cafeteria, store, coffee cart, pharmacy, hoptel, etc.) to link the topic to a setting outside of the office; every 1-hour visit included 45 minutes of learning in the SFVAHCS OTP outpatient clinic and 15 minutes of practicing around the SFVAHCS. Topics were selected from existing manuals, books, and brochures [163-167], and topics were broad yet relevant to most individuals with CUD.

The number of actual study visits during the study period to complete the 36 total hours of training was flexible for participants in both arms to help with study attendance. However, the maximum number of training hours of computer-based training and/or therapist-based training was limited to a total of 2 hours per study visit to help prevent participant fatigue in both arms.

Study Measurements

After a participant was invited for a screening visit after the telephone screening interview (~10 minutes), initial assessments were conducted over three screening visits to assess each participant for study eligibility (Table 1.3). Screening visit #1 was allotted for ~2.5 hours, screening visit #2 (neurocognitive testing) was allotted for ~3 hours, and screening visit #3 was allotted for ~3 hours. After obtaining the relevant written screening consent forms, each participant's demographic, psychiatric, medical, substance, family, and social history was collected (interviewer-administered). A directly observed urine toxicology was obtained on all screening and subsequent study visits. A mental status examination (clinical interview by the principal investigator, who is a psychiatrist) was performed at each visit to screen for any immediate safety concerns (e.g., suicidal or homicidal ideations with intent/plan) and potentially exclude participants who endorsed such concerns. A physical examination and vital signs were only completed if none was documented in the patient's SFVAHCS electronic medical record within the past 12 months. Collateral history from the medical record, primary care physician, and/or outpatient addiction treatment team was obtained as clinically necessary. In the third screening visit, the relevant written study consent forms were obtained.

Assessments for psychiatric symptoms and disorders included the Mini International Neuropsychiatric Interview (MINI) for Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [168] (interviewer-administered), the Beck Depression Inventory-II (BDI-II) [145] (self-report), the State-Trait Anxiety Inventory (STAI) [169] (self-report), and screening for Attention-Deficit Hyperactivity Disorder (ADHD) based on DSM-5 criteria [170] (interviewer-administered clinical interview). The MINI has similar reliability and validity properties to the Structured Clinical Interview Patient Edition (SCID-P) for DSM-III-R and the Composite International Diagnostic Interview (CIDI), but can be administered in a much shorter period of time [168, 171]. The BDI-II has high internal consistency, capacity to discriminate between depressed and non-depressed participants, and good concurrent, content, and structural validity [172]. The STAI has very good to excellent internal consistency in a variety of samples and has good evidence for convergent validity by significantly correlating with other measures of anxiety, though discriminant validity is limited [173].

The Timeline Followback (TLFB) Method [174, 175] (interviewer-administered) was used to assess route, frequency, quantity, dollar value of use, and craving severity for alcohol, anxiolytics, caffeine, cocaine and other stimulants (e.g., amphetamine, methamphetamine), hallucinogens, heroin and other opioids, inhalants, marijuana, phencyclidine, tobacco, and other substances (e.g., barbiturates, bath salts, steroids). The TLFB has good test-retest reliability [176] and validity with biological measures of substance use, such as urine tests [177, 178]. The Addiction Severity Index(ASI) [179] (interviewer-administered) was used to assess life domains relevant to individuals with substance use disorders. The ASI has good test-retest reliability [180-182], internal consistency, inter-rater reliability, concurrent validity [182-186], and construct validity [187]. The Treatment Services Review (TSR) [188] (interviewer-administered) and the Medication Recommendation Tracking Form (MRTF) [189] (interviewer-administered) were used to assess concurrent non-study-related treatments that participants were receiving. The TSR has adequate test-rest reliability, concurrent validity, and discriminant validity [188, 190].

The MRTF has been feasible in studies of bipolar disorder [189, 191] but will need further reliability and validation studies in addiction populations.

The Cocaine Effects Questionnaire (CEQ) [192] (self-report), the Obsessive-Compulsive Cocaine Scale (OCCS) [193, 194] (self-report), the Cocaine Craving Questionnaire-General (CCQ-Gen) [195] (self-report), and the Cocaine Craving Questionnaire–Weiss (CCQ-Weiss) [196, 197] (self-report) were used assess the effects of cocaine and domains relevant to individuals with CUD. The CEQ has good construct and concurrent validity as compared with measures of similar constructs and cocaine use [192]. The OCCS has good internal consistency, test-retest reliability, predictive validity, and convergent validity [194]. The CCQ-Gen has moderate to high reliability and good concurrent validity [195]. The CCQ-Weiss has high internal consistency and good predictive validity for short-term initiation of abstinence [197]. The University of Rhode Island Change Assessment (URICA) [198] (self-report) was used to assess an individual's motivation for change. The URICA has good internal consistency [199] and construct validity in addiction populations, but the predictive validity is limited [200].

The Clinical Global Impression (CGI) Scale (Observer [CGI-O] & Self [CGI-S]) [201] was used to assess participants' global functioning. However, this measure has limited reliability and validity in clinical samples [202]. The Sheehan Disability Scale (SDS) [203] (self-report) was used to assess functional disability in work/school, social life, and family life/home responsibilities. While the SDS has reliability and validity data in psychiatric populations such as mood disorders, anxiety disorders, and pathological gambling [204-206], there are no specific data in addiction populations. The Drug User Quality of Life Scale (DUQOL) [143, 144] (interviewer-administered) was used to assess quality of life areas relevant to individuals with substance use disorders. The DUQOL has good internal consistency, test-retest reliability, criterion validity, content validity, convergent validity, and discriminant validity in addiction populations [143, 144, 207]. The Multiple Errands Test (MET) (interviewer-administered, adapted to the SFVAHCS) [208-210] was used to assess real-world cognitive functional

performance based on tasks that participants performed around the SFVAHCS. The MET has no specific reliability or validity data in addiction populations.

Instead of relying on measures to assess one or two cognitive domains and because the cognitive effects of the interventions in this study have not been previously tested, a broad neurocognitive battery was used to assess cognition across multiple domains [211] (Table 1.4). The complex domains of attention, memory, executive function, and impulsivity were each assessed with multiple measures and modalities (self-report, interviewer-administered, paper and pen, computer) at screening, end of treatment, and three-month follow-up.

The computerized Cocaine Implicit Association Test (IAT) [212-214] was used to assess attentional bias towards cocaine-related cues. While the IAT has been used in addiction populations [213, 215, 216], there are no specific reliability or validity data in such populations. The Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test [217] (Conditions 1, 2, 3, and 5), the Wechsler Adult Intelligence Scale – 4th Edition (WAIS-IV) [218] Coding, and the WAIS-IV Symbol Search were used to assess visual attention and processing speed. The WAIS-IV Digit Span and the WAIS-IV Arithmetic were used to assess working memory. While the D-KEFS [31, 219-221] and WAIS-IV [222-224] have been used in addiction populations, there are no specific reliability or validity data in cocaine use disorder populations. The Hopkins Verbal Learning Test-Revised (HVLT-R) [225, 226] was used to assess verbal learning and memory. The Brief Visuospatial Memory Test-Revised (BVMT-R) [227] was used to assess visuospatial learning and memory. While the HVLT-R and the BVMT-R have reliability and validity data [228-231], there are no specific reliability or validity data in cocaine use disorder populations.

The D-KEFS and the Wisconsin Card Sorting Test (Computer Version 4) [232, 233] (WCST-CV4) were used to assess various types of executive function. The D-KEFS Tower Test was used to assess planning, rule learning, inhibition, and cognitive set. The D-KEFS Trail Making Test (Condition 4) was used to assess cognitive flexibility. The D-KEFS Color-Word

Interference Test was used to assess inhibition and switching. The WCST-CV4 was used to assess problem-solving, abstract reasoning, and shifting set. While the WCST-CV4 has reliability and validity data in various populations [234, 235], there are no specific reliability or validity data in cocaine use disorder populations.

Several measures were used to assess various types of impulsivity [236-238]. The Barratt Impulsiveness Scale (BIS) [239, 240] (second version, self-report) was used to assess motor and nonplanning attention. While the BIS has adequate reliability and validity in neuropsychiatric populations [241, 242] and has been used in addiction populations [242], there are no specific reliability or validity data in cocaine use disorder populations. The UPPS-P (urgency, premeditation, perseverance, sensation seeking, and positive urgency) Impulsive Behavior Scale [243, 244] (self-report) was used to assess urgency, sensation-seeking, premeditation, and perseverance. While the UPPS-P has been used in various populations [245, 246], there are no specific reliability or validity data in cocaine use disorder populations.

The computerized Conners' Continuous Performance Test (CPT) (3rd Edition) [247] was used to assess omissions, commissions, and perseverations. While the CPT has adequate reliability and validity in psychiatric populations [248, 249], there are no specific reliability or validity data in cocaine use disorder populations. The computerized Iowa Gambling Task (IGT) [250] was used to assess decision-making. The IGT has no specific reliability or validity data in cocaine use disorder populations [251-256]. The Monetary Choice Questionnaire (MCQ) (self-report, PhenX Toolkit version) [257, 258] was used to assess delayed reward discounting. The MCQ has no specific reliability or validity data in cocaine use disorder populations. The computerized Balloon Analogue Risk Task (BART) [259] was used to assess risk-taking. Participants were paid in cash (rounded up to the nearest dollar) for the dollar amount that they earned on the BART. The BART has good test-retest reliability in healthy individuals [251, 260, 261], but there are no specific reliability or validity data in cocaine use disorder populations.

The Wechsler Test of Adult Reading (WTAR) [146] was used to assess premorbid intellectual function. While the WTAR has been good reliability and validity in other populations [262-264], there are no specific reliability or validity data in cocaine use disorder populations. The Mini-Mental State Examination (MMSE) [147] was used as a general cognitive screen. The MMSE has no specific reliability or validity data in cocaine use disorder populations. The WTAR and MMSE were only administered once during the second screening visit.

Additional measures were administered during the study period, end-of-treatment, and three-month follow-up (Table 1.5). Each end-of-treatment visit and each three-month follow-up visit was allotted for ~3 hours. The Systematic Assessment for Treatment Emergent Events (SAFTEE) form (interviewer-administered) [265] was used to systematically monitor participants for the development of any new medical or psychiatric symptoms. The SAFTEE has no specific reliability or validity data in cocaine use disorder populations [266-269]. The Credibility/Expectancy Questionnaire (CEQ) (self-report) [270] was used asses participants' expectancy for improvement and credibility of the study interventions, but has no specific reliability or validity data in cocaine use disorder populations. The Computer System Usability Questionnaire (self-report) [271] was used to assess participants' satisfaction with using the computerized parts of the study intervention, but has no specific reliability or validity data in cocaine use disorder populations. The Game Training Questionnaire (self-report) [272] was used to assess whether participants perceived the computer training to be effective (e.g., reaction time, memory, reasoning ability, etc.) and how the participants perceived the computer training (enjoyable, challenging, frustrating, motivated), but has no specific reliability or validity data in cocaine use disorder populations. A Research Study Payment Questionnaire (self-report) [273-275] was created to assess on what participants used the cash that was paid during this study (same phrasing of categories as used in [275]), but has no specific reliability or validity data in cocaine use disorder populations.

Blinding

Ideally, those who assessed the primary outcomes would be blinded to the study arm. However, since this was a pilot study with limited funding through a career development award and turnover of non-permanent research assistants during the study period, outcomes were assessed by whichever staff was practically available to assess the outcomes at a given study visit.

Adherence/Quality Assurance

All participants came to the SFVAHCS OTP outpatient clinic to complete all screening, study, end of treatment, and follow-up visit tasks. Research assistants were trained on all tasks and supervised by the principal investigator. Measures of adherence to the study interventions included the number of visits attended and the number of homework assignments completed.

Power/Sample Size

Because this study was a pilot trial, the initial goals were to assess feasibility of enrollment and acceptability of all study procedures by participants. However, a power/sample size calculation was still completed prior to this trial in order to help inform the conduct of a larger trial with cognitive, substance use, and quality of life outcomes.

Effect sizes and confidence intervals were estimated, though there is caution regarding the use of pilot studies to guide power calculations for study proposals [276]. A pilot study of 40 completers (n = 20 per arm) was deemed to be feasible and realistic with the inherent budget limitations of a career developmental award. With an alpha level of 0.05, 80% power, and a 1:1 allocation ratio of Cog-Rehab arm to control arm, the minimum detectable effect size to detect with this sample size would be a large effect (e.g., 1 to 1.5 standard deviation change on a neurocognitive measure).

For cognitive outcomes, the literature gives some guidance on the anticipated effect sizes with similar cognitive outcomes as used in this study; however, the control groups used in these studies were not necessarily similar to that used in this study. In 14 psychotic patients, the

cognitive-adaptation manual used in this study had small to medium effects (Cohen's *d* = 0.22 - 0.61) on various cognitive domains [131] when combined with pharmacotherapy; the control group was pharmacotherapy alone. PSSCogRehab as an adjunct to standard of care long-term SUD residential treatment had a small effect (*d* = 0.37) on improving cognition in those with CUD and other SUDs (*n* = 160) [68]; the control group was an equally intensive attention control treatment (computer-assisted typing) similar to what is being used in this study. In primarily individuals with CUD (*n* = 27), PSSCogRehab as an adjunct to standard of care SUD treatment at a treatment facility had small effects (d = 0.06 - 0.29) on various cognitive domains [69]; the control group was similar to PSSCogRehab in all essential features, except for providing correct answers and module progression and compensation yoked to an individual in the active group. While most of these effect sizes are small to medium, we expect that because our Cog-Rehab arm is a combination of treatments, the effect sizes from this combination will be larger than what has been previously seen in the literature.

For substance use outcomes, drug counseling has had small to medium effects on decreasing drug use [277]. Because drug counseling is being used in both arms and is influenced by the 12-step philosophy, data from the Cocaine Collaborative Treatment Study show that active participation in 12-step activities had small effects on decreasing cocaine use (*d* = 0.14 - 0.47) [278]. We contacted members of the Cocaine Collaborative Treatment Study for guidance on estimating the effect size of drug counseling on decreasing cocaine use in cognitively impaired individuals with CUD. As cognitively impaired individuals with CUD may represent those who have CUD with a more medium/severe level of pathology from cerebral perfusion or metabolism anomalies [24, 47], the effect size of drug counseling on decreasing cocaine use in cognitively impaired individuals with CUD is highly unlikely to be medium/large and is more likely to be small. By potentially improving attention/memory/executive function deficits more effectively in the Cog-Rehab arm compared to the Control arm, we expect to achieve a more powerful effect on decreasing cocaine use in the Cog-Rehab arm due to

participants being able to better focus, attend to, remember, and think during the drug counseling content.

For quality of life outcomes, there are no prior reports of the Drug User Quality of Life Scale with drug counseling, the cognitive-adaptation manual, the PSSCogRehab software, or psychoeducation. The literature gives some guidance on the anticipated effect sizes with similar outcomes. In 14 psychotic patients, the cognitive-adaptation manual had medium effects (d = 0.52 - 0.67) on total functional capacity and quality of life [131]. Thus, in this study, we would expect effect sizes at least this big.

Statistical Analysis

All data were stored in a custom-made Microsoft Access database for this study (Quicksilver Consulting; El Cerrito, California). The initial goals were to assess feasibility of enrollment and acceptability of all study procedures by participants. Feasibility of enrollment was assessed by tracking the number of telephone calls received, number of telephone screens actually completed, number of telephone callers set up for the 1st screening visit, number of callers who completed all screening visits in person, number of participants randomized, and number of participants who completed the entire study. The Computer System Usability Questionnaire and the Game Training Questionnaire helped assess acceptability of the study procedures. The distributions of variables will be examined and described as appropriate. The results of these analyses will be described in a second paper.

DISCUSSION

This paper describes a novel protocol for a pilot 12-week, randomized, parallel-group outpatient study of treatment-seeking adults at the SFVAHCS with CUD who were mild-to-moderately cognitively impaired and dissatisfied with their quality of life. Because existing models of cognitive rehabilitation have yielded small to medium effect sizes in improving cognition in CUD, newer models of cognitive rehabilitation are needed to improve cognition more effectively. Most prior studies use a single approach to improving cognition; this study

used a combined approach, hypothesizing that using two approaches to improving cognition could result in greater benefits than a single approach alone.

Strengths

First, this study adapted cognitive rehabilitation principles from the OT field to treat cognitive impairment in CUD. Second, OT-based cognitive-adaptation techniques were combined with computer-cognitive-remediation techniques to represent a newer model of cognitive rehabilitation in an effort to improve cognition more effectively in CUD. Third, this study collected a comprehensive set of psychiatric, substance use, and neurocognitive measures in order to demonstrate proof-of-concept of the study intervention and to gather preliminary data of the study intervention's impact on different domains associated with CUD. Finally, this study was conducted at a VA hospital in patients with complex comorbidities in an effort to increase external validity to patients with CUD in other clinical settings.

Limitations

This study had several limitations. First, the interventions were labor-intensive and required a substantial amount of training before delivery to participants, which was possible in a research setting. However, such a labor-intensive approach may not be easily scalable in a community addiction treatment setting. Second, most community-based addiction treatment programs will not have access to extensive neurocognitive assessments as conducted in this study, which limits the detailed assessment of various cognitive domains in patients treated in a community setting. Third, the burden on the participants was quite high, which may limit study participation, study completion, and ability to recruit (especially if cash incentives are not given in a community addiction treatment setting).

Fourth, this study combined cognitive-adaptation techniques and cognitive-remediation techniques in the Cog-Rehab arm and did not determine which techniques are better or worse. Each set of techniques had its own contribution, and the study used a comprehensive approach to treat cognitive impairment. This study could not determine which active ingredient would

impact outcomes, though we were not planning on testing for efficacy in this study; the active ingredient can be teased out in future larger studies. Fifth, those who assessed the primary outcomes were not necessarily blinded to the study arm. Non-blinding could have biased how some study staff assessed participants.

Sixth, because this study recruited individuals with at least mild cognitive impairment, the results from this study would not apply to those with no cognitive impairment or cognitive impairment not detected by classical neurocognitive measures (e.g., social cognition [279, 280], compulsivity [281]). Finally, study participants were required to be in at least 3 months of remission from their CUD diagnosis. Because this study recruited relatively stable participants from a substance use perspective, the results from this study may not be generalizable to those who are actively using cocaine or are trying to stop using cocaine.

CONCLUSION

CUD remains a significant public health problem in the U.S., and cognitive impairment moderates clinical outcomes in CUD. This first of three papers describes the protocol for a pilot randomized controlled trial of OT-based cognitive rehabilitation for CUD. Integrating OT-based cognitive rehabilitation in a comprehensive treatment plan for CUD could have a direct and significant positive impact on the public health burden of this population. The second paper will discuss recruitment numbers, feasibility and acceptability of interventions, and statistical analysis of collected assessments. The third and final paper will be a secondary analysis of the Multiple Errands Test as associated with the neurocognitive assessments.

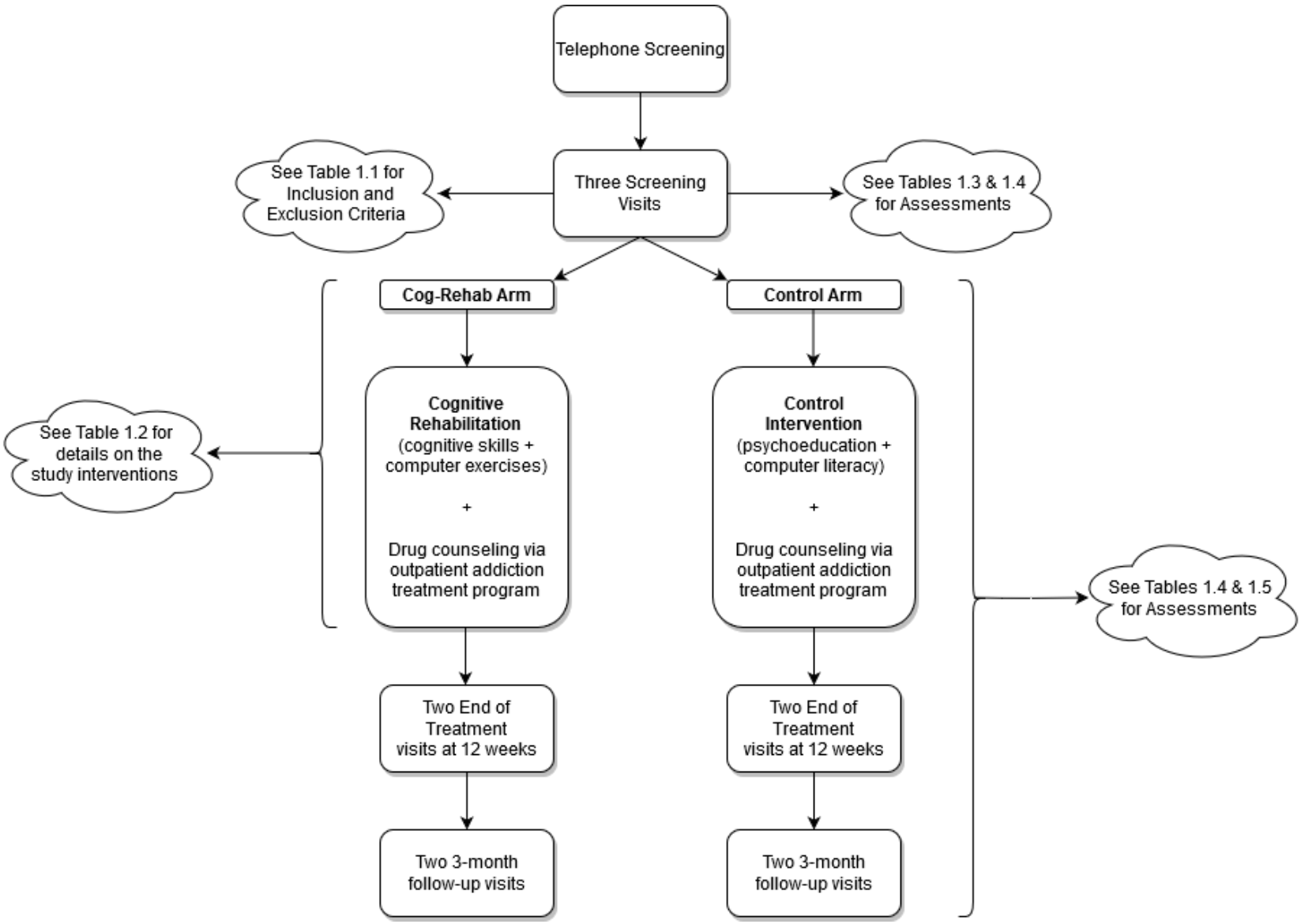


Figure 1.1. Overall Study Flow Diagram.

Table 1.1. Inclusion and Exclusion Criteria.

Inclusion Criteria
Age 18-65
Primary cocaine use disorder (based on DSM-5 criteria) and at least 3 months of remission (confirmed with urine tox)
At least mild cognitive impairment, defined as = or > 1.5 standard deviations impairment on any 2 performance-based neurocognitive measures
Needing to change quality of life, defined as self-identifying at least 2 life areas as needing to change on the Drug User Quality of Life Scale
A Veteran at the San Francisco Veterans Affairs Health Care System
Currently receiving weekly drug counseling (individual or group; at least 1 hour/week) through an outpatient substance use disorder treatment program
Exclusion Criteria
Inability to speak, read, write, and understand English
Inadequate hearing or vision
Concurrent substance use disorder (except tobacco or caffeine) not in at least 3 months of remission
A psychiatric disorder that will interfere with study participation or will make participation hazardous (e.g., psychosis, suicidal or homicidal ideations, severe anxiety)
A depressive disorder classified as severe, defined as a Beck Depression Inventory-II score >29
Current diagnosis of a bipolar disorder needing acute inpatient psychiatric hospitalization
Currently symptomatic from attention-deficit/hyperactivity disorder (DSM-5 criteria)
Any learning disorder, any type of dementia, any type of delirium, or an amnestic disorder due to any general medical condition
Wechsler Test of Adult Reading standard score <70
Mini-Mental State Examination score <24
Current use of scheduled (i.e., prescribed) regular (i.e., daily) psychotropics or other medicines with a high likelihood of sedation & cognitive impairment (e.g., benzodiazepines, clozapine, anticholinergics)
Currently prescribed stimulants (e.g., methylphenidate) or cognitive enhancers (e.g., donepezil, memantine)
Active medical illnesses – uncontrolled diabetes, uncontrolled hypertension, uncontrolled thyroid dysfunction, or uncontrolled B12/folate deficiency; central nervous system illness with potential cognitive aspects (Parkinson's, or Huntington's dementia); Cirrhosis with complications (e.g., ascites, encephalopathy, jaundice, gastrointestinal bleeding); Needing acute medical hospitalization from HIV sequelae, such as HIV-related opportunistic infection
Any history of any type of stroke or brain hemorrhage
Any history of traumatic brain injury, intracranial pathology (e.g., tumor), or brain surgery
Currently on probation or parole
Concurrent participation in another study that medically/administratively interferes with this study

Table 1.2. Active "Cog-Rehab" Arm and Control Arm.

	Active "Cog-Rehab" Arm – OT-based Cognitive Rehabilitation	**Control Arm – Control for therapist & computer interaction**
Week	***Adaptation tasks (taught by a therapist)***	***Psychoeducation (taught by a therapist)***
1	Introduction & Calendars (1 hour)	Etiologies of psychiatric symptoms (1 hour)
2	Prospective memory (1 hour)	Types of psychotherapy (1 hour)
3	Prospective memory (1 hour)	What is depression? (1 hour)
4	Vigilance (1 hour)	Antidepressants – not just for depression (1 hour)
5	Vigilance (1 hour)	What is anxiety? (1 hour)
6	Verbal learning & memory (1 hour)	Anti-anxiety meds – not just for anxiety (1 hour)
7	Verbal learning & memory (1 hour)	What does "bipolar" mean? (1 hour)
8	Verbal learning & memory (1 hour)	Mood stabilizers – not just for "bipolar" (1 hour)
9	Cognitive flexibility (1 hour)	Antipsychotics – not just for psychosis (1 hour)
10	Cognitive flexibility (1 hour)	Psycho-pharm vs. alternative therapies (1 hour)
11	Cognitive flexibility (1 hour)	Risks associated with treatment withdrawal (1 hour)
12	Conclusion & Review (1 hour)	Conclusion & Review (1 hour)
Week	***Remediation tasks (computer)***	***Typing Tutorial / Computer Literacy (computer)***
1	Attention training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
2	Attention training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
3	Attention training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
4	Attention training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
5	Memory training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
6	Memory training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
7	Memory training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
8	Memory training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
9	Executive function training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
10	Executive function training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
11	Executive function training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)
12	Executive function training (1 hour)	Typing Tutorial / Computer Literacy (1 hour)

Table 1.3. Screening Assessments.

Screening Assessments	Telephone Screen	Visit 1	Visit 2	Visit 3
Telephone screening consent, Telephone screen	X			
Screening consent, Screening quiz, Consent to contact for future research, "Consent for use of picture and/or voice" form, HIPAA Consent/Authorization for Use & Release of Individually Identifiable Health Information for VHA Research (VA form 10-0493)		X		
Physical examination, Vital signs (weight, blood pressure, respiratory rate, pulse, temperature) [Physical examination and vital signs will only be completed if none documented within the past 12 months.]		X		
Demographic/psychiatric/substance/medical/family/social history, Mental status exam, Urine tox (direct observe)		X		
Mini International Neuropsychiatric Interview (MINI) for DSM-5, Beck Depression Inventory-II, DSM-5 criteria for ADHD, Addiction Severity Index, Timeline Followback Method for the past 90 days, 28-day Treatment Services Review, Medication Recommendation Tracking Form, State-Trait Anxiety Inventory (STAI)		X		
Collateral history from the medical record/primary care physician/outpatient addiction treatment team as necessary		X		
Neurocognitive testing (see Table 1.4), Mental status exam, Urine tox (direct observe)			X	
Multiple Errands Test (MET), Cocaine Effects Questionnaire, Obsessive-Compulsive Cocaine Scale, Cocaine Craving Questionnaire-General, Cocaine Craving Questionnaire –Weiss, Sheehan Disability Scale (SDS), Drug User Quality of Life Scale (DUQOL), University of Rhode Island Change Assessment (URICA)				X
Inclusion/exclusion criteria checklist, Study consent procedure note, Study quiz, Study consent if inclusion/exclusion criteria met, Randomization procedure checklist, Mental status exam, Urine tox (direct observe)				X
Timeline Followback Method (TLFB) for the past week, Medication Recommendation Tracking Form				X
Clinical Global Impression (CGI) Scale (Observer [CGI-O] & Self [CGI-S]), 7-day Treatment Services Review				X
Revocation of Authorization VHA Research form (VA form 10-10116), Study Completion form & Closing Out Checklist as needed		X	X	X

Table 1.4. Neurocognitive Assessments.

Domain		Assessment	Screening Visit #2	End of Treatment and at 3-month Follow-up
Premorbid Intellectual Function		Wechsler Test of Adult Reading	X	
General Cognitive Screen		Mini-Mental State Examination	X	
Attentional Bias		Cocaine Implicit Association Test	X	X
Attention (Visual) & Processing Speed		Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (Conditions 1, 2, 3, & 5 at each visit)	X	X
		Wechsler Adult Intelligence Scale – 4th Edition (WAIS-IV) Coding	X	X
		WAIS-IV Symbol Search	X	X
Memory	Working Memory	WAIS-IV Digit Span	X	X
		WAIS-IV Arithmetic	X	X
	Verbal Learning & Memory	Hopkins Verbal Learning Test-Revised (Forms 3, 5, and 6 at respective visits)	X	X
	Visuospatial Learning & Memory	Brief Visuospatial Memory Test-Revised (Forms 3, 5, and 6 at respective visits)	X	X
Executive Function	Planning, Rule Learning, Inhibition & Cognitive Set	D-KEFS Tower Test	X	X
	Cognitive Flexibility	D-KEFS Trail Making Test (Condition 4 at each visit)	X	X
	Inhibition & Switching	D-KEFS Color-Word Interference Test	X	X
	Problem-Solving, Abstract Reasoning & Shifting Set	Wisconsin Card Sorting Test – Computer Version 4	X	X
Impulsivity	Attention, Motor & Nonplanning	Barratt Impulsiveness Scale second version	X	X
	Urgency, Sensation-Seeking, Premeditation & Perseverance	UPPS-P Impulsive Behavior Scale	X	X
	Omissions, Commissions & Perseverations	Conners' Continuous Performance Test 3rd Edition	X	X
	Decision-Making	Iowa Gambling Task	X	X
	Delayed Reward Discounting	Monetary Choice Questionnaire (PhenX Toolkit)	X	X
	Risk-Taking	Balloon Analogue Risk Task	X	X

Table 1.5. Assessments During the Study, End-of-Treatment, and Follow-up.

