Targeting Self-regulatory Deficits Through Cognitive Remediation Intervention

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Protocol Title: Targeting self-regulatory deficits through cognitive remediation intervention

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Version Date: 03022019

(*If applicable*) Clinicaltrials.gov Registration #: Click or tap here to enter text.

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The overarching objective of this supplement application is to apply a behavioral medicine approach to validate a novel set of interventions that may be used to both study and treat cognitive-affective dysfunctions implicated in self-regulation. By systematically characterizing and addressing cognitive-affective processes, we aim to accelerate assessment and treatment efforts in disorders characterized by dysfunction in self-regulation, including substance use disorders (SUDs). The proposed research will evaluate the possibility of modifying cognitive-affective deficits that hinder self-regulation using a focused skill-building approach targeting three domains demonstrated to be disrupted in SUDs: executive function, negative emotionality, and incentive salience.

We are proposing a small randomized clinical trial in which 100 substance users will complete the existing Psychotherapy Development Center (PDC) pretreatment assessment battery as well as a novel battery of assays to evaluate cognitive-affective functioning. These batteries will be administered before and after the intervention (cognitive training tasks) to help examine the generalizability of any training effects to related cognitive training tasks (tasks that the participant was not specifically trained on). These related tasks will also help quantify participants' potential responsiveness to treatment and, as such, may help bridge the gap between behavior, mechanism, and treatment.

After completing pretreatment assessments, participants will be randomized to either a (1) cognitive remediation program (training tasks) specifically designed to address cognitive-affective dysregulation or (2) control tasks (verbal fluency tasks). Tasks will be completed twice per week for 4 weeks, after which assessment batteries will be repeated. Finally, we will evaluate real-world behavior and the durability of the training via a one-month follow-up, which will include assessment of substance use as well as the cognitive-affective battery. Our primary Specific Aim will be to evaluate the efficacy of the cognitive-remediation program relative to the control condition control on the indicators of cognitive-affective functioning and substance use, testing the hypothesis that individuals randomized to the cognitive remediation program will demonstrate improved functioning on the cognitive-affective battery as well as reduced substance abuse. We will also explore potential moderators of response to the training, including baseline measures of cognitive-affective function.

Our long term goal is to enhance outcomes of effective 'top down' treatments like cognitive behavior therapy (CBT) and contingency management by combining them with brief 'bottom up' interventions that address, more directly, underlying mechanistic deficits that impact self-regulation and ultimately the maintenance of SUDs. The proposed research will lay the foundation for a more thorough evaluation of 'mechanism matched cognitive remediation' (1). Translation of these findings is expected to eventually allow clinician to match cognitive remediation interventions to the respective core deficits of their patients. Targeted intervention strategies such as these are likely to improve outcomes for multiple externalizing disorders, including SUDs. Moreover, as they are brief and administered via computer, the potential dissemination of these treatments could be more efficient, cost-effective, and implemented in a wider variety of settings (e.g., primary care, rural areas) than traditional behavior change interventions.

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.

Two years

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Cognitive-Affective factors and substance use disorders (SUDs):
SUDs rank among the most widespread and costly illnesses in the US (17, 18). Although multiple factors contribute to the development and maintenance of SUDs, core neurobiological and psychological processes are commonly implicated in the development and maintenance of SUDs and other externalizing disorders (e.g., antisocial personality, attention deficit-hyperactivity, conduct). In particular, these disorders are characterized by marked dysfunction in self-regulation, subserved by impairments in executive function and hyper-reactivity of negative emotionality and incentive salience (19, 20). Dysfunctions in these domains are mirrored in the tendency for individuals with SUDs to demonstrate strong attentional orienting to motivationally salient cues (21), failure to inhibit reward seeking responses (22), difficulty classifying rare or unexpected stimuli in the oddball task (23), deficits in distress tolerance (24), and poor delay discounting during gambling tasks (25). In these instances, individuals with SUDs react strongly to motivationally salient information (e.g., unexpected information, goal-relevant reward, punishment, threat), particularly when they are prepared to make a practiced, dominant response. Accordingly, reactivity to affective information (incentive or negative emotion) and deficiencies in executive function may disinhibit individuals with SUDs to engage in pleasure-seeking (e.g., substance use), display extraverted interpersonal tendencies, and to act in an impulsive manner, particularly when in an affectively charged situation. Thus, interventions that directly target these underlying cognitive-affective deficits are a novel and promising strategy to enhance intervention effectiveness.

