Official Title: Compensatory Cognitive Training Via Telehealth for Veterans With Alcohol Use Disorders

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Title
Compensatory Cognitive Training Via Telehealth for Veterans with Alcohol Use Disorders

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Specific Aims/Purpose

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Prior research conducted by our team at the VA Portland Healthcare System (VAPORHCS) has demonstrated that Compensatory Cognitive Training (CCT) reduces cognitive problems and improves compensatory cognitive strategy use among Veterans with a history of mild traumatic brain injury (Pagulayan et al., 2017; Storzbach et al., 2017) and mild cognitive impairment (Huckans et al., 2013; Huckans et al., 2010). Motivationally Enhanced Compensatory Cognitive Training for Addictions (ME-CCT-A) is a promising manualized cognitive rehabilitation therapy for addictions that was developed and piloted by the original developers of CCT (Huckans et al., 2018). This study extends our research by evaluating ME-CCT-A delivered via telehealth in the context of early remission from alcohol use disorder (AUD). The specific aims of the study include:

Aim 1. Evaluate feasibility and acceptability in a pilot trial of ME-CCT-A delivered via telehealth in Veterans in early remission from AUDs.

> **Hypothesis 1:** We hypothesize that ME-CCT-A will be feasible and acceptable in a pilot trial of ME-CCT-A delivered via telehealth.

Aim 2. Assess the preliminary efficacy of ME-CCT-A delivered via telehealth on objective cognitive performance, daily functioning, subjective cognitive complaints, and psychiatric and substance use outcomes.

> **Hypothesis 2:** We hypothesize that ME-CCT-A will improve objective cognitive performance, daily functioning, subjective cognitive complaints, and psychiatric and substance use outcomes in Veterans in early remission from AUDs.

Scientific Rationale and Significance

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Alcohol use disorders (AUDs) are highly disabling yet treatable conditions that pose a significant burden to individuals and society due to the high rates of morbidity, mortality, and economic costs associated with the condition. Veterans are at elevated risk for developing AUDs due to high rates of trauma exposure, readjustment stressors, and heavy alcohol consumption normalized within military cultures (Meadows et al., 2022; Straus et al., 2020). AUDs are among the most common psychiatric conditions

nationally; the lifetime prevalence of AUDs is 29.1% with a 12-month prevalence of 13.9% (Grant et al., 2015). Rates of AUDs are even higher among Veterans; the lifetime prevalence of AUDs for Veterans is 35.8% with a 12-month prevalence of 15.1% (Boden & Hoggatt, 2018). According to the Centers for Disease Control, AUDs costs the United States $249 billion annually (Sacks JJ, 2015). The costs associated with AUDs are numerous, with the largest contributors being healthcare expenses, criminal justice expenses, losses to workplace productivity, and motor vehicle crashes (Rehm & Shield, 2019; Rehm, 2009; Sacks JJ, 2015).

Despite the high prevalence and costs associated with AUDs, treatment rates for the general population remain low with only 17.3% of people with AUDs receiving treatment, indicating a treatment gap of 82.7% (Mekonen et al., 2021). For those who enter treatment, relapse rates for current substance use treatment programs remain very high (~40-60%), often with more than half of individuals relapsing within six months of completing treatment (Moos & Moos, 2006; NIDA, 2020). Treatment rates for AUD within the VA are slightly higher, with approximately 25% of Veterans with an AUD receiving specialty addictions treatment for AUD (Williams et al., 2021).

Telehealth can play a considerable role in increasing access to evidence-based treatments for Veterans with AUDs. The US Department of Veterans Affairs (VA) has expanded access to virtual visits (i.e., VA Video Connect) throughout the COVID-19 pandemic (Connolly et al., 2021). From February 2020 to November 2020, weekly telehealth visits increased by 1,653% with over 40,000 telehealth visits completed daily (US Department of Veteran Affairs, 2021). Preliminary research indicates that there is little difference between evidenced-based treatments (EBTs) delivered in-person versus via telehealth (Fiacco et al., 2021; Lin et al., 2019; Shigekawa et al., 2018; Young, 2012). A recent rapid review of telehealth for SUDs highlighted strong support for telehealth as an addition to standard care, as it improved abstinence from alcohol and increased treatment retention (Uhl et al., 2022). A systemic review of group-based treatments delivered via telehealth indicated high patient and provider satisfaction and showed similar outcomes to in-person groups (Gentry et al., 2019). Telehealth can eliminate barriers to Veterans accessing EBTs and has many documented advantages, including improved access to EBTs, cost effectiveness, convenience, greater retention of materials, time saving effects, greater privacy, and increased flexibility for both Veterans and providers (Elnitsky CA, 2013; Frost et al., 2022; Kintzle et al., 2022).

Most individuals entering treatment for AUDs present with cognitive deficits across a range of cognitive domains, including attention, memory, and executive functions, and these deficits frequently persist for six months or longer following remission (Bruijnen et al., 2019; Glass et al., 2009; Le Berre et al., 2017; Stavro et al., 2013). Cognitive deficits are associated with increased relapse rates, less treatment compliance, and poorer treatment outcomes in individuals seeking substance use treatment (Czapla et al., 2016; Mahoney, 2019; Schmidt et al., 2017). Despite the high rates of cognitive impairments among adults with AUDs and their negative impact on treatment outcomes, current evidence-based pharmacotherapies and behavioral treatments for AUDs do not specifically treat or address cognitive symptoms. Accessible (e.g., brief, manualized, delivered via telehealth) and effective treatments for Veterans with AUDs and cognitive deficits are urgently needed.