Assessments During the Study, End-of-Treatment and Follow-up	Study Weeks 1-12 (1-2 visits/week)	End of Treatment		3-month follow-up	
	Visits 4-39	Visit 40	Visit 41	Visit 42	Visit 43
Mental status exam, U-tox	Completed at every study visit	X	X	X	X
Credibility/Expectancy Questionnaire, Game Training Questionnaire Part 1	Completed only once at study week 1				
TLFB, Systematic Assessment for Treatment and Emergent Events (SAFTEE) form, CGI-O, CGI-S, Medication Recommendation Tracking Form	Completed once per each study week (not done at every visit)		X		X
7-day Treatment Services Review	Completed once per each study week (not done at every visit)		X		
Neurocognitive testing (see Table 1.4)		X		X	
DUQOL, MET, SDS, Cocaine Effects Questionnaire, Obsessive-Compulsive Cocaine Scale, Cocaine Craving Questionnaire-General, Cocaine Craving Questionnaire –Weiss, BDI-2, STAI, URICA			X		X
Addiction Severity Index, Timeline Followback Method for the past 90 days, 28-day Treatment Services Review, Research Study Payment Questionnaire					X
Computer System Usability Questionnaire, Game Training Questionnaire Part 2			X		
Collateral history from the medical record/primary care physician/outpatient addiction treatment team as necessary, Revocation of Authorization as necessary (VA form 10-10116), Study Completion form & Closing Out Checklist as needed	Completed as needed				
Serious Adverse Events – report on occurrence	Report on occurrence				

Chapter 1 References

1. NIDA. *Cocaine: Abuse and Addiction*. Research Report Series 2009 9/10/2014]; Available from: http://www.drugabuse.gov/sites/default/files/cocainerrs.pdf.
2. NIDA. *What is the scope of cocaine use in the United States?* . 2016; Available from: https://www.drugabuse.gov/publications/research-reports/cocaine/what-scope-cocaine-use-in-united-states.
3. Czermainski, F.R., et al., *Assessment of inhibitory control in crack and/or cocaine users: a systematic review.* Trends Psychiatry Psychother, 2017. 39(3): p. 216-225.
4. Frazer, K.M., Q. Richards, and D.R. Keith, *The long-term effects of cocaine use on cognitive functioning: A systematic critical review.* Behav Brain Res, 2018. 348: p. 241-262.
5. Hall, M.G., et al., *Neuropsychological comparisons of cocaine versus methamphetamine users: A research synthesis and meta-analysis.* Am J Drug Alcohol Abuse, 2018. 44(3): p. 277-293.
6. Potvin, S., et al., *Cocaine and cognition: a systematic quantitative review.* J Addict Med, 2014. 8(5): p. 368-76.
7. Spronk, D.B., et al., *Characterizing the cognitive effects of cocaine: a comprehensive review.* Neurosci Biobehav Rev, 2013. 37(8): p. 1838-59.
8. Wood, S., et al., *Psychostimulants and cognition: a continuum of behavioral and cognitive activation.* Pharmacol Rev, 2014. 66(1): p. 193-221.
9. Jovanovski, D., S. Erb, and K.K. Zakzanis, *Neurocognitive deficits in cocaine users: a quantitative review of the evidence.* J Clin Exp Neuropsychol, 2005. 27(2): p. 189-204.
10. Beatty, W.W., et al., *Neuropsychological performance of recently abstinent alcoholics and cocaine abusers.* Drug Alcohol Depend, 1995. 37(3): p. 247-53.

11. Bolla, K.I., R. Rothman, and J.L. Cadet, *Dose-related neurobehavioral effects of chronic cocaine use.* J Neuropsychiatry Clin Neurosci, 1999. 11(3): p. 361-9.

12. Hoff, A.L., et al., *Effects of crack cocaine on neurocognitive function.* Psychiatry Res, 1996. 60(2-3): p. 167-76.

13. Ardila, A., M. Rosselli, and S. Strumwasser, *Neuropsychological deficits in chronic cocaine abusers.* Int J Neurosci, 1991. 57(1-2): p. 73-9.

14. O'Malley, S., et al., *Neuropsychological impairment in chronic cocaine abusers.* Am J Drug Alcohol Abuse, 1992. 18(2): p. 131-44.

15. Mittenberg, W. and S. Motta, *Effects of chronic cocaine abuse on memory and learning.* Arch Clin Neuropsychol, 1993. 8(6): p. 477-83.

16. Gottschalk, C., et al., *Cognitive function and cerebral perfusion during cocaine abstinence.* Am J Psychiatry, 2001. 158(4): p. 540-5.

17. Cunha, P.J., et al., *[Neuropsychological impairments in crack cocaine-dependent inpatients: preliminary findings].* Rev Bras Psiquiatr, 2004. 26(2): p. 103-6.

18. Manschreck, T.C., et al., *Freebase cocaine and memory.* Compr Psychiatry, 1990. 31(4): p. 369-75.

19. Schrimsher, G.W., J.D. Parker, and R.S. Burke, *Relation between cognitive testing performance and pattern of substance use in males at treatment entry.* Clin Neuropsychol, 2007. 21(3): p. 498-510.

20. Horner, M.D., *Attentional functioning in abstinent cocaine abusers.* Drug Alcohol Depend, 1999. 54(1): p. 19-33.

21. Rosselli, M. and A. Ardila, *Cognitive effects of cocaine and polydrug abuse.* J Clin Exp Neuropsychol, 1996. 18(1): p. 122-35.

22. Browndyke, J.N., et al., *Examining the effect of cerebral perfusion abnormality magnitude on cognitive performance in recently abstinent chronic cocaine abusers.* J Neuroimaging, 2004. 14(2): p. 162-9.

23. Verdejo-Garcia, A., et al., *Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse.* Neuropsychol Rev, 2004. 14(1): p. 1-41.

24. Strickland, T.L., et al., *Cerebral perfusion and neuropsychological consequences of chronic cocaine use.* J Neuropsychiatry Clin Neurosci, 1993. 5(4): p. 419-27.

25. Berry, J., et al., *Neuropsychological deficits in abstinent cocaine abusers: preliminary findings after two weeks of abstinence.* Drug Alcohol Depend, 1993. 32(3): p. 231-7.

26. Beveridge, T.J., et al., *Review. Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys.* Philos Trans R Soc Lond B Biol Sci, 2008. 363(1507): p. 3257-66.

27. Fernandez-Serrano, M.J., et al., *Neuropsychological consequences of alcohol and drug abuse on different components of executive functions.* J Psychopharmacol, 2010. 24(9): p. 1317-1332.

28. Bolla, K.I., J.L. Cadet, and E.D. London, *The neuropsychiatry of chronic cocaine abuse.* J Neuropsychiatry Clin Neurosci, 1998. 10(3): p. 280-9.

29. Di Sclafani, V., et al., *Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence.* Drug Alcohol Depend, 2002. 66(2): p. 161-71.

30. NIDA-Conf. *Developing Behavioral Treatments for Drug Abusers with Cognitive Impairments* 2003.

31. Vonmoos, M., et al., *Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset.* Br J Psychiatry, 2013. 203(1): p. 35-43.

32. Vonmoos, M., et al., *Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study.* Neuropsychopharmacology, 2014. 39(9): p. 2200-10.

33. Teichner, G., M.D. Horner, and R.T. Harvey, *Neuropsychological predictors of the attainment of treatment objectives in substance abuse patients.* Int J Neurosci, 2001. 106(3-4): p. 253-63.

34. Teichner, G., et al., *Substance abuse treatment outcomes for cognitively impaired and intact outpatients.* Addict Behav, 2002. 27(5): p. 751-63.

35. Vik, P.W., et al., *Cognitive impairment in substance abuse.* Psychiatr Clin North Am, 2004. 27(1): p. 97-109, ix.

36. Rolland, B., et al., *A Patient-Tailored Evidence-Based Approach for Developing Early Neuropsychological Training Programs in Addiction Settings.* Neuropsychol Rev, 2019. 29(1): p. 103-115.

37. Butler, K. and B. Le Foll, *Impact of Substance Use Disorder Pharmacotherapy on Executive Function: A Narrative Review.* Front Psychiatry, 2019. 10: p. 98.

38. Parsons, O.A., K.W. Schaeffer, and S.W. Glenn, *Does neuropsychological test performance predict resumption of drinking in posttreatment alcoholics?* Addict Behav, 1990. 15(3): p. 297-307.

39. Gregson, R.A. and G.M. Taylor, *Prediction of relapse in men alcoholics.* J Stud Alcohol, 1977. 38(9): p. 1749-60.

40. Fals-Stewart, W. and J. Schafer, *The relationship between length of stay in drug-free therapeutic communities and neurocognitive functioning.* J Clin Psychol, 1992. 48(4): p. 539-43.

41. Bates, M.E., et al., *Cognitive impairment influences drinking outcome by altering therapeutic mechanisms of change.* Psychol Addict Behav, 2006. 20(3): p. 241-53.

42. Aharonovich, E., E. Nunes, and D. Hasin, *Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment.* Drug Alcohol Depend, 2003. 71(2): p. 207-11.

43. Aharonovich, E., et al., *Cognitive deficits predict low treatment retention in cocaine dependent patients.* Drug Alcohol Depend, 2006. 81(3): p. 313-22.

44. Fox, H.C., E.D. Jackson, and R. Sinha, *Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes.* Psychoneuroendocrinology, 2009. 34(8): p. 1198-207.

45. Katz, E.C., et al., *Cognitive ability as a factor in engagement in drug abuse treatment.* Am J Drug Alcohol Abuse, 2005. 31(3): p. 359-69.

46. Hudetz, J.A., et al., *Postoperative cognitive dysfunction in older patients with a history of alcohol abuse.* Anesthesiology, 2007. 106(3): p. 423-30.

47. Goldstein, R.Z., et al., *Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex.* Neuropsychologia, 2004. 42(11): p. 1447-58.

48. Vocci, F.J., *Cognitive remediation in the treatment of stimulant abuse disorders: a research agenda.* Exp Clin Psychopharmacol, 2008. 16(6): p. 484-97.

49. Sofuoglu, M., *Cognitive enhancement as a pharmacotherapy target for stimulant addiction.* Addiction, 2010. 105(1): p. 38-48.

50. Sofuoglu, M., et al., *Galantamine improves sustained attention in chronic cocaine users.* Exp Clin Psychopharmacol, 2011. 19(1): p. 11-9.

51. Brady, K.T., K.M. Gray, and B.K. Tolliver, *Cognitive enhancers in the treatment of substance use disorders: clinical evidence.* Pharmacol Biochem Behav, 2011. 99(2): p. 285-94.

52. Sofuoglu, M., et al., *Cognitive Function as a Transdiagnostic Treatment Target in Stimulant Use Disorders.* J Dual Diagn, 2016. 12(1): p. 90-106.

53. Cook, J., et al., *Managing attention deficit hyperactivity disorder in adults using illicit psychostimulants: A systematic review.* Aust N Z J Psychiatry, 2017. 51(9): p. 876-885.

54. Salloum, I.M. and E.S. Brown, *Management of comorbid bipolar disorder and substance use disorders.* Am J Drug Alcohol Abuse, 2017. 43(4): p. 366-376.

55. Simon, N., B. Rolland, and L. Karila, *Methylphenidate in Adults with Attention Deficit Hyperactivity Disorder and Substance Use Disorders.* Curr Pharm Des, 2015. 21(23): p. 3359-66.

56. Nunes, E.V. and F.R. Levin, *Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis.* JAMA, 2004. 291(15): p. 1887-96.

57. Swann, A.C., *The strong relationship between bipolar and substance-use disorder.* Ann N Y Acad Sci, 2010. 1187: p. 276-93.

58. San, L., B. Arranz, and J. Martinez-Raga, *Antipsychotic drug treatment of schizophrenic patients with substance abuse disorders.* Eur Addict Res, 2007. 13(4): p. 230-43.

59. Goldstein, R.A., C. DesLauriers, and A.M. Burda, *Cocaine: history, social implications, and toxicity--a review.* Dis Mon, 2009. 55(1): p. 6-38.

60. Gallelli, L., et al., *Drug-Drug Interactions in Cocaine-users and their Clinical Implications.* Curr Drug Abuse Rev, 2017. 10(1): p. 25-30.

61. NIDA. *Research Report Series: "Prescription Drugs: Abuse and Addiction"*. 2011 2/3/2012]; Available from: http://www.drugabuse.gov/sites/default/files/rrprescription.pdf.

62. Midgley, M., *Mitigating the prescription drug abuse epidemic.* J Healthc Risk Manag, 2017. 36(3): p. 16-20.

63. McHugh, R.K., S. Nielsen, and R.D. Weiss, *Prescription drug abuse: from epidemiology to public policy.* J Subst Abuse Treat, 2015. 48(1): p. 1-7.

64. Monheit, B., D. Pietrzak, and S. Hocking, *Prescription drug abuse - A timely update.* Aust Fam Physician, 2016. 45(12): p. 862-866.

65. Scheurich, A., et al., *Neuropsychological status of alcohol-dependent patients: increased performance through goal-setting instructions.* Alcohol Alcohol, 2004. 39(2): p. 119-25.

66. Fadardi, J.S. and W.M. Cox, *Reversing the sequence: reducing alcohol consumption by overcoming alcohol attentional bias.* Drug Alcohol Depend, 2009. 101(3): p. 137-45.

67. Fals-Stewart, W. and S. Lucente, *The effect of cognitive rehabilitation on the neuropsychological status of patients in drug abuse treatment who display neurocognitive impairment.* Rehabilitation Psychology, 1994. 39(2): p. 75-94.

68. Fals-Stewart, W. and W.K. Lam, *Computer-assisted cognitive rehabilitation for the treatment of patients with substance use disorders: a randomized clinical trial.* Exp Clin Psychopharmacol, 2010. 18(1): p. 87-98.

69. Bickel, W.K., et al., *Remember the future: working memory training decreases delay discounting among stimulant addicts.* Biol Psychiatry, 2011. 69(3): p. 260-5.

70. Gordon, S.M., B.P. Kennedy, and J.D. McPeake, *Neuropsychologically impaired alcoholics: assessment, treatment considerations, and rehabilitation.* J Subst Abuse Treat, 1988. 5(2): p. 99-104.

71. Grohman, K., W. Fals-Stewart, and K. Donnelly, *Improving treatment response of cognitively impaired veterans with neuropsychological rehabilitation.* Brain Cogn, 2006. 60(2): p. 203-4.

72. Peterson, M.A., et al., *Cognitive recovery following alcohol detoxification: A computerised remediation study.* Neuropsychological Rehabilitation: An International Journal, 2002. 12(1): p. 63 - 74.

73. Brooks, S.J., et al., *The impact of cognitive training in substance use disorder: the effect of working memory training on impulse control in methamphetamine users.* Psychopharmacology (Berl), 2017. 234(12): p. 1911-1921.

74. Brooks, S.J., et al., *Psychological intervention with working memory training increases basal ganglia volume: A VBM study of inpatient treatment for methamphetamine use.* Neuroimage Clin, 2016. 12: p. 478-91.

75. Rass, O., et al., *A randomized controlled trial of the effects of working memory training in methadone maintenance patients.* Drug Alcohol Depend, 2015. 156: p. 38-46.

76. Schulte, M.H.J., et al., *The effect of N-acetylcysteine and working memory training on neural mechanisms of working memory and cue reactivity in regular cocaine users.* Psychiatry Res Neuroimaging, 2019. 287: p. 56-59.

77. Wanmaker, S., et al., *The efficacy of a working memory training in substance use patients: A randomized double-blind placebo-controlled clinical trial.* J Clin Exp Neuropsychol, 2018. 40(5): p. 473-486.

78. Zhu, Y., et al., *A Newly Designed Mobile-Based Computerized Cognitive Addiction Therapy App for the Improvement of Cognition Impairments and Risk Decision Making in Methamphetamine Use Disorder: Randomized Controlled Trial.* JMIR Mhealth Uhealth, 2018. 6(6): p. e10292.

79. Manning, V., et al., *Combining approach bias modification with working memory training during inpatient alcohol withdrawal: an open-label pilot trial of feasibility and acceptability.* Subst Abuse Treat Prev Policy, 2019. 14(1): p. 24.

80. Strickland, J.C., et al., *Feasibility, Acceptability, and Initial Efficacy of Delivering Alcohol Use Cognitive Interventions via Crowdsourcing.* Alcohol Clin Exp Res, 2019. 43(5): p. 888-899.

81. Hendershot, C.S., et al., *Randomized trial of working memory training as an adjunct to inpatient substance use disorder treatment.* Psychol Addict Behav, 2018. 32(8): p. 861-872.

82. Khemiri, L., et al., *Working Memory Training in Alcohol Use Disorder: A Randomized Controlled Trial.* Alcohol Clin Exp Res, 2019. 43(1): p. 135-146.

83. Staiger, P.K., et al., *A randomised controlled trial examining the efficacy of smoking-related response inhibition training in smokers: a study protocol.* BMC Public Health, 2018. 18(1): p. 1226.

84. Manning, V., et al., *Protocol for a randomised controlled trial of cognitive bias modification training during inpatient withdrawal from alcohol use disorder.* Trials, 2018. 19(1): p. 598.

85. Verdejo-Garcia, A., *Cognitive training for substance use disorders: Neuroscientific mechanisms.* Neurosci Biobehav Rev, 2016. 68: p. 270-281.

86. Bell, M.D., N.A. Vissicchio, and A.J. Weinstein, *Cognitive Training and Work Therapy for the Treatment of Verbal Learning and Memory Deficits in Veterans With Alcohol Use Disorders.* J Dual Diagn, 2016. 12(1): p. 83-9.

87. Gunn, R.L., et al., *Predictors of Effective Working Memory Training in Individuals with Alcohol Use Disorders.* Alcohol Clin Exp Res, 2018. 42(12): p. 2432-2441.

88. Snider, S.E., et al., *Working Memory Training Improves Alcohol Users' Episodic Future Thinking: A Rate-Dependent Analysis.* Biol Psychiatry Cogn Neurosci Neuroimaging, 2018. 3(2): p. 160-167.

89. Bickel, W.K., L. Moody, and A. Quisenberry, *Computerized Working-Memory Training as a Candidate Adjunctive Treatment for Addiction.* Alcohol Res, 2014. 36(1): p. 123-6.

90. Sampedro-Piquero, P., et al., *Neuroplastic and cognitive impairment in substance use disorders: a therapeutic potential of cognitive stimulation.* Neurosci Biobehav Rev, 2018.

91. Wiers, R.W., *Cognitive Training in Addiction: Does It Have Clinical Potential?* Biol Psychiatry Cogn Neurosci Neuroimaging, 2018. 3(2): p. 101-102.

92. Gamito, P., et al., *Cognitive Training through mHealth for Individuals with Substance Use Disorder.* Methods Inf Med, 2017. 56(2): p. 156-161.

93. McClure, S.M. and W.K. Bickel, *A dual-systems perspective on addiction: contributions from neuroimaging and cognitive training.* Ann N Y Acad Sci, 2014. 1327: p. 62-78.

94. Rinck, M., et al., *Relapse prevention in abstinent alcoholics by cognitive bias modification: Clinical effects of combining approach bias modification and attention bias modification.* J Consult Clin Psychol, 2018. 86(12): p. 1005-1016.

95. Felton, J.W., et al., *Improvement of Working Memory is a Mechanism for Reductions in Delay Discounting Among Mid-Age Individuals in an Urban Medically Underserved Area.* Ann Behav Med, 2019.

96. Kaag, A.M., et al., *A high working memory load prior to memory retrieval reduces craving in non-treatment seeking problem drinkers.* Psychopharmacology (Berl), 2018. 235(3): p. 695-708.

97. Loughead, J., et al., *Can brain games help smokers quit?: Results of a randomized clinical trial.* Drug Alcohol Depend, 2016. 168: p. 112-118.

98. Goldman, R.S. and M.S. Goldman, *Experience-dependent cognitive recovery in alcoholics: a task component strategy.* J Stud Alcohol, 1988. 49(2): p. 142-8.

99. Goldstein, G., et al., *Rehabilitation during alcohol detoxication in comorbid neuropsychiatric patients.* J Rehabil Res Dev, 2005. 42(2): p. 225-34.

100. Forsberg, L.K. and M.S. Goldman, *Experience-dependent recovery of cognitive deficits in alcoholics: extended transfer of training.* J Abnorm Psychol, 1987. 96(4): p. 345-53.

101. Roehrich, L. and M.S. Goldman, *Experience-dependent neuropsychological recovery and the treatment of alcoholism.* J Consult Clin Psychol, 1993. 61(5): p. 812-21.

102. Wetzig, D.L. and S.I. Hardin, *Neurocognitive deficits of alcoholism: an intervention.* J Clin Psychol, 1990. 46(2): p. 219-29.

103. Unterholzner, G., E. Sagstetter, and M.G. Bauer, *[A multi-stage cognitive training program for improving cognitive functions of chronic alcoholic patients].* Z Klin Psychol Psychopathol Psychother, 1992. 40(4): p. 378-95.

104. Stringer, A.Y. and M.S. Goldman, *Experience-dependent recovery of block design performance in male alcoholics: strategy training versus unstructured practice.* J Stud Alcohol, 1988. 49(5): p. 406-11.

105. Forsberg, L.K. and M.S. Goldman, *Experience-dependent recovery of visuospatial functioning in older alcoholic persons.* J Abnorm Psychol, 1985. 94(4): p. 519-29.

106. Hansen, L., *Treatment of reduced intellectual functioning in alcoholics.* J Stud Alcohol, 1980. 41(1): p. 156-8.

107. Godfrey, H.P. and R.G. Knight, *Cognitive rehabilitation of memory functioning in amnesiac alcoholics.* J Consult Clin Psychol, 1985. 53(4): p. 555-7.

108. Velligan, D.I. and J.M. Gonzalez, *Rehabilitation and recovery in schizophrenia.* Psychiatr Clin North Am, 2007. 30(3): p. 535-48.

109. Blundon, G. and E. Smits, *Cognitive rehabilitation: a pilot survey of therapeutic modalities used by Canadian occupational therapists with survivors of traumatic brain injury.* Can J Occup Ther, 2000. 67(3): p. 184-96.

110. Poole, J., et al., *Statement: occupational therapy services management of persons with cognitive impairments.* Am J Occup Ther, 1991. 45(12): p. 1067-8.

111. Dirette, D.K., J. Hinojosa, and G.J. Carnevale, *Comparison of remedial and compensatory interventions for adults with acquired brain injuries.* J Head Trauma Rehabil, 1999. 14(6): p. 595-601.

112. Fan, Q., L. Liao, and G. Pan, *The Application of Cognitive Remediation Therapy in The Treatment of Mental Disorders.* Shanghai Arch Psychiatry, 2017. 29(6): p. 373-375.

113. Jahshan, C., Y. Rassovsky, and M.F. Green, *Enhancing Neuroplasticity to Augment Cognitive Remediation in Schizophrenia.* Front Psychiatry, 2017. 8: p. 191.

114. Penades, R., et al., *Neuroimaging studies of cognitive remediation in schizophrenia: A systematic and critical review.* World J Psychiatry, 2017. 7(1): p. 34-43.

115. Winkens, I., et al., *Efficacy of time pressure management in stroke patients with slowed information processing: a randomized controlled trial.* Arch Phys Med Rehabil, 2009. 90(10): p. 1672-9.

116. Engelberts, N.H., et al., *The effectiveness of cognitive rehabilitation for attention deficits in focal seizures: a randomized controlled study.* Epilepsia, 2002. 43(6): p. 587-95.

117. Ownsworth, T.L. and K. McFarland, *Memory remediation in long-term acquired brain injury: two approaches in diary training.* Brain Inj, 1999. 13(8): p. 605-26.

118. Hux, K., et al., *Effect of training frequency on face-name recall by adults with traumatic brain injury.* Brain Inj, 2000. 14(10): p. 907-20.

119. von Cramon, D.Y., G. Matthes-von Cramon, and N. Mai, *Problem-solving deficits in brain-injured patients: A therapeutic approach.* Neuropsychol Rehabil, 1991. 1(1): p. 45-64.

120. Levine, B., et al., *Rehabilitation of executive functioning: an experimental-clinical validation of goal management training.* J Int Neuropsychol Soc, 2000. 6(3): p. 299-312.

121. Stringer, A.Y., *Ecologically-oriented neurorehabilitation of memory: robustness of outcome across diagnosis and severity.* Brain Inj, 2011. 25(2): p. 169-78.

122. Toglia, J., et al., *A multicontext approach to promoting transfer of strategy use and self regulation after brain injury: An exploratory study.* Brain Inj, 2010. 24(4): p. 664-77.

123. Solanto, M.V., et al., *Development of a new psychosocial treatment for adult ADHD.* J Atten Disord, 2008. 11(6): p. 728-36.

124. Londos, E., et al., *Effects of a goal-oriented rehabilitation program in mild cognitive impairment: a pilot study.* Am J Alzheimers Dis Other Demen, 2008. 23(2): p. 177-83.

125. Velligan, D.I., et al., *Randomized controlled trial of the use of compensatory strategies to enhance adaptive functioning in outpatients with schizophrenia.* Am J Psychiatry, 2000. 157(8): p. 1317-23.

126. Milders, M., B. Deelman, and I. Berg, *Rehabilitation of memory for people's names.* Memory, 1998. 6(1): p. 21-36.

127. Ho, M.R. and T.L. Bennett, *Efficacy of neuropsychological rehabilitation for mild-moderate traumatic brain injury.* Arch Clin Neuropsychol, 1997. 12(1): p. 1-11.

128. Twamley, E.W., C.Z. Burton, and L. Vella, *Compensatory cognitive training for psychosis: who benefits? Who stays in treatment?* Schizophr Bull, 2011. 37 Suppl 2: p. S55-62.

129. Shum, D., et al., *A randomized controlled trial of prospective memory rehabilitation in adults with traumatic brain injury.* J Rehabil Med, 2011. 43(3): p. 216-23.

130. Twamley, E.W., *Cognitive Training Individual Manual*. 2006, University of California, San Diego.

131. Twamley, E.W., et al., *Development and Pilot Testing of a Novel Compensatory Cognitive Training Intervention for People with Psychosis.* Am J Psychiatr Rehabil, 2008. 11(2): p. 144-163.

132. White, S., *Let's get organized: an intervention for persons with co-occurring disorders.* Psychiatr Serv, 2007. 58(5): p. 713.

133. Yohman, J.R., K.W. Schaeffer, and O.A. Parsons, *Cognitive training in alcoholic men.* J Consult Clin Psychol, 1988. 56(1): p. 67-72.

134. Hannon, R., et al., *Memory retraining with adult male alcoholics.* Arch Clin Neuropsychol, 1989. 4(3): p. 227-32.

135. Gutman, S.A., *Why Addiction has a Chronic, Relapsing Course. The Neurobiology of Addiction: Implications for Occupational Therapy Practice.* Occupational Therapy in Mental Health, 2006. 22(2): p. 1-29.

136. Ostlund, S.B. and B.W. Balleine, *On habits and addiction: An associative analysis of compulsive drug seeking.* Drug Discov Today Dis Models, 2008. 5(4): p. 235-245.

137. Volkow, N.D., et al., *Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies.* Neurobiol Learn Mem, 2002. 78(3): p. 610-24.

138. Gillen, G., *Cognitive and Perceptual Rehabilitation: Optimizing Function*. 2009: Mosby Elsevier.

139. Burke, J.M., et al., *A process approach to memory book training for neurological patients.* Brain Inj, 1994. 8(1): p. 71-81.

140. Boman, I.L., et al., *Cognitive training in home environment.* Brain Inj, 2004. 18(10): p. 985-95.

141. Trombly, C.A., et al., *Occupational therapy and achievement of self-identified goals by adults with acquired brain injury: phase II.* Am J Occup Ther, 2002. 56(5): p. 489-98.

142. van Heugten, C.M., R.W. Ponds, and R.P. Kessels, *Brain training: hype or hope?* Neuropsychol Rehabil, 2016. 26(5-6): p. 639-44.

143. Hubley, A.M., L.B. Russell, and A. Palepu, *Injection Drug Use Quality of Life scale (IDUQOL): a validation study.* Health Qual Life Outcomes, 2005. 3: p. 43.

144. Hubley, A.M. and A. Palepu, *Injection Drug User Quality of Life Scale (IDUQOL): findings from a content validation study.* Health Qual Life Outcomes, 2007. 5: p. 46.

145. Beck, A.T., R.A. Steer, and G.K. Brown, *BDI-II Manual (2nd edition)*. 2nd ed. 1996, San Antonio: Harcourt Brace & Company.

146. Wechsler, D.A., *Wechsler Test of Adult Reading*. 2001, San Antonio, TX: The Psychological Corporation.

147. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res, 1975. 12(3): p. 189-98.

148. *Research Randomizer*. 2019 06/30/2019]; Available from: https://www.randomizer.org/.

149. NPO. *Neuropsychonline*. 2011; Available from: https://www.neuropsychonline.com/.

150. Chen, S.H., et al., *The effectiveness of computer-assisted cognitive rehabilitation for persons with traumatic brain injury.* Brain Inj, 1997. 11(3): p. 197-209.

151. Elgamal, S., et al., *Successful computer-assisted cognitive remediation therapy in patients with unipolar depression: a proof of principle study.* Psychol Med, 2007. 37(9): p. 1229-38.

152. Shin, S.H., M.H. Ko, and Y.H. Kim, *Effect of Computer-Assisted Cognitive Rehabilitation Program for Patients with Brain Injury.* J Korean Acad Rehabil Med, 2002. 26(1): p. 1-8.

153. Hogarty, G.E., et al., *Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior.* Arch Gen Psychiatry, 2004. 61(9): p. 866-76.

154. Batchelor, J., et al., *Cognitive rehabilitation of severely closed-head-injured patients using computer-assisted and noncomputerized treatment techniques.* J Head Trauma Rehabil, 1988. 3(3): p. 78-85.

155. Bell, M., et al., *Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance.* Arch Gen Psychiatry, 2001. 58(8): p. 763-8.

156. Burda, P.C., et al., *Computer-assisted cognitive rehabilitation of chronic psychiatric inpatients.* Computers in Human Behavior, 1994. 10(3): p. 359-368.

157. Ruff, R.M., et al., *Neuropsychological rehabilitation: An experimental study with head-injured patients.* J Head Trauma Rehabil, 1989. 4(3): p. 20-36.

158. Vinogradov, S., M. Fisher, and E. de Villers-Sidani, *Cognitive training for impaired neural systems in neuropsychiatric illness.* Neuropsychopharmacology, 2012. 37(1): p. 43-76.

159. Genevsky, A., et al., *Cognitive training in schizophrenia: a neuroscience-based approach.* Dialogues Clin Neurosci, 2010. 12(3): p. 416-21.

160. McGurk, S.R., et al., *A meta-analysis of cognitive remediation in schizophrenia.* Am J Psychiatry, 2007. 164(12): p. 1791-802.

161. Wykes, T. and V. Huddy, *Cognitive remediation for schizophrenia: it is even more complicated.* Curr Opin Psychiatry, 2009. 22(2): p. 161-7.

162. *Typing Master*. 2019; Available from: http://www.typingmaster.com/typing-tutor/free-download.html.

163. Walsh, J., *Psychoeducation in Mental Health*. 2010, Chicago, IL: Lyceum Books.

164. Colom, F.V. and E. Vieta, *Psychoeducation Manual for Bipolar Disorder*. 2006: Cambridge University Press.

165. Lefley, H.P., *Family Psychoeducation for Serious Mental Illness*. 2009: Oxford University Press.

166. APA. *Let's Talk Facts*. 2005 7/10/2011]; Available from: http://www.healthyminds.org/Functional-Library/brochures.aspx.

167. Chew, R.H., R.E. Hales, and S.C. Yudofsky, *What Your Patients Need to Know About Psychiatric Medications, 2nd Edition*. 2009: American Psychiatric Publishing.