Translating mechanism into intervention:
Cognitive-affective impairments are a persistent and functionally relevant feature of multiple disorders, including SUDs (26-30). Such impairments span multiple domains and are more closely linked to functional outcomes than severity of clinical symptomatology, making them a priority for treatment development (27, 28, 31, 32). Increasingly, there is strong interest in understanding the mechanisms of behavior change and developing effective interventions that capitalize on this understanding (3). One promising and innovative intervention strategy is cognitive remediation. Cognitive remediation encompasses a diverse array of "interventions that aim to improve (neuro)cognitive functions (attention, memory, executive function, social cognition, or metacognition) with the goal of durability and generalization" (33). Some evidence suggests the promise of this approach for SUDs (34, 35), although early efforts to use this treatment approach for SUDs has failed to assess the translation of specific skills to generalizable skills. Additionally, most of this early work has either provided non-specific training (e.g., general executive functioning or attention bias modification) or training on a single dysfunction (e.g., distress tolerance) that did not necessarily capitalize on our understanding of the multifaceted cognitive-affective deficits affecting individuals with SUDs. Recent research suggests it is possible to identify cognitive-affective processes that are dysfunctional in SUDs and related disorders, target those cognitive-affective processes, and bring about change in those processes using a systematic approach to cognitive remediation tailored to specific self-regulatory deficits: Co-investigator Dr. Baskin-Sommers (1) designed a cognitive remediation program for incarcerated individuals with SUDs (see Preliminary Studies). This program was developed to target specific cognitive-affective deficits in two antisocial

subtypes (psychopathic and externalizing) with co-morbid SUDs. There is a large body of evidence suggesting that individuals with psychopathy + SUDs are characterized by impairments in modulating attention to accommodate multiple streams of information, whereas individuals with externalizing/antisocial personality disorder + SUDs demonstrate exaggerated responses to affective information and various kinds of motivational cues, in combination with reduced regulatory capacity (36). Training that used a multi-task package designed to target the specific cognitive-affective deficits associated with either subtype (psychopathic versus externalizing) led to improvement on both trained and non-trained tasks, with improved outcomes for individuals who received the type of training tailored to the deficits associated with their subtype. This SOBC supplement would extend this work by testing the cognitive remediation strategy used for the externalizing subtype in a heterogeneous sample of individuals with substance use disorders.

Dr. Baskin-Sommers' recently published cognitive remediation study in offenders (1) represents a proof of concept study for the proposed SOBC supplement (see Figure 1). Training designed to target affective self-regulation and remedy the distinct deficits associated with SUD-offender subtypes resulted in specific and differential improvement on trained and non-trained tasks. Moreover, analyses demonstrated that using three tasks to tap cognitive-affective dysfunction from multiple angles was a stronger predictor of change than any single task. Finally, unpublished analysis showed that individuals who received training that matched their cognitive-affective deficits had fewer disciplinary reports in prison two months following the training. Together, these tasks highlight the utility of targeting cognitive-affective functions through targeted computerized tasks and the generalizability of change to other tasks and to real-world behavior.

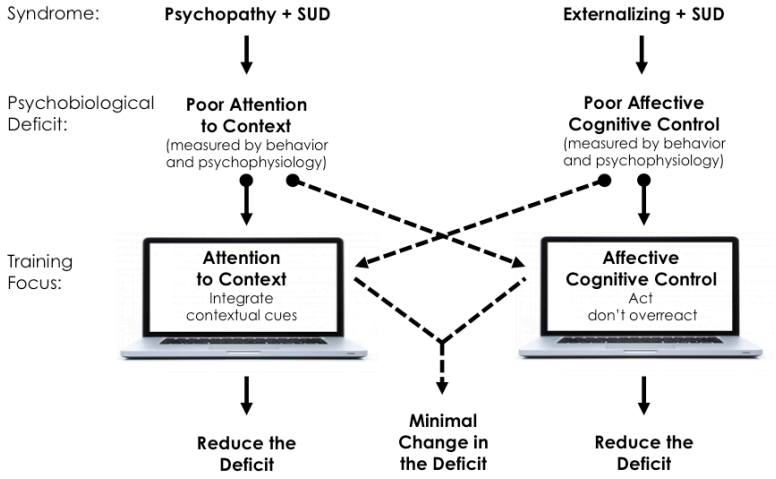

Figure 1. Overview of study design, Baskin-Sommers et al (2105). Proposed SOBC project uses cognitive remediation tasks targeted for improved affective-cognitive control (boxed area)

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Overview:

The proposed SOBC supplement project will be conducted at the Substance Abuse Treatment Unit (SATU) and Adult Outpatient Psychiatric Services (IOP) in New Haven. One hundred substance

users will be randomized, via a computerized urn randomization program (55) we have used in multiple previous trials (9, 10, 37, 56, 57) to either the cognitive remediation package or a control condition (computerized verbal fluency tasks), with trainings conducted twice per week for 4 weeks. Training will be conducted as an add-on to the participants' ongoing standard treatment at the clinic.