Motivationally Enhanced Compensatory Cognitive Training for Addictions (ME-CCT-A) is a manualized group-based behavioral intervention (8 weeks, 2 hour per week) designed to improve cognitive functioning in Veterans with substance use disorders (SUDs) and cognitive complaints. ME-CCT-A is an adaptation of CCT initially developed by clinicians and researchers at the VA Portland Healthcare System and VA San Diego Healthcare System (Storzbach et al., 2017). CCT draws from the empirical and theoretical literature on compensatory strategy training for conditions characterized by cognitive complaints and impairments, including mild traumatic brain injury (Storzbach et al., 2017), psychosis

(Twamley et al., 2012), and mild cognitive impairment (Huckans et al., 2010). ME-CCT-A is a comprehensive treatment in that it addresses multiple types of symptoms and concerns that interfere with recovery from addictions – cognitive impairments, neuropsychiatric symptoms, and lifestyle patterns that increase risk of cognitive impairment, poor health, and relapse. In addition to training in compensatory cognitive skills, ME-CCT-A includes mindfulness practices and motivational interviewing techniques (Miller, 2013) to boost the adoption of lifestyle strategies (e.g., nutrition, exercise) that improve cognition and overall health (Gomez-Pinilla, 2006). ME-CCT-A is designed to be easy to administer and as an adjunct to standard SUD treatment programs. While initially designed to be delivered in-person, ME-CCT-A can be delivered through virtual platforms with little to no modification of the content and structure of the intervention.

VA-SPECIFIC REQUIREMENT (relevance to VA mission):

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Given the high rate of AUDs among Veterans, the prevalence of cognitive impairments among those with AUDs, and the negative impact of cognitive impairments on treatment outcomes, an evidence-based cognitive training intervention that optimally addresses the complex needs of Veterans with AUDs and cognitive impairments is of critical importance. To our knowledge, no studies have been conducted to evaluate the efficacy of a telehealth-delivered, manualized comprehensive compensatory cognitive training intervention with Veterans with addictions and cognitive deficits. This study will allow us to optimize ME-CCT-A for the telehealth format and assess the feasibility, acceptability, and preliminary efficacy of the intervention in preparation for a larger-scale pilot randomized control trial.

Preliminary Studies

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Ms. Shirley (Co-PI) has extensive training and experience in conducting, pilot testing, and publishing studies on CCT with Veterans. Ms. Shirley's research and clinical experiences have informed her knowledge of the importance of utilizing neuropsychological assessment and evidence-based treatments in the management of cognitive impairment across a range of conditions, such as mild cognitive impairment (MCI), traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), and substance use disorders (SUDs). From 2018 to present, Ms. Shirley has served as the study clinician administering the clinical protocol of a multi-site VA-funded randomized control trial that evaluates the efficacy of CCT for Veterans with MCI (O'Neil, IRB#4101). She has collected pilot data on CCT in Veterans with substance use disorders alongside one of the originators of CCT, Marilyn Huckans, PhD (O'Neil, IRB#4018). In addition to expertise in CCT, Ms. Shirley's research has examined the adverse psychiatric, cognitive, and physical health effects following chronic use and during protracted abstinence from SUDs. From 2018 to present, she has served as study coordinator of a project investigating brain dysfunction in Veterans with AUDs following treatment for Hepatitis C (Loftis, IRB#3967). She has analyzed data collected by the Methamphetamine Use Research Center (MARC) and published multiple manuscripts examining differences in cognition, psychiatric symptoms, and physical health during active use and remission from methamphetamine (MA) and opioids. This project is a logical extension of her interest and experience in cognitive rehabilitation interventions and years of collaboration with the Compensatory Cognitive Training Research Program (led by her academic/research mentor, Maya O'Neil, PhD [Co-PI]) at VAPORHCS and OHSU.

Ms. Shirley's recent published work related to CCT and SUDs are noted below:

1. **Shirley, K.,** Sano, E., & O'Neil, M. (2023). Pilot trial of Compensatory Cognitive Training with Veterans in Remission from Alcohol Use Disorders. Abstract selected for poster presentation at the Annual RSA Scientific Meeting, Bellevue, Washington.
2. Loftis, J.M., Firsick, E., **Shirley, K.**, Le-Cook, A., Sano, E., Hudson, R., & Moorman, J. (2023). Inflammatory and Mental Health Sequelae of COVID-19. *Comprehensive Psychoneuroendocrinology* (Under Review).
3. **Shirley, K.,** O'Neil, M., Boyd, S., & Loftis, J.M. (2023). Differences in Rates of Impairment in Adults Who Use Methamphetamine Using Two Sets of Demographically Corrected Norms. *Applied Neuropsychology: Adult*.
4. **Shirley, K**. & Loftis, J. M. (2022). A Spotlight on HCV and SARS-CoV-2 Co-infection and Brain Function. *Pharmacology, Biochemistry and Behavior.*
5. **Shirley, K.,** Firsick, E., Sano, E., O'Neil, M., & Loftis, J. (2022). Comparison of Self-Reported Psychiatric Symptom Severity in Adults Who Use Methamphetamine Versus Methamphetamine and Opioid Co-use. Abstract selected for poster presentation at the Association for Psychological Science Annual Convention, Chicago, Illinois.
6. **Shirley, K.,** O'Neil, M., & Loftis, J. (2022). Potential for Inflated Norms in Neuropsychological Assessment of Individuals Who Use Methamphetamine. Abstract selected for poster presentation at the International Neuropsychological Society 50th Annual Meeting, New Orleans, Louisiana.
7. Huckans, M., Boyd, S., Moncrief, G., Hantke, N., Winters, B., **Shirley, K.,** Sano, E., McCready, H., Dennis, L., Kohno, M., Hoffman, W., & Loftis, J. (2021). Cognition during Active Methamphetamine Use Versus Remission. *Journal of Clinical and Experimental Neuropsychology.*
8. O'Neil, M. E., Cameron, D., **Shirley, K.,** Sano, E., Twamley, E., Williams, R., Turner, A., Pagulayan, K., Roost, M., Jak, A., Storzbach, D., & Huckans, M. (2021). Change in Learning and Memory Partially Mediates Effects of Compensatory Cognitive Training on Self-Reported Cognitive Symptoms. *Journal of Head Trauma Rehabilitation*.
9. Loftis, J., Firsick, E., **Shirley, K.,** & Hoffman, W. (2021). Effects of Alcohol Use Disorder and Chronic Viral Infection on Neurocircuitry and Behavior. Abstract selected for oral presentation (given by Loftis) at the Psychiatric Research Society Annual Meeting, Park City, Utah.