168. Sheehan, D.V., et al., *The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.* J Clin Psychiatry, 1998. 59 Suppl 20: p. 22-33;quiz 34-57.

169. Spielberger, C.D., et al., *Manual for the State-Trait Anxiety Inventory*. 1983: Consulting Psychologists Press, Inc.

170. APA, *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition ed. 2013, Arlington, VA: American Psychiatric Association.

171. Amorim, P., et al., *DSM-IH-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI.* Eur Psychiatry, 1998. 13(1): p. 26-34.

172. Wang, Y.P. and C. Gorenstein, *Psychometric properties of the Beck Depression Inventory-II: a comprehensive review.* Braz J Psychiatry, 2013. 35(4): p. 416-31.

173. Elwood, L.S., K. Wolitzky-Taylor, and B.O. Olatunji, *Measurement of anxious traits: a contemporary review and synthesis.* Anxiety Stress Coping, 2012. 25(6): p. 647-66.

174. Fals-Stewart, W., et al., *The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties.* J Consult Clin Psychol, 2000. 68(1): p. 134-44.

175. Carey, K.B., et al., *Temporal stability of the timeline followback interview for alcohol and drug use with psychiatric outpatients.* J Stud Alcohol, 2004. 65(6): p. 774-81.

176. Robinson, S.M., et al., *Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use.* Psychol Addict Behav, 2014. 28(1): p. 154-62.

177. Hersh, D., et al., *The validity of self-reported cocaine use in two groups of cocaine abusers.* J Consult Clin Psychol, 1999. 67(1): p. 37-42.

178. Hjorthoj, C.R., A.R. Hjorthoj, and M. Nordentoft, *Validity of Timeline Follow-Back for self-reported use of cannabis and other illicit substances--systematic review and meta-analysis.* Addict Behav, 2012. 37(3): p. 225-33.

179. McLellan, A.T., et al., *The Fifth Edition of the Addiction Severity Index.* J Subst Abuse Treat, 1992. 9(3): p. 199-213.

180. Drake, R.E., G.J. McHugo, and J.C. Biesanz, *The test-retest reliability of standardized instruments among homeless persons with substance use disorders.* J Stud Alcohol, 1995. 56(2): p. 161-7.

181. McCusker, J., et al., *Test-retest reliability of the Addiction Severity Index composite scores among clients in residential treatment.* The American Journal on Addictions, 1994. 3(3): p. 254-262.

182. Zanis, D.A., et al., *Reliability and validity of the Addiction Severity Index with a homeless sample.* J Subst Abuse Treat, 1994. 11(6): p. 541-8.

183. Hodgins, D.C. and N. el-Guebaly, *More data on the Addiction Severity Index. Reliability and validity with the mentally ill substance abuser.* J Nerv Ment Dis, 1992. 180(3): p. 197-201.

184. Joyner, L.M., J.D. Wright, and J.A. Devine, *Reliability and validity of the addiction severity index among homeless substance misusers.* Subst Use Misuse, 1996. 31(6): p. 729-51.

185. McLellan, A.T., et al., *New data from the Addiction Severity Index. Reliability and validity in three centers.* J Nerv Ment Dis, 1985. 173(7): p. 412-23.

186. Kosten, T.R., B.J. Rounsaville, and H.D. Kleber, *Concurrent validity of the addiction severity index.* J Nerv Ment Dis, 1983. 171(10): p. 606-10.

187. Leonhard, C., et al., *The Addiction Severity Index: a field study of internal consistency and validity.* J Subst Abuse Treat, 2000. 18(2): p. 129-35.

188. McLellan, A.T., et al., *A new measure of substance abuse treatment. Initial studies of the treatment services review.* J Nerv Ment Dis, 1992. 180(2): p. 101-10.

189. Reilly-Harrington, N.A., et al., *The Medication Recommendation Tracking Form: a novel tool for tracking changes in prescribed medication, clinical decision making,*

and use in comparative effectiveness research. J Psychiatr Res, 2013. 47(11): p. 1686-93.

190. Cacciola, J.S., et al., *Initial reliability and validity studies of the revised Treatment Services Review (TSR-6).* Drug Alcohol Depend, 2008. 92(1-3): p. 37-47.

191. Reilly-Harrington, N.A., et al., *Tracking medication changes to assess outcomes in comparative effectiveness research: A bipolar CHOICE study.* J Affect Disord, 2016. 205: p. 159-164.

192. Rohsenow, D.J., et al., *The Cocaine Effects Questionnaire for patient populations: development and psychometric properties.* Addict Behav, 2004. 29(3): p. 537-53.

193. Vorspan, F., et al., *The Obsessive-Compulsive Cocaine Scale (OCCS): a pilot study of a new questionnaire for assessing cocaine craving.* Am J Addict, 2012. 21(4): p. 313-9.

194. Jardin, B.F., et al., *The Obsessive Compulsive Cocaine Scale: assessment of factor structure, reliability, and validity.* Addict Behav, 2011. 36(12): p. 1223-7.

195. Tiffany, S.T., et al., *The development of a cocaine craving questionnaire.* Drug Alcohol Depend, 1993. 34(1): p. 19-28.

196. Weiss, R.D., et al., *The relationship between cocaine craving, psychosocial treatment, and subsequent cocaine use.* Am J Psychiatry, 2003. 160(7): p. 1320-5.

197. Weiss, R.D., et al., *Early prediction of initiation of abstinence from cocaine. Use of a craving questionnaire.* Am J Addict, 1997. 6(3): p. 224-31.

198. McConnaughy, E.N., J.O. Prochaska, and W.F. Velicer, *Stages of change in psychotherapy: Measurement and sample profiles.* Psychotherapy: Theory, Research and Practice, 1983. 20: p. 368-375.

199. Pantalon, M.V., et al., *The URICA as a measure of motivation to change among treatment-seeking individuals with concurrent alcohol and cocaine problems.* Psychol Addict Behav, 2002. 16(4): p. 299-307.

200. Field, C.A., et al., *Construct, concurrent and predictive validity of the URICA: data from two multi-site clinical trials.* Drug Alcohol Depend, 2009. 101(1-2): p. 115-23.

201. Guy, W., *ECDEU Assessment Manual for Psychopharmacology.* US Department of Health, and Welfare, 1976: p. 534-537.

202. Forkmann, T., et al., *The Clinical Global Impression Scale and the influence of patient or staff perspective on outcome.* BMC Psychiatry, 2011. 11: p. 83.

203. Sheehan, D.V., K. Harnett-Sheehan, and B.A. Raj, *The measurement of disability.* Int Clin Psychopharmacol, 1996. 11 Suppl 3: p. 89-95.

204. Arbuckle, R., et al., *The psychometric validation of the Sheehan Disability Scale (SDS) in patients with bipolar disorder.* Psychiatry Res, 2009. 165(1-2): p. 163-74.

205. Coles, T., et al., *Psychometric evaluation of the Sheehan Disability Scale in adult patients with attention-deficit/hyperactivity disorder.* Neuropsychiatr Dis Treat, 2014. 10: p. 887-95.

206. Hodgins, D.C., *Reliability and validity of the Sheehan Disability Scale modified for pathological gambling.* BMC Psychiatry, 2013. 13: p. 177.

207. Brogly, S., et al., *Towards more effective public health programming for injection drug users: development and evaluation of the injection drug user quality of life scale.* Subst Use Misuse, 2003. 38(7): p. 965-92.

208. Alderman, N., et al., *Ecological validity of a simplified version of the multiple errands shopping test.* J Int Neuropsychol Soc, 2003. 9(1): p. 31-44.

209. Dawson, D.R., et al., *Further development of the Multiple Errands Test: standardized scoring, reliability, and ecological validity for the Baycrest version.* Arch Phys Med Rehabil, 2009. 90(11 Suppl): p. S41-51.

210. Shallice, T. and P.W. Burgess, *Deficits in strategy application following frontal lobe damage in man.* Brain, 1991. 114 (Pt 2): p. 727-41.

211. Roebuck-Spencer, T.M., et al., *Cognitive Screening Tests Versus Comprehensive Neuropsychological Test Batteries: A National Academy of Neuropsychology Education Paperdagger.* Arch Clin Neuropsychol, 2017. 32(4): p. 491-498.

212. Meade, A.W., *FreeIAT: An Open-Source Program to Administer the Implicit Association Test.* Applied Psychological Measurement, 2009. 33(8): p. 643.

213. Wiers, R.W., K. Houben, and J. de Kraker, *Implicit cocaine associations in active cocaine users and controls.* Addict Behav, 2007. 32(6): p. 1284-9.

214. Greenwald, A.G., B.A. Nosek, and M.R. Banaji, *Understanding and using the implicit association test: I. An improved scoring algorithm.* J Pers Soc Psychol, 2003. 85(2): p. 197-216.

215. Marhe, R., et al., *Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: an ecological momentary assessment study.* J Consult Clin Psychol, 2013. 81(1): p. 1-12.

216. Waters, A.J., R. Marhe, and I.H. Franken, *Attentional bias to drug cues is elevated before and during temptations to use heroin and cocaine.* Psychopharmacology (Berl), 2012. 219(3): p. 909-21.

217. Delis, D.C., E. Kaplan, and J.H. Kramer, *The Delis-Kaplan Executive Function System*. 2001, San Antonio, TX: The Psychological Corporation.

218. Wechsler, D.A., *Wechsler Adult Intelligence Scale - Fourth Edition*. 2008, San Antonio, TX: Pearson Assessment.

219. Delis, D.C., et al., *Reliability and validity of the Delis-Kaplan Executive Function System: an update.* J Int Neuropsychol Soc, 2004. 10(2): p. 301-3.

220. Nyongesa, M.K., et al., *Assessing Executive Function in Adolescence: A Scoping Review of Existing Measures and Their Psychometric Robustness.* Front Psychol, 2019. 10: p. 311.

221. Reske, M., D.C. Delis, and M.P. Paulus, *Evidence for subtle verbal fluency deficits in occasional stimulant users: quick to play loose with verbal rules.* J Psychiatr Res, 2011. 45(3): p. 361-8.

222. Bowde, S.C., et al., *Factorial invariance for combined Wechsler Adult Intelligence Scale-Revised and Wechsler Memory Scale-Revised scores in a sample of clients with alcohol dependency.* Clin Neuropsychol, 2001. 15(1): p. 69-80.

223. Latvala, A., et al., *Cognitive functioning in substance abuse and dependence: a population-based study of young adults.* Addiction, 2009. 104(9): p. 1558-68.

224. Polunina, A.G. and D.M. Davydov, *EEG correlates of Wechsler Adult Intelligence Scale.* Int J Neurosci, 2006. 116(10): p. 1231-48.

225. Brandt, J., *The hopkins verbal learning test: Development of a new memory test with six equivalent forms.* Clinical Neuropsychologist, 1991. 5(2): p. 125-142.

226. Benedict, R.H.B., et al., *Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability.* The Clinical Neuropsychologist, 1998. 12(1): p. 43-55.

227. Benedict, H.R.B., *Brief Visuospatial Memory Test - Revised*. 1997, Odessa, FL: Psychological Assessment Resources, Inc.

228. de Caneda, M.A.G., et al., *The Reliability of the Brief Visuospatial Memory Test - Revised in Brazilian multiple sclerosis patients.* Dement Neuropsychol, 2018. 12(2): p. 205-211.

229. Kane, K.D. and B.P. Yochim, *Construct validity and extended normative data for older adults for the Brief Visuospatial Memory Test, Revised.* Am J Alzheimers Dis Other Demen, 2014. 29(7): p. 601-6.

230. Shapiro, A.M., et al., *Construct and concurrent validity of the Hopkins Verbal Learning Test-revised.* Clin Neuropsychol, 1999. 13(3): p. 348-58.

231. Woods, S.P., et al., *Test-retest reliability of component process variables within the Hopkins Verbal Learning Test-Revised.* Assessment, 2005. 12(1): p. 96-100.

232. Heaton, R.K., et al., *Wisconsin Card Sorting Test Manual, Revised and Expanded.* 1993, Orlando, FL: Psychological Assessment Resources.

233. Fortuny, L.A. and R.K. Heaton, *Standard versus computerized administration of the wisconsin card sorting test.* The Clinical Neuropsychologist, 1996. 10(4): p. 419-424.

234. Chiu, E.C., et al., *Validity of the Wisconsin Card Sorting Test in patients with stroke.* Disabil Rehabil, 2018. 40(16): p. 1967-1971.

235. Kopp, B., F. Lange, and A. Steinke, *The Reliability of the Wisconsin Card Sorting Test in Clinical Practice.* Assessment, 2019: p. 1073191119866257.

236. Arce, E. and C. Santisteban, *Impulsivity: a review.* Psicothema, 2006. 18(2): p. 213-20.

237. Chamberlain, S.R. and B.J. Sahakian, *The neuropsychiatry of impulsivity.* Curr Opin Psychiatry, 2007. 20(3): p. 255-61.

238. Chamorro, J., et al., *Impulsivity in the general population: a national study.* J Psychiatr Res, 2012. 46(8): p. 994-1001.

239. Patton, J.H., M.S. Stanford, and E.S. Barratt, *Factor structure of the Barratt impulsiveness scale.* J Clin Psychol, 1995. 51(6): p. 768-74.

240. Stanford, M.S., et al., *Fifty years of the Barratt Impulsiveness Scale: An update and review.* Personality and Individual Differences, 2009. 47(5): p. 385-395.

241. Spinella, M., *Normative data and a short form of the Barratt Impulsiveness Scale.* Int J Neurosci, 2007. 117(3): p. 359-68.

242. Stanford, M., et al., *Fifty years of the Barratt Impulsiveness Scale: An update and review.* Personality and Individual Differences, 2009. 47: p. 385-395.

243. Whiteside, S.P. and D.R. Lynam, *The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity.* Personality and Individual Differences, 2001. 30(4): p. 669-689.

244. Whiteside, S.P., et al., *Validation of the UPPS impulsive behaviour scale: a four-factor model of impulsivity.* European Journal of Personality, 2005. 19(7): p. 559-574.

245. Dugre, J.R., et al., *The Psychometric Properties of a Short UPPS-P Impulsive Behavior Scale Among Psychiatric Patients Evaluated in an Emergency Setting.* Front Psychiatry, 2019. 10: p. 139.

246. Fernandez-Serrano, M.J., et al., *Neuropsychological profiling of impulsivity and compulsivity in cocaine dependent individuals.* Psychopharmacology (Berl), 2012. 219(2): p. 673-83.

247. Conners, C.K., *Conners Continuous Performance Test- Third Edition (Conners CPT 3) & Conners Continuous Auditory Test of Attention (Conners CATA): Technical Manual.* 2014, New York: Multi-Health Systems Inc.

248. Shaked, D., et al., *Reliability and validity of the Conners' Continuous Performance Test.* Appl Neuropsychol Adult, 2019: p. 1-10.

249. Rapisarda, A., et al., *The continuous performance test, identical pairs: norms, reliability and performance in healthy controls and patients with schizophrenia in Singapore.* Schizophr Res, 2014. 156(2-3): p. 233-40.

250. Bechara, A., et al., *Insensitivity to future consequences following damage to human prefrontal cortex.* Cognition, 1994. 50(1-3): p. 7-15.

251. Buelow, M.T. and W.R. Barnhart, *Test-Retest Reliability of Common Behavioral Decision Making Tasks.* Arch Clin Neuropsychol, 2018. 33(1): p. 125-129.

252. Buelow, M.T. and J.A. Suhr, *Construct validity of the Iowa Gambling Task.* Neuropsychol Rev, 2009. 19(1): p. 102-14.

253. Kjome, K.L., et al., *Relationship between impulsivity and decision making in cocaine dependence.* Psychiatry Res, 2010. 178(2): p. 299-304.

254. Lin, C.H., et al., *Reexamining the validity and reliability of the clinical version of the iowa gambling task: evidence from a normal subject group.* Front Psychol, 2013. 4: p. 220.

255. Vadhan, N.P., et al., *Decision-making in long-term cocaine users: Effects of a cash monetary contingency on Gambling task performance.* Drug Alcohol Depend, 2009. 102(1-3): p. 95-101.

256. Verdejo-Garcia, A., et al., *The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task.* Drug Alcohol Depend, 2007. 90(1): p. 2-11.

257. Kirby, K.N., N.M. Petry, and W.K. Bickel, *Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls.* J Exp Psychol Gen, 1999. 128(1): p. 78-87.

258. *Monetary-Choice Questionnaire*. 2016; Available from: https://www.phenxtoolkit.org/protocols/view/530301.

259. Lejuez, C.W., et al., *Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART).* J Exp Psychol Appl, 2002. 8(2): p. 75-84.

260. Weafer, J., M.J. Baggott, and H. de Wit, *Test-retest reliability of behavioral measures of impulsive choice, impulsive action, and inattention.* Exp Clin Psychopharmacol, 2013. 21(6): p. 475-81.

261. White, T.L., C.W. Lejuez, and H. de Wit, *Test-retest characteristics of the Balloon Analogue Risk Task (BART).* Exp Clin Psychopharmacol, 2008. 16(6): p. 565-70.

262. Dykiert, D. and I.J. Deary, *Retrospective validation of WTAR and NART scores as estimators of prior cognitive ability using the Lothian Birth Cohort 1936.* Psychol Assess, 2013. 25(4): p. 1361-6.

263. Green, R.E., et al., *Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR).* J Clin Exp Neuropsychol, 2008. 30(2): p. 163-72.

264. Whitney, K.A., et al., *Validity of the Wechsler Test of Adult Reading (WTAR): effort considered in a clinical sample of U.S. military veterans.* Appl Neuropsychol, 2010. 17(3): p. 196-204.

265. Johnson, B.A., N. Ait-Daoud, and J.D. Roache, *The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field.* J Stud Alcohol Suppl, 2005(15): p. 157-67; discussion 140.

266. Guy, W., et al., *Intra-interrater reliability of SAFTEE using videotape interviews and clinical trial data.* Psychopharmacol Bull, 1987. 23(1): p. 93-6.

267. Guy, W., et al., *Reliability and validity of SAFTEE: preliminar analyses.* Psychopharmacol Bull, 1986. 22(2): p. 397-401.

268. Jacobson, A.F., et al., *Interrater agreement and intraclass reliability measures of SAFTEE in psychopharmacologic clinical trials.* Psychopharmacol Bull, 1986. 22(2): p. 382-8.

269. Jacobson, A.F., et al., *Interrater agreement and reliability measures of SAFTEE: general inquiry vs. systematic inquiry.* Psychopharmacol Bull, 1987. 23(1): p. 97-101.

270. Devilly, G.J. and T.D. Borkovec, *Psychometric properties of the credibility/expectancy questionnaire.* J Behav Ther Exp Psychiatry, 2000. 31(2): p. 73-86.

271. Lewis, J.R., *IBM computer usability satisfaction questionnaires: Psychometric evaluation and instructions for use.* International Journal of Human-Computer Interaction, 1995. 7(1): p. 57-78.

272. Boot, W.R., et al., *Video games as a means to reduce age-related cognitive decline: attitudes, compliance, and effectiveness.* Front Psychol, 2013. 4: p. 31.

273. Festinger, D.S., et al., *Do research payments precipitate drug use or coerce participation?* Drug Alcohol Depend, 2005. 78(3): p. 275-81.

274. Festinger, D.S., et al., *Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion.* Drug Alcohol Depend, 2008. 96(1-2): p. 128-35.

275. Festinger, D.S. and K.L. Dugosh, *Paying substance abusers in research studies: where does the money go?* Am J Drug Alcohol Abuse, 2012. 38(1): p. 43-8.

276. Kraemer, H.C., et al., *Caution regarding the use of pilot studies to guide power calculations for study proposals.* Arch Gen Psychiatry, 2006. 63(5): p. 484-9.

277. Woody, G.E., *Research findings on psychotherapy of addictive disorders.* Am J Addict, 2003. 12 Suppl 2: p. S19-26.

278. Weiss, R.D., et al., *The effect of 12-step self-help group attendance and participation on drug use outcomes among cocaine-dependent patients.* Drug Alcohol Depend, 2005. 77(2): p. 177-84.

279. Bora, E. and N. Zorlu, *Social cognition in alcohol use disorder: a meta-analysis.* Addiction, 2017. 112(1): p. 40-48.

280. Yacubian, J. and C. Buchel, *The genetic basis of individual differences in reward processing and the link to addictive behavior and social cognition.* Neuroscience, 2009. 164(1): p. 55-71.

281. Lee, R.S.C., S. Hoppenbrouwers, and I. Franken, *A Systematic Meta-Review of Impulsivity and Compulsivity in Addictive Behaviors.* Neuropsychol Rev, 2019. 29(1): p. 14-26.

Chapter 2 Abstract

Background: Cognitive impairment is common in adults with cocaine use disorder and can reduce the effectiveness of treatment. Effectively treating cognitive impairment as part of a comprehensive treatment plan for adults with cocaine use disorder (CUD) could potentially improve important clinical outcomes, such as abstinence, quality of life, and treatment completion (e.g., cognitive-behavioral therapy, therapeutic community). Because existing models of cognitive rehabilitation have yielded small to medium effect sizes in improving cognition in CUD, newer models of cognitive rehabilitation are needed to improve cognition more effectively in CUD.

Aims: Practitioners in the occupational therapy (OT) field work on improving the function of various cognitively impaired populations by using cognitive-adaptation techniques to enhance cognition in daily quality of life/function. OT can address the cognitive and problem-solving deficits that lead to a breakdown in daily life skills. A model of OT-based cognitive rehabilitation in CUD may strongly improve cognition, ultimately improving important clinical outcomes. The long-term goals of this research program are to examine improvement in cognition, cocaine abstinence, and daily quality of life/function from a novel model of OT-based cognitive rehabilitation. This randomized pilot trial was needed to address potential areas of uncertainty before conducting a future larger definitive randomized controlled trial (RCT).

Methods: This paper describes the feasibility, acceptability, and preliminary effect sizes for a pilot 12-week, randomized, parallel group outpatient study of 31 treatment-seeking adults (age 18-65) with CUD (with 3 or more months of remission) who were mild-to-moderately cognitively impaired and dissatisfied with their quality of life. Participants were randomized to a Cog-Rehab arm (drug counseling + OT-based cognitive rehabilitation), or to a Control arm (drug counseling + psychoeducation/computer exercises). Acceptability of study procedures was assessed at the end of treatment with the Computer System Usability Questionnaire [range from 1 (strongly agree) to 7 (strongly disagree)] and the Game Training Questionnaire. Urine toxicology at each

visit tested for cocaine, marijuana, opiates, methamphetamines, amphetamine, phencyclidine, benzodiazepines, and barbiturates. Attention, memory, executive function, and impulsivity neurocognitive assessments were conducted at baseline, end of treatment (12 weeks), and follow-up (24 weeks). For each measure, an effect size was calculated by subtracting mean change in Cog-Rehab Arm from mean change in Control Arm and dividing by the pooled standard deviation. A positive sign for a between-group effect size for neurocognitive assessments means favoring the Cog-Rehab arm, and a negative sign for an effect size means favoring the Control arm.

Results: 100% of enrolled study participants completed all study procedures (16 Cog-Rehab arm, 15 Control arm). Study participants had a mean age of 57.5 years (SD 5.8), 30 (96.8%) were male, 19 (61.3%) were Black, 12 (38.7%) were White, 6 (19.4%) were Latino, 15 (48.4%) were single, and had a mean education of 12.8 years (SD 1.4). Participants in both groups were similar in sex, age, education, race, ethnicity, marital status, retirement status, and handedness. Based on the Computer System Usability Questionnaire, participants in the Cog-Rehab and Control arms had similar ratings on the mean overall satisfaction score (1.9 vs. 2.0, $P = 0.90$). Based on the Game Training Questionnaire, participants in the Cog-Rehab and Control arms had similar ratings for whether they perceived the computer training to be enjoyable (81.3% vs. 60%, Fisher's exact p = 0.19). Participants in the Cog-Rehab arm completed a significantly greater percentage of homework assignments (65.3%) than those in the Control arm (32.7%) [$X^2(2) = 36.2$; $P < 0.0001$]. There were no significant differences between groups in relapse to any substance at any timepoint. Most of the between-group effect sizes for neurocognitive measures and functional assessments had 95% confidence intervals that crossed zero. Some significant between-group effect sizes were found for certain neurocognitive measures (favoring Cog-Rehab arm: attentional bias 1.0, attention 0.7, visual memory 0.8, executive function 1.0) and one functional assessment (favoring Cog-Rehab arm: Drug User Quality of Life Score 0.8).

Discussion: This study found that a novel OT-based approach for improving cognition in adults with CUD and cognitive impairment is feasible and acceptable and provides preliminary evidence for efficacy based on effect sizes. CUD remains a significant public health problem in the U.S., and effectively treating cognitive impairment as part of a comprehensive treatment plan for CUD could potentially improve important clinical outcomes. Based on this pilot trial's feasibility, acceptability, and preliminary effect sizes, we believe a definitive RCT is warranted.

Chapter 2 Main Body

INTRODUCTION

Cocaine use disorders (CUDs) remain a significant U.S. public health problem [282, 283]. Relapse to cocaine use among those with a CUD is common [284, 285], with data showing that less than 25% of those with CUD remain abstinent over a 1-year period after participating in outpatient empirically-based behavioral (individual or group) and pharmacologic therapies [286]. Cognitive impairment in those with substance use disorders (SUDs) [287-291] is associated with relapse [292, 293], lower likelihood of treatment completion (e.g., cognitive-behavioral therapy, therapeutic community) [294-298], lower motivation [299], and worse quality of life [300, 301]. Effectively treating cognitive impairment as part of a comprehensive treatment plan for CUD could potentially improve important clinical outcomes, such as abstinence, quality of life, and treatment completion. Because existing models of cognitive rehabilitation have yielded small to medium effect sizes in improving cognition in CUD [302-305] (e.g., working memory training, combination of working memory training and medication), newer models of cognitive rehabilitation are needed to enhance existing models and to improve cognition more effectively.

One field where practitioners work on improving the function of various cognitively impaired patients (e.g., stroke, traumatic brain injury, schizophrenia) by using cognitive-adaptation/compensation to enhance cognition in daily quality of life/function [306-316] is occupational therapy (OT). OT can address the cognitive and problem solving deficits that lead to a breakdown in daily life skills [317]. A model of OT-based cognitive rehabilitation in CUD may strongly improve cognition, ultimately improving important clinical outcomes.

The effectiveness of OT-based cognitive rehabilitation in treating cognitive impairment in CUD has not been examined through research. This study was a pilot 12-week, randomized, parallel-group outpatient study of treatment-seeking (for cognitive difficulties) adults (age 18-65) with CUD (with 3 or months of remission) who were mild-to-moderately cognitively impaired and

dissatisfied with their quality of life. Participants were randomized to a Cog-Rehab arm (drug counseling + OT-based cognitive rehabilitation), or to a Control arm (drug counseling + psychoeducation/computer literacy).

This randomized pilot trial was needed to address potential areas of uncertainty before conducting a future larger definitive randomized controlled trial. Areas of uncertainty included feasibility of recruiting adults with CUD with 3 or months of remission, feasibility of randomizing participants who met strict eligibility criteria, feasibility and acceptability of completing a lengthy neurocognitive battery at three timepoints, feasibility and acceptability of completing the complex interventions in the Cog-Rehab and Control arms, feasibility of completing homework assignments during the study period, and feasibility and acceptability of attending lengthy study visits at three timepoints. Observing how these areas of uncertainty unfolded in this pilot trial helped determine the feasibility of conducting a larger future definite randomized controlled trial.

The overall project aims were to examine the improvement in cognition, examine the improvement in cocaine abstinence, and examine the improvement in daily quality of life/function from a novel model of OT-based cognitive rehabilitation. The first of three papers described the protocol for the pilot study. This second paper will discuss recruitment, feasibility and acceptability of assessments and interventions, and estimate effect sizes for clinical outcomes. The CONSORT extension to randomized pilot and feasibility trials was used as a guide for this second paper [318]. The third and final paper will be a secondary analysis of the Multiple Errands Test as associated with the neurocognitive assessments.

METHODS

Overall Study Design

This study was a randomized, parallel-group outpatient study of adults with CUD who had 3 months of self-reported remission from cocaine use and were seeking treatment for cognitive difficulties. If a potential participant met criteria based on a telephone interview, the participant was then scheduled for an in-person screening visit. The study protocol can be

accessed by contacting the principal investigator. No changes were made to this protocol after the trial started.

Study Setting

This study was conducted at the San Francisco Veterans Affairs Health Care System (SFVAHCS) between 7/1/2014 and 6/30/2019. This study was registered on clinicaltrials.gov (NCT01684293). This study was approved by both the University of California, San Francisco (UCSF) Institutional Review Board (IRB) and the SFVAHCS Clinical Research Workgroup. All participants were paid in cash (US dollars) for their study participation. The funding source (National Institute on Drug Abuse) had no role in the design of this study and had no role during its execution, analyses, interpretation of the data, or decision to submit results.

Study Recruitment

Word-of-mouth and flyers around the SFVAHCS were used to recruit potential participants for treatment-seeking adults with CUD. Because the principal investigator's office was located in the opioid treatment program (OTP) clinic, most participants came through word-of-mouth from the OTP clinic.

Verbal consent was used to conduct the screening telephone interview. If the potential participant met criteria based on the telephone interview, the individual was then scheduled for the first screening visit. During the first screening visit, the screening consent form for the screening process was reviewed by the principal investigator, any questions answered, and the written screening consent form was signed by the individual after the individual passed a first screening consent quiz. For participants who passed the first and second screening visits, a third screening visit was scheduled. Neurocognitive testing occurred during the second screening visit. During the third screening visit, after reviewing all screening data (inclusion and exclusion criteria list in chapter #1), the written study consent form was signed by the participant after the participant passed a second study consent quiz. The Multiple Errands Test was also administered at the third screening visit.

Study Randomization

Participants were randomized in a 1:1 allocation ratio to the Cog-Rehab arm or the Control arm. Simple randomization with no restriction or blocking was completed using the Research Randomizer website [319]. No steps were taken to conceal the sequence. The principal investigator generated the random allocation sequence, enrolled and consented participants, and assigned participants to interventions.

Study Intervention

Because the intervention in this study was a new intervention that had not been tested previously in a clinical setting, the IRB and the research team wanted to ensure that participants in both arms were receiving some form of substance use disorder treatment. As a result, weekly individual or group drug counseling (choice was up to each participant) was required for study participation.

In the Cog-Rehab arm, OT-based cognitive rehabilitation consisted of adaptation strategies taught by a therapist (Bachelors level research assistant) and remediation techniques practiced on a computer. The active Cog-Rehab arm consisted of 36 hours of training (24 hours computer-based, 12 hours therapist-based) over a 12-week study period. The online software PSSCogRehab [320] was used for the 24 hours of computer-cognitive-remediation (4 modules [Attention, Memory, Executive, and Problem Solving]). The 12-visit cognitive-adaptation individual manual by Twamley et al [308, 321] was used for the 12 hours of therapist-based training. A homework assignment was given for 11 out of the 12 therapist-based training visits; each assignment helped reinforce the content discussed in the therapist-based training visit.