Several variables will be assessed. Demographic variables will include gender, race, and level of education. Person-specific variables will include type and severity of substance use disorder, personality characteristics, and treatment readiness. Pre- and post-training testing will evaluate change in cognitive-affective targets, with a one-month follow-up period to evaluate both the durability of training effects as well as impact on real-world behaviors (substance use).

This project will benefit the Parent award (P50 DA 0009241) by enabling us to evaluate how individuals with varying levels of these cognitive-affective deficits respond to study interventions and hence inform future projects which could address whether addressing these deficits via cognitive remediation improves response to empirically validated therapies via 'mechanism-matched' cognitive remediation.

Diagnostic and Baseline Assessments:
After providing written informed consent (see Human Subjects), participants will complete the following components of the Parent award (Psychotherapy Development Center, PDC) Core assessment battery to facilitate comparison with ongoing/previous Center studies:

- *Structured Clinical Interview for DSM-5* (SCID) (58) (59), including antisocial personality disorder.
- The *Brief Symptom Index (*BSI) (60) is a widely used 53-item inventory of psychiatric symptoms.
- *Substance Use Calendar.* Self-reports of substance use (cocaine, alcohol, opioids, marijuana, other illicit drugs, and nicotine) are documented at each contact via the Substance Use Calendar. Similar to the Time Line Follow-Back (61), the Substance Use Calendar assesses substance use on a daily basis.
- *State-Trait Anxiety Inventory (STAI)* is a widely-used measure of consistent and transient stress and anxiety (62).
- *Distress Tolerance.* (24, 63, 64) is commonly measured using the Mirror Tracing Persistence Task (65).
- *Shipley Institute of Living Scale* (66) is included as a widely used measure of general intelligence.
- *Balloon Analog Risk Task (BART)* is a computerized measure of risk-taking (67).
- *Five-trial adjusting delay discounting task* is a brief computerized measure of delay discounting (Koffarnus & Bickel, 2014).

Baseline Cognitive-Affective Assessments:
This battery includes three tasks that have been previously used to tap the cognitive-affective processes associated with SUDs and other externalizing disorders.

- *Incentivized n-Back task* includes manipulations of working memory load, response prepotency, and incentivized performance (trial-by-trial feedback using monetary reward and punishment) to examine the integrity of cognitive control functions necessary for successful regulation of behavior. In this task, participants view a series of letters. Participants are instructed to monitor the letters and

respond with a button press if the preceding letter in the *n*-back position is different from the current letter (e.g., a mismatch trial). Participants are instructed to withhold their response when the preceding letter matched the current stimulus (e.g., a match trial). The majority of trials are mismatch trials (80%), whereas match trials are infrequent (20%). The task also includes a manipulation of working memory load. In the low load (1-back) condition, participants are instructed to determine whether the currently presented letter matched the immediately preceding letter in the sequence. In the high load (2-back) condition, participants are required to monitor and maintain the stimulus information in working memory in order to determine whether the letter stimulus 2 positions earlier matched the current letter. Finally, the task manipulates incentives on a subset of trials; in separate blocks participants received reward (sound of a coin drop and the addition of 5 cents) following a correct response or punishment following an incorrect response (aversive .5s 100dB noise blast and the loss of 5 cents). The primary dependent variable will be task performance. The Incentivized *n*-Back task is thus used to assess relevant processes because deficits because it evaluates a person's tendency to over-allocate attention to motivationally-salient information (22, 74).

Post-Treatment Follow- Assessments:
At the end of the 4 weeks, the participant will be asked to fill out more questionnaires (see table below), provide a urine and breath specimen for drug and alcohol testing, and be interviewed again. This assessment session will take about 1 hour.

Study assessments schedule:

Instrument/task	Rater	Screen	Week 0	Training	Week 4	Follow-up
Informed consent quiz	P	x				
Demographics and medical history	P	x				
Locator form	RA					
SCID for DSM-5	RA	x				
Shipley	P	x				
Inclusion/exclusion	RA	x				
Urn randomization	RA	x				
Utox and BAC	RA	x	x	x	x	x
BSI	P		x		x	x
Substance Use Calendar	RA		x	x	x	x
State-Trait Anxiety	P		x		X	x
Distress Tolerance	RA		X		X	x
BART	RA		X		X	x
5-Item Delay Discounting	RA		X		X	X
Incentivized n-back	RA		X		X	X
Externalizing Spectrum Inventory	P		x			
Perceived Stress Scale	P		x			x
Circumstance, Motivation, Readiness Scale for Treatment	P		x			x

Interventions:

Participants will be randomized to one of 2 training conditions, to be completed twice per week over 4 weeks, *in addition* to standard treatment at SATU/IOP, which typically consists of weekly group meetings, case management and random urine toxicology screening. Each training session will be 30-45 minutes (time variability depends on speed of reading instructions and choices made in the tasks). Across all weeks the participant will complete approximately six hours of training.