Dr. Maya O'Neil's (Co-PI) research focuses on treatment, assessment, and health services related to PTSD and TBI, as well as common comorbidities, such as cognitive impairment. Dr. O'Neil is currently funded on a 5-year career development award (CDA) through the VA's rehabilitation research and development program piloting the efficacy and feasibility of CCT for PTSD (O'Neil #3500). In addition, Dr. O'Neil is the site primary investigator of a multi-site, VA-funded, randomized control trial that evaluates the efficacy of CCT for Veterans with MCI (O'Neil #4101) as well as a principal- and co-investigator on numerous grants that investigate cognitive functioning and mental health. Dr. O'Neil has worked closely and collaborated with the developers of CCT on multiple projects and papers.

Dr. O'Neil's recent published works related to CCT are noted below:

1. Keller, A.V., Clark, J.M.R., Maye, J.E., Jak, A.J., **O'Neil, M.E.**, Williams, R.M., Turner, A.P., Pagulayan, K.F., & Twamley, E.W. (2023). Neuropsychological predictors of posttraumatic stress disorder and depressive symptom improvement in compensatory cognitive training for Veterans with a history of mild traumatic brain injury. Abstract selected for poster presentation at the 51st Annual Meeting of the International Neuropsychological Society, San Diego, CA.
2. Clark, J.M.R., Mahmood, Z., Jak, A.J., Huckans, M., **O'Neil, M.E.**, Roost, M., Williams, R.M., Turner, A.P., Pagulayan, K.F., Storzbach, D., & Twamley, E.W. (2022). Neuropsychological

performance and functional capacity following mild traumatic brain injury in Veterans. *Journal of Head Trauma Rehabilitation.*
3. Clark, J.M.R., Keller, A.V., Maye, J.E., Jak, A.J., Huckans, M., **O'Neil, M.E.**, Roost, M.S., Williams, R.M., Turner, A.P., Pagulayan, K.F., Storzbach, D., & Twamley, E.W. (2021). Neuropsychological predictors of posttraumatic stress disorder and depressive symptom improvement in compensatory cognitive training for Veterans with a history of mild traumatic brain injury. *Journal of Head Trauma Rehabilitation*.
4. **O'Neil, M.E.,** Cameron, D.C., Shirley, K., Sano, E., Twamley, E., Williams, R., Turner, A., Pagulayan, K., Roost, M., Jak, A., Storzbach, D., Huckans, M. (2021). Change in learning and memory partially mediates effects of compensatory cognitive training on self-reported cognitive symptoms. *Journal of Head Trauma Rehabilitation*.
5. Mahmood, Z., Clark, J.M.R., Jak, A.J., Huckans, M., **O'Neil, M.E.,** Roost, M.S., Williams, R.M., Pagulayan, K.F., Turner, A.P., Storzbach, D., & Twamley, E.W. (2020). Predictors of intervention adherence in compensatory cognitive training for Veterans with a history of mild traumatic brain injury. *Journal of Head Trauma Rehabilitation.*
6. Clark, J.M.R., Mahmood, Z., Huckans, M., **O'Neil, M.E.**, Jake, A.J., Williams, R.M., Turner, A.P., Pagulayan, K.F., Roost, M.S., Callahan, M.L., Storzbach, D.M., & Twamley, E.W. (2019). Correlates of PTSD symptom improvement in Veterans with a history of mild traumatic brain injury receiving compensatory cognitive training. Abstract selected for poster presentation at the 14th Annual Lewis L. Judd Young Investigators Symposium, UCSD Department of Psychiatry, La Jolla, CA.
7. **O'Neil, M.E.,** Pagulayan, K.*, Turner, A., White, R., Laman-Maharg, B., Storzbach, D., Twamley, E., (2017). Mental health does not moderate compensatory cognitive training efficacy for Veterans with a history of mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation. [*Shared first authorship]*
8. Storzbach, D., Twamley, E., Roost, M., Golshan, S., Williams, R., **O'Neil, M.E.,** Jak, A., Turner, A., Kowalski, H., Pagulayan, K., Huckans, M. (2016). Compensatory cognitive training for Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Veterans with mild traumatic brain injury. *Journal of Head Trauma Rehabilitation.*

Research Design and Methods

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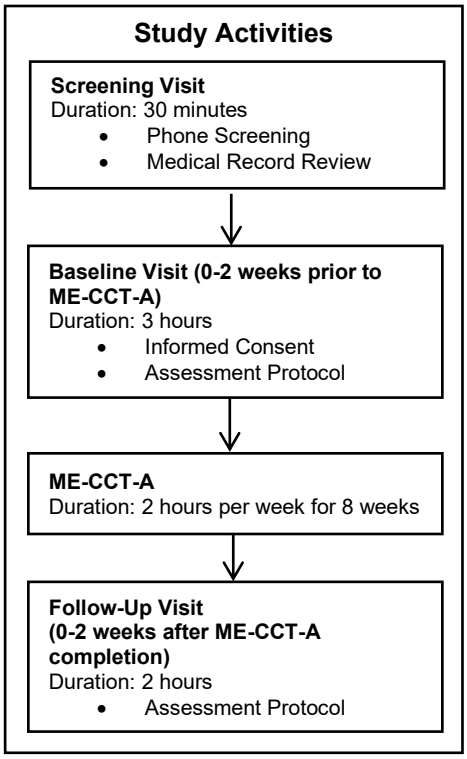
Overview: We will enroll up to 30 Veterans and assess feasibility, acceptability, and preliminary efficacy of ME-CCT-A via telehealth. Veterans will receive ME-CCT-A via telehealth and undergo two study evaluations (baseline and 8 weeks) while also continuing with their usual medical, psychiatric, psychotherapeutic, and/or substance use treatment. Feasibility will be assessed by examining data on recruitment and retention rates, rate of completion of the intervention, and feasibility of testing procedures and data collection methods. Acceptability will be assessed through feedback surveys after study completion. We will assess the preliminary efficacy of ME-CCT-A on objective cognitive performance, daily functioning, subjective cognitive complaints, and psychiatric and substance use outcomes.