To control for therapist interaction and computer interaction in the Cog-Rehab arm, the Control arm tasks consisted of psychoeducation taught by a therapist (Bachelors level research assistant) and computer literacy exercises; no cognitive rehabilitation occurred in the Control arm. The Control arm also consisted of 36 hours of training (24 hours computer-based, 12 hours therapist-based) over a 12-week study period. The software Typing Master [322] and computer

literacy topics (e.g., Microsoft Word, Excel, PowerPoint, etc.) were used for 24 hours of computer typing exercises. Psychoeducation focusing on general behavioral health topics was used for the 12 hours of therapist-based training; no specific manual was used, but a list of topics was compiled for the purpose of this study. A homework assignment was given for 11 out of the 12 therapist-based training visits; each assignment helped reinforce the content discussed in the therapist-based training visit.

To increase generalizability to daily function [323-327], a part of each session in both arms occurred in various settings around the Veterans Affairs hospital where the study took place (e.g., cafeteria, store, coffee cart, etc.). Further details on the intervention were described in the first paper.

Study Measurements

Feasibility data were collected throughout the enrollment, intervention, and follow-up periods. Feasibility measures included: a) ability to recruit adults with CUD with 3 or months of remission, b) ability to randomize participants who met strict eligibility criteria, c) ability to complete a lengthy neurocognitive battery at three timepoints, d) ability to complete the complex interventions in the Cog-Rehab and Control arms, e) ability to complete eleven homework assignments during the study period, and f) ability to complete outcome assessments at three timepoints.

Metrics of tracking feasibility included the number of telephone calls received, number of telephone screens actually completed, number of telephone callers set up for the 1st screening visit, number of callers who completed all screening visits in person, number of participants randomized, number of participants who completed the entire study, number of total study visits attended, and percent of homework assignments completed during the study period (out of eleven homework assignments).

Acceptability of study procedures was assessed at the end of treatment with the Computer System Usability Questionnaire and the Game Training Questionnaire. The 19-item

self-report Computer System Usability Questionnaire (CSUQ) [328] was used to assess participants' satisfaction with using the computerized parts of the study intervention; each item had seven answer choices, ranging from 1 (strongly agree) to 7 (strongly disagree), and four scores were calculated (overall satisfaction, system usefulness, information quality, interface quality). The self-report Game Training Questionnaire (GTQ) [329] assessed how the participants perceived the computer training (4-item Part 2 – enjoyable, challenging, frustrating, motivated); each question had seven answer choices, ranging from very strongly disagree to very strongly agree.

Outcome measures for a future definitive randomized controlled trial were included in this pilot trial to assess the feasibility of research staff administering these measures and the feasibility of participants completing these measures and to provide proof-of-concept by estimating effect sizes. Sociodemographics were collected at baseline by self-report via a structured interview. Clinical characteristics were collected at baseline by various methods, such as self-report and the interviewer-administered Mini International Neuropsychiatric Interview (MINI) for Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [330]. Urine toxicologies were conducted at baseline, during the treatment period, end of treatment, and follow-up. Urine toxicology at each visit tested for cocaine, marijuana, opiates, methamphetamines, amphetamine, phencyclidine, benzodiazepines, and barbiturates using the rapid one-step Alere iScreen drugs of abuse screening test card (Alere; Portsmouth, Virginia).

The Wechsler Test of Adult Reading (WTAR) [331] was used to assess premorbid intellectual function. The Mini-Mental State Examination (MMSE) [332] was used as a general cognitive screen. The WTAR and MMSE were only administered once at baseline.

Attention neurocognitive assessments at baseline, end of treatment, and follow-up included the Cocaine Implicit Association Test (Cocaine IAT), Delis–Kaplan Executive Function System (D-KEFS) Trail Making Test (Number Sequencing subtest), and Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Processing Speed Composite (Coding and Symbol

Search). The computerized Cocaine Implicit Association Test (IAT) [333-336] was used to assess attentional bias towards cocaine-related cues. The GNB (Greenwald, Nosek, and Banaji) score for the IAT is approximately similar to an effect size measure (such as Cohen's *d*; full details described elsewhere [335, 336]). Positive values reflected positive valence towards a concept (towards cocaine in this study), and negative values reflected negative valence away from a concept (away from cocaine in this study). For the D-KEFS [337], scaled scores were used for the Trail Making Test Number Sequencing subtest. The WAIS-IV [338] Processing Speed Composite Score was interpreted as an intelligence quotient standard score (mean = 100; standard deviation = 15; lower score means worse performance).

Memory neurocognitive assessments at baseline, end of treatment, and follow-up included the WAIS-IV Working Memory Composite (Digit Span and Arithmetic), Hopkins Verbal Learning Test-Revised (HVLT-R), and Brief Visuospatial Memory Test-Revised (BVMT-R). The WAIS-IV [338] Working Memory Composite Score was interpreted as an intelligence quotient standard score (mean = 100; standard deviation = 15; lower score means worse performance). For the HVLT-R [339, 340] and BVMT-R [341], T-scores (mean = 50; standard deviation = 10; lower score means worse performance) were used for all scores.

Executive function neurocognitive assessments at baseline, end of treatment, and follow-up included the D-KEFS Trail Making Test (Number-Letter Switching subtest) and Wisconsin Card Sorting Test (Computer Version 4) [WCST]. Scaled scores were used for the D-KEFS Trails Number-Letter Switching subtest. T-scores were used for the computerized WCST [342, 343] Total Errors score.

Impulsivity neurocognitive assessments at baseline, end of treatment, and follow-up included the Barratt Impulsiveness Scale (BIS), UPPS-P (urgency, premeditation, perseverance, sensation seeking, positive urgency) Impulsive Behavior Scale, and Iowa Gambling Task (IGT). For the 30-item self-report BIS [344, 345], each item had four answer choices (1 to 4), and the total score was calculated. For the 50-item self-report UPPS-P [346,

347], each item had four answer choices (1 [agree strongly] to 4 [disagree strongly]), and a Sensation seeking score was calculated. For the computerized IGT [348], T-scores were used for all scores.

Quality of life and functional assessments at baseline, end of treatment, and follow-up included the Drug User Quality of Life Scale (DUQOL) and Multiple Errands Test (MET). For the 22-item DUQOL [349, 350], each item had seven answer choices (1 [very dissatisfied] to 7 [very satisfied]). A total score was calculated from the 22 items. Regarding the MET [351-353], a performance efficiency score was calculated (total tasks completed / total locations visited), and a normalized performance efficiency score was calculated (performance efficiency score / 1.625 [the ideal performance efficiency score, based on 13 tasks / 8 locations = 1.625]).

No changes were made to the measures after this pilot trial commenced. Criteria to judge whether to proceed with a future definitive randomized controlled trial included achieving the six feasibility measures specified above. No interim analyses of measures were planned.

Stopping guidelines for the entire study were not considered at study inception. However, all adverse events reported by a participant or observed by research staff would have been individually listed on an Adverse Event Form. Should any serious and/or unexpected adverse events have occurred, procedures were in place to notify (within 24 hours) the IRB, State of California Committee for the Protection of Human Subjects, Quality Improvement Unit at the IRB, the NIDA Project Officer, and the Data Safety Monitoring Board (consisted of three psychiatrists at the SFVAHC who were not affiliated with this study). Relevant data and any available follow-up reports would have been reported to the Project Officer and to NIDA via the Serious Adverse Event Tracking and Reporting System. The entire team would have determined whether the seriousness of the event warranted removal of the participant from the study.

Blinding

Ideally, those who assessed the primary outcomes would be blinded to the study arm. However, since this was a pilot study with limited funding through a career development award and turnover of non-permanent research assistants during the study period, outcomes were assessed by whichever staff was practically available to assess the outcomes at a given study visit; some staff were aware of the study arm assignments. Participants were aware of which intervention they received.

Adherence/Quality Assurance

All participants came to the SFVAHCS OTP outpatient clinic to complete all screening, study, end of treatment, and follow-up visit tasks. Research assistants were trained on all tasks and supervised by the principal investigator; participants' charts were audited periodically for data integrity by the principal investigator and the SFVAHCS research compliance officer. Adherence to the study interventions by study staff was assessed with study session checklists.

Statistical Analysis

All data for each participant were first stored in a dedicated study binder for each participant. Data were then entered into a custom-made Microsoft Access database for this study (Quicksilver Consulting; El Cerrito, California) by research assistants. Data from this Microsoft Access database were then converted to Stata files using Stat/Transfer version 14 for Windows (Circle Systems, Inc.; Seattle, Washington.) All analyses were finally conducted using Stata/SE 16.1 for Windows (5/20/2020 revision; StataCorp, LLC; College Station, Texas).

The distributions of variables were examined and described as appropriate with descriptive statistics (e.g., mean, standard deviation, percentage). Baseline sociodemographics and clinical characteristics of the Cog-Rehab Arm and the Control Arm were compared using t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. These techniques also were used to compare feasibility and acceptability measures between groups. For each measure, an effect size was calculated by subtracting mean change in Cog-

Rehab Arm from mean change in Control Arm and dividing by the pooled standard deviation. Three between-group effect sizes were calculated for each measure: a) end of treatment change from baseline, b) follow-up change from baseline, and c) follow-up change from end of treatment. Effect sizes generally >=0.2 are considered small, >=0.5 are considered medium, and >=0.8 are considered large [354]. A positive sign for an effect size means favoring the Cog-Rehab arm, and a negative sign for an effect size means favoring the Control arm.

RESULTS

Description of Study Participants

Out of 143 telephone calls received (Figure 2.1), eighty-five screening phone calls were completed. Fifty-eight potential callers did not call back, despite research staff returning their phone call. Out of those 85 phone calls, 12 callers declined to participate, 38 callers were initially ineligible over the phone, and 36 callers were scheduled for an in-person screening visit. Four callers did not show up for the first screening visit and were also deemed ineligible, bringing the total ineligible callers to 42. Thirty-two callers were screened in person, one of whom was severely depressed and excluded at the first in-person screening visit. Thirty-one participants were randomized in the study.

Reasons for declining to participate (Figure 2.1) included living too far away, being too busy to participate, and not interested in the study. Reasons for ineligibility (Figure 2.1) included having a high suicide risk flag in the medical record, severe depression, having an active serious medical issue, taking an exclusionary medication, not showing up for the first screening visit, not being a cocaine user, having active legal issues, still using cocaine or another illicit drug, being over the age of 65, and being banned from the clinic for assaultive behavior. Sixteen participants completed the Cog-Rehab arm, and fifteen participants completed the Control arm.

Overall, study participants had a mean age of 57.5 years (SD 5.8), 30 (96.8%) were male, 19 (61.3%) were Black, 12 (38.7%) were White, 6 (19.4%) were Latino, 15 (48.4%) were single, and had a mean education of 12.8 years (SD 1.4). Participants in both groups (Table

2.1) were similar in sex, age, education, race, ethnicity, marital status, retirement status, and handedness. Control arm participants were significantly older when they became regular cocaine users (age 29) than Cog-Rehab arm participants (age 23) [t(29) = -2.2; -11.4 to -0.5; P = 0.03]. Participants in both groups had similar psychiatric diagnoses.

Feasibility and Acceptability Assessments and Urine Toxicology Assessments

Metrics of tracking feasibility included the number of telephone calls received (143 calls), number of telephone screens actually completed (85 screened), number of telephone callers set up for the 1st screening visit (36 callers), number of callers who completed all screening visits in person (31 callers), number of participants randomized (31 participants), number of participants who completed the entire study (31 participants: 16 Cog-Rehab arm, 15 Control arm), and number of total study visits attended (participants in both arms attended all study visits). Participants in the Cog-Rehab arm completed a significantly greater percentage of homework assignments (65.3%) than those in the Control arm (32.7%) [$X^2(2) = 36.2$; $P < 0.0001$].

Acceptability of study procedures was assessed at the end of treatment with the Computer System Usability Questionnaire and the Game Training Questionnaire (Table 2.2). Based on the Computer System Usability Questionnaire, participants in the Cog-Rehab and Control arms had similar ratings [range from 1 (strongly agree) to 7 (strongly disagree)] on the mean overall satisfaction score (1.9 vs. 2.0, $P = 0.90$), mean system usefulness score (2.0 vs. 2.1, $P = 0.84$), mean information quality score (2.0 vs. 2.0, $P = 1.0$), and mean interface quality score (1.9 vs. 2.0, $P = 0.88$). Based on the Game Training Questionnaire, participants in the Cog-Rehab and Control arms had similar ratings for whether they perceived the computer training to be enjoyable (81.3% vs. 60%, Fisher's exact p = 0.19), challenging (56.3% vs. 66.7%, Fisher's exact p = 0.40), frustrated (31.3% vs. 13.3%, Fisher's exact p = 0.20), and motivated (62.5% vs. 60%, Fisher's exact p = 0.06).

There were no significant differences between the number of participants in both arms that relapsed to any substance during the treatment period, end of treatment, and follow-up (Table 2.3).

Neurocognitive Measures and Functional Assessments

Research staff were able to administer all measures to participants. Participants were able to complete a lengthy neurocognitive battery at three timepoints. Overall, study participants had a mean WTAR score of 95.2 (SD 13.7) and a mean MMSE score of 28.1 (SD 1.3). Participants in both groups did not differ significantly on these measures.

For the change from baseline to end of treatment effect sizes (Tables 2.4 and 2.5), most of the between-group effect sizes had 95% confidence intervals that crossed zero. A significant medium effect size was observed for the BVMT-R Total Recall T-score (0.8, favoring the Cog-Rehab arm). While some measures had effect sizes that appeared to favor the Cog-Rehab arm (e.g., Cocaine Implicit Association Test, D-KEFS Trails Number-Letter Switching, Wisconsin Card Sorting Test, UPPS-P Sensation seeking, Barratt Impulsiveness Scale, Drug User Quality of Life Scale, Multiple Errands Test), the 95% confidence intervals crossed zero for these effect sizes.

For the change from end of treatment to follow-up effect sizes (Tables 2.4 and 2.5), most of the between-group effect sizes had 95% confidence intervals that crossed zero. A significant large effect size was observed for the Cocaine Implicit Association Test GNB score (1.0, favoring the Cog-Rehab arm), even though there was no significant between-group effect size from baseline to end of treatment for this measure. A significant medium effect size was observed for the D-KEFS Trails Number Sequencing scaled score (0.7, favoring the Cog-Rehab arm), even though there was no significant between-group effect size from baseline to end of treatment for this measure. While some measures had effect sizes that appeared to favor the Cog-Rehab arm (e.g., WAIS-IV Processing Speed, WAIS-IV Working Memory, HVLT-R,) or the

Control arm (e.g., Barratt Impulsiveness Scale, Multiple Errands Test), the 95% confidence intervals crossed zero for these effect sizes.

Most of the change from baseline to follow-up between-group effect sizes (Tables 2.4 and 2.5) for the between-group effect sizes had 95% confidence intervals that crossed zero. For the between-group effect size for the BVMT-R Total Recall T-score, the effect was maintained from baseline to follow-up (significant large effect size 0.8, favoring the Cog-Rehab arm). A significant large effect size was observed for the Wisconsin Card Sorting Test Total Errors T-score (1.0, favoring the Cog-Rehab arm), even though there were no significant between-group effect sizes from baseline to end of treatment or from end of treatment to follow-up for this measure. A significant medium effect size was observed for the Drug User Quality of Life Scale total score (0.8, favoring the Cog-Rehab arm), even though there were no significant between-group effect sizes from baseline to end of treatment or from end of treatment to follow-up for this measure. While some measures had effect sizes that appeared to favor the Cog-Rehab arm (e.g., HVLT-R, UPPS-P Sensation seeking) or the Control arm (e.g., Cocaine Association Implicit Test, Iowa Gambling Task), the 95% confidence intervals crossed zero for these effect sizes.

DISCUSSION

100% of enrolled study participants completed all study procedures (16 Cog-Rehab arm, 15 Control arm). Regarding feasibility measures: a) we were able to recruit adults with CUD with 3 or months of remission, b) we were able to randomize participants who met strict eligibility criteria, c) participants were able to complete a lengthy neurocognitive battery at three timepoints, d) participants were able to complete the complex interventions in the Cog-Rehab and Control arms, e) not all participants were able to complete eleven homework assignments during the study period, and f) participants were able to complete outcome assessments at three timepoints. Research staff were able to administer all measures to participants.

Though all participants attended all study visits, participants in the Cog-Rehab arm completed a significantly greater percentage of homework assignments than those in the Control arm. At the end of treatment, participants in both arms had similar high (strongly agree) usability and acceptability ratings for study procedures and had similar ratings for how they perceived the computer training (highly enjoyable, moderately challenging, low frustration, moderately motivated).

While we were hoping to see improvements on all neurocognitive measures and functional assessments since the cognitive rehabilitation content targeted all domains, most of the between-group effect sizes for neurocognitive measures and functional assessments had 95% confidence intervals that crossed zero. Some significant between-group effect sizes were found; however, given the sheer number of neurocognitive measures administered and a small study sample size, one explanation for these significant findings is chance.

A significant medium effect size that favored the Cog-Rehab arm was observed for the BVMT-R Total Recall from baseline to the end of treatment, and a significant large effect size that favored the Cog-Rehab arm was observed for the BVMT-R Total Recall from baseline to follow-up. Aside from chance, perhaps the Cog-Rehab intervention had a true effect on a measure of visual memory since visual memory training was a component of the intervention. A significant medium effect size that favored the Cog-Rehab arm was observed for the D-KEFS Trails Number Sequencing from end of treatment to follow-up. Aside from chance, an explanation for this finding is not apparent at this time and will need to be explored in a future definitive RCT.

A significant large effect size that favored the Cog-Rehab arm was observed for the Cocaine Implicit Association Test GNB score from end of treatment to follow-up. The lower the GNB score, the greater the level of attentional bias away from cocaine. Cog-Rehab arm participants decreased in their mean GNB score (attentional bias away from cocaine), and Control arm participants increased in their mean GNB score (attentional bias towards cocaine).

Since Cog-Rehab arm participants were taught skills to help their cognitive impairment (whereas Control arm participants were not taught such skills), perhaps Cog-Rehab arm participants began to realize the deleterious effects of cocaine and started to become biased away from cocaine-related cues. This preliminary explanation will need further exploration in a future definitive RCT.

A significant large effect size that favored the Cog-Rehab arm was observed for the Wisconsin Card Sorting Test Total Errors from baseline to follow-up. A significant medium effect size that favored the Cog-Rehab arm was observed for the Drug User Quality of Life Scale total score from baseline to follow-up. Aside from chance, these significant effect sizes were perhaps related to Control arm participants worsening over time due to not receiving an intervention to target their cognitive impairment. Also, the effect sizes for both of these measures from baseline to end of treatment were in the same direction, even though they were not significant.

Another explanation for some of the significant effect sizes for neurocognitive measures is participants could have "trained to the task" [355]. For example, the computer exercises contain exercises that are similar to the Wisconsin Card Sorting Test. Visual exercises are integrated into the therapist training, and thus may explain the significant results on the BVMT-R. The future definitive RCT must be careful to not include outcome measures that are too similar to the cognitive training being delivered to participants.

Though the intervention was complex and there were many assessments, participants completed all assessments. In this study, participants were assessed comprehensively with various assessments – feasibility, acceptability, psychiatric, clinical, neurocognitive, quality of life, function – which we felt was important to understand participants fully, rather than focus only on one or two aspects of their lives. Even though some measures showed medium to large effect sizes that favored the Cog-Rehab participants, most quality of life and functional assessments showed similarity in both groups across timepoints. Only using neurocognitive measures in this study would have given an impression that participants' cognition meaningfully

improved. Other than the one significant medium effect size that favored the Cog-Rehab arm for the Drug User Quality of Life Scale (which could have been due to chance), having complementary quality of life and functional assessments showed that improvements on neurocognitive measures didn't necessarily transfer into real-world functional improvements.

This difficulty in transfer to real-world functional improvements has also been observed in other populations, such as persons with traumatic brain injury [356, 357], schizophrenia [358], and older adults [359]. Techniques that are being used concurrently with cognitive training in these other populations to help with transfer to functional improvements include vocational rehabilitation, self-awareness training, virtual reality training, videoconferencing, and social skills training. Adding such techniques to cognitive training for persons with substance use disorder can be explored in a future definitive RCT.

Strengths

First, we collected a comprehensive set of psychiatric, substance use, and neurocognitive measures in order to demonstrate proof-of-concept of the study intervention and to gather preliminary data of the study intervention's impact on different domains associated with CUD. Second, we conducted this study at a veteran's hospital in patients with complex comorbidities in an effort to maximize internal validity for this little-studied population.

Third, the interventions in this study were relatively low technology to implement by research staff with a college degree. The interventions were feasible and acceptable to participants, as participants attended study visits and none dropped out. Finally, quality of life and functional assessments helped complement the neurocognitive assessments in assessing the overall impact of the intervention.

Limitations

This study had several limitations. First, though the interventions were low technology, the interventions were still labor-intensive and required a substantial amount of training before delivery to participants. Such a labor-intensive approach may not be easily scalable in a

community addiction treatment setting. If this intervention proved to be efficacious in a future definitive RCT, it would likely need to be effective on a larger scale. Second, though participants completed all of their study visits, this was likely due to being paid in cash for each study visit. Adherence may not be as high for patients in an outpatient clinical setting without such external cash incentives.

Third, this study combined cognitive-adaptation techniques and cognitive-remediation techniques in the Cog-Rehab arm and did not determine which techniques were better or worse. Each set of techniques had its own contribution, and the study used a comprehensive approach to treat cognitive impairment. This study could not determine which active ingredient would impact outcomes, though we were not planning on testing for efficacy in this study; the active ingredient can be teased out in a future definitive RCT. Fourth, study staff were aware of the randomization sequence, and those who assessed the primary outcomes were not necessarily blinded to the study arm. Non-blinding could have biased how some study staff assessed participants. These limitations can be addressed in a future definitive RCT.

Fifth, because this study recruited individuals with at least mild cognitive impairment, the results from this study may not generalize to those with no cognitive impairment or cognitive impairment not detected by classical neurocognitive measures (e.g., social cognition [360, 361], compulsivity [362]). Sixth, the homework assignments in the Control arm were either likely difficult to complete or not engaging enough to complete. The content of the homework assignments would need to be revisited before conducting a future definitive RCT. Finally, study participants were required to be in at least 3 months of remission from their CUD diagnosis. Because this study recruited relatively stable participants from a substance use perspective, the results from this study may not generalize to those who are actively using cocaine or are trying to stop using cocaine.

CONCLUSIONS

CUD remains a significant public health problem in the U.S., and effectively treating cognitive impairment as part of a comprehensive treatment plan for CUD could potentially improve important clinical outcomes. The first of three papers described the protocol for a pilot randomized controlled trial of OT-based cognitive rehabilitation for CUD. Integrating OT-based cognitive rehabilitation in a comprehensive treatment plan for CUD could have a direct and significant positive impact on the public health burden of this population.

This second paper shows the feasibility, acceptability, and preliminary effect sizes of an OT-based intervention to improve cognitive function in patients with CUD. Participants in both arms had similar high usability and acceptability ratings for study procedures and had similar ratings for how they perceived the computer training. Participants in the Cog-Rehab arm completed a significantly greater percentage of homework assignments than those in the Control arm. At follow-up, there were no significant differences between groups in relapse to any substance. Most of the between-group effect sizes for neurocognitive measures and functional assessments had 95% confidence intervals that crossed zero. Some significant between-group effect sizes were found for certain neurocognitive measures (attentional bias, attention, visual memory, executive function) and one functional assessment (Drug User Quality of Life Scare).

Based on this pilot trial's feasibility, acceptability, and preliminary effect sizes, we believe a definitive RCT is warranted. Key elements of this definitive RCT include having adequate sample size and power to test the efficacy of the interventions, selecting a priori primary and secondary outcomes, refining the content of the Control arm homework assignments to improve homework completion percentage, decreasing the number of assessments to limit participant burden (e.g., limiting neurocognitive assessments to 1 hour, removing neurocognitive assessments that are too similar to the computer exercises), decreasing the number of hours of computer exercises to limit participant burden, blinding research staff who assess outcomes,

concealing the randomization sequence from research staff, using other contingency management techniques for motivation instead of cash, selecting a more standardized control intervention, and implementing interim analyses and stopping rules. The third and final paper will be a secondary analysis of the Multiple Errands Test as associated with the neurocognitive assessments.

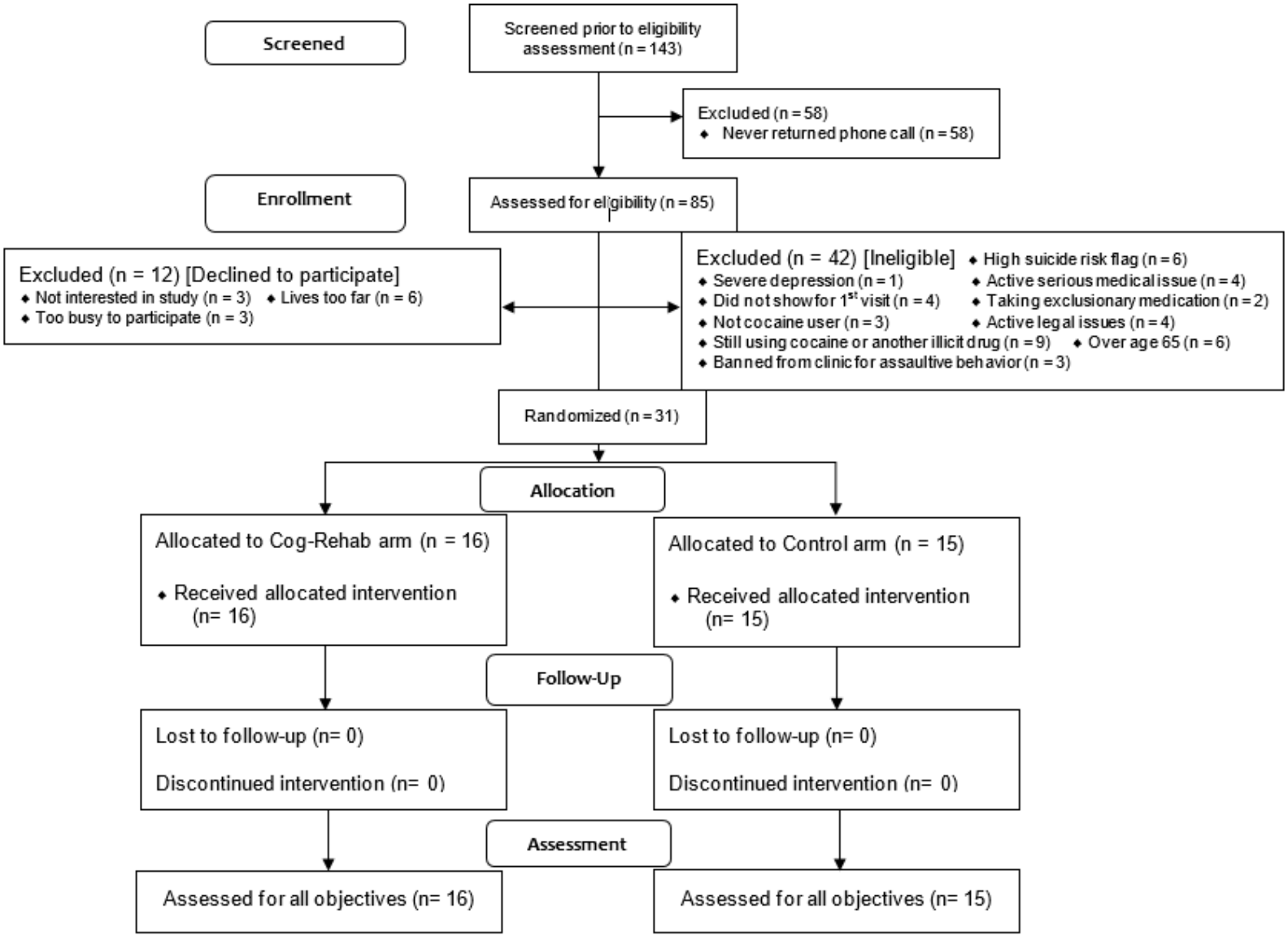


Figure 2.1. Participant CONSORT Flow Diagram.

Table 2.1. Baseline Sociodemographics and Clinical Characteristics.

*Mean (Standard Deviation) ^n (%)

Measure	*Cog-Rehab Arm (n = 16)*	*Control Arm (n = 15)*
Age in years*	57.2 (3.9)	57.9 (7.4)
Male^	16 (100%)	14 (93.3%)
Black^	8 (50%)	11 (73.3%)
White^	8 (50%)	4 (26.7%)
American Indian/Alaska Native^	5 (31.3%)	2 (13.3%)
Latino^	4 (25%)	2 (13.3%)
Single/Never Married^	7 (43.8%)	8 (53.3%)
Divorced^	7 (43.8%)	6 (40%)
Education in years*	12.6 (1.3)	13.1 (1.4)
Retired/Disability over past 3 years^	13 (81.3%)	13 (86.7%)
Right-handed^	12 (75%)	14 (93.3%)
Cocaine – age in years when first tried*	19.9 (6.1)	24.7 (9.9)
Cocaine – age in years of regular use* (started using 3x/week or more)	22.9 (5.5)	28.9 (9.0)
Cocaine – net years used* (total years used minus abstinence)	21.9 (9.2)	21.8 (10.0)
MINI (Mini-International Neuropsychiatric Interview) depressive disorder current diagnosis^	2 (12.5%)	2 (13.3%)
MINI depressive disorder past diagnosis^	12 (75%)	6 (40%)
MINI depressive disorder recurrent diagnosis^	9 (56.3%)	6 (40%)
MINI PTSD (Posttraumatic Stress Disorder) current diagnosis^	6 (37.5%)	7 (46.7%)
MINI alcohol use disorder past 12 months diagnosis^	6 (37.5%)	2 (13.3%)
MINI cannabis use disorder past 12 months diagnosis^	5 (31.3%)	2 (13.3%)
MINI opioid use disorder past 12 months diagnosis^	6 (37.5%)	5 (33.3%)
Prescribed methadone as part of opioid treatment program^	5 (31.3%)	7 (46.7%)

Table 2.2. Acceptability Assessments at End of Treatment.

CSUQ = Computer System Usability Questionnaire GTQ = Game Training Questionnaire

*Mean (Standard Deviation) ^n (%)

For statistical analyses for each measure between groups, the point estimate, the confidence interval, and the *P*-value are listed.

	End of Treatment	
Measure	*Cog-Rehab Arm (n = 16)*	*Control Arm (n = 15)*
CSUQ – overall satisfaction score*	1.9 (1.3)	2.0 (1.5)
	t(29) = -0.1; -1.1 to 1.0; *P* = 0.90	
CSUQ system usefulness score*	2.0 (1.3)	2.1 (1.5)
	t(29) = -0.2; -1.1 to 0.9; *P* = 0.84	
CSUQ information quality score*	2.0 (1.3)	2.0 (1.6)
	t(29) = 0.01; -1.1 to 1.1; *P* = 1.0	
CSUQ interface quality score*	1.9 (1.4)	2.0 (1.7)
	t(29) = -0.2; -1.2 to 1.0; *P* = 0.88	
GTQ #2 – Question #1 (enjoyable)^	13 (81.3%) agree	9 (60%) agree
	Fisher's exact p = 0.19	
GTQ #2 – Question #2 (challenging)^	9 (56.3%) agree	10 (66.7%) agree
	Fisher's exact p = 0.40	
GTQ #2 – Question #3 (frustrated)^	5 (31.3%) agree	2 (13.3%) agree
	Fisher's exact p = 0.20	
GTQ #2 – Question #4 (motivated)^	10 (62.5%) agree	9 (60%) agree
	Fisher's exact p = 0.06	

Table 2.3. Urine Toxicology Assessments at Baseline, During Treatment Period, End of Treatment, and Follow-up.