Control condition. Participants randomized to this condition will complete a computerized verbal flexibility task (Text Twist). An active computer-based control was selected as it provides a rigorous comparison to intervention and will help address concerns that any game-style activities will produce improvements by controlling for computer time and game experiences, as well as non-specific elements such as support, attention, study contact, activation, and motivation. It is possible an active and engaging control condition may produce modest neurocognitive change in some domains, but available data indicate the control condition is not likely to influence the target-specific processes associated with self-regulation (75).

Cognitive Remediation tasks: The target training focuses on providing individuals with practice inhibiting, learning, and making decisions *within affective contexts*. Well-validated tasks that have been reliably shown to tap these processes, and are amenable to repeated administration, were selected. Each of these tasks taps the underlying domains of self-regulatory dysfunction (executive function, negative emotionality, incentive salience). Thus, this training package more directly builds on previous work that establishes the importance of *dual demands on cognitive and affective processes associated with regulation of behavior*. Moreover, it addresses the complex cognitive-affective dysfunctions in self-regulation from multiple angles rather than targeting or tapping a single process that is likely entrapped within a more multi-faceted dysfunction. The basic structure of this training has been successfully implemented in Dr. Baskin-Sommers' previous work (1). The three tasks will address inhibition in the face of reward, cost-benefit decision-making in the face of uncertainty, and working memory in the face of distress. These three tasks provide measures of the target processes of interest, but are distinct from the pre-post measures, so as to measure the transfer of skills from one setting to another (i.e., generalizability).

Rewarded Stop Signal task (15 minutes). The Stop Signal task provides a measure of reward approach motivation (Go reaction time) and ability to inhibit motor behavior (Stop reaction time) under conditions of high motivation to approach. An interesting dissociation emerges, such that some people (high reward sensitivity) are faster at going and worse at stopping under higher reward (76), some people (impulsive) are faster at going but worse at stopping (77), and others are faster at going but show no reward effect on stopping (78). In order to measure these individual differences, we have developed a version of the task in which participants are given information on the reward value of each upcoming trial, with 75% of (standard) trials awarded 2 points for correct performance, and 25% high reward trials receiving 50 points for correct performance (1). All participants start with a neutral block and then enter the reward block where they view stimuli of circles (Go), but some circles will have a ton played which indicates that no response should be given (Stop). A dual staircase tracking procedure is used, with a separate mean calculated for both the standard and the high reward trials. We specifically selected a version utilizing a cue at the beginning of each trial, as pretrial cues can modulate Go reaction time on both simple reaction time and stop signal reaction time paradigms (79, 80).

Decision-Making during Ambiguity (15 min). This is a financial decision-making task in which the amounts of favorable and unfavorable information regarding an ambiguous financial prospect will be parametrically manipulated (81). On each trial, participants are presented with a (distinct) virtual "bag"

of exactly 100 poker chips, all of which were colored either red or blue. For this bag, participants receive partial information about the number of red and blue chips in the bag. Parametrically varying the number of red chips and blue chips shown to participants allows for a trial-wise calibration of the availability of favorable or unfavorable information. Participants are asked to indicate whether they want to select a chip from the bag (giving them a chance to get a winning chip) or get 5 points for certain. The task consists of 56 trials. Each trial begins with a fixation cross, after which participants view the available information about the bag's contents versus the 5 point guarantee. Participants select which option they want for the current round by pressing the left or right key. Participants are not placed under time constraints for responding.

Paced Auditory Serial Addition Task (PASAT; 7 min) (82) The PASAT is a cognitive task purported to measure working memory, speed of information processing, and sustained and divided attention. It is a measure of many functional domains, but primarily relates to a participant's ability to persist in the face of emotional reactions (i.e., distress tolerance) to the task's demands. For this task, numbers are sequentially flashed on a computer screen, and participants are asked to add the presented number to the one previously presented. For example, if the digits '3', '6' and '2' were presented, the participant would respond with the correct sums, which are '9' and then '8'. Participants provide answers by using the mouse to click on the correct answer on a number pad displayed on the screen. Participants are told that their score increases by one point with each correct answer and that incorrect answers or omissions would not affect their total score. However, if they provide an incorrect answer or omitted a response, participants would hear a loud noise blast presented over headphones. The task consists of three levels with varying latencies between number presentations. Specifically, the first level of the PASAT provides a 3-s latency between number presentations (i.e., low difficulty) for 2 minutes, the second level provides a 2-s latency for the first 2 minutes and a 1-s latency for the last minute (i.e., medium difficulty), and the third level provides a 1-s latency (i.e., high difficulty) until terminated, up to 7 minutes.

Total Protocol Completion Time:
From consent to the completion of the study, participants will complete approximately 10-12 hours of study-related activities.