Intervention: Once at least 4 eligible Veterans have completed baseline visits, the 8-week group will begin via telehealth. The virtual group will be held through VA Video Connect or another VA-approved video meeting tool. Group sessions will last for 2 hours and consist of interactive didactic information and discussion and activities that introduce a variety of cognitive strategies and external aids. Ms. Shirley (Co-PI) and/or another study staff member will run the CCT groups. Intervention materials will be mailed to participants prior to group start date. Attendance of each Veteran at each session will be noted. Individual make-up sessions will be offered to Veterans who miss a session, and attendance at make-ups will be recorded.



ME-CCT-A Treatment Manual: The structure of the intervention is determined by the ME-CCT-A treatment manual, which has been tailored to each cognitive domain commonly affected by SUDs (Huckans et al., 2018). Session materials correspond to compensatory cognitive training for difficulties with learning, memory, processing speed, executive functioning (multitasking abilities), verbal functioning, concentration, and attention. Additionally, session content in the updated manual is tailored to address other symptoms related to SUDs that might be influencing cognitive functioning and incorporates motivational interviewing methods. Table 1 outlines the structure and content of the ME-CCT-A treatment manual and group sessions.

Table 1. ME-CCT-A Session Content

Session	Major Concepts	Examples of Strategies	Session Activities	Home Exercise
1	Intro and SUD/cognitive functioning psychoeducation	Creating a "home" for important items	Day planner use	Finding a home for the day planner
2	Organization and prospective memory Part I	Time management	Scheduling and concrete goal setting	Practice using the calendar
3	Organization and prospective memory Part II	Daily and weekly planning sessions	Enter lists and activities into the calendar	Follow through with planning sessions
4	Attention and concentration	Paying attention during meetings and conversations	Practicing paying attention during conversations	Active listening once a day
5	Learning and memory	Internal and external memory strategies	Practice memory strategies	Practice using a strategy everyday
6	Problem-solving and cognitive flexibility	Evaluating costs and benefits to identify better choices	6-step problem-solving method	Practice problem-solving with 2 life goals
7	Planning and goal setting	Goal setting	Identify and re-evaluate priorities	Practice planning a goal
8	Skill integration and review	Review, practice, goals, and planning for the future	How to maintain skills and apply them to goals	Provided with additional SUD-related resources

Assessment Protocol: Veterans will complete the virtual assessment battery (see Table 2) at baseline (approximately 0-2 weeks prior to ME-CCT-A) and follow-up (approximately 0-2 weeks following ME-CCT-A completion). The battery consists of performance-based tests of objective cognition functioning and functional capacity and self-report measures of subjective cognitive complaints/functioning, substance use, engagement in targeted lifestyle practices associated with improved cognition, and engagement in protective activities/factors associated with reduced relapse. The Client Satisfaction Questionnaire (CSQ-8) and a series of structured, open-ended questions specific to the study intervention will be included at follow-up to assess Veterans' satisfaction with the virtual CCT intervention. Assessments will take approximately 2 hours.

The cognitive domains were selected for assessment because previous research by our group has demonstrated that SUDs can be associated with significant impairments in attention, memory, and executive functions, and because ME-CCT-A includes cognitive strategy training that specifically targets each of those domains (Huckans et al., 2021; Huckans, Fuller, Wheaton, et al., 2015; Huckans, Fuller, Chalker, et al., 2015; Huckans et al., 2010; Storzbach et al., 2017). Measures were selected because of their sound psychometric properties and their ability to be conducted virtually. Each neuropsychological measure has more than one form, minimizing test-retest confounds at our two assessment visits. Assessment measures will be scored according to standardized test procedures. All assessments will be administered by Ms. Shirley (Co-PI) or another approved study member and supervised by Maya O'Neil, Ph.D. (Co-PI), who is a licensed, credentialed, and privileged VA neuropsychologist.

Table 2. Assessment Protocol	
Measure	**Construct Assessed**
Objective Cognitive Functioning and Functional Capacity (Neuropsychological Tests)	
Wide Range Achievement Test 5 (WRAT5)	Reading ability, premorbid IQ estimate (baseline only)
Neuropsychological Assessment Battery (NAB) Attention Module subtest: Digit Span	Auditory attention capacity and working memory
NAB Attention Module subtest: Driving Scenes	Visual attention and working memory
NAB Memory Module subtest: List Learning	Verbal learning and memory
NAB Memory Module subtest: Shape Learning	Visual learning and memory
NAB Memory Module subtest: Medication Instructions	Verbal learning and memory relevant to everyday functioning
NAB Memory Module subtest: Name, Address, and Phone Number	Verbal learning and memory relevant to everyday functioning
NAB Executive Functions Module subtest: Judgment	Everyday problem-solving/executive function
NAB Executive Functions Module subtest: Categories	Mental flexibility and categorization
Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency	Language
Self-report Measures (Questionnaire Battery)	
Brief Addiction Monitor (BAM)	Substance use factors; Risk/protective factors
Prospective-Retrospective Memory Questionnaire (PRMQ)	Cognitive symptoms
Portland Cognitive Strategies Scale 2.0 (PCSS)	Compensatory cognitive strategy use
PROMIS–57 Profile v2.1	Physical, mental, and social health
PROMIS v2.0 Cognitive Function 8a	Subjective cognitive functioning
Client Satisfaction Questionnaire (CSQ-8)	Satisfaction with the intervention (follow-up only)
Timeline Followback (TLFB)	Alcohol and cannabis consumption over a given time period
Alcohol Use Disorders Identification Test (AUDIT-C)	Alcohol use

ANALYTIC PLAN.
All data analyses will be conducted by study personnel with expertise in statistics, using Excel, SPSS, or other statistical software approved by the VA.