^n (%)

For statistical analyses for each measure between groups at each timepoint, the point estimate, the confidence interval, and the *P*-value are listed.

	Baseline		During Treatment Period		End of Treatment		Follow-up	
Measure	*Cog-Rehab Arm (n = 16)*	*Control Arm (n = 15)*	*Cog-Rehab Arm (n = 16)*	*Control Arm (n = 15)*	*Cog-Rehab Arm (n = 16)*	*Control Arm (n = 15)*	*Cog-Rehab Arm (n = 16)*	*Control Arm (n = 15)*
# of participants positive for cocaine^	0	0	1 (6.3%)	4 (26.7%)	1 (6.3%)	2 (13.3%)	1 (6.3%)	2 (13.3%)
			Fisher's exact p = 0.17		Fisher's exact p = 0.60		Fisher's exact p = 0.60	
# of participants positive for marijuana^	5 (31.3%)	3 (20%)	7 (43.8%)	5 (33.3%)	4 (25%)	2 (13.3%)	3 (18.8%)	4 (26.7%)
	Fisher's exact p = 0.69		Fisher's exact p = 0.72		Fisher's exact p = 0.65		Fisher's exact p = 0.69	
# of participants positive for opiates^	3 (18.8%)	1 (6.7%)	4 (25%)	7 (46.7%)	3 (18.8%)	3 (20%)	2 (12.5%)	6 (40%)
	Fisher's exact p = 0.60		Fisher's exact p = 0.27		Fisher's exact p = 1.0		Fisher's exact p = 0.11	
# of participants positive for methamphetamines^	1 (6.3%)	0	1 (6.3%)	2 (13.3%)	1 (6.3%)	0	1 (6.3%)	0
	Fisher's exact p = 1.0		Fisher's exact p = 0.60		Fisher's exact p = 1.0		Fisher's exact p = 1.0	
# of participants positive for amphetamines^	1 (6.3%)	0	3 (18.8%)	2 (13.3%)	1 (6.3%)	0	1 (6.3%)	0
	Fisher's exact p = 1.0		Fisher's exact p = 1.0		Fisher's exact p = 1.0		Fisher's exact p = 1.0	
# of participants positive for phencyclidine^	0	0	0	1 (6.7%)	0	0	0	0
			Fisher's exact p = 0.48					
# of participants positive for benzodiazepines^	0	0	1 (6.3%)	2 (13.3%)	0	0	0	0
			Fisher's exact p = 0.60					
# of participants positive for barbiturates^	0	0	0	1 (6.7%)	0	0	0	0
			Fisher's exact p = 0.48					
# of participants positive for any substance^	5	3	7	7	4	3	3	6
	Fisher's exact p = 0.69		Fisher's exact p = 1.0		Fisher's exact p = 1.0		Fisher's exact p = 0.25	

Table 2.4. Between-Group Effect Sizes for Attention and Memory Neurocognitive Measures.

Effect size calculated by subtracting mean change in Cog-Rehab Arm from mean change in Control Arm and dividing by the pooled baseline standard deviation.
For calculating the "Follow-Up Change from End of Treatment" effect size, the pooled end of treatment standard deviation was used.
A positive sign for an effect size means favoring the Cog-Rehab arm, and a negative sign for an effect size means favoring the Control arm.
GNB = Greenwald, Nosek, and Banaji D-KEFS = Delis–Kaplan Executive Function System WAIS-IV = Wechsler Adult Intelligence Scale Fourth Edition
HVLT-R = Hopkins Verbal Learning Test-Revised BVMT-R = Brief Visuospatial Memory Test-Revised

Neurocognitive Domain	Measure	Timepoint	Cog-Rehab Arm (*n* = 16) Mean (standard deviation)	Control Arm (*n* = 15) Mean (standard deviation)	Between-Group Effect Size (95% confidence interval)
Attention	Cocaine Implicit Association Test – GNB Score	Baseline	-0.1 (0.4)	-0.2 (0.4)	
		Change from Baseline to End of Treatment	0.1 (0.5)	-0.1 (0.6)	-0.5 (-1.2 to 0.2)
		Change from Baseline to Follow-Up	-0.1 (0.3)	0.2 (0.4)	0.6 (-0.1 to 1.3)
		Change from End of Treatment to Follow-Up	-0.2 (0.6)	0.3 (0.4)	1.0 (0.2 to 1.7)
	D-KEFS Trails Number Sequencing – Scaled score	Baseline	8.8 (2.9)	9.3 (2.8)	
		Change from Baseline to End of Treatment	0.9 (3.3)	1.7 (2.3)	-0.3 (-1.0 to 0.5)
		Change from Baseline to Follow-Up	1.6 (3.4)	1.4 (1.8)	0.1 (-0.6 to 0.8)
		Change from End of Treatment to Follow-Up	0.7 (0.8)	-0.3 (1.7)	0.7 (0.003 to 1.5)
	WAIS-IV Processing Speed Composite	Baseline	88.4 (8.9)	83.9 (22.6)	
		Change from Baseline to End of Treatment	2.9 (4.9)	5.9 (21.9)	-0.2 (-0.9 to 0.5)
		Change from Baseline to Follow-Up	4.4 (5.6)	5.1 (19.8)	-0.1 (-0.8 to 0.7)
		Change from End of Treatment to Follow-Up	1.4 (5.5)	-0.9 (9.1)	0.3 (-0.4 to 1.0)
Memory	WAIS-IV Working Memory Composite	Baseline	85.7 (9.4)	81.4 (20.8)	
		Change from Baseline to End of Treatment	5.8 (5.3)	5.9 (17.3)	-0.004 (-0.7 to 0.7)
		Change from Baseline to Follow-Up	8.3 (8.2)	6.6 (20.4)	0.1 (-0.6 to 0.8)
		Change from End of Treatment to Follow-Up	2.4 (5.3)	0.7 (5.4)	0.3 (-0.4 to 1.0)
	HVLT-R Total Recall T-score	Baseline	27.8 (8.9)	26.1 (8.3)	
		Change from Baseline to End of Treatment	4.9 (8.8)	3.4 (9.8)	0.2 (-0.5 to 0.9)
		Change from Baseline to Follow-Up	8.1 (7.4)	2.7 (7.7)	0.7 (-0.02 to 1.4)
		Change from End of Treatment to Follow-Up	3.1 (7.5)	-0.7 (7.9)	0.5 (-0.2 to 1.2)
	BVMT-R Total Recall T-score	Baseline	32.1 (6.6)	29.7 (8.6)	
		Change from Baseline to End of Treatment	6.2 (8.2)	0.3 (7.7)	0.8 (0.01 to 1.5)
		Change from Baseline to Follow-Up	6.4 (7.7)	1.1 (5.1)	0.8 (0.1 to 1.5)
		Change from End of Treatment to Follow-Up	0.2 (5.8)	0.8 (8.8)	-0.1 (-0.8 to 0.6)

Table 2.5. Between-Group Effect Sizes for Executive Function & Impulsivity Neurocognitive Measures and Functional Assessments.

Effect size calculated by subtracting mean change in Cog-Rehab Arm from mean change in Control Arm and dividing by the pooled baseline standard deviation.
For calculating the "Follow-Up Change from End of Treatment" effect size, the pooled end of treatment standard deviation was used.
A positive sign for an effect size means favoring the Cog-Rehab arm, and a negative sign for an effect size means favoring the Control arm.
D-KEFS = Delis–Kaplan Executive Function System UPPS-P = urgency, premeditation, perseverance, sensation seeking, positive urgency

Neurocognitive Domain	Measure	Timepoint	Cog-Rehab Arm (*n* = 16) Mean (standard deviation)	Control Arm (*n* = 15) Mean (standard deviation)	Between-Group Effect Size (95% confidence interval)
Executive Function	D-KEFS Trails Number-Letter Switching – Scaled score	Baseline	7.6 (3.9)	8.6 (3.5)	
		Change from Baseline to End of Treatment	0.9 (2.7)	-0.1 (3.2)	0.4 (-0.4 to 1.1)
		Change from Baseline to Follow-Up	1.9 (2.5)	1.4 (1.9)	0.2 (-0.5 to 0.9)
		Change from End of Treatment to Follow-Up	0.9 (2.9)	1.5 (3.3)	-0.2 (-0.9 to 0.5)
	Wisconsin Card Sorting Test – Total Errors T-score	Baseline	34.1 (8.3)	40.6 (16.6)	
		Change from Baseline to End of Treatment	8.1 (18.4)	-5.4 (19.5)	0.7 (-0.02 to 1.4)
		Change from Baseline to Follow-Up	13.8 (20.0)	-6.3 (20.3)	1.0 (0.2 to 1.7)
		Change from End of Treatment to Follow-Up	5.8 (19.9)	-0.9 (7.4)	0.5 (-0.3 to 1.2)
Impulsivity	UPPS-P Sensation seeking	Baseline	2.8 (0.5)	2.5 (0.6)	
		Change from Baseline to End of Treatment	1.89e-0.09 (0.2)	-0.1 (0.6)	0.3 (-0.4 to 1.0)
		Change from Baseline to Follow-Up	-0.1 (0.3)	-0.2 (0.7)	0.3 (-0.4 to 1.0)
		Change from End of Treatment to Follow-Up	-0.1 (0.2)	-0.1 (0.2)	0.2 (-0.5 to 0.9)
	Barratt Impulsiveness Scale – Total Score	Baseline	72.4 (12.6)	73.3 (13.5)	
		Change from Baseline to End of Treatment	-1.5 (5.6)	-4.1 (7.3)	0.4 (-0.3 to 1.1)
		Change from Baseline to Follow-Up	-2.9 (7.8)	-3.6 (8.4)	0.1 (-0.6 to 0.8)
		Change from End of Treatment to Follow-Up	-1.4 (4.5)	0.5 (5.1)	-0.4 (-1.1 to 0.3)
	Iowa Gambling Task – Net Total T-score	Baseline	52.1 (12.1)	45.9 (7)	
		Change from Baseline to End of Treatment	-0.6 (18.0)	3.3 (7.4)	-0.3 (-1.0 to 0.4)
		Change from Baseline to Follow-Up	-3.6 (14.2)	1.5 (9.7)	-0.4 (-1.1 to 0.3)
		Change from End of Treatment to Follow-Up	-3.1 (14.9)	-1.7 (8.8)	-0.1 (-0.8 to 0.6)
	Drug User Quality of Life Scale – Total score	Baseline	4.3 (0.8)	5.1 (0.9)	
		Change from Baseline to End of Treatment	0.4 (0.5)	0.1 (0.8)	0.5 (-0.3 to 1.2)
		Change from Baseline to Follow-Up	0.4 (0.3)	-0.2 (1.0)	0.8 (0.02 to 1.5)
		Change from End of Treatment to Follow-Up	0.03 (0.4)	-0.2 (0.9)	0.4 (-0.3 to 1.1)
	Multiple Errands Test – normalized performance efficiency score	Baseline	0.5 (0.2)	0.4 (0.1)	
		Change from Baseline to End of Treatment	0.2 (0.3)	0.1 (0.2)	0.4 (-0.3 to 1.1)
		Change from Baseline to Follow-Up	0.1 (0.3)	0.2 (0.3)	-0.3 (-1.0 to 0.4)
		Change from End of Treatment to Follow-Up	-0.01 (0.3)	0.2 (0.3)	-0.6 (-1.3 to 0.1)

Chapter 2 References

282. NIDA. *Cocaine: Abuse and Addiction*. Research Report Series 2009 9/10/2014]; Available from: http://www.drugabuse.gov/sites/default/files/cocainerrs.pdf.

283. NIDA. *What is the scope of cocaine use in the United States?* . 2016; Available from: https://www.drugabuse.gov/publications/research-reports/cocaine/what-scope-cocaine-use-in-united-states.

284. Hanlon, C.A., L.T. Dowdle, and J.L. Jones, *Biomarkers for Success: Using Neuroimaging to Predict Relapse and Develop Brain Stimulation Treatments for Cocaine-Dependent Individuals.* Int Rev Neurobiol, 2016. 129: p. 125-56.

285. Roncero, C., et al., *Cocaine relapse and health-related quality of life: a 23 weeks study.* Actas Esp Psiquiatr, 2019. 47(2): p. 37-44.

286. Sinha, R., *New findings on biological factors predicting addiction relapse vulnerability.* Curr Psychiatry Rep, 2011. 13(5): p. 398-405.

287. Teichner, G., M.D. Horner, and R.T. Harvey, *Neuropsychological predictors of the attainment of treatment objectives in substance abuse patients.* Int J Neurosci, 2001. 106(3-4): p. 253-63.

288. Teichner, G., et al., *Substance abuse treatment outcomes for cognitively impaired and intact outpatients.* Addict Behav, 2002. 27(5): p. 751-63.

289. Vik, P.W., et al., *Cognitive impairment in substance abuse.* Psychiatr Clin North Am, 2004. 27(1): p. 97-109, ix.

290. Rolland, B., et al., *A Patient-Tailored Evidence-Based Approach for Developing Early Neuropsychological Training Programs in Addiction Settings.* Neuropsychol Rev, 2019. 29(1): p. 103-115.

291. Butler, K. and B. Le Foll, *Impact of Substance Use Disorder Pharmacotherapy on Executive Function: A Narrative Review.* Front Psychiatry, 2019. 10: p. 98.

292. Parsons, O.A., K.W. Schaeffer, and S.W. Glenn, *Does neuropsychological test performance predict resumption of drinking in posttreatment alcoholics?* Addict Behav, 1990. 15(3): p. 297-307.

293. Gregson, R.A. and G.M. Taylor, *Prediction of relapse in men alcoholics.* J Stud Alcohol, 1977. 38(9): p. 1749-60.

294. Fals-Stewart, W. and J. Schafer, *The relationship between length of stay in drug-free therapeutic communities and neurocognitive functioning.* J Clin Psychol, 1992. 48(4): p. 539-43.

295. Bates, M.E., et al., *Cognitive impairment influences drinking outcome by altering therapeutic mechanisms of change.* Psychol Addict Behav, 2006. 20(3): p. 241-53.

296. Aharonovich, E., E. Nunes, and D. Hasin, *Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment.* Drug Alcohol Depend, 2003. 71(2): p. 207-11.

297. Aharonovich, E., et al., *Cognitive deficits predict low treatment retention in cocaine dependent patients.* Drug Alcohol Depend, 2006. 81(3): p. 313-22.

298. Fox, H.C., E.D. Jackson, and R. Sinha, *Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes.* Psychoneuroendocrinology, 2009. 34(8): p. 1198-207.

299. Katz, E.C., et al., *Cognitive ability as a factor in engagement in drug abuse treatment.* Am J Drug Alcohol Abuse, 2005. 31(3): p. 359-69.

300. Hudetz, J.A., et al., *Postoperative cognitive dysfunction in older patients with a history of alcohol abuse.* Anesthesiology, 2007. 106(3): p. 423-30.

301. Goldstein, R.Z., et al., *Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex.* Neuropsychologia, 2004. 42(11): p. 1447-58.

302. Fals-Stewart, W. and W.K. Lam, *Computer-assisted cognitive rehabilitation for the treatment of patients with substance use disorders: a randomized clinical trial.* Exp Clin Psychopharmacol, 2010. 18(1): p. 87-98.

303. Bickel, W.K., et al., *Remember the future: working memory training decreases delay discounting among stimulant addicts.* Biol Psychiatry, 2011. 69(3): p. 260-5.

304. Schulte, M.H.J., et al., *The effect of N-acetylcysteine and working memory training on neural mechanisms of working memory and cue reactivity in regular cocaine users.* Psychiatry Res Neuroimaging, 2019. 287: p. 56-59.

305. Wanmaker, S., et al., *The efficacy of a working memory training in substance use patients: A randomized double-blind placebo-controlled clinical trial.* J Clin Exp Neuropsychol, 2018. 40(5): p. 473-486.

306. Levine, B., et al., *Rehabilitation of executive functioning: an experimental-clinical validation of goal management training.* J Int Neuropsychol Soc, 2000. 6(3): p. 299-312.

307. Shum, D., et al., *A randomized controlled trial of prospective memory rehabilitation in adults with traumatic brain injury.* J Rehabil Med, 2011. 43(3): p. 216-23.

308. Twamley, E.W., et al., *Development and Pilot Testing of a Novel Compensatory Cognitive Training Intervention for People with Psychosis.* Am J Psychiatr Rehabil, 2008. 11(2): p. 144-163.

309. Stringer, A.Y., *Ecologically-oriented neurorehabilitation of memory: robustness of outcome across diagnosis and severity.* Brain Inj, 2011. 25(2): p. 169-78.

310. Toglia, J., et al., *A multicontext approach to promoting transfer of strategy use and self regulation after brain injury: An exploratory study.* Brain Inj, 2010. 24(4): p. 664-77.

311. Solanto, M.V., et al., *Development of a new psychosocial treatment for adult ADHD.* J Atten Disord, 2008. 11(6): p. 728-36.

312. Londos, E., et al., *Effects of a goal-oriented rehabilitation program in mild cognitive impairment: a pilot study.* Am J Alzheimers Dis Other Demen, 2008. 23(2): p. 177-83.

313. Velligan, D.I., et al., *Randomized controlled trial of the use of compensatory strategies to enhance adaptive functioning in outpatients with schizophrenia.* Am J Psychiatry, 2000. 157(8): p. 1317-23.

314. Milders, M., B. Deelman, and I. Berg, *Rehabilitation of memory for people's names.* Memory, 1998. 6(1): p. 21-36.

315. Ho, M.R. and T.L. Bennett, *Efficacy of neuropsychological rehabilitation for mild-moderate traumatic brain injury.* Arch Clin Neuropsychol, 1997. 12(1): p. 1-11.

316. Twamley, E.W., C.Z. Burton, and L. Vella, *Compensatory cognitive training for psychosis: who benefits? Who stays in treatment?* Schizophr Bull, 2011. 37 Suppl 2: p. S55-62.

317. Gutman, S.A., *Why Addiction has a Chronic, Relapsing Course. The Neurobiology of Addiction: Implications for Occupational Therapy Practice.* Occupational Therapy in Mental Health, 2006. 22(2): p. 1-29.

318. Eldridge, S.M., et al., *CONSORT 2010 statement: extension to randomised pilot and feasibility trials.* Bmj, 2016. 355: p. i5239.

319. *Research Randomizer*. 2019 06/30/2019]; Available from: https://www.randomizer.org/.

320. NPO. *Neuropsychonline*. 2011; Available from: https://www.neuropsychonline.com/.

321. Twamley, E.W., *Cognitive Training Individual Manual*. 2006, University of California, San Diego.

322. *Typing Master*. 2019; Available from: http://www.typingmaster.com/typing-tutor/free-download.html.

323. Gillen, G., *Cognitive and Perceptual Rehabilitation: Optimizing Function*. 2009: Mosby Elsevier.

324. Burke, J.M., et al., *A process approach to memory book training for neurological patients.* Brain Inj, 1994. 8(1): p. 71-81.

325. Boman, I.L., et al., *Cognitive training in home environment.* Brain Inj, 2004. 18(10): p. 985-95.

326. Trombly, C.A., et al., *Occupational therapy and achievement of self-identified goals by adults with acquired brain injury: phase II.* Am J Occup Ther, 2002. 56(5): p. 489-98.

327. van Heugten, C.M., R.W. Ponds, and R.P. Kessels, *Brain training: hype or hope?* Neuropsychol Rehabil, 2016. 26(5-6): p. 639-44.

328. Lewis, J.R., *IBM computer usability satisfaction questionnaires: Psychometric evaluation and instructions for use.* International Journal of Human-Computer Interaction, 1995. 7(1): p. 57-78.

329. Boot, W.R., et al., *Video games as a means to reduce age-related cognitive decline: attitudes, compliance, and effectiveness.* Front Psychol, 2013. 4: p. 31.

330. Sheehan, D.V., et al., *The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.* J Clin Psychiatry, 1998. 59 Suppl 20: p. 22-33;quiz 34-57.

331. Wechsler, D.A., *Wechsler Test of Adult Reading*. 2001, San Antonio, TX: The Psychological Corporation.

332. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res, 1975. 12(3): p. 189-98.

333. Meade, A.W., *FreeIAT: An Open-Source Program to Administer the Implicit Association Test.* Applied Psychological Measurement, 2009. 33(8): p. 643.

334. Wiers, R.W., K. Houben, and J. de Kraker, *Implicit cocaine associations in active cocaine users and controls.* Addict Behav, 2007. 32(6): p. 1284-9.

335. Greenwald, A.G., B.A. Nosek, and M.R. Banaji, *Understanding and using the implicit association test: I. An improved scoring algorithm.* J Pers Soc Psychol, 2003. 85(2): p. 197-216.

336. Meade, A.W. *FreeIAT Home*. 2019; Available from: https://meade.wordpress.ncsu.edu/freeiat-home/.

337. Delis, D.C., E. Kaplan, and J.H. Kramer, *The Delis-Kaplan Executive Function System*. 2001, San Antonio, TX: The Psychological Corporation.

338. Wechsler, D.A., *Wechsler Adult Intelligence Scale - Fourth Edition*. 2008, San Antonio, TX: Pearson Assessment.

339. Brandt, J., *The hopkins verbal learning test: Development of a new memory test with six equivalent forms.* Clinical Neuropsychologist, 1991. 5(2): p. 125-142.

340. Benedict, R.H.B., et al., *Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability.* The Clinical Neuropsychologist, 1998. 12(1): p. 43-55.

341. Benedict, H.R.B., *Brief Visuospatial Memory Test - Revised*. 1997, Odessa, FL: Psychological Assessment Resources, Inc.

342. Heaton, R.K., et al., *Wisconsin Card Sorting Test Manual, Revised and Expanded.* 1993, Orlando, FL: Psychological Assessment Resources.

343. Fortuny, L.A. and R.K. Heaton, *Standard versus computerized administration of the wisconsin card sorting test.* The Clinical Neuropsychologist, 1996. 10(4): p. 419-424.

344. Patton, J.H., M.S. Stanford, and E.S. Barratt, *Factor structure of the Barratt impulsiveness scale.* J Clin Psychol, 1995. 51(6): p. 768-74.

345. Stanford, M.S., et al., *Fifty years of the Barratt Impulsiveness Scale: An update and review.* Personality and Individual Differences, 2009. 47(5): p. 385-395.

346. Whiteside, S.P. and D.R. Lynam, *The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity.* Personality and Individual Differences, 2001. 30(4): p. 669-689.

347. Whiteside, S.P., et al., *Validation of the UPPS impulsive behaviour scale: a four-factor model of impulsivity.* European Journal of Personality, 2005. 19(7): p. 559-574.

348. Bechara, A., et al., *Insensitivity to future consequences following damage to human prefrontal cortex.* Cognition, 1994. 50(1-3): p. 7-15.

349. Hubley, A.M., L.B. Russell, and A. Palepu, *Injection Drug Use Quality of Life scale (IDUQOL): a validation study.* Health Qual Life Outcomes, 2005. 3: p. 43.

350. Hubley, A.M. and A. Palepu, *Injection Drug User Quality of Life Scale (IDUQOL): findings from a content validation study.* Health Qual Life Outcomes, 2007. 5: p. 46.

351. Alderman, N., et al., *Ecological validity of a simplified version of the multiple errands shopping test.* J Int Neuropsychol Soc, 2003. 9(1): p. 31-44.

352. Dawson, D.R., et al., *Further development of the Multiple Errands Test: standardized scoring, reliability, and ecological validity for the Baycrest version.* Arch Phys Med Rehabil, 2009. 90(11 Suppl): p. S41-51.

353. Shallice, T. and P.W. Burgess, *Deficits in strategy application following frontal lobe damage in man.* Brain, 1991. 114 (Pt 2): p. 727-41.

354. Cohen, J., *Statistical power analysis for the behavioral sciences*. 1988, Hillsdale, N.J.: L. Erlbaum Associates.

355. Keefe, R.S., et al., *Report From the Working Group Conference on Multisite Trial Design for Cognitive Remediation in Schizophrenia.* Schizophr Bull, 2010.

356. Messinis, L., et al., *Cognitive Neurorehabilitation in Acquired Neurological Brain Injury.* Behav Neurol, 2019. 2019: p. 8241951.

357. Stephens, J.A., K.N. Williamson, and M.E. Berryhill, *Cognitive Rehabilitation After Traumatic Brain Injury: A Reference for Occupational Therapists.* OTJR (Thorofare N J), 2015. 35(1): p. 5-22.

358. Bowie, C.R., *Cognitive remediation for severe mental illness: state of the field and future directions.* World Psychiatry, 2019. 18(3): p. 274-275.

359. Ball, K., et al., *Effects of cognitive training interventions with older adults: a randomized controlled trial.* JAMA, 2002. 288(18): p. 2271-81.

360. Bora, E. and N. Zorlu, *Social cognition in alcohol use disorder: a meta-analysis.* Addiction, 2017. 112(1): p. 40-48.

361. Yacubian, J. and C. Buchel, *The genetic basis of individual differences in reward processing and the link to addictive behavior and social cognition.* Neuroscience, 2009. 164(1): p. 55-71.

362. Lee, R.S.C., S. Hoppenbrouwers, and I. Franken, *A Systematic Meta-Review of Impulsivity and Compulsivity in Addictive Behaviors.* Neuropsychol Rev, 2019. 29(1): p. 14-26.

Chapter 3 Abstract

Background: The Multiple Errands Test (MET) is an interviewer-administered measure used to assess real-world cognitive functional performance based on completing a series of tasks outside of the traditional office setting. Tasks include purchasing an item, writing the names of items, and finding the price of items. These tasks are to be completed under a set of rules, such as spending as little money as possible and doing the tasks in any order. The MET has undergone various revisions since it was originally created. The MET version used in this study, the MET-Revised (MET-R), uses more objective scoring metrics by raters than the traditional MET. Whereas the MET includes metrics such as “inefficiencies”, “strategies”, and “interpretation failures” that are more open to subjective impressions when scored by raters, the MET-R instead has scoring metrics such as “number of locations visited”, “number of tasks completed”, and “number of rule breaks” that are more objective when scored by raters. The MET has been used in substance use disorder population and has been found to have small associations with the executive function domain when compared with traditional neurocognitive measures. It is unclear whether the difference in scoring metrics between the MET and the MET-R means that the various revisions of the MET are assessing different cognitive domains. Understanding on what cognitive domains the MET-R maps may be helpful in using the MET-R as a more time-efficient way to assess cognition in substance use disorder populations, compared to a lengthy neurocognitive battery.

Aim: The aim of this study was to assess whether performance on the MET-R by adult veterans with a primary cocaine use disorder is associated with domains of attention, memory, executive function, and impulsivity on a comprehensive neurocognitive battery. Similar to the MET, we hypothesized that MET-R performance would be more strongly correlated with the domain of executive function than the domains of attention, memory, or impulsivity.

Methods: This paper is a secondary analysis of data from a pilot clinical trial (n = 31), where the MET-R was administered along with a comprehensive neurocognitive battery. The measures

from the neurocognitive battery were organized into four domains (attention, memory, executive function, impulsivity) and nine sub-domains. For the linear regression model, the outcome variable was baseline MET-R performance efficiency T-score, and the predictor variable was baseline neurocognitive domain or sub-domain composite T-score. All neurocognitive measures were adjusted for age, sex, and education. The model was also adjusted for age in years of regular cocaine use.

Results: Study participants had a mean age of 57.5 years (SD 5.8), 30 (96.8%) were male, 19 (61.3%) were Black, 12 (38.7%) were White, 6 (19.4%) were Latino, 15 (48.4%) were single, and had a mean education of 12.8 years (SD 1.4). The mean composite T-scores for neurocognitive subdomains were as low as 33 (SD 8.1) for the verbal memory sub-domain and as high as 49.3 (SD 7.4) for the decision-making sub-domain. MET-R performance was significantly associated only with the overall impulsivity neurocognitive domain (adjusted coefficient 0.8, 95% CI 0.2 to 1.3) but no other domains.

Conclusion: This is the first paper to assess MET-R performance in a sample of persons with substance use disorders. MET-R performance was significantly associated only with the overall impulsivity neurocognitive domain but no other domains. The MET-R may be uniquely measuring the domain of impulsivity that is not captured by traditional neurocognitive testing. The MET-R will need testing in larger samples of persons with substance use disorders to determine whether it is clinically meaningful or correlated with other health outcomes.

Chapter 3 Main Body

INTRODUCTION

Cognitive impairment in those with substance use disorders (SUDs) [363-367] is associated with relapse [368, 369], lower likelihood of treatment completion [370-374], lower motivation [375], and worse quality of life [376, 377]. Effectively treating cognitive impairment as part of a comprehensive treatment plan for CUD could potentially improve important clinical outcomes, such as abstinence, quality of life, and treatment completion.

While assessment of cognition through traditional comprehensive neurocognitive batteries is ideal [378], these batteries can take several hours and lead to significant burden and fatigue for patients in a clinical setting and participants in a clinical research setting. In addition, such batteries may not be ecologically valid, as structured neurocognitive batteries in a research setting may not capture the unstructured nature of cognitive demands in everyday real-world tasks [379]. To address the shortcomings of traditional neurocognitive batteries, different types of unstructured tests have been created in an attempt to better capture the cognitive demands of everyday activities in real-world settings [379]. Examples include the Twenty Questions from the Delis-Kaplan Executive Function System, the Rivermead Behavioural Memory Test-Third Edition [379], and the Multiple Errands Test [380].

The Multiple Errands Test (MET) is a 30-40 minute interviewer-administered measure used to assess real-world cognitive functional performance based on completing a series of tasks outside of the traditional office setting [380]. Tasks include purchasing an item, writing the names of items, and finding the price of items. These tasks are to be completed under a set of rules, such as spending as little money as possible and doing the tasks in any order. The MET has been used in various populations, such as persons with brain injury [381, 382], multiple sclerosis [383], Parkinson’s disease [384], stroke [385], bipolar disorder [386], schizophrenia [387], obsessive-compulsive disorder [388], and substance use disorders [389]. The MET has undergone various revisions since it was originally created, such as the virtual MET [388], the

MET Hospital Version [390], the Chinese MET [391], the Big-Store MET [392], the MET Simplified Version [393], the MET Home Version [394], and the MET-Revised (MET-R) [385].

The MET has been used in substance use disorder populations [395, 396] and has been found to have small associations with the executive function domain [389] when compared with traditional neurocognitive measures. For example, in a study of 60 participants with alcohol, cocaine and heroin use disorders [389], the largest Pearson's correlations were -0.34 for task failures and the Letters and Numbers Test, and -0.31 for interpretation failures and the Zoo Map Test. However, the MET-R (also estimated to be 30-40 minutes in length) uses slightly different scoring metrics than the traditional MET. Whereas the MET includes metrics such as "inefficiencies", "strategies", and "interpretation failures" that are more open to subjective impressions when scored by raters, the MET-R instead has scoring metrics such as "number of locations visited", "number of tasks completed", and "number of rule breaks" that are more objective when scored by raters. The MET-R was specifically developed to provide an objective scoring system for raters [385] compared to the MET. It is unclear whether this difference in scoring metrics between the MET and the MET-R means that the various revisions of the MET are assessing different cognitive domains. Understanding on what cognitive domains the MET-R maps may be helpful in using the MET-R as a more time-efficient way to assess cognition in substance use disorder populations, compared to a lengthy neurocognitive battery which can take up to 2-3 hours.