5. Genetic Testing N/A ☒

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

Participants will be 100 individuals (aged 18 and older) enrolled in outpatient (non-methadone/buprenorphine) treatment for any substance use disorder (other than PCP) at the Substance Abuse Treatment Unit in New Haven. As the goal of this project is to develop interventions that address self-regulation across multiple disorders, we will recruit individuals who have a range of substance use disorders and levels of severity. Otherwise, inclusion criteria are relatively broad and intended primarily to exclude individuals who are insufficiently stable to complete an outpatient trial of 4 weeks duration, who are highly unlikely to be located for assessment interviews, or who have a significant history of head injury or other condition that would confound interpretation of study findings. Individuals who are currently physically dependent on opioids, alcohol, or other substances and who require detoxification will be referred appropriately and invited to be re-screened following detoxification and stabilization. Completion of assessment instruments requires a minimum of a 4th grade reading level.

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion and exclusion criteria
Participants will be included who:

- Are between ages 18 and 50.
- Meet current DSM-5 criteria for an alcohol, stimulant, cannabis, or opioid use disorder.
- Are sufficiently stable for 4 weeks of outpatient treatment.
- Are willing to provide locator information.
- Are fluent in English and have a 4th grader or higher reading level

Individuals will be excluded who:

- Meet DSM-5 criteria for a bipolar or schizophrenic disorder.
- Who have a legal case pending such that incarceration during the 4-week protocol is likely.
- Are physically dependent on alcohol, opioids or benzodiazepines or who report recent PCP use.
- Have a baseline Shipley estimated IQ less than 70
- Have 3 or more head injuries with loss of consciousness for over 30 minutes or lasting effects
- Have a history of chronic illness or neurological disorders (e.g., epilepsy or stroke) that would complicate evaluation of effects of cognitive training

9. How will eligibility be determined, and by whom? Write here

Following provision of written informed consent, baseline assessments will be completed with the research assistants. These will include demographic data, SCID interview for DSM-5, Shipley, and a brief medical history for determination of eligibility.

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

1. *Cognitive remediation training and control condition*.
Cognitive remediation is safe, inexpensive, portable, and easy to administer. The cognitive training tasks proposed here have been used safely with similar populations in previous work (1, 85). Thus, the potential dissemination of these treatments could be more efficient, cost-effective, and implemented in a wider variety of settings than traditional behavior change interventions. The

computerized control condition is safe, consisting of simple verbal fluency tasks. Importantly, the skills needed to complete these games are non-specific and distinct from those required for the cognitive remediation training. Both the experimental and control condition will be administered in addition to standard treatment (TAU, treatment as usual) at the SATU/IOP clinic, which typically consists of weekly group meetings, urine toxicology screening, and case management. Thus, psychological risks appear to be minimal and not different from those of equivalent non-study psychotherapeutic interventions.

We believe that there are very few risks to participating in this treatment. We would like participants to tell us about any times they use alcohol or illegal drugs while they are in the study. It is not illegal to report past substance use. Also, we know that stopping alcohol or substance use can be quite difficult. In order to be helpful to participants, we simply need to know about their alcohol or substance use. The urine drug tests and the breathalyzer tests for alcohol enables us to be certain of our results. The only way participants might be dismissed from the study is if they repeatedly do not come to treatment or violate the rules of this clinical program. We would only ask that they do their best to stop using alcohol or drugs, be honest about themselves and their problems and to be available at their appointment times for both the research assistant and counselor.

2. *Urine and breath specimen collection*
Urine and breath specimens are collected primarily as safeguards to participants and should add no risks other than those normally associated with these procedures.

3. *Rating scale and questionnaires.*
These are all non-invasive, should add no risk, and have been used without difficulty or any adverse events in our previous studies with this population. The major disadvantage is the time taken to complete them. Our past experience with these measures indicates that they are acceptable to patients. Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only patients' code numbers will be recorded on the forms themselves to protect confidentiality**.**

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

Assessment of risks versus benefits requires some description of the individuals to be treated. The study population is at high risk for a number of cognitive and psychiatric problems; this is also a population at high risk for treatment failure, either by treatment dropout or continued illicit substance use. The behavioral therapies tested here carry minimal risk and will be implemented as adjuncts to standard outpatient treatment at this comprehensive treatment center. We believe we have included adequate safeguards for participants to address the ethical questions, regular contacts with program staff and close monitoring of symptoms, and procedures to withdraw from study treatments participants who show significant deterioration or adverse events. Thus, the potential benefits for individuals and society at large are high; and the risk/benefit ratio appears favorable toward the proposed study treatments.