Phase 2, Aim 2 *Feasibility and Acceptability*: Descriptive statistics will characterize the feasibility of recruiting and retaining Veterans. Recruitment will be deemed feasible if we successfully screen for eligibility 50% of Veterans referred to the study and enroll 75% of screened Veterans who meet all study inclusion criteria. Retention will be deemed successful if we achieve 75% completion for post-treatment assessments. Chi-square tests of association and t-tests will compare demographic and clinical characteristics of successfully versus unsuccessfully recruited and retained Veterans to identify characteristics of Veterans who may require more intensive recruitment or retention efforts in a future trial. Acceptability will be assessed through surveys on treatment satisfaction (i.e., CSQ-8 with additional study-specific items) following group completion. Treatment will be deemed acceptable if ≥ 70% of Veterans score ≥ 24 on the CSQ-8.

Phase 2, Aim 3 *Preliminary Efficacy***:** Descriptive statistics and exploratory analyses will be used to assess the normality of the data and homogeneity of variance. Although our small sample size will limit our power to detect significant differences between pre- and post-treatment measures, we will

conduct preliminary analyses using t-tests to examine whether pre-post changes are in the expected directions. We will examine effect size (Cohen's d) and significance of our measures.

Study Population

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

The proposed study is conducted at a single site. We propose to enroll up to 30 Veterans in this pilot trial. Because our primary purposes are to examine feasibility and acceptability to Veterans with AUD, achieving adequate statistical power is not a primary concern of this pilot clinical trial. Results from this study with a sample size of up to 30, combined with comparisons to similar studies of CCT with other Veteran groups (e.g., those with mild TBI history), will provide adequate information on expected effect size to allow for estimations of statistical power for a future proposal of a larger pilot trial.

Inclusion criteria include:1) Male and female Veterans (>18 years) who meet criteria for AUD in early remission (>1 month, <12 months remission) based on the DSM-5 (American Psychiatric Association, 2013); 2) Concern about a mild cognitive decline that has been identified by the Veteran or a knowledgeable informant (e.g., SUD treatment providers), and the Veteran wants treatment for their cognitive concerns; and 3) Access to internet and webcam.

Exclusion criteria include: 1) Intoxication or impaired capacity to understand study risks and benefits; 2) Major Neurocognitive Disorder, dementia, or neurodegenerative disorder (e.g., Alzheimer's Disease); and/or 3) Auditory or visual impairments that would prevent ability to participate in the cognitive rehabilitation group or benefit from compensatory strategies.

Eligibility will be established by electronic medical record review and will be confirmed by the Veteran during the initial phone call.

1. ***VA-SPECIFIC REQUIREMENT (inclusion of non-Veterans):***

☑ N/A. The study does not include non-Veterans.

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

Subject Identification/Recruitment

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Recruitment, eligibility screening, consenting, study visits, and CCT groups will be conducted by approved clinical research staff. A Waiver of Authorization and Informed Consent Process for Screening/Recruitment Purposes will be obtained to facilitate subject identification and recruitment.

1. Potential participants who meet the study criteria will be recruited into this study through word-of-mouth referrals from clinicians at VAPORHCS, primarily through the neuropsychology clinic, SUD treatment program, and outpatient mental health clinic. Study announcements and study advertisements will be disseminated to mental health and SUD providers at VAPORHCS to assist with recruitment. Research staff may contact patients who indicate to their clinicians that they are interested in participating. Potential participants may also contact the study personnel after learning

of the study (e.g., from advertisements). Initial phone screening will be done for each subject when they contact the lab and are interested in participating. The potential participant will be screened by study personnel using a screening form. A study member will give regular presentations of the study at Substance Abuse Treatment Program (SATP) access meetings. Attendance at these recruitment meetings by potential subjects is entirely voluntary. Potential subjects will be given the IRB-approved advertisement with contact information and asked to call the contact number if they are interested in participation.

2. IRB-approved flyers will be posted in designated research advertisement space at VAPORHCS, which includes elevators and lobby spaces, as well as common spaces at OHSU and in the community.
3. Social media will be utilized for recruitment purposes. Study advertisements will be posted on VAPORHCS sponsored social media accounts including internal publication/promotion (Weekly E-news employee newsletter and Employee SharePoint E-Post) and external publication/promotion (VA Social Media Sites including VAPORHCS Facebook and Twitter pages, Public VAPORHCS Web Page, Quarterly Veteran Connection Newsletter, and Email Updates through GovDelivery). All recruitment advertisements will ask prospective participants to telephone research staff if they are interested in participating. Email or social media messaging will not be utilized. Craigslist will also be utilized for recruitment. The study coordinator will create Craigslist postings that include a text version of the IRB approved study advertisement. Email responses to the Craigslist posting will be disabled so subjects will only be able to respond via telephone. All potential participants will be screened using the screening form when they contact research staff.
4. The Corporate Data Warehouse (CDW) will be utilized to compile a list of potential participants. IRB-approved study staff will use this list to conduct medical chart reviews (i.e., CPRS) to identify Veterans who meet study criteria, do not meet exclusion criteria, are able to provide informed consent, can attend visits virtually, and may be interested in participating in the research. Veterans who are identified as eligible will be sent a letter from the Mental Health Clinical Director, a letter of introduction from the study team, the study flyer, and a form with the option to opt-in or opt-out to hearing more about the research either by calling study staff or returning the enclosed opt-in/opt-out form. A self-addressed, postage-paid return envelope will be included for the Veteran's convenience. The letter will also state that if study staff does not receive a response within two weeks, the Veteran may be contacted by phone to verify receipt of the letter and be given the option to be mailed a second letter (if not received). Only verification of Veteran's address will be obtained for those who did not receive a letter. Study staff will call all Veterans who indicate interest to provide more information about the study, answer any questions the Veteran may have, and, if applicable, schedule the initial baseline visit.

An appointment confirmation letter will be mailed to a participant after they have scheduled their initial visit. An appointment confirmation letter will also be sent prior to their follow-up visit. If a participant is enrolled in the study and not returning phone calls to schedule additional research visits, a no-show letter will be sent in the mail asking the participant to contact the research coordinator to discuss their interest in their continued involvement in the research study. If the research coordinator does not hear back from the participant within two weeks of sending the letter, the participant will be disenrolled from the research study.