The aim of this study was to assess whether performance on the MET-R by adult veterans with a primary cocaine use disorder is associated with domains of attention, memory, executive function, and impulsivity on a comprehensive neurocognitive battery. This paper is a secondary analysis of data from a pilot clinical trial (n = 31), where the MET-R was administered at baseline along with a comprehensive neurocognitive battery. Similar to the MET, we hypothesized that MET-R performance would be more strongly correlated with the domain of executive function than the domains of attention, memory, or impulsivity.

METHODS

Overall Study Design

The data used for this analysis came from a randomized, parallel-group outpatient study of treatment-seeking adult veterans with a primary cocaine use disorder and cognitive impairment. The full details of the study have been described in a previous paper (see Chapter #1).

Study Setting

This study was conducted at the San Francisco Veterans Affairs Health Care System (SFVAHCS) between 7/1/2014 and 6/30/2019. This study was registered on clinicaltrials.gov (NCT01684293). This study was approved by both the University of California, San Francisco (UCSF) Institutional Review Board (IRB) and the SFVAHCS Clinical Research Workgroup. All participants were paid in cash (US dollars) for their study participation ($15 for each study visit). The funding source (National Institute on Drug Abuse) had no role in the design of this study and had no role during its execution, analyses, interpretation of the data, or decision to submit results.

Study Recruitment

Word-of-mouth and flyers around the SFVAHCS were used to recruit potential participants. Participants signed a written informed consent form to participate.

Neurocognitive Measures

The full list of measures is described in a previous paper (see Chapter #1). This study was especially relevant for this analysis, because neurocognitive measures and the MET-R were collected at baseline. The neurocognitive measures were organized into four neurocognitive domains (attention, memory, executive function, impulsivity) and nine sub-domains (Table 3.1). All measures were adjusted for age, sex, and education, and all measures were converted to T-scores (mean = 50, SD = 10, range 0 to 100) before creating composite scores for each neurocognitive domain and sub-domain.

Attention neurocognitive assessments included the Delis–Kaplan Executive Function System (D-KEFS) Trail Making Test (Conditions 1, 2, 3, and 5), and Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Coding and Symbol Search. For the D-KEFS [397], scaled scores were converted to T-scores. The WAIS-IV [398] Coding and Symbol Search scaled scores were converted to T-scores. The attention domain was divided into a visual attention sub-domain (D-KEFS Trail Making Test) and a processing speed sub-domain (WAIS-IV Coding and Symbol Search).

Memory neurocognitive assessments included the WAIS-IV Digit Span and Arithmetic, Hopkins Verbal Learning Test-Revised (HVLT-R), and Brief Visuospatial Memory Test-Revised (BVMT-R). The WAIS-IV [398] Digit Span and Arithmetic scaled scores were converted to T-scores. For the HVLT-R [399, 400] and BVMT-R [401], T-scores were calculated from the raw scores. The memory domain was divided into a working memory sub-domain (WAIS-IV Digit Span and Arithmetic), a verbal memory sub-domain (HVLT-R), and a visuospatial memory sub-domain (BVMT-R).

Executive function neurocognitive assessments included the D-KEFS Tower Test, D-KEFS Trail Making Test (Condition 4), D-KEFS Color-Word Interference Test, and Wisconsin Card Sorting Test (Computer Version 4) [WCST]. The scaled scores for the D-KEFS tests were converted to T-scores. For the WCST [402, 403], T-scores were calculated from the raw scores. The executive function domain was divided into a cognitive flexibility sub-domain (D-KEFS Tower Test, Trail Making Test, and Color-Word Interference Test) and a set shifting sub-domain (WCST).

Impulsivity neurocognitive assessments included the Conners' Continuous Performance Test (CPT) 3rd Edition and the Iowa Gambling Task (IGT). For the computerized CPT [404], T-scores were calculated from the raw scores. For this analysis, the T-scores were reverse-scored to ensure that a higher T-score means better performance. For the computerized IGT [405], T-

scores were calculated from the raw scores. The impulsivity domain was divided into a continuous performance sub-domain (Conners' CPT) and a decision-making sub-domain (IGT).

MET-R Description and Procedure

Because the MET is administered in real-world settings, local versions have to be developed since each setting is unique and no two real-world settings are exactly alike. The MET is an example of a performance-based test that requires performing tasks in a setting of unpredictability, interpersonal interactions, social demands, noise, and little or no assistance from the staff administering the test [385, 406, 407]. The MET-R was specifically developed to provide an objective scoring system for raters [385] compared to the MET. The MET-R used in this study was adapted to the SFVAHCS. Adaptation means that a map of the SFVAHCS had to be created for participants to use (Figure 3.1), and tasks that could be completed at the SFVAHCS based on the SFVAHCS environment had to be created (Figure 3.2). There are no previous reliability and validity data on the MET-R at the SFVAHCS since this version was newly adapted for this study.

A map of the SFVAHCS is given to each participant (Figure 3.1). This map contains a key of locations around the SFVAHCS where participants can complete the necessary tasks. The participant is given an instruction sheet of the tasks to complete (Figure 3.2). Tasks include mailing an item, purchasing items, making a phone call, obtaining answers to questions, meeting the examiner at a certain place and time, and talking to the staff person after completing certain tasks. This instruction sheet also contains a list of rules to follow while completing the tasks. Rules include not spending more than a certain dollar amount, not going back into a previously visited area, not buying more than 2 items at a location, and not speaking to the staff person unless it is part of the exercise.

The participant is also provided with a sports watch to wear during the test which tracks distance traveled while walking around the SFVAHCS, number of calories burned while walking around the SFVAHCS, and number of steps taken while walking around the SFVAHCS. The

participant is also given a clipboard, pen, stamp, and a $10-bill. The staff person administering the MET-R follows behind the participant around the SFVAHCS with a stopwatch, pen, clipboard, and a recording and scoring sheet (Figure 3.3). The recording and sheet contain items that the staff person has to complete as the participant is doing the test and after the participant finishes the test. Items to record include the number of locations visited, the number of items completed, and the number of rules broken.

The MET-R scores include distance traveled while walking around the SFVAHCS, number of calories burned while walking around the SFVAHCS, number of steps taken while walking around the SFVAHCS, total completion time, number of locations visited, number of tasks completed, and number of rule breaks. A performance efficiency score was calculated (total tasks completed / total locations visited). For this paper, the performance efficiency score was determined to be the key outcome of interest. The performance efficiency score was converted to a T-score.

Blinding

Ideally, those who assessed the primary outcomes would be blinded to the study arm. However, since this was a pilot study with limited funding through a career development award and turnover of non-permanent research assistants during the study period, outcomes were assessed by whichever staff was practically available to assess the outcomes at a given study visit.

Adherence/Quality Assurance

All participants came to the SFVAHCS to complete all visit tasks. A Standard Operating Procedure (SOP) manual for the neurocognitive testing and the MET-R was created for research staff. Research assistants were trained on all tasks and supervised by the principal investigator. Research staff were trained on materials needed, organization of materials, pre-test administration procedures, verbal scripts to read to participants, test administration procedures, end of test administration procedures, post-test administration procedures, and

scoring procedures. The principal investigator personally observed all research assistants performing all neurocognitive testing and MET-R administration on at least 3 participants initially. All research assistants were expected to finish scoring the same day of test administration. Scoring of all measures on all participants was double-checked by the principal investigator, and any errors or discrepancies were immediately corrected. All participants' charts (no specific sampling plan) were audited yearly for data integrity by the principal investigator and the SFVAHCS research compliance officer.

Statistical Analysis

Stata/SE 16.1 (update level 5/20/2020) was used for all descriptive and linear regression analyses. Standard descriptive statistics were used to summarize MET-R performance (e.g., mean, standard deviation). For the linear regression model, the outcome variable was baseline MET-R performance efficiency T-score, and the predictor variable was baseline neurocognitive domain or sub-domain composite T-score. All neurocognitive measures were adjusted for age, sex, and education. The model was also adjusted for age in years of regular cocaine use (started using 3x/week or more), since Control arm participants were significantly older when they became regular cocaine users (age 29) than Cog-Rehab arm participants (age 23) [t(29) = -2.2; -11.4 to -0.5; P = 0.03].

Linear regression models were checked for linearity, normality, constant variance (homoscedasticity), outlying/high leverage/influential points, and multicollinearity. Linearity was assessed using component plus residual (CPR) plots with the LOWESS smooth option. Normality was assessed using quantile plots of residuals against the quantiles of the normal distribution (qnorm), kernel density plots of the residuals (kdensity), and the ladder-of-powers quantile-normal plots (qladder). Constant variance was assessed by residual versus predictor (RVP) plots of continuous predictors and residual versus fitted (RVF) plots. To account for heteroskedasticity, heteroskedasticity consistent (hc3) standard errors were used [408-410]. Outlying/high leverage/influential points were assessed using boxplots to detect outlying values

among the dfbetas; no observations had absolute dfbetas greater than 2. Multicollinearity was assessed analyzing the variance inflation factor values after each regression model; no observations had values greater than 10.

RESULTS

Participant Characteristics

Overall, study participants had a mean age of 57.5 years (SD 5.8), 30 (96.8%) were male, 19 (61.3%) were Black, 12 (38.7%) were White, 6 (19.4%) were Latino, 15 (48.4%) were single, and had a mean education of 12.8 years (SD 1.4). Participants in both groups (Table 3.2) were similar in sex, age, education, race, ethnicity, marital status, retirement status, and handedness. Control arm participants were significantly older when they became regular cocaine users (age 29) than Cog-Rehab arm participants (age 23) [t(29) = -2.2; -11.4 to -0.5; P = 0.03]. Participants in both groups had similar psychiatric diagnoses.

Summary Statistics of Neurocognitive Domains and MET-R

The mean composite T-scores for neurocognitive domains (Table 3.3) were as low as 33 (SD 8.1) for the verbal memory sub-domain and as high as 49.3 (SD 7.4) for the decision-making sub-domain. Regarding the MET-R (Table 3.3), the mean time of completion was 19.9 minutes (SD 5), the mean number of tasks completed was 8.4 (SD 1.9), the mean number of locations visited was 13.3 (SD 4.1), the mean number of rule breaks was 4.7 (SD 1.6), and the mean performance efficiency T-score was 50 by definition.

Association between MET-R Performance Efficiency T-Score and Neurocognitive Domain Composite T-Scores

Normality, constant variance, outlying/high leverage/influential points, and multicollinearity assumptions for the linear regression models were met (Figure 3.4). For the linearity assumption, there was noise in the tails for the neurocognitive domain composite T-scores, but such noise is not unexpected for a study with a small sample size.

The 95% confidence intervals for most of the adjusted coefficients crossed 0 (Table 3.4). However, MET-R performance was significantly associated with the overall impulsivity neurocognitive domain (adjusted coefficient 0.8, 95% CI 0.2 to 1.3). Though not statistically significant, the continuous performance sub-domain had an adjusted coefficient of 0.4, and the adjusted coefficient was 0.3 for the decision-making sub-domain, overall executive function domain, cognitive flexibility sub-domain, overall memory domain, and verbal memory sub-domain.

DISCUSSION

This is the first paper to assess MET-R performance in a sample of persons with substance use disorders. In a sample of veterans with a primary cocaine use disorder, MET-R performance was significantly associated only with the overall impulsivity neurocognitive domain (adjusted coefficient 0.8, 95% CI 0.2 to 1.3) but no other domains. Though the impulsivity sub-domains were not significant, perhaps the overall impulsivity domain being significant was due to elimination of noise when taking the average of the impulsivity sub-domains and creating an overall impulsivity domain score.

To our knowledge, other versions of the MET [381, 384, 411] and the previous study of participants with alcohol, cocaine and heroin use disorders [389] have focused on the executive function domain but have not separately assessed the domain of impulsivity. Perhaps the objective scoring nature of the MET-R, as opposed to the scoring of the MET that is more subject to interpretation depending on the rater, is tapping into the overall impulsivity domain more than other domains. Since MET-R performance is defined as tasks/locations, perhaps an association with overall impulsivity means that participants are simply performing more tasks in a frantic manner due to the unstructured nature of the MET-R. Participants may be performing more tasks chaotically without any upfront plan. This explanation will need to be further explored in a larger study with more power.

Though the associations with other neurocognitive domains and sub-domains were not statistically significant, the adjusted coefficients were in the 0.3 to 0.4 range. This study only had power to detect overall large effects (e.g., Cohen's F-squared = 0.35; Cohen's d = 1.04; Cohen's q = 1.12). Perhaps other neurocognitive domains and sub-domains would become statistically significant in a larger study with more power, and the clinical significance of such statistical findings will need to be explored in this larger study. The MET-R will also need further testing in larger samples of persons with substance use disorders to establish comparability with neurocognitive measures. If the MET-R performance is indeed captured by several cognitive domains than just one domain (such as executive function or impulsivity), the MET-R could potentially be a more time-efficient way to assess cognition (mean 19.9 minutes [SD 5] in this study) than a lengthy neurocognitive battery which can take up to 2-3 hours.

Strengths

First, this study collected a comprehensive set of neurocognitive measures, which allowed for the investigation of the association between neurocognitive domains and MET-R performance. Second, we conducted this study at a veteran's hospital in patients with complex comorbidities in an effort to maximize internal validity for this little-studied population. Finally, the MET-R is a relatively low technology measure to implement by research staff with a college degree.

Limitations

First, the sample size for this analysis was small, and this study is underpowered. The results are perhaps false-negative due to the small sample size. A larger sample size will be needed to better tease out which neurocognitive domains may be best associated with MET-R performance. Second, most community-based addiction treatment programs will not have access to extensive neurocognitive assessments as conducted in this study, which limits the detailed assessment of various cognitive domains in patients treated in a community setting.

Third, a more rigorous program of training research assistants with formal proficiency checks could have been implemented. Since this was a pilot study, the principal investigator was able to double-check all of the research assistants' work. This level of double-checking may not be possible in a larger trial, and this limitation will need to be addressed in a larger study. Finally, despite the inherent unpredictability in performance-based tests like the MET-R and local versions needing to be developed due to the uniqueness of each setting, the MET-R that was adapted to the SFVAHCS will still need independent reliability and validity testing in a separate study due to psychometric concerns.

CONCLUSION

In a sample of veterans with a primary cocaine use disorder, MET-R performance was significantly associated only with the overall impulsivity neurocognitive domain but no other domains. The MET-R may be uniquely measuring the domain of impulsivity that is not captured by traditional neurocognitive testing. The MET-R will need testing in larger samples of persons with substance use disorders to determine whether it is clinically meaningful or correlated with other health outcomes. The MET-R could potentially become a more time-efficient way to assess cognition in outpatient clinical settings and community-based addiction treatment programs, rather than a lengthy neurocognitive battery.

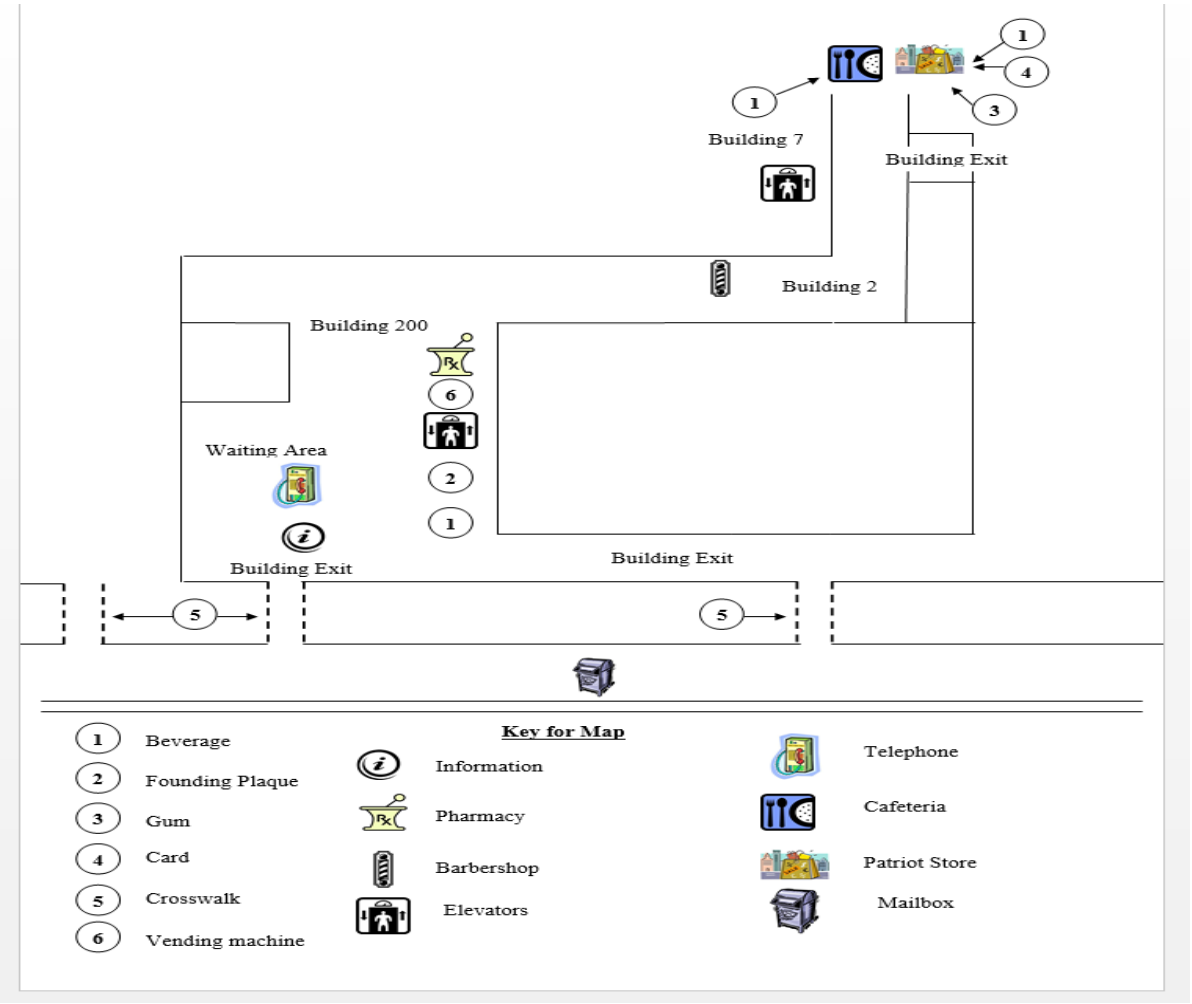


Figure 3.1. Multiple Errands Test-Revised Map.

Instructions: In this exercise, you should complete the following tasks.

Do the following:

- Mail something to Dr. Giles at Samuel Merritt University
- Get a beverage and give it to the examiner
- Get gum
- Get a card
- Telephone Dr. Raj at 415-745-0206 and say what time it is
- Sign the back of the envelope

You must meet me at the elevators 10 minutes after you have started the exercise, and tell me the time

Obtain the following information and write it in the spaces below:
What is the price of a candybar? _____
What is the opening time of the barbershop on Monday? _____
What is the closing time of the pharmacy on Friday? _____
When was the San Francisco VA founded? _____
Where are the prices listed on the Patriot Store deodorants? _____

- Tell me when you have completed the exercise
- Begin this test when you are ready. Tell me when you begin.

Please read the rules out loud and repeat them back to the examiner:

Rules

- *You should complete all of these tasks, but you may do so in any order*
- *You should spend no more than $4.50*
- *You should buy no more than two items in the Patriot Store*
- *You should complete this exercise as quickly as possible without taking risks*
- *You should stay on the main floor of the hospital*
- *You should not enter any hospital treatment areas or staff only areas*
- *You should not go back into an area you have already been in*
- *You should use the crosswalk when crossing the street*
- *You should follow the Patriot Store's posted rules*
- *You should only go outside of the hospital building once*
- *Do not speak to the examiner unless it is part of the exercise*

Dr. Giles
Samuel Merritt University
450 30th Street, 4th Floor
Oakland, CA 94609

Figure 3.2. Multiple Errands Test-Revised Instruction Sheet.

A. Distance traveled in miles (based on GPS sports watch):_____
B. Number of calories burned (based on GPS sports watch):_____
C. Total number of steps (based on GPS sports watch):_____
D. How many minutes of the test elapsed when at elevators? (based on examiner's stopwatch):_____
E. Total time to complete (based on examiner's stopwatch):_____
F. Indicate whether each of the following locations was visited:

- Cafeteria Y N If >1 once, #:_____
- Patriot Store Y N If >1 once, #:_____
- Elevators Y N If >1 once, #:_____
- Barbershop Y N If >1 once, #:_____
- Pharmacy Y N If >1 once, #:_____
- Founding Plaque/Information desk for this information Y N If >1 once, #:_____
- Phone – Waiting Area (if uses own phone, this counts) Y N If >1 once, #:_____
- Mailbox Y N If >1 once, #:_____
- Other:_____ #:_____ Other:_____ #:_____ Other:_____ #:_____
- Other:_____ #:_____ Other:_____ #:_____ Other:_____ #:_____
- Other:_____ #:_____ Other:_____ #:_____ Other:_____ #:_____
- Other:_____ #:_____ Other:_____ #:_____ Other:_____ #:_____
- Other:_____ #:_____ Other:_____ #:_____ Other:_____ #:_____

G. Total number of locations visited:_____
H. Indicate whether each item was fully completed or not (add any comments):

1) Mail something… Y N _____
2) Get a beverage…. Y N _____
3) Get gum… Y N _____
4) Get a card… Y N _____
5) Telephone… Y N _____
6) Sign the back… Y N _____
7) Meet at elevators… Y N _____
8) Price of candybar Y N _____
9) Barbershop time Y N _____
10) Pharmacy time Y N _____
11) SF VA founded Y N _____
12) Deodorants' price location Y N _____
13) Tell me when completed… Y N _____

I. Total number of tasks completed:_____
J. Did participant follow each rule? (add any comments):

1) Complete all tasks… Y N _____
2) Spending <= $4.50 Y N _____
3) Buy <=2 items in Patriot Store Y N _____
4) Complete w/o risks… Y N _____
5) Stay on main floor Y N _____
6) Not enter treatment area.. Y N _____
7) Not go back into an area.. Y N _____
8) Use crosswalk Y N _____
9) Follow Patriot Store's rules Y N _____
10) Go outside only once Y N _____
11) Not speak to examiner… Y N _____

K. Total number of rule breaks:_____
L. **Participant's Performance Efficiency**
(Total # of tasks completed) / (Total # of locations) = _____ (2 decimal places)
Optimal Performance Efficiency is 1.625 (based on 13 tasks/8 locations).
Normalize participant's efficiency:
(Participant's performance efficiency) / (1.625) = _____ (2 decimal places)
M. Self-rating of performance:_____ Self-rating of familiarity with the VA:_____

Figure 3.3. Multiple Errands Test-Revised Recording and Scoring Sheet.

The following nine items are listed in Figures 3.5 to 3.17 (from left to right):

Row #1
1. Linearity – Component Plus Residual (CPR) plot with the LOWESS smooth option for the neurocognitive sub-domain composite T-score
2. Linearity – Kernel density plot for the neurocognitive sub-domain composite T-score
3. Linearity – Graph matrix for baseline MET-R Performance Efficiency T-Score (dependent variable), neurocognitive sub-domain composite T-score (independent variable), and age in years of regular cocaine use (adjusted variable)

Row #2
1. Normality – Quantile plot of residuals against the quantiles of the normal distribution for the baseline MET-R Performance Efficiency T-Score
2. Normality – Kernel density plot of the residuals for the baseline MET-R Performance Efficiency T-Score
3. Normality – Ladder-of-powers quantile-normal plot for the baseline MET-R Performance Efficiency T-Score

Row #3
1. Constant variance – Residual versus fitted (RVF) plot
2. Outlying/high leverage/influential points – Boxplot to detect outlying values among the dfbetas
3. Multicollinearity – variance inflation factor (vif) value

Sample Stata Code for checking above assumptions for linear regression:

Linearity
regress metIT VerbMemComp AgeRegularUse5, vce(hc3)
cprplot VerbMemComp, lowess → Row #1, #1
cprplot AgeRegularUse5, lowess
kdensity VerbMemComp, normal → Row #1, #2
kdensity AgeRegularUse5, normal
graph matrix metIT VerbMemComp AgeRegularUse5 → Row #1, #3

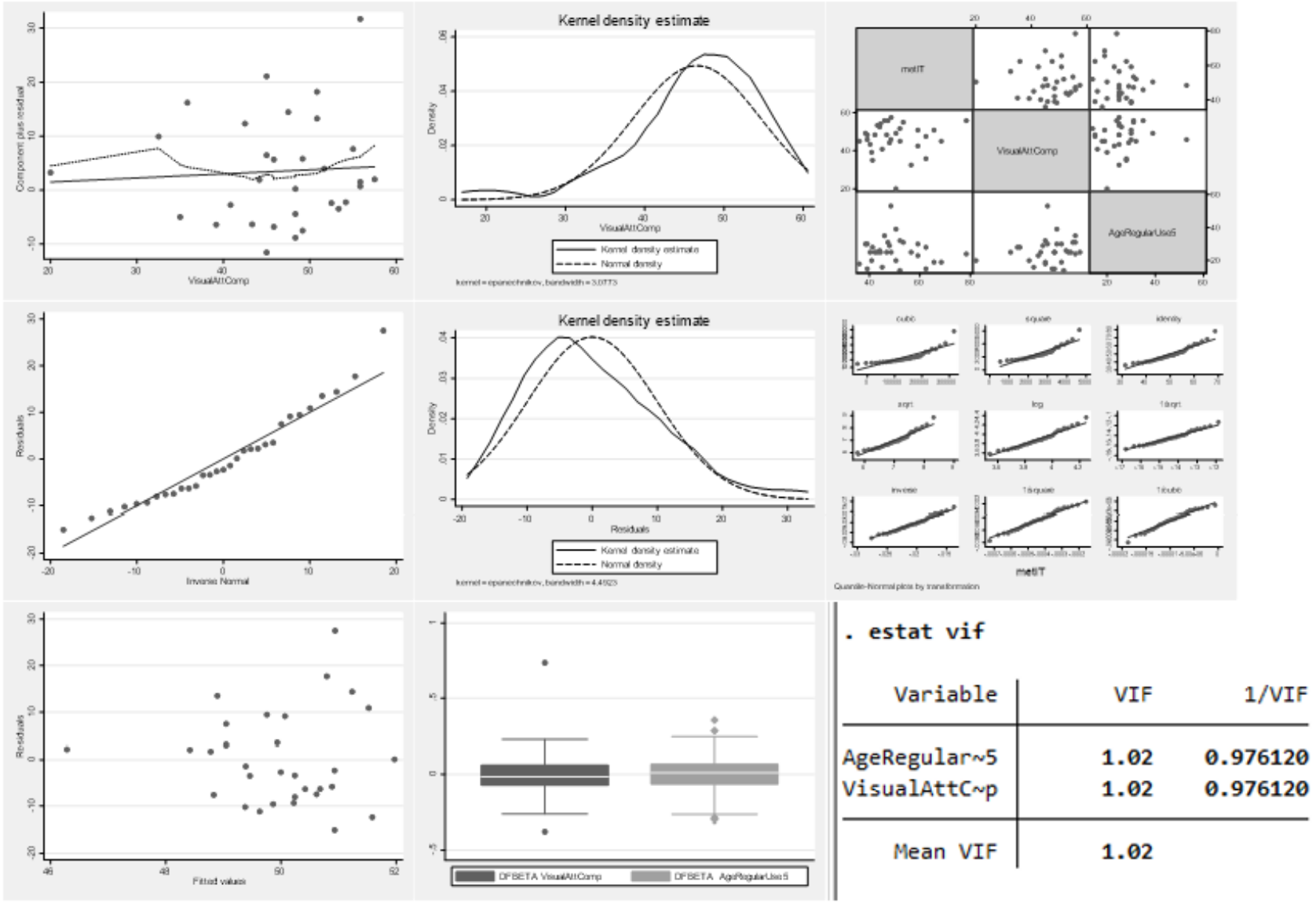
Normality
regress metIT VerbMemComp AgeRegularUse5, vce(hc3)
predict metITresid, residual
qnorm metITresid → Row #2, #1
kdensity metITresid, normal → Row #2, #2
qladder metIT → Row #2, #3

Constant Variance
regress metIT VerbMemComp AgeRegularUse5, vce(hc3)
rvfplot → Row #3, #1
rvpplot AgeRegularUse5

Outlying/high leverage/influential points
regress metIT VerbMemComp AgeRegularUse5
dfbeta
graph box _dfbeta_* → Row #3, #2

Multicollinearity
regress metIT VerbMemComp AgeRegularUse5, vce(hc3)
estat vif → Row #3, #3

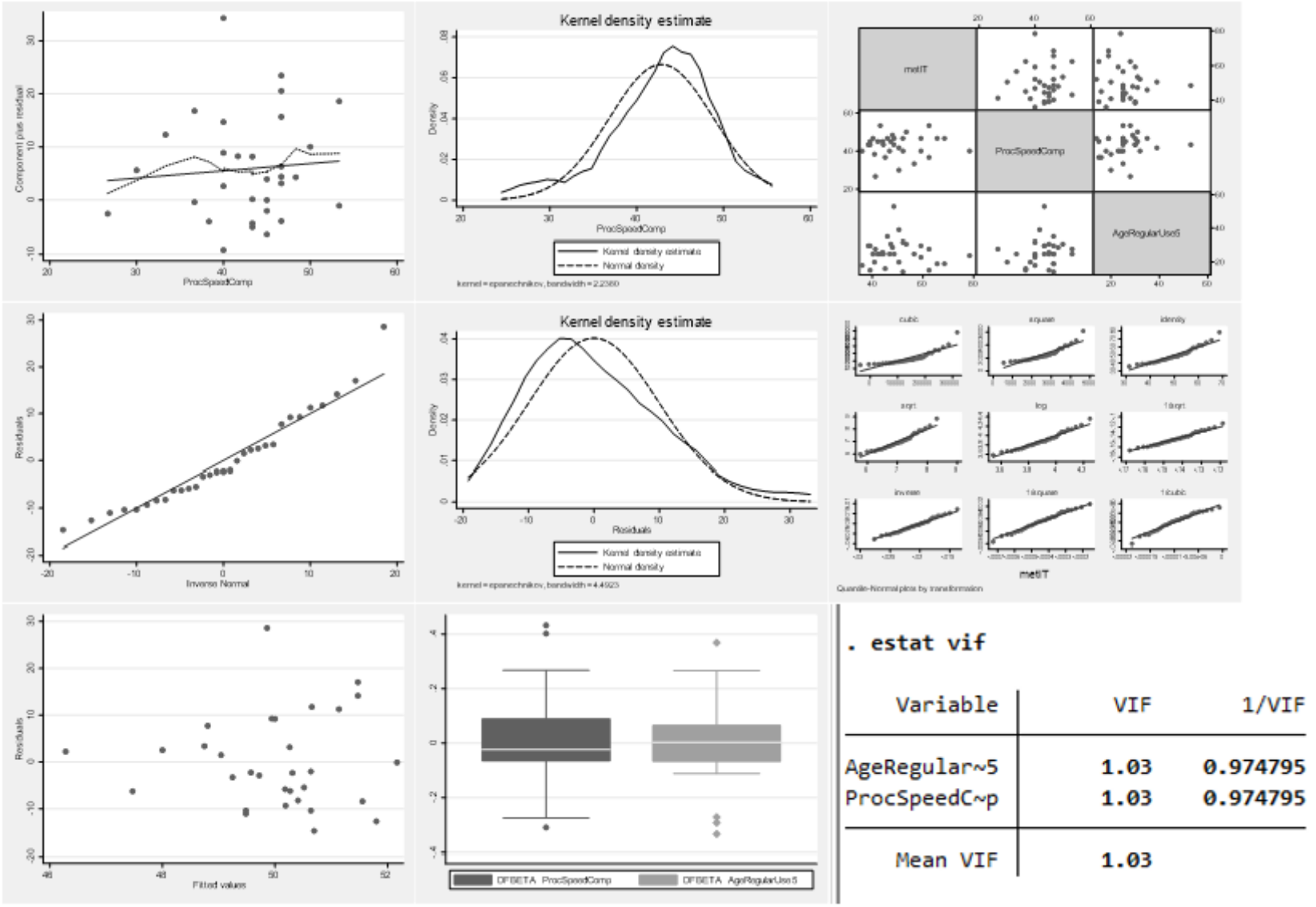
Figure 3.4. Stata Code for Linear Regression Assumptions.