We will recruit participants via flyers distributed at the clinic and via direct referral from clinicians, following procedures we have worked out through multiple previous studies at this site (86-94). The

screening of patients using the inclusion and exclusion criteria, and the urine toxicology screens and SCIDs, will minimize the risk of including participants who are not appropriate for this low-risk study. On-site medical staff and frequent visits and monitoring by research staff will minimize the risks of adverse events and assure that they are managed quickly if they do occur. Study physicians are available on call, including nights and weekends, to answer patient concerns.

Participants will be withdrawn from the treatment arm if they show severe psychological or symptomatic deterioration, unacceptable levels of adverse events as determined by the SATU/IOP program director or if clinically necessary for ethical or safety purposes. Participants dropped from the study for these reasons or because they wish to withdraw will be offered treatment as usual at SATU/IOP or be referred to a higher level of care, such as an inpatient facility, when appropriate. For all participants, if an emergent medical, psychiatric, or substance abuse issue emerges from any treatment or test given as part of the proposed study, these will be assessed through the SATU/IOP physician and appropriate referral or treatment will be delivered. Private referral and/or hospitalization may also be offered according to the participants' needs and wishes.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates

1. Procedures to ensure the validity and integrity of the data

Multiple measures are in place to ensure the validity and integrity of the data. First, all research staff receive Human Subjects Protection training, as well as training in Good Clinical Practice. Weekly research meetings for all research staff take place, in addition to weekly project-specific measures, as a forum for in-service training as well as to discuss questions regarding issues that arise in complex clinical research protocols. Adherence to protocol procedures will be monitored using individual supervision conducted by the PI. Multiple research staff are cross-trained to 'cover' for each other; thus, review by multiple staff with oversight by the PI facilitates early identification of errors and oversight. The Data Manager conducts weekly quality assurance checks of research charts and Case Report Form (CRFs).

2. Procedures to guarantee the accuracy and completeness of the data during data collection, entry, transmission, and analysis.

As CRFs are completed, they are scanned in and processed by the Data Manager. The electronic images are verified by the Data Manager using Teleforms, and transferred to the database. The Data Manager processes the assessments on a daily basis, checks for missing data, logical inconsistencies, and reports any errors back to the Research Assistants. Any necessary corrections are done by direct entry and documented in the system and on the CRF logs.

3. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will monitor the proposed project because this population might be considered vulnerable due to their substance use. This board, already in place for all projects affiliated with the P50 Psychotherapy Development Center (PDC), is composed of Yale investigators who are independent of the parent trials and experienced in various aspects of the conduct of clinical trials for the treatment of addictive disorders (Drs. Sherry McKee, Declan Barry, and Jenifer Edelman). Dr. Carroll has developed a standard DSMB report form that has been used in all PDC and PDC-related trials that summarizes on a quarterly basis:

1. Recruitment, retention, and follow-up rates for the study and compares them to target rates.
2. Rates of data completeness and availability of primary outcome data
3. Occurrence of AEs and SAEs
4. Report of study progress since the last report.
5. Rates of recruitment of women, minorities, and children with respect to targeted rates.

These reports will be generated by the Data Managers each quarter, signed and reviewed by Dr. Baskin-Sommers prior to their submission to the DSMB.

Because the projected effect sizes may not be large enough for detection during interim analyses, we are not proposing a preliminary analysis of accumulating efficacy and safety data by treatment assignment. Instead, we propose to submit a quarterly report of aggregate data to the DSMB members that contains screening data, baseline demographics, retention data, serious adverse events data, as well as accrual status including projections, times to milestones, and any other data that will help in the assessment of the clinical trial. Based on this report, each DSMB member will complete a form making one of two recommendations: 1) continue recruitment as planned; or 2) schedule formal DSMB meeting immediately. If any DSMB member recommends a meeting, this will be scheduled within one week, minutes will be kept, the report will be reviewed with the PI, and the committee will vote on whether the study should: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop recruiting pending further investigation. If, after this meeting, any DSMB member votes to stop recruitment or requests a protocol modification, the Yale IRB will be informed.

4. Reporting of Serious Adverse Events (SAEs)

SAEs will be systematically assessed at each clinic visit. We have worked out these procedures in multiple clinical trials of behavioral interventions). The most common SAEs are expected to be overnight hospitalizations for reasons related to substance use, psychiatric, or medical problems. All events meeting FDA definition for SAEs (any medical occurrence that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; creates persistent or significant disability/incapacity, or a congenital anomaly/birth defect will be reported) will result in immediate notification (within 1 hour of staff learning of SAE) to the study Principal Investigator (Dr. Baskin-Sommers), Psychotherapy Development Center (PDC) regulatory coordinator, and on-site SATU/IOP clinic director (or their designee). Within 24 hours, staff will complete the study SAE Form (without PHI) and send this to the same three individuals.