Inclusion of women and minorities in this pilot study is appropriate and is encouraged. Subject selection is based only on the criteria described in the subject eligibility section. Women and minorities are not excluded from the study solely based on either of those demographic characteristics. Because sex effects may be observed, we will make every effort to enroll equal numbers of men and women. Given that all research participants will be Veterans treated within the VAPORHCS, children will not be included in this study.

Informed Consent & HIPAA Authorization

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The procedure for collecting informed consent and HIPAA authorization will be conducted via phone, video, mail, or secured/encrypted email as described in these steps:

Preliminary eligibility and screening phone call: For Veterans who are recruited into this study through referrals from clinicians, word of mouth at VAPORHCS, or after seeing a study flier, the research team members will conduct a chart screen and phone call to determine preliminary eligibility. Eligible participants who have given their permission during the screening call with a study staff member will be informed to expect a packet in the mail or electronically via DocuSign. Potential participants will be advised of potential risks when returning signed documents through the mail. A packet containing the Informed Consent Form, HIPAA, subject reimbursement forms, and self-report measures will be sent to their home address (along with a self-addressed, stamped envelope [SASE]) or sent via DocuSign. Informed consent will either be obtained at the end of this call or conducted during a separate pre-arranged phone or video appointment. The packet will contain a reminder for the recipient to not sign the documents prior to their next scheduled contact time with study staff.

Informed consent: During the phone call or video visit with research personnel, the research team member will review the Informed Consent Form with the participant. Participants will be informed that they are being asked to participate in a research study. They will be told the nature of the procedures and informed of the risks associated with their participation, asked to read the consent form, and encouraged to ask questions or discuss any pertinent issues. Participants will be informed that the research project is voluntary, that participation can be stopped at any time and that participation will not impact any care, services, employment, or benefits they receive at the VAPORHCS. Participants will also be informed that they will be compensated for time. All research volunteers will be asked to sign the consent form and HIPAA authorization after they have read it and discussed the study with research personnel. If they give verbal consent to participate, they will be instructed to sign the ICF and HIPAA form. Veterans will be provided instructions for returning signed documents via DocuSign. Alternatively, participants have the option to place the signed forms into the SASE and mail back as soon as possible. For participants who choose to return the signed forms by mail, research data will be collected from the participant prior to the study team receiving the signed informed consent forms and HIPAA authorization. Participants may withdraw their consent at any time and may withdraw from the study at any time.

4. ***VAPORHCS-SPECIFIC REQUIREMENT (inclusion of those with impaired decision-making capacity):***

☑ N/A. The study does not include those with impaired decision-making capacity

Risks and Side Effects:

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

Patients may become upset or experience cravings for nicotine, drugs, or alcohol while answering personal questions during the interview and assessment. Participants may also become bored, fatigued, frustrated, or upset while completing cognitive tasks or questionnaires. There are also risks to confidentiality, particularly of sensitive information about alcohol and drug use and abuse.

This is a low-risk study. Benefits to society include advancing research on a potentially efficacious treatment for Veterans with cognitive impairments in recovery from addictions. There are currently no FDA-approved medications for cognitive impairments due to AUD, and there are currently few, if any, manualized behavioral therapies for adults with cognitive impairments during recovery from AUD. Thus, the potential large benefits to society outweigh the potential minimal risks to subjects in this study.

Since study activities involve contact with participants via telephone or video, study team members will only contact Veterans from a private area so no one outside of the study team can overhear the conversation or have access to research information or protected health information. The study team member that conducts a study activity via telephone or video will obtain the address of the Veteran's location where they will participate and the contact information of a person at or near the Veteran's location who can be called in the case of emergency. If there is not a person at or near the Veteran's location available in case of emergency, the study team member will notify the Veteran that they will call 911 if there is an emergency and provide the 911 dispatch with the Veteran's address. Veterans will participate via phone or video only if they have a safe, private location from which to participate. No video or audio recordings will be made during any of the research procedures.

Neuropsychological measures are considered intellectual property and one of the risks of administering them through telehealth is a possibility of unauthorized reuse or sharing of the measures. To protect neuropsychological intellectual property, study staff will inform Veterans at the beginning of each assessment session that they cannot record or otherwise preserve test stimuli shown over the computer.

Additional Participant Safeguards:

☑ N/A. The study does not include vulnerable populations and/or those with impaired decision-making capacity.

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

VAPORHCS-SPECIFIC REQUIREMENT (inclusion of those with impaired decision-making capacity):

☑ N/A. The study does not include those with impaired decision-making capacity

Suicidality*:*

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

VA-SPECIFIC REQUIREMENT:

☐ N/A. The study does not include a population of subjects who are potentially suicidal.

If participants present with high risk for suicide (e.g., report suicidal plans or intentions), study staff will follow the following protocol, one step at a time until the participant is transferred to an appropriate provider for follow-up assessment and care: 1) Contact Maya O'Neil, PhD (Co-PI) or other IRB-approved responsible clinician of the study to assess the participant and determine if follow-up care is needed (e.g., open up virtual "room" for responsible clinician to join the video and ensure connection is established before ending the study visit). 2) Work with the participant to identify and contact the primary VA mental health or medical provider so the s/he can conduct an assessment and provide follow-up care as needed (i.e., alert provider by phone, through Teams, or encrypted email and send request for provider to join the call). 3) Use the emergency procedures for VVC to connect the participant to e911 services or contact local emergency services if the participant is not in an area in which 911 is available.

Benefits:

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

This study involves an intervention that may directly benefit the participants. There are general benefits to science and medicine in that the knowledge gained from this study may help to validate a new evidence-based treatment for individuals who are suffering from cognitive impairment due to AUD. Additionally, participants may benefit from the study if abnormal results are discovered through the study procedures (e.g., undiagnosed depression) and the participant is then referred to a provider for follow-up care. This study has the potential to benefit Veterans by improving our understanding of cognitive rehabilitation interventions for Veterans with AUDs.