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.02	0.976120
VisualAttC~p	1.02	0.976120
Mean VIF	1.02	

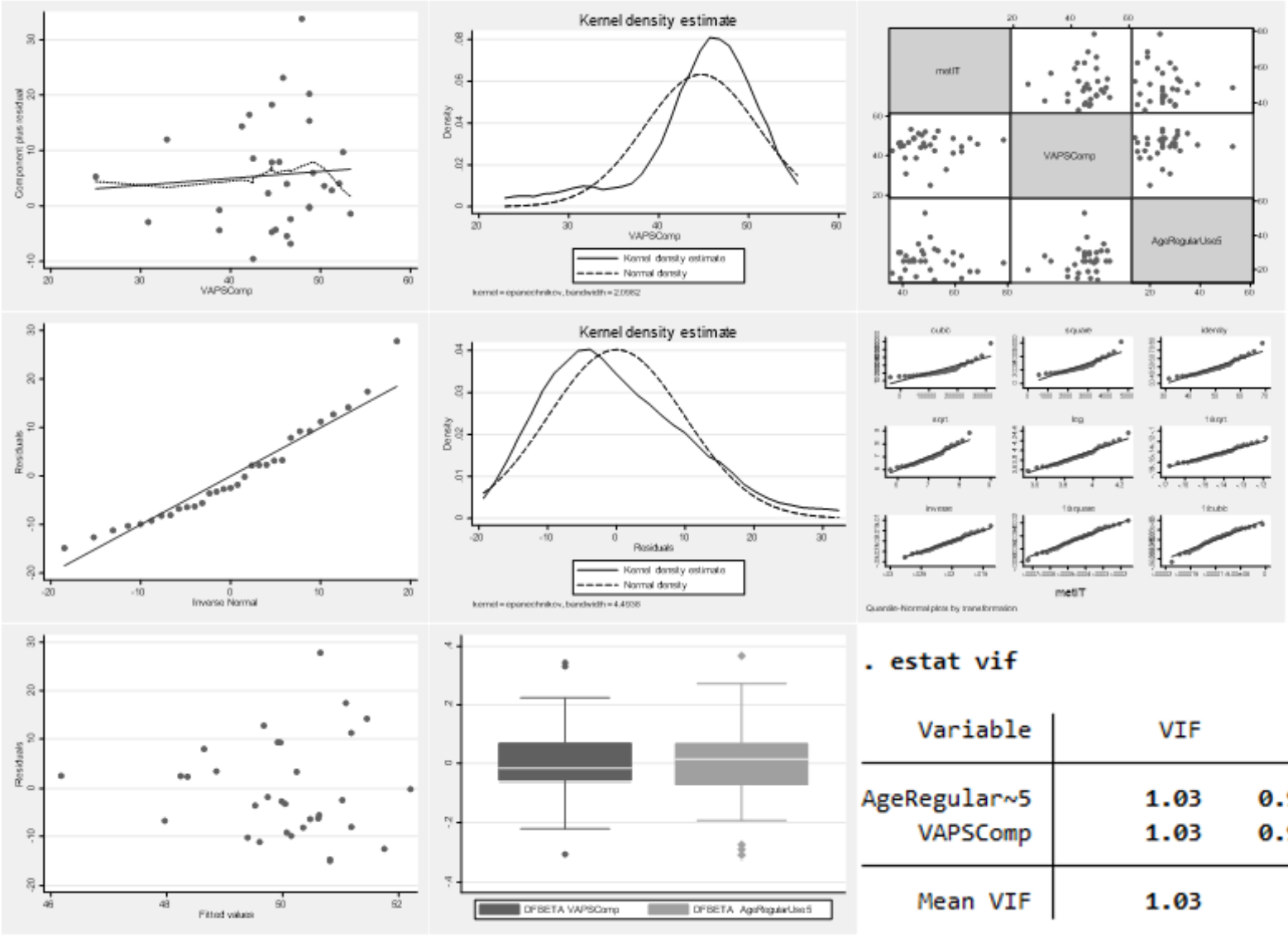
Figure 3.5. Visual Attention Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.03	0.974795
ProcSpeedC~p	1.03	0.974795
Mean VIF	1.03	

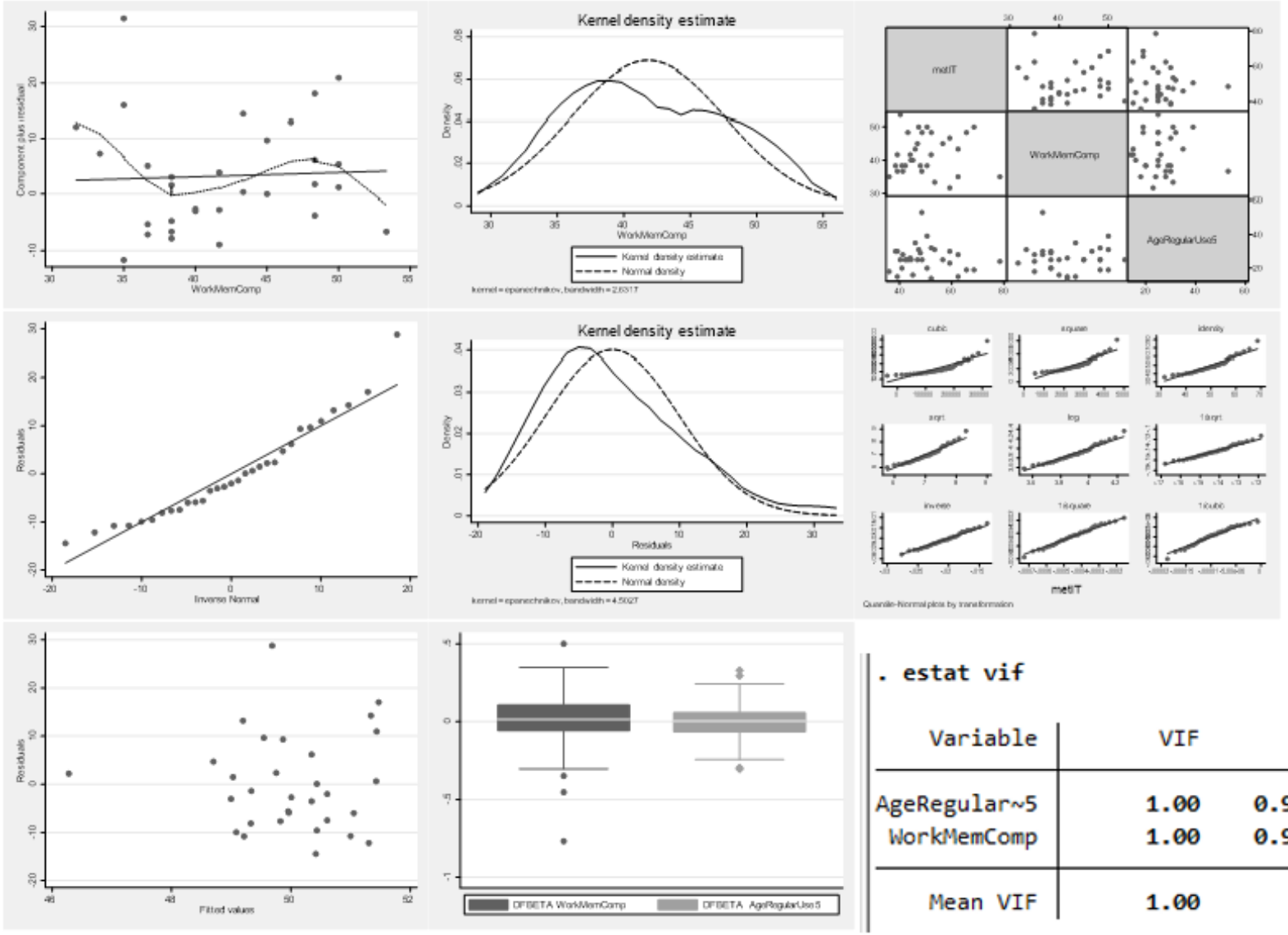
Figure 3.6. Processing Speed Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.03	0.969629
VAPSComp	1.03	0.969629
Mean VIF	1.03	

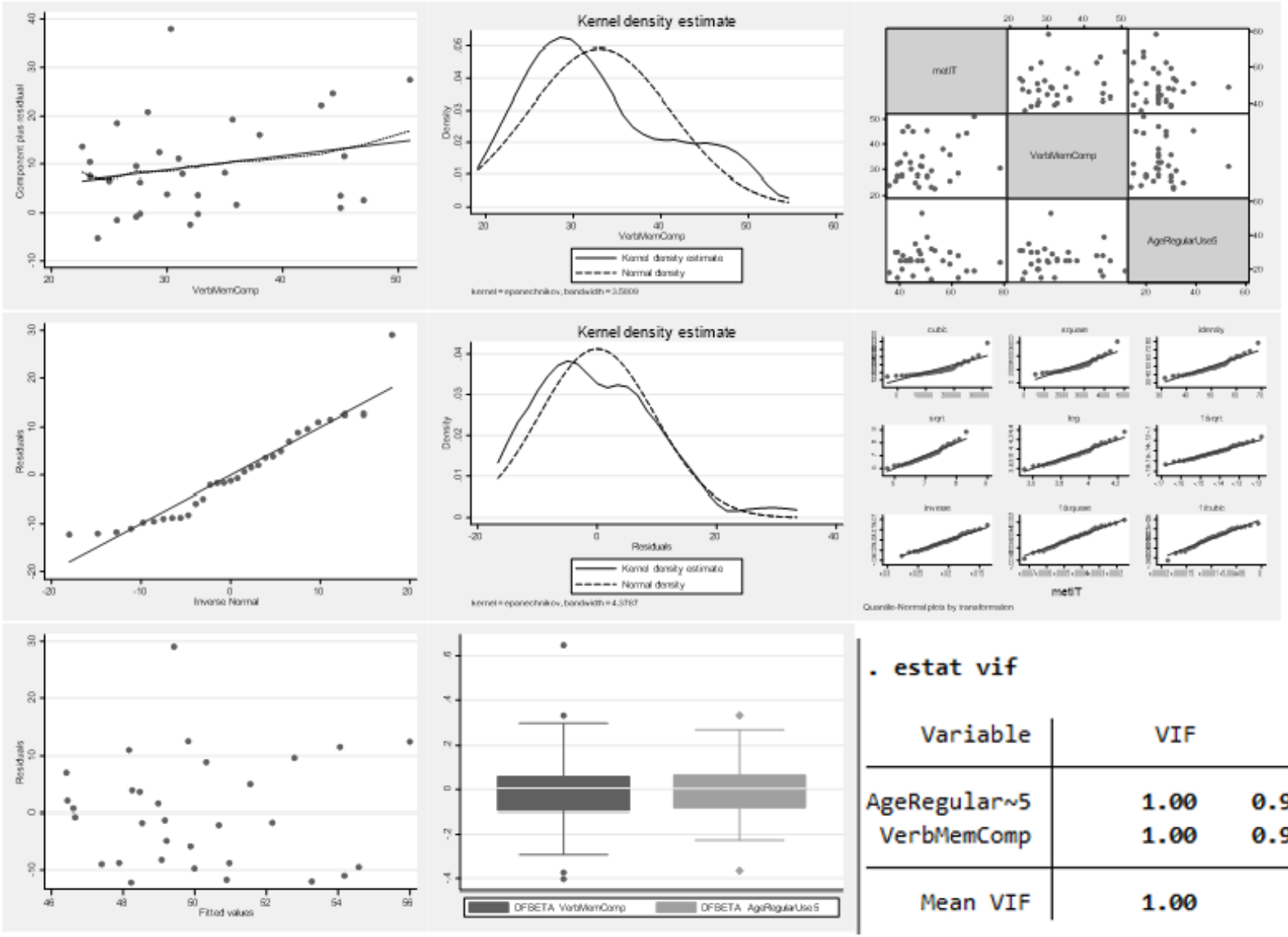
Figure 3.7. Overall Attention Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.00	0.999896
WorkMemComp	1.00	0.999896
Mean VIF	1.00	

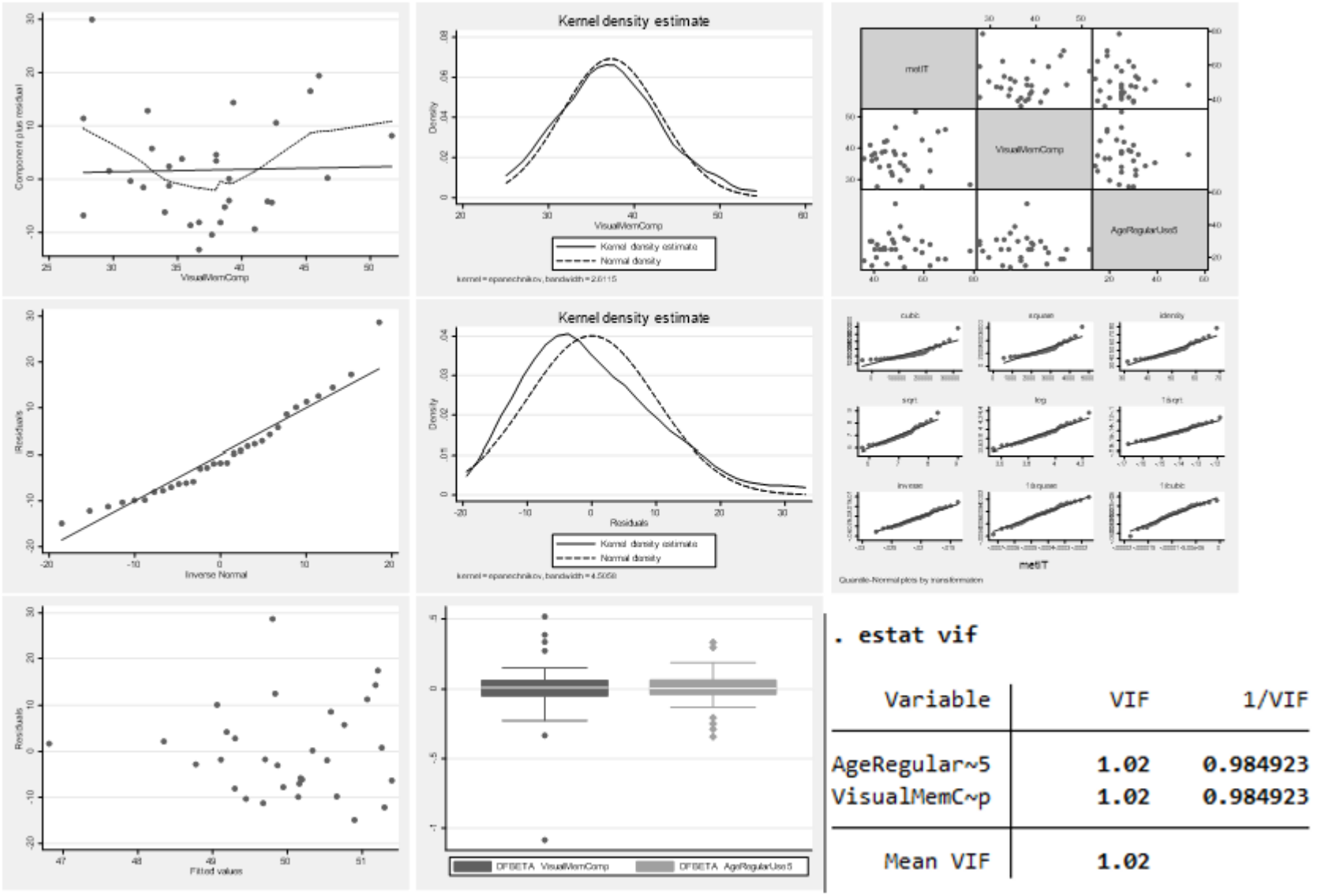
Figure 3.8. Working Memory Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.00	0.997973
VerbMemComp	1.00	0.997973
Mean VIF	1.00	

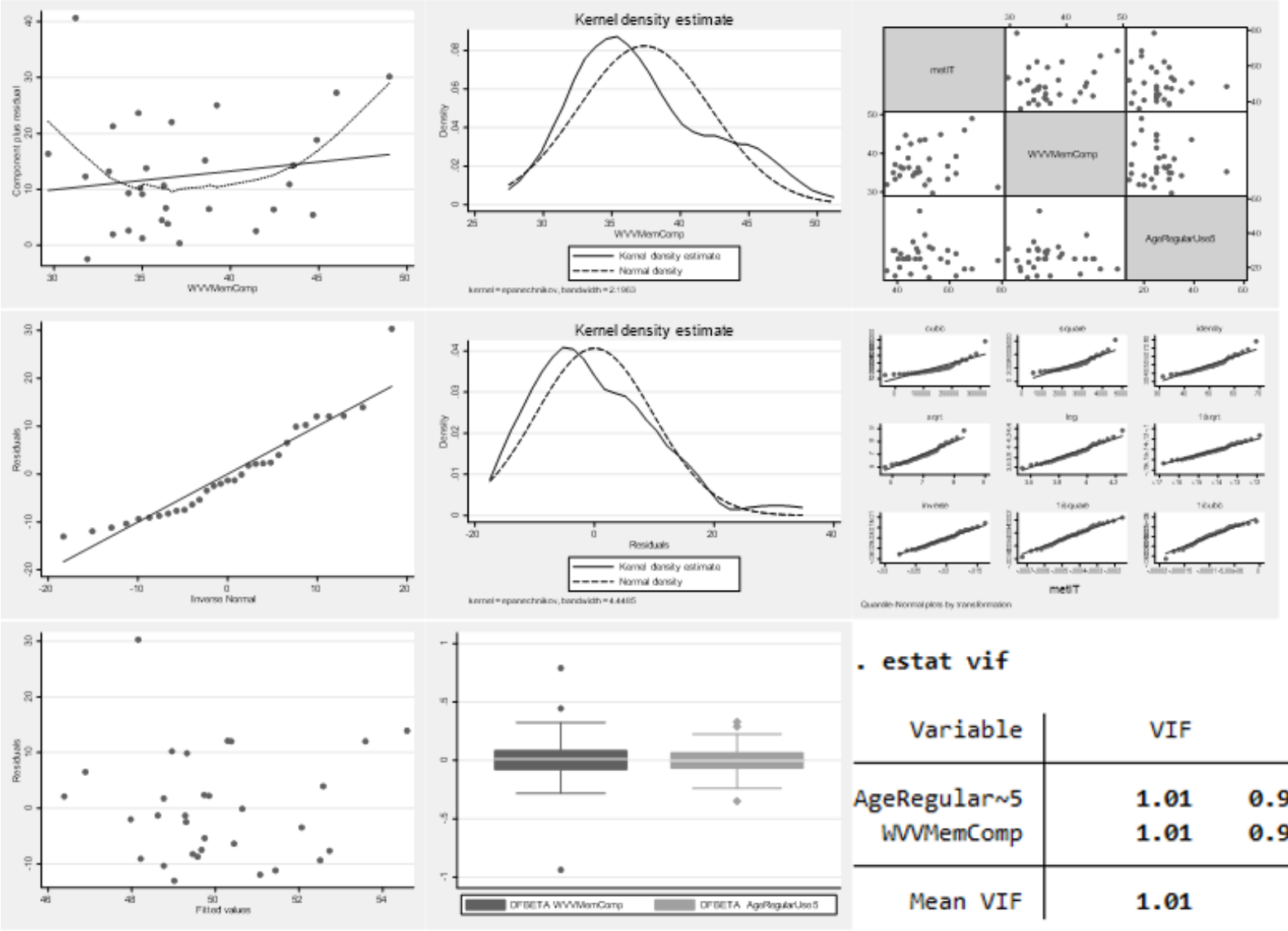
Figure 3.9. Verbal Memory Composite – Statistical Assumptions




```
. estat vif

    Variable |       VIF       1/VIF
-------------+----------------------
AgeRegular~5 |      1.02    0.984923
VisualMemC~p |      1.02    0.984923
-------------+----------------------
    Mean VIF |      1.02
```

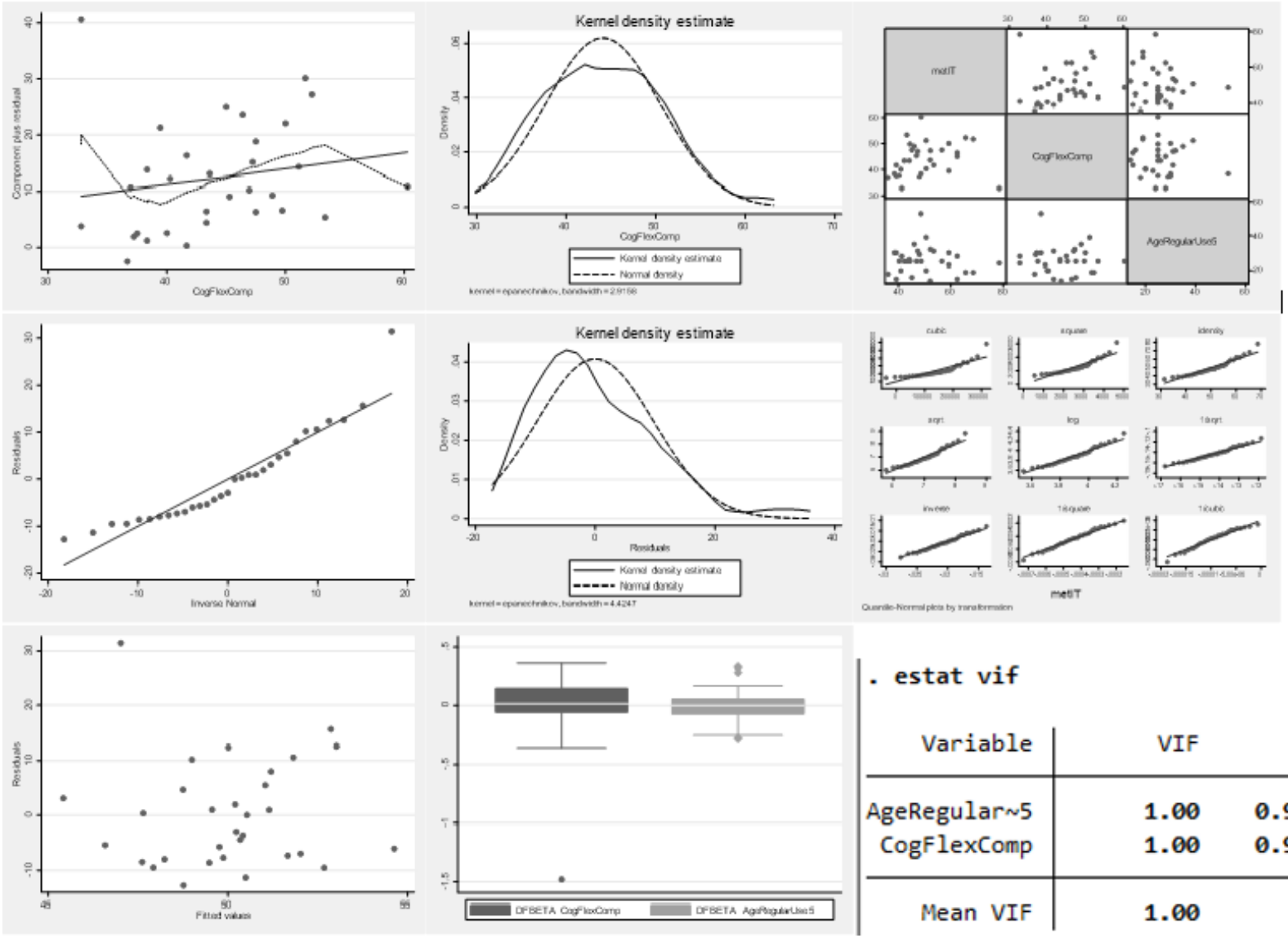
Figure 3.10. Visuospatial Memory Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.01	0.993947
WVVMemComp	1.01	0.993947
Mean VIF	1.01	

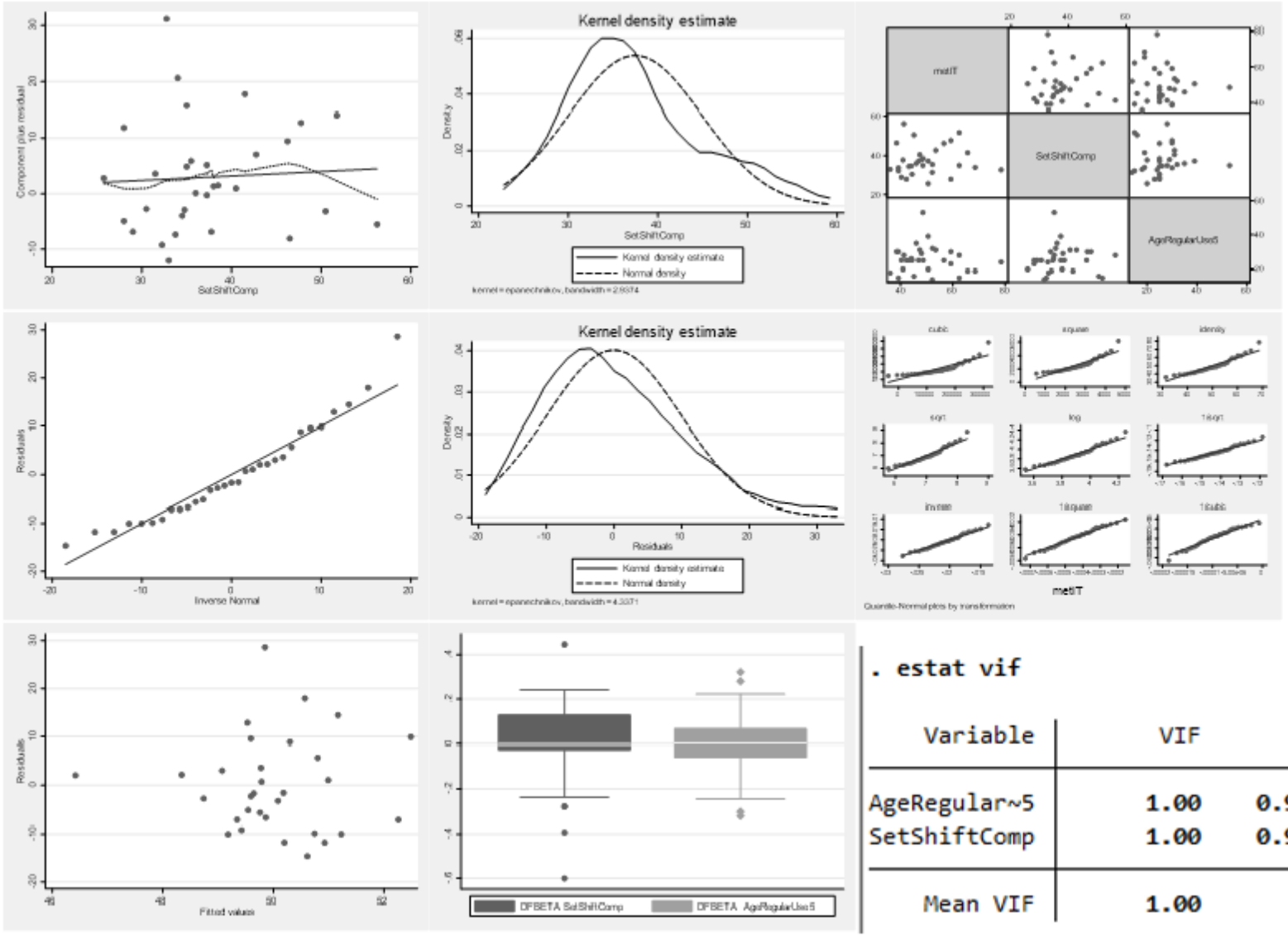
Figure 3.11. Overall Memory Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.00	0.996438
CogFlexComp	1.00	0.996438
Mean VIF	1.00	

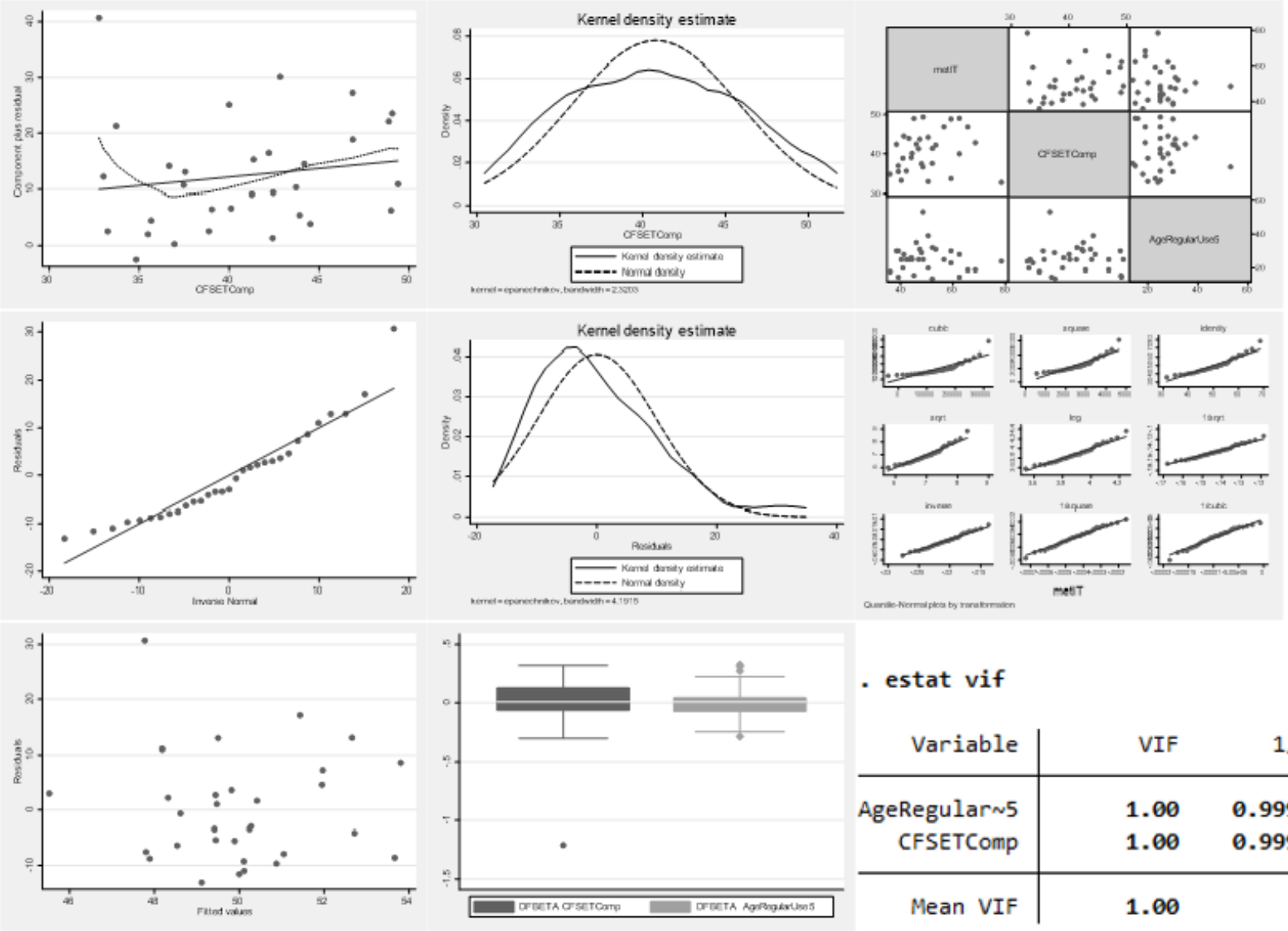
Figure 3.12. Cognitive Flexibility Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.00	0.999431
SetShiftComp	1.00	0.999431
Mean VIF	1.00	