As part of this initial report, Dr. Baskin-Sommers will provide an evaluation of the SAE with regard to its: 1) grade of risk (none, mild, moderate, severe, life-threatening or disabling; fatal; 2) attribution of relatedness to study (unrelated/not, unlikely/remotely, possibly, probably, definitely); 3) level of anticipation/expectedness given the risks of study population or protocol (anticipated, anticipated but at frequency greater than expected, unanticipated); 4) categorization (death, life threatening, hospitalization, disability, birth anomaly/defect, medical intervention required to prevent death/disability); 5) resolution (recovered/resolved, recovering/resolving, not recovered/resolved, fatal, lost to follow-up). This evaluation will be documented on study SAE Form. The PDC regulatory coordinator or designee will follow up with Dr. Baskin-Sommers or study staff until the SAE resolution (5) is considered resolved and any updates documented and reported appropriately.

The Yale Human Investigations Committee (HIC) must be informed with 5 days of any SAE that Dr. Baskin-Sommers judges to be unanticipated (or anticipated but occurring greater than expected) and (possibly, probably, definitely) related to study participation. The HIC form must be completed either electronically through COEUS, faxed to the HIC office, or hand delivered. A copy of this HIC form will be forwarded to the PDC regulatory coordinator or designee. Yale's File Transfer Facility or other secure system must be used if personal health information is included on this form.

The NIDA Program Office must be informed of any SAE that results in death or which Dr. Baskin-Sommers judges as sufficiently life threatening that death might have occurred if medical or psychiatric intervention were not provided. This report is made to NIDA regardless of whether the SAE was study related or unanticipated. Dr. Baskin-Sommers and study staff will provide a follow-up report to the PDC regulatory coordinator or designee with 48 hours of the event so that NIDA's SAE form can be completed and submitted. Copies of this form will be distributed to the PDC PI (Dr. Carroll), study co-investigators, all DSMB members, and the on-site program director. Yale's File Transfer Facility or other secure system must be used if personal health information is included on this form. Within one week, the PDC PI or Scientific Director will confer with DSMB members to determine if a meeting should occur.

In addition to the SAE forms completed, a progress note in the study clinical chart must be made that provides a detailed narrative description of the event with a co-signature by supervisory personnel.

All SAEs regardless of grade, relatedness, anticipation, categorization, or resolution will be summarized in quarterly DSMB reports and annual reports to the Yale HIC.

We will report all major protocol amendments or changes in the informed consent form to the NIDA Project Officer as well as any temporary or permanent suspension of patient accrual

d. For multi-site studies for which the Yale PI serves as the lead investigator: **N/A**
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

13. Statistical Considerations: Describe the statistical analyses that support the study design.

Data will be collected, managed and analyzed through the standard procedures of the PDC as described in detail in the parent grant. Regarding statistical power, Dr. Baskin-Sommers' previous study using a similar cognitive remediation battery (1) with 55 participants revealed an effect size of d =.42 for the malleability of performance on the training, with 92% power. A sample size of 100 will allow us to evaluate the effect of ongoing substance use as a moderator of treatment response at 80% power. We have established that we can recruit and treat a sample of this size in the one-year time allotment of the SOBC supplement. Our rates of end of treatment assessment and follow-up in Center trials is 90% or above, enabling us to conduct true intention to treat analyses with minimal statistical imputation (48, 49, 83). General Linear Modeling will be used to examine change in performance on these tasks over time. Using General Linear Modeling as we have in previous Center-supported studies (10, 37, 49, 57, 84), we will evaluate the extent to which participants who receive cognitive remediation show significantly greater improvement across time in the cognitive-affective assessment battery than those who receive the control training. Additionally, structural equation modeling (SEM) and latent profile analysis (LPA) will be used to examine variable-centered (correlation between measures) versus person-centered (profiles of individuals) alternatives. SEM with maximum-likelihood estimation will be used to test the association between pre-post measures and SUD-related behaviors. LPA, whereby each individual is assigned to a mutually exclusive assay class (i.e. profile) based on a data-driven analytic strategy, will be used to test the association between each individual's pre-post profile and treatment response. Moreover, we will use regression discontinuity analyses compare observations clustered closely on either side of a process-level threshold around a particular intervention. This analysis would allow us to examine the local average treatment effects on pre-post measures in a non-parametric data-driven manner.

Timeline	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Recruit 3 participants/week	x	x	x	x	x	x	x	x	x			
Participant 100 completes 4 week treatment											x	
Participant 100 completes 1 month follow-up												x
Data analysis and preparation of reports												x

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

B. DRUGS/BIOLOGICS ☒N/A

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

4. Use of Placebo: ☒Not applicable to this research project

B. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: 100
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings (Criagslist)	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☒ Departmental/Center website	☐ Television
☐ Medical record review*	☒ Departmental/Center research boards	☒ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☒ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☒ Other: Direct referral from clinicians to RA		

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. Flyers and direct clinician referral. Flyers will be posted throughout SATU, IOP, and on websites (Craigslist, Department/Center website). Additionally, all clinicians will be given a "Client Interest Sheet" that describes the basic study and asks clients to contact study personnel.