Protected Health Information:

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

VA-SPECIFIC REQUIREMENTS:

As part of the study, we will collect the following individually identifiable health information from each participant: information from their VA Health Records such as diagnoses, progress notes, medication, lab and radiology findings; specific information concerning alcohol and drug abuse and HIV status; demographic information such as name, race, gender, age, birthdate, address, phone number, and clinic visit dates; questionnaires and neuropsychological measures. This information is necessary for our research because we plan to use medical record information to confirm eligibility and clinical participation in CCT. We will use contact information to reach participants and for scheduling. We will use demographic information to describe our sample (i.e., sample characteristics) and to determine if they moderate study outcomes. Questionnaires and neuropsychological measures will help us determine if CCT is efficacious and address our study aims.

Collaborative Research

VA-SPECIFIC REQUIREMENTS:

☐ N/A. The study does not include Collaborative Research.

This study is being reviewed by OHSU-VA joint IRB and utilizes OHSU's REDCap. All study procedures are conducted on VAPORHCS property by VA staff on VA time.

Resources Available
VA-SPECIFIC REQUIREMENT:

All research study visits are conducted through phone or video, but the Co-PIs' existing research spaces (Portland campus: Bldg. 104, P3, Rooms B2G-151 and B2G-153; Building 103, Room E-136) may be utilized to conduct the remote research study visits. Study staff will utilize video-capable computers either in the Co-PI's personal office/research spaces or from secure locations in their own homes.

This project is a logical extension of Ms. Shirley (Co-PI), Dr. O'Neil (Co-PI), and Dr. Loftis' (Co-I) existing research programs, which focus on the effects of SUDs and the development of novel treatments for cognitive impairment. Pilot data from this study will be used to submit future VA and NIH grants. Thus, it is reasonable that Ms. Shirley, Dr. O'Neil, and Dr. Loftis will be using a small portion of their own protected research time, research staff's time, and their research space on this pilot project so that they may obtain continued funding for their research programs.

Notably, similar interventions are currently regularly offered to Veterans at VAPORHCS, including Veterans with MCI, TBI, and PTSD through the neuropsychology clinic as part of normal clinical care. Whereas in the past these groups were offered to patients by VA-paid clinicians, this project will now enable research-funded staff to offer the same groups to patients (likely freeing up clinicians for additional clinical work). Thus, this project offers important clinical services to Veterans at VAPORHCS as a benefit to the hospital. However, because there is not sufficient data in the literature to know whether these interventions are effective with adults with AUD, we are offering them for research purposes only, rather than as standard clinical care.

Subject Compensation/Payment:

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

VA-SPECIFIC REQUIREMENTS:

☐ N/A. The study does not include subject compensation/payment.

Subjects will be reimbursed $50 for the initial baseline assessment visit. Subjects who participate in the follow-up visits will receive an additional $50. Payment will be provided in the form of an Amazon.com gift card. This compensation is reasonable and commensurate with the expected contributions of the participant. The amount of payment and terms of the payment are described in the informed consent form. Payments are fair and appropriate and do not constitute (or appear to constitute) undue pressure or influence on, or coercion of, the prospective research subjects to volunteer for or continue participation in the research study.

Privacy and Confidentiality:

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

All study data derived from subject procedures will be obtained specifically for research purposes. Research records will be maintained according to the VA research records retention schedule. Data will be stored in a manner intended to preserve patient confidentiality. Hard-copy protected health information (PHI) will be stored in locked cabinets in the PIs' VA office and laboratory space. Electronic PHI will be stored on servers behind the VA firewall accessed by password-protected VA computers. Each subject is assigned a unique identifier (study ID) based on a study identifier and number (*i.e*., CCTA-xxx). Only coded or de-identified data, not PHI, are used for analysis. The file linking the study ID to the patient's name will be stored in a separate password-protected file on a secure server behind the VA firewall.

Coded data will be stored on OHSU's REDCap application, a highly secure and robust web-based research data collection and management system. No identifiable information will be entered into this application at any time. The statisticians will not have access to the code or PHI at any time. The spreadsheet linking the code to the subject will remain behind the VA firewall at VAPORHCS. Once the study has ended, the link will be stored by the VAPORHCS Research & Development Service.

Data will be collected and stored in a manner intended to preserve patient confidentiality. To preserve privacy, only approved study personnel will conduct study visits or access study records. All study visits will occur in private offices to preserve participants' privacy.

Certificate of Confidentiality

To further protect subject's privacy and confidentiality, the investigators will obtain a Certificate of Confidentiality from the National Institute of Health. With this Certificate, the investigators cannot be forced (for example by court subpoena) to disclose information that may identify subjects in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

The informed consent document will include a statement that this study has a Certificate of Confidentiality and will describe the type of information that will be included in the subjects VHA medical record.

VA-SPECIFIC REQUIREMENTS:

☑ N/A. The study does not include a Certificate of Confidentiality.

Information and/or Specimen Management

VA-SPECIFIC REQUIREMENTS:

All study data derived from subject procedures will be obtained specifically for research purposes. Data will be stored in a manner intended to preserve patient confidentiality. Raw data (*e.g.,* collected from neuropsychiatric assessment visit procedures) will be stored in locked cabinets and on password protected computers in limited access folders behind the VA firewall. Each subject is assigned a unique identifier (study ID) based on a study identifier and number (i.e., CCTA-xxx). Only coded or de-identified data, not PHI, are used for analysis. Coded data will also be stored on OHSU's REDCap application, a highly secure and robust web-based research data collection and management system. The file linking the unique identifier with the patient's name will be stored in a separate password-protected file on a secure computer behind the VA firewall. Consent forms and the key linking names to identifiers will be stored in locked file cabinets or on password protected computers in limited access folders behind the VA firewall, and the key and consents will be stored

separately from the de-identified data files. Once the study has ended, the link will be stored by the VAPORHCS Research & Development Service.