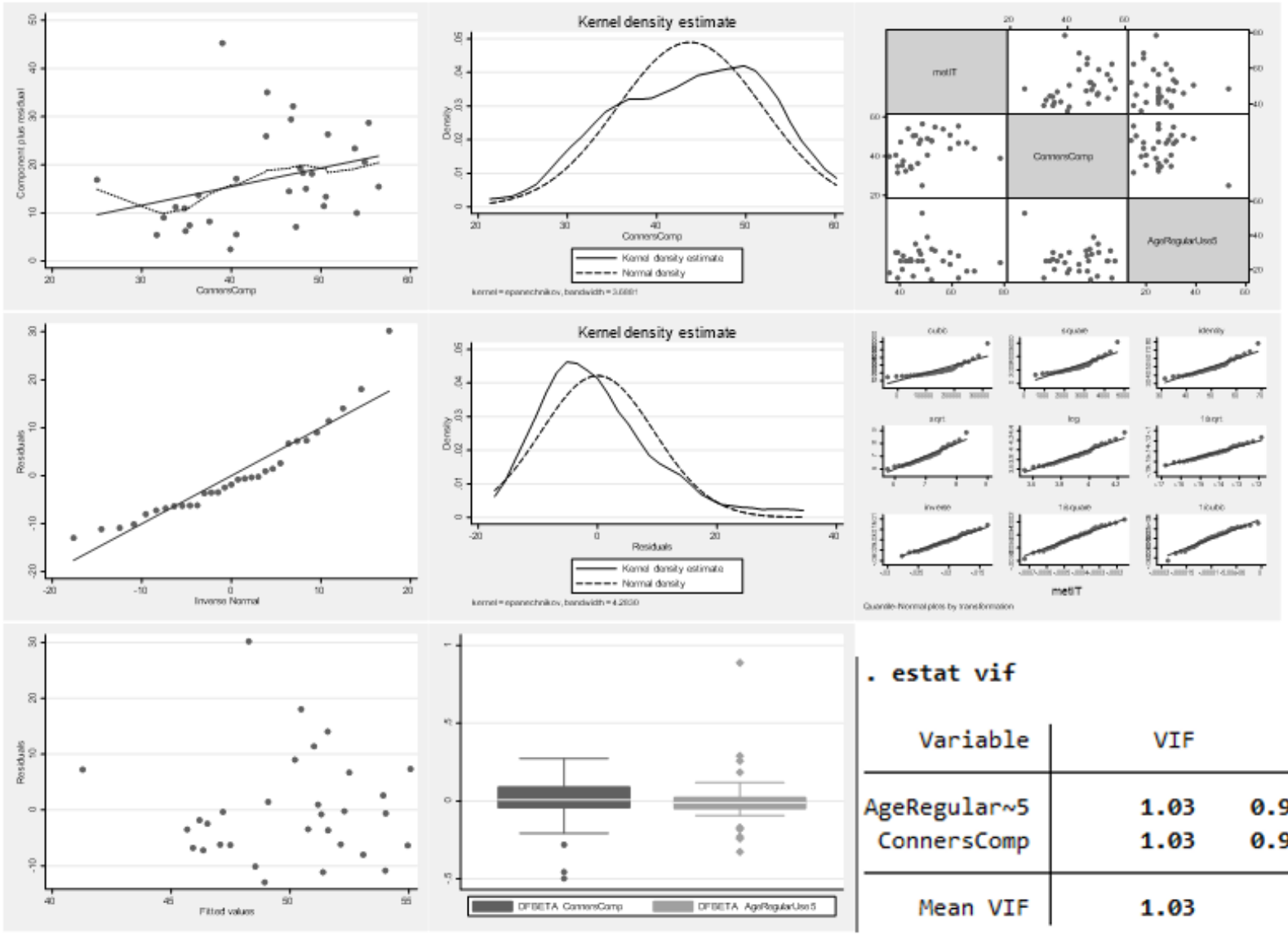
Figure 3.13. Set Shifting Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.00	0.999590
CFSETComp	1.00	0.999590
Mean VIF	1.00	

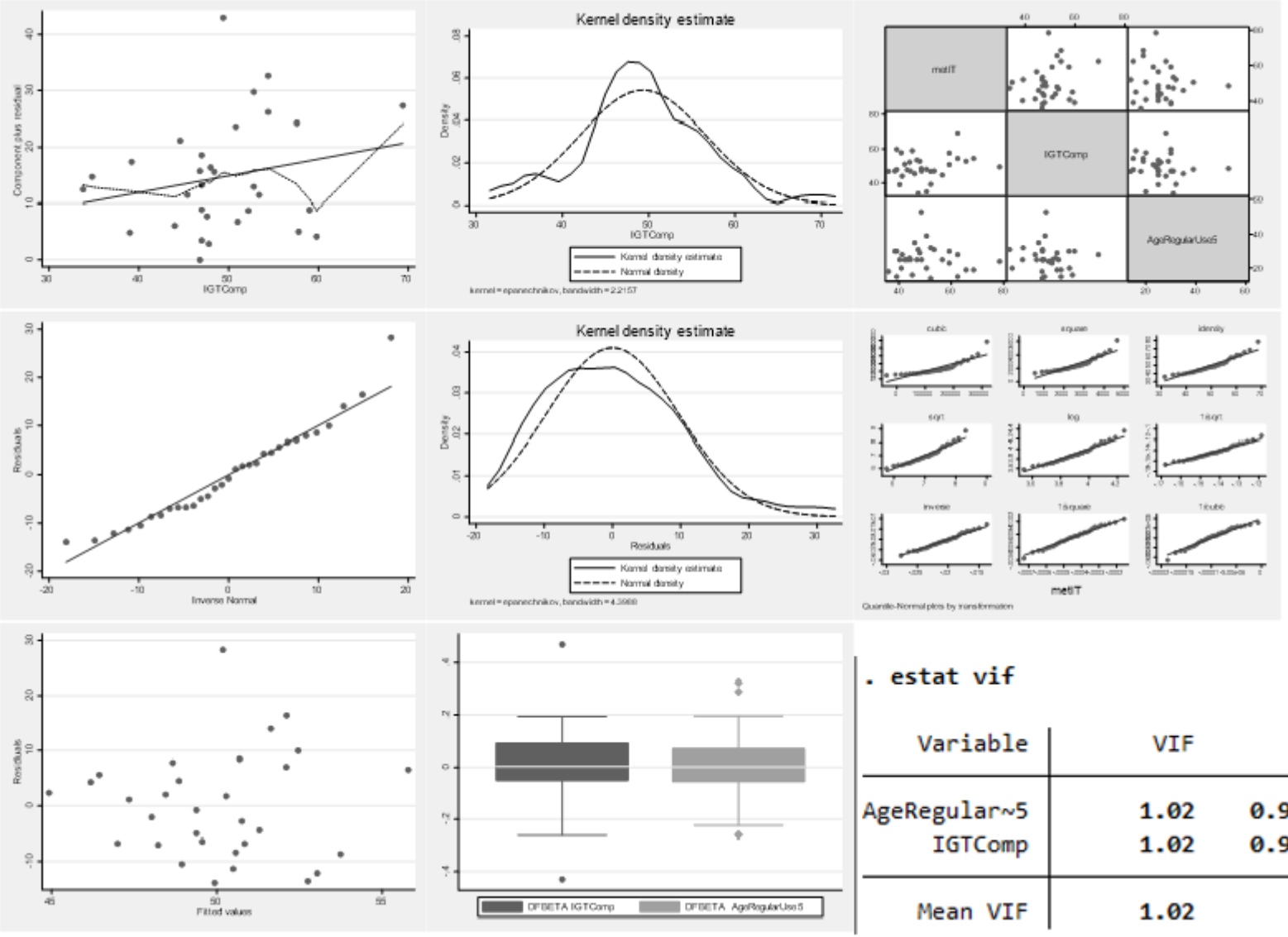
Figure 3.14. Overall Executive Function Composite – Statistical Assumptions



. estat vif

Variable	VIF	1/VIF
AgeRegular~5	1.03	0.970676
ConnersComp	1.03	0.970676
Mean VIF	1.03	

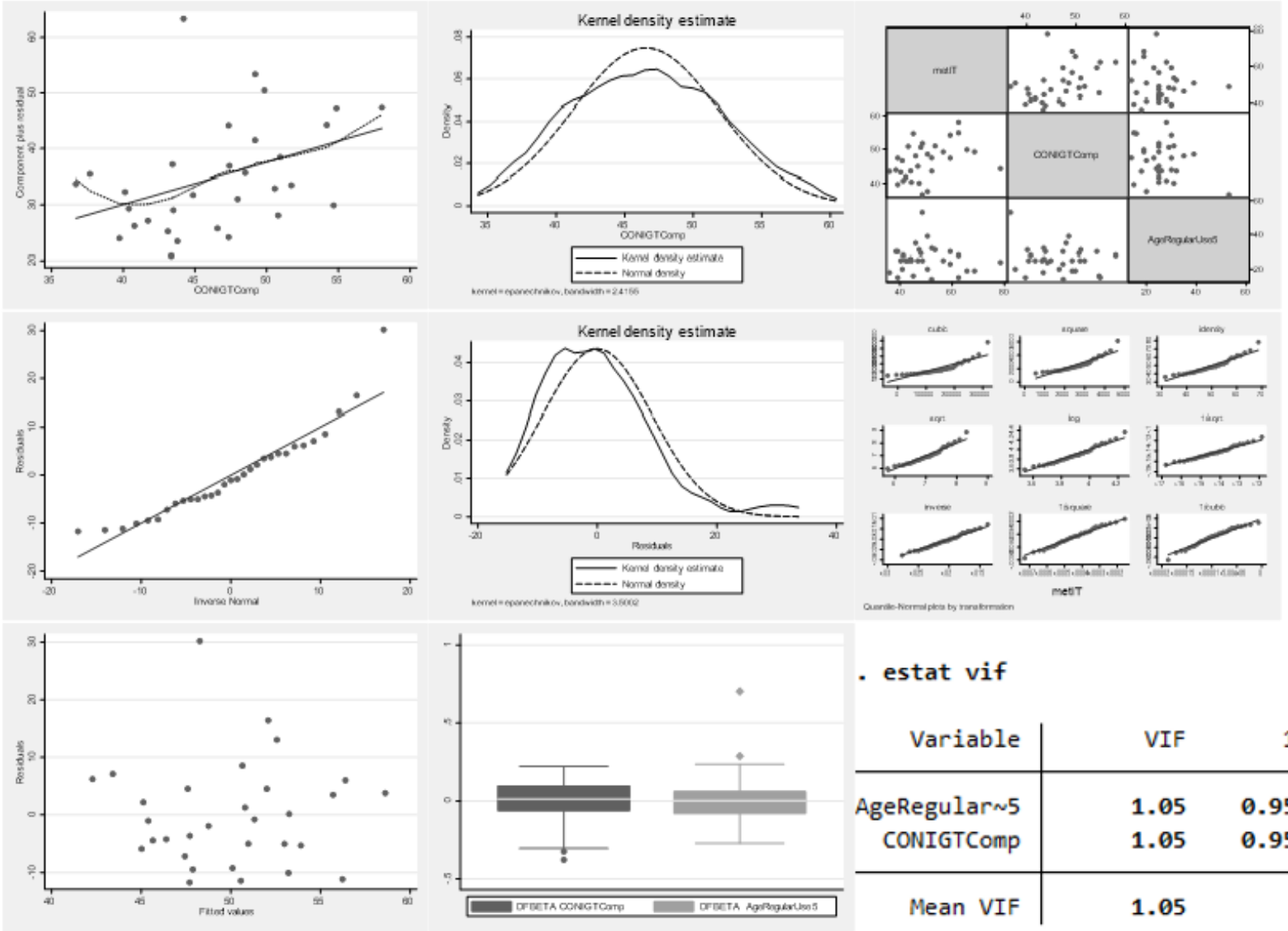
Figure 3.15. Continuous Performance Composite – Statistical Assumptions




```
. estat vif

    Variable |      VIF      1/VIF
-------------+----------------------
AgeRegular~5 |     1.02   0.984078
     IGTComp |     1.02   0.984078
-------------+----------------------
    Mean VIF |     1.02
```

Figure 3.16. Decision-Making Composite – Statistical Assumptions




```
. estat vif
```

Variable	VIF	1/VIF
AgeRegular~5	1.05	0.952609
CONIGTComp	1.05	0.952609
Mean VIF	1.05	

Figure 3.17. Overall Impulsivity Composite – Statistical Assumptions

Table 3.1. Neurocognitive Domains based on Neurocognitive Measures.

D-KEFS = Delis–Kaplan Executive Function System WAIS-IV = Wechsler Adult Intelligence Scale Fourth Edition

Domain	Sub-Domain		Measure	Score Modifications
Attention	Visual Attention		Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test Condition 1 (visual scanning, scaled), Condition 2 (number sequencing, scaled) Condition 3 (letter sequencing, scaled), Condition 5 (motor speed, scaled)	Converted to T-score
	Processing Speed		WAIS-IV Coding (scaled score)	Converted to T-score
			WAIS-IV Symbol Search (scaled score)	Converted to T-score
Memory	Working Memory		WAIS-IV Digit Span (scaled score)	Converted to T-score
			WAIS-IV Arithmetic (scaled score)	Converted to T-score
	Verbal Memory		Hopkins Verbal Learning Test-Revised (T-score) [Trial 1 immediate recall, Delayed recall, Retention]	Already in T-score
	Visuospatial Memory		Brief Visuospatial Memory Test-Revised (T-score) [Trial 1 immediate recall, Delayed recall, Learning]	Already in T-score
Executive Function	Cognitive Flexibility (Paper-based)	Planning, Rule Learning, Inhibition & Cognitive Set	D-KEFS Tower Test (scaled)	Converted to T-score
		Cognitive Flexibility	D-KEFS Trail Making Test (Condition 4, scaled)	Converted to T-score
		Inhibition & Switching	D-KEFS Color-Word Interference Test (Condition 1 scaled, Condition 2 scaled, Condition 3 scaled, Condition 4 scaled)	Converted to T-score
	Set Shifting (Computer-based)	Problem-Solving, Abstract Reasoning & Shifting Set	Wisconsin Card Sorting Test – Computer Version 4 (computer) (T-score) [Perseverative responses, Perseverative errors, Nonperseverative errors, %Conceptual level responses]	Already in T-score
Impulsivity	Continuous Performance	Omissions, Commissions & Perseverations (Computer-based)	Conners' Continuous Performance Test 3rd Edition (computer) (T-score) (D', omissions, commissions, perseverations, hit reaction time, hit reaction time standard deviation, variability, block change, inter-stimulus interval change)	Reverse-scored to ensure higher T-score means better performance
	Decision-Making	Decision-Making (Computer-based)	Iowa Gambling Task (computer) (T-score) (Net 1, Net 2, Net 3, Net 4, Net 5)	Already in T-score

Table 3.2. Participant Characteristics.

*Mean (Standard Deviation) ^n (%)

Measure	*Cog-Rehab Arm (n = 16)*	*Control Arm (n = 15)*
Age in years*	57.2 (3.9)	57.9 (7.4)
Male^	16 (100%)	14 (93.3%)
Black^	8 (50%)	11 (73.3%)
White^	8 (50%)	4 (26.7%)
American Indian/Alaska Native^	5 (31.3%)	2 (13.3%)
Latino^	4 (25%)	2 (13.3%)
Single/Never Married^	7 (43.8%)	8 (53.3%)
Divorced^	7 (43.8%)	6 (40%)
Education in years*	12.6 (1.3)	13.1 (1.4)
Retired/Disability over past 3 years^	13 (81.3%)	13 (86.7%)
Right-handed^	12 (75%)	14 (93.3%)
Cocaine – age in years when first tried*	19.9 (6.1)	24.7 (9.9)
Cocaine – age in years of regular use* (started using 3x/week or more)	22.9 (5.5)	28.9 (9.0)
Cocaine – net years used* (total years used minus abstinence)	21.9 (9.2)	21.8 (10.0)
MINI (Mini-International Neuropsychiatric Interview) depressive disorder current diagnosis^	2 (12.5%)	2 (13.3%)
MINI depressive disorder past diagnosis^	12 (75%)	6 (40%)
MINI depressive disorder recurrent diagnosis^	9 (56.3%)	6 (40%)
MINI PTSD (Posttraumatic Stress Disorder) current diagnosis^	6 (37.5%)	7 (46.7%)
MINI alcohol use disorder past 12 months diagnosis^	6 (37.5%)	2 (13.3%)
MINI cannabis use disorder past 12 months diagnosis^	5 (31.3%)	2 (13.3%)
MINI opioid use disorder past 12 months diagnosis^	6 (37.5%)	5 (33.3%)
Prescribed methadone as part of opioid treatment program^	5 (31.3%)	7 (46.7%)

Table 3.3. Summary Statistics of Neurocognitive Domains and Multiple Errands Test-Revised.

* Greater the T-score, better the performance

Domain	**Sub-Domain***	**Mean (Standard Deviation)** *n* = 31
Attention	Visual Attention (paper-based) composite T-score	46.6 (8.1)
	Processing Speed (paper-based) composite T-score	42.8 (6.0)
Overall Attention Composite T-score		44.7 (6.3)
Memory	Working Memory (verbally-based) composite T-score	41.8 (5.8)
	Verbal Memory (verbally-based) composite T-score	33.0 (8.1)
	Visuospatial Memory (paper-based) composite T-score	37.3 (5.8)
Overall Memory Composite T-score		37.4 (4.8)
Executive Function	Cognitive Flexibility (paper-based) measures composite T-score	44.1 (6.4)
	Set Shifting (computer-based) measures composite T-score	37.5 (7.4)
Overall Executive Function Composite T-score		40.8 (5.1)
Impulsivity	Continuous Performance (paper-based) measures composite T-score	43.7 (8.1)
	Decision-Making (computer-based) measures composite T-score	49.3 (7.4)
Overall Impulsivity Composite T-score		46.5 (5.3)

MET-R Scores*	**Mean (Standard Deviation)** *n* = 31
Distance traveled in miles	0.4 (0.2)
Number of calories burned	61.4 (26.3)
Number of steps taken	759.9 (389.6)
Time (in minutes) when at elevators	13.6 (6.2)
Time (in minutes) to complete MET-R	19.9 (5.0)
Number of locations visited	13.3 (4.1)
Number of tasks completed	8.4 (1.9)
Number of rule breaks	4.7 (1.6)
Self-rating of performance (scale of 0 to 100)	65.9 (19.4)
Self-rating of familiarity with the Veterans Affairs Hospital (scale of 0 to 100)	73.1 (15.3)
Performance efficiency score	0.7 (0.3)
Performance efficiency score – T-score	50.0 (10.0) [range 36.0 to 78.5]

Table 3.4. Association between Multiple Errands Test-Revised Performance Efficiency T-Score and Neurocognitive Domain Composite T-Scores.

All analyses (n = 31) were adjusted for age, sex, education, and age in years of regular cocaine use.

Domain	Sub-Domain	Adjusted coefficient 95% Confidence Interval
Attention	Visual Attention (paper-based) composite T-score	0.1 (-0.4 to 0.5)
	Processing Speed (paper-based) composite T-score	0.1 (-0.5 to 0.7)
Overall Attention Composite T-score		0.1 (-0.3 to 0.6)
Memory	Working Memory (verbally-based) composite T-score	0.1 (-0.7 to 0.9)
	Verbal Memory (verbally-based) composite T-score	0.3 (-0.2 to 0.8)
	Visuospatial Memory (paper-based) composite T-score	0.1 (-0.8 to 0.9)
Overall Memory Composite T-score		0.3 (-0.7 to 1.4)
Executive Function	Cognitive Flexibility (paper-based) measures composite T-score	0.3 (-0.6 to 1.1)
	Set Shifting (computer-based) measures composite T-score	0.1 (-0.5 to 0.6)
Overall Executive Function Composite T-score		0.3 (-0.7 to 1.3)
Impulsivity	Continuous Performance (paper-based) measures composite T-score	0.4 (-0.02 to 0.8)
	Decision-Making (computer-based) measures composite T-score	0.3 (-0.2 to 0.8)
Overall Impulsivity Composite T-score		0.8 (0.2 to 1.3)

Chapter 3 References

363. Teichner, G., M.D. Horner, and R.T. Harvey, *Neuropsychological predictors of the attainment of treatment objectives in substance abuse patients.* Int J Neurosci, 2001. 106(3-4): p. 253-63.

364. Teichner, G., et al., *Substance abuse treatment outcomes for cognitively impaired and intact outpatients.* Addict Behav, 2002. 27(5): p. 751-63.

365. Vik, P.W., et al., *Cognitive impairment in substance abuse.* Psychiatr Clin North Am, 2004. 27(1): p. 97-109, ix.

366. Rolland, B., et al., *A Patient-Tailored Evidence-Based Approach for Developing Early Neuropsychological Training Programs in Addiction Settings.* Neuropsychol Rev, 2019. 29(1): p. 103-115.

367. Butler, K. and B. Le Foll, *Impact of Substance Use Disorder Pharmacotherapy on Executive Function: A Narrative Review.* Front Psychiatry, 2019. 10: p. 98.

368. Parsons, O.A., K.W. Schaeffer, and S.W. Glenn, *Does neuropsychological test performance predict resumption of drinking in posttreatment alcoholics?* Addict Behav, 1990. 15(3): p. 297-307.

369. Gregson, R.A. and G.M. Taylor, *Prediction of relapse in men alcoholics.* J Stud Alcohol, 1977. 38(9): p. 1749-60.

370. Fals-Stewart, W. and J. Schafer, *The relationship between length of stay in drug-free therapeutic communities and neurocognitive functioning.* J Clin Psychol, 1992. 48(4): p. 539-43.

371. Bates, M.E., et al., *Cognitive impairment influences drinking outcome by altering therapeutic mechanisms of change.* Psychol Addict Behav, 2006. 20(3): p. 241-53.

372. Aharonovich, E., E. Nunes, and D. Hasin, *Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment.* Drug Alcohol Depend, 2003. 71(2): p. 207-11.

373. Aharonovich, E., et al., *Cognitive deficits predict low treatment retention in cocaine dependent patients.* Drug Alcohol Depend, 2006. 81(3): p. 313-22.

374. Fox, H.C., E.D. Jackson, and R. Sinha, *Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes.* Psychoneuroendocrinology, 2009. 34(8): p. 1198-207.

375. Katz, E.C., et al., *Cognitive ability as a factor in engagement in drug abuse treatment.* Am J Drug Alcohol Abuse, 2005. 31(3): p. 359-69.

376. Hudetz, J.A., et al., *Postoperative cognitive dysfunction in older patients with a history of alcohol abuse.* Anesthesiology, 2007. 106(3): p. 423-30.

377. Goldstein, R.Z., et al., *Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex.* Neuropsychologia, 2004. 42(11): p. 1447-58.

378. Roebuck-Spencer, T.M., et al., *Cognitive Screening Tests Versus Comprehensive Neuropsychological Test Batteries: A National Academy of Neuropsychology Education Paperdagger.* Arch Clin Neuropsychol, 2017. 32(4): p. 491-498.

379. Howieson, D., *Current limitations of neuropsychological tests and assessment procedures.* Clin Neuropsychol, 2019. 33(2): p. 200-208.

380. Shallice, T. and P.W. Burgess, *Deficits in strategy application following frontal lobe damage in man.* Brain, 1991. 114 (Pt 2): p. 727-41.

381. Alderman, N., et al., *Ecological validity of a simplified version of the multiple errands shopping test.* J Int Neuropsychol Soc, 2003. 9(1): p. 31-44.

382. Tranel, D., J. Hathaway-Nepple, and S.W. Anderson, *Impaired behavior on real-world tasks following damage to the ventromedial prefrontal cortex.* J Clin Exp Neuropsychol, 2007. 29(3): p. 319-32.

383. Roca, M., et al., *Cognitive deficits in multiple sclerosis correlate with changes in fronto-subcortical tracts.* Mult Scler, 2008. 14(3): p. 364-9.

384. Cipresso, P., et al., *Virtual multiple errands test (VMET): a virtual reality-based tool to detect early executive functions deficit in Parkinson's disease.* Front Behav Neurosci, 2014. 8: p. 405.

385. Morrison, M.T., et al., *Multiple Errands Test-Revised (MET-R): A Performance-Based Measure of Executive Function in People With Mild Cerebrovascular Accident.* Am J Occup Ther, 2013. 67(4): p. 460-8.

386. Torralva, T., et al., *Deficits in tasks of executive functioning that mimic real-life scenarios in bipolar disorder.* Bipolar Disord, 2012. 14(1): p. 118-25.

387. Caletti, E., et al., *Neuropsychology, social cognition and global functioning among bipolar, schizophrenic patients and healthy controls: preliminary data.* Front Hum Neurosci, 2013. 7: p. 661.

388. Pedroli, E., et al., *A Computational Approach for the Assessment of Executive Functions in Patients with Obsessive-Compulsive Disorder.* J Clin Med, 2019. 8(11).

389. Valls-Serrano, C., et al., *Development of a Contextualized Version of the Multiple Errands Test for People with Substance Dependence.* J Int Neuropsychol Soc, 2018. 24(4): p. 347-359.

390. Maeir, A., S. Krauss, and N. Katz, *Ecological Validity of the Multiple Errands Test (MET) on Discharge from Neurorehabilitation Hospital.* OTJR (Thorofare N J), 2011. 31(1): p. S38-46.

391. Lai, F.H., et al., *The validity, reliability and clinical utility of a performance-based executive function assessment in people with mild to moderate dementia.* Aging Ment Health, 2019: p. 1-9.

392. Antoniak, K., et al., *Developing and Validating a Big-Store Multiple Errands Test.* Front Psychol, 2019. 10: p. 2575.

393. Castiel, M., et al., *Use of the Multiple Errands Test-Simplified Version in the assessment of suboptimal effort.* Neuropsychol Rehabil, 2012. 22(5): p. 734-51.

394. Burns, S.P., et al., *In-home contextual reality: a qualitative analysis using the Multiple Errands Test Home Version (MET-Home).* Neuropsychol Rehabil, 2018: p. 1-15.

395. Valls-Serrano, C., A. Caracuel, and A. Verdejo-Garcia, *Goal Management Training and Mindfulness Meditation improve executive functions and transfer to ecological tasks of daily life in polysubstance users enrolled in therapeutic community treatment.* Drug Alcohol Depend, 2016. 165: p. 9-14.

396. Valls-Serrano, C., A. Verdejo-Garcia, and A. Caracuel, *Planning deficits in polysubstance dependent users: Differential associations with severity of drug use and intelligence.* Drug Alcohol Depend, 2016. 162: p. 72-8.

397. Delis, D.C., E. Kaplan, and J.H. Kramer, *The Delis-Kaplan Executive Function System*. 2001, San Antonio, TX: The Psychological Corporation.

398. Wechsler, D.A., *Wechsler Adult Intelligence Scale - Fourth Edition*. 2008, San Antonio, TX: Pearson Assessment.

399. Brandt, J., *The hopkins verbal learning test: Development of a new memory test with six equivalent forms.* Clinical Neuropsychologist, 1991. 5(2): p. 125-142.

400. Benedict, R.H.B., et al., *Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability.* The Clinical Neuropsychologist, 1998. 12(1): p. 43-55.

401. Benedict, H.R.B., *Brief Visuospatial Memory Test - Revised*. 1997, Odessa, FL: Psychological Assessment Resources, Inc.

402. Heaton, R.K., et al., *Wisconsin Card Sorting Test Manual, Revised and Expanded.* 1993, Orlando, FL: Psychological Assessment Resources.

403. Fortuny, L.A. and R.K. Heaton, *Standard versus computerized administration of the wisconsin card sorting test.* The Clinical Neuropsychologist, 1996. 10(4): p. 419-424.

404. Conners, C.K., *Conners Continuous Performance Test- Third Edition (Conners CPT 3) & Conners Continuous Auditory Test of Attention (Conners CATA): Technical Manual.* 2014, New York: Multi-Health Systems Inc.

405. Bechara, A., et al., *Insensitivity to future consequences following damage to human prefrontal cortex.* Cognition, 1994. 50(1-3): p. 7-15.

406. Hamera, E. and C.E. Brown, *Developing a context-based performance measure for persons with schizophrenia: the test of grocery shopping skills.* Am J Occup Ther, 2000. 54(1): p. 20-5.

407. Hamera, E., M. Rempfer, and C. Brown, *Performance in the "real world": update on test of grocery shopping skills (TOGSS).* Schizophr Res, 2005. 78(1): p. 111-2; author reply 113-4.

408. MacKinnon, J.G. and H. White, *Some heteroskedasticity-consistent covariance matrix estimators with improved finite sample properties.* Journal of Econometrics, 1985. 29(3): p. 305-325.

409. Dudgeon, P., *Some Improvements in Confidence Intervals for Standardized Regression Coefficients.* Psychometrika, 2017. 82(4): p. 928-951.

410. Long, J.S. and L.H. Ervin, *Using Heteroscedasticity Consistent Standard Errors in the Linear Regression Model.* The American Statistician, 2000. 54(3): p. 217-224.

411. Dawson, D.R., et al., *Further development of the Multiple Errands Test: standardized scoring, reliability, and ecological validity for the Baycrest version.* Arch Phys Med Rehabil, 2009. 90(11 Suppl): p. S41-51.

Publishing Agreement

It is the policy of the University to encourage open access and broad distribution of all theses, dissertations, and manuscripts. The Graduate Division will facilitate the distribution of UCSF theses, dissertations, and manuscripts to the UCSF Library for open access and distribution. UCSF will make such theses, dissertations, and manuscripts accessible to the public and will take reasonable steps to preserve these works in perpetuity.

I hereby grant the non-exclusive, perpetual right to The Regents of the University of California to reproduce, publicly display, distribute, preserve, and publish copies of my thesis, dissertation, or manuscript in any form or media, now existing or later derived, including access online for teaching, research, and public service purposes.

DocuSigned by:
Rajkumar Kalapatapu
9517D18FE8F049F...
Author Signature

5/29/2020
Date