Disclosure/Sharing:

VA-SPECIFIC REQUIREMENTS:

☑ N/A. The study does not include disclosure/sharing outside the IRB-approved VAPORHCS study personnel.

Transfer of Data Ownership

VA-SPECIFIC REQUIREMENTS:

☑ N/A. The study does not include transfer of data ownership.

Web Application(s), Mobile Device(s) and/or Mobile Application(s):

VA-SPECIFIC REQUIREMENTS:

☐ N/A. The study does not include web application(s), mobile device(s) and/or mobile application(s).

A study team member will schedule study visits and CCT sessions with the Veteran and then send the Veteran a link for VVC through the Virtual Care Manager platform (no direct email contact between Veteran and study personnel will be initiated; all contact will be through the Virtual Care Manager or other VA-approved scheduling systems to ensure that no PHI is sent over email). VVC precautions for safety will be verified (i.e., veteran's physical address at time of appointment in case of emergency). No recordings will take place during study visits or CCT sessions.

VA REDCap will not be utilized for this study since VA REDCap is an intranet-only application that would require participants to have an active VA network account to be able to complete questionnaires within the application. Instead, OHSU's REDCap server will be utilized to store questionnaire data. Veterans will have the choice of either completing questionnaires online (through OHSU REDCap) or on paper. If the Veteran chooses to complete the questionnaires online, a link to the online questionnaires will be sent in the mail in their appointment confirmation letter. If the Veteran chooses to complete the questionnaires on paper, the paper questionnaires will be sent in the same envelope as their appointment confirmation letter. Only coded data will be stored on OHSU's REDCap application, a highly secure and robust web-based research data collection and management system. The questionnaires will have an alphanumeric code that will be linked to the participants' names in a separate spreadsheet that will remain behind the VA firewall at VAPORHCS. No identifiable information will be entered into REDCap at any time.

Data and Safety Monitoring Plan (DSMP)

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

VA-SPECIFIC REQUIREMENTS:

Monitoring human participant recruitment, neuropsychiatric data collection, and data entry will be performed by the Co-PIs and study staff. Any adverse events will be reported immediately to the Co-PIs who will evaluate the patient and determine if any additional evaluation or treatment is needed. Ms. Shirley will ensure that adverse events are properly reported to the IRB. The study staff will examine all cumulative adverse events quarterly to determine if there are any systematic problems. The balance of risk to benefit will be continuously monitored by the Co-PIs, and the study may be modified or terminated if risks begin to outweigh benefit.

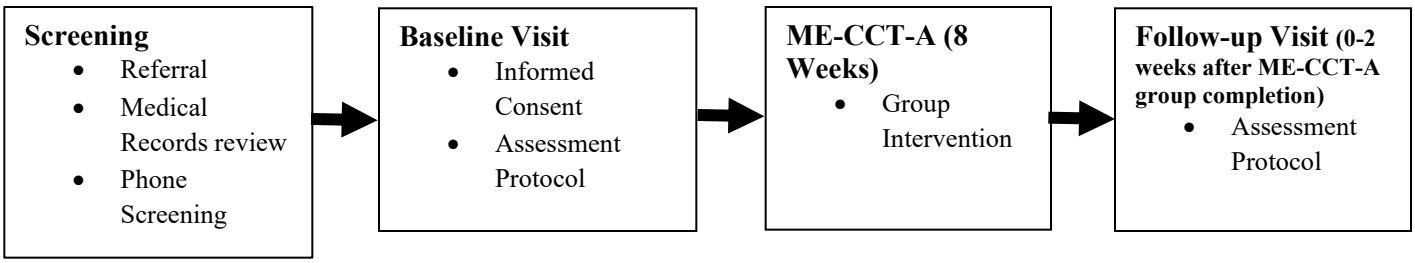
Study staff is trained on the protocols to ensure that procedures are being conducted within the scope of the approved protocols. Maya O'Neil, PhD, (Co-PI), a licensed psychologist and neuropsychologist, supervises Ms. Shirley (Co-PI) and other clinical research staff in the administration and scoring of neuropsychological tests and psychological measures. Recruitment and enrollment will be reviewed monthly in meetings with Ms. Shirley and Dr. O'Neil. At these meetings, the research team will problem solve recruitment issues to ensure that projected enrollment numbers are obtained. Ms. Shirley will check procedures (at least monthly) to verify that they are being conducted per the approved protocol, including the responsibilities and roles for gathering and monitoring data. The data are recorded by research staff as it is collected, and data accuracy is verified by double scoring, data entry, and visual verification.

Step-by-Step Guidance on Conducting the Study

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

The study procedures and timeline are outlined in **Figure 2** below.

Figure 2. Study Flow Chart and Activities



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Appendix – Supporting Documents List

☐ See sponsor/3rd party protocol for requested information in this section. Indicate what heading/subheading in the 3rd party protocol that the information is located:

Questionnaires and surveys
Portland Cognitive Strategies Scale 2.0 (PCSS)
Brief Addiction Monitor (BAM)
Prospective-Retrospective Memory Questionnaire (PRMQ)
PROMIS–57 Profile v2.1
PROMIS v2.0 Cognitive Function 8a
Client Satisfaction Questionnaire (CSQ-8)
Timeline Followback (TLFB)
Alcohol Use Disorders Identification Test (AUDIT-C)

Neuropsychological assessments
Wide Range Achievement Test, Fifth Edition (WRAT5™)
Neuropsychological Assessment Battery (NAB) Attention Module subtests: Digit Span; Driving Scenes
Neuropsychological Assessment Battery (NAB) Memory Module subtests: List Learning; Shape Learning; Medication Instructions; Name, Address, and Phone Number
Neuropsychological Assessment Battery (NAB) Executive Function Module subtests: Judgment; Categories
Delis-Kaplan Executive Function System (D-KEFS) subtest: Verbal Fluency

Other documents
Appointment confirmation letters (baseline and follow-up)
No contact letter
Clinical interview forms (baseline and follow-up)
Screening form (prior to enrollment)
PI recruitment letter