Clinicians will mention, in-person, that a study is being conducted at SATU/IOP. If a client expresses interest, the clinician will have the client fill out the "Client Interest Sheet."

b. Describe how potential subjects are contacted. Potential participants will be contacted via two options. One option will be that the client takes a flyer tab and calls the research staff via phone. That phone call will be used to set up an in person screen, where a consent form will be presented. The other option will be that a clinician provides the client with a "Client Contact Sheet" and then the client calls staff to set-up an initial in-person screen.

c. Who is recruiting potential subjects? Research staff and indirectly clinic staff who refer

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☐Yes, some of the subjects

☒No

If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.) N/A

Choose one:

☐ For entire study

☐ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *Write here*

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

A trained research staff member will obtain written informed consent prior to any study related procedures. The informed consent process will be conducted in a private, quiet setting. The staff member and the participant will discuss the basic components described in the consent form. These include: participation is voluntary and participants may withdraw without consequences to clinic services received, purpose, procedures, randomization, visit schedule, risks and benefits, potential compensation, alternatives to study participation, and confidentiality. The consent form describing each of these components will be reviewed and approved by the Yale School of Medicine Institutional Review Board (Human Investigations Committee) prior to enrolling any participants. Potential participants will be provided an opportunity to ask questions and time to consider his/her decision to participate. A comprehension quiz will be given to ensure the participant has an adequate understanding of study as we have done in multiple previous studies (87, 93, 95-97). A copy of the consent form will be given to the participant.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

We require participants to read and write in English, and we routinely use a multiple-choice test after review of the consent form to determine that participants understand the key points of the research. The research staff reviews the test with the participant and clarifies any question which was incorrectly answered.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒Not Requesting any consent waivers

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

   No PHI will be collected on study CRFs. We only collect protocol session dates which are changed to "number of sessions completed" if data sets are released to other Yale investigators.

2. How will the research data be collected, recorded and stored?

   All research staff and clinicians receive annual Good Clinical Practice, Human Subjects Protection, and HIPAA training through the Yale School of Medicine. Our data collection and management procedures are fully compliant with HIPAA. In addition:

   - Our study forms have been designed to avoid collecting identifiable information (e.g., no PHI is collected on CRFs). We generally collect only protocol session dates. These are changed to 'number of sessions completed' if data sets are released to other Yale investigators.
   - Research data are collected on CRFs, and sent to data managers in our research offices on a closed secure network. All computers used by research staff are password protected. No identifying information is on CRFs.
   - The screening of patients using the inclusion and exclusion criteria, and the comprehensive evaluations will minimize the risk of including subjects with insignificant substance use (or who are otherwise inappropriate for the study).
   - Confidentiality in regards to collected materials will be maintained via a numbered reference system maintained by the Project Director. Participants' names will appear only on the consent form, HIPPA authorization form, and "key" form kept by the Project Director.
   - Limits to confidentiality include only disclosure of acute suicidality, homicidality, or abuse of a minor, as is standard in clinical practice.
   - Data are stored at our secure data management center; data sets do not include identifying information. At the conclusion of the study, all locator data are destroyed. Source data is generally destroyed 3 years after completion of the study at a secure location and destroyed by Shred-It.
   - The funding agency, NIDA, may access the data for routine audits.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   See above

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   Data are stored at our secure data management center; data sets do not include identifying information. At the conclusion of the study, all locator data are destroyed. Source data is generally destroyed 3 years after completion of the study at a secure location and destroyed by Shred-It.

6. If appropriate, has a Certificate of Confidentiality been obtained?

   Will be applied for pending HIC approval. The Certificate of Confidentiality is being obtained to protect client's omission of substance use and/or a toxicology screen. If the participant tests positive, results will be stored as a part of our research record on the secure server.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The major potential benefit to participants is in potential reduction of substance use and improvements in cognitive affective functioning via the study treatments, which may, in turn, foster improvement in participants' legal, medical, interpersonal, psychological and occupational functioning.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Individuals who do not wish to participate or who are ineligible for the trial will continue to receive standard treatment at SATU/IOP.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   All participants will be offered compensation for time spent completing study assessments including $35 for the pre-treatment assessment, $10 for each training session, $35 for posttreatment assessment, $50 bonus for completing all training sessions and scheduled assessments and $50 for the one-month follow-up. The possible total is $250 for completing all timepoints. Payments to the participants will be prorated for those who withdraw prematurely; that is, they will receive payment only for those assessments they complete.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   Subjects will not be charged for ancillary treatments or evaluations they receive at the clinic. Subjects will be charged for treatment as usual at the clinic; where most patients receive treatment with no-out of pocket expenses or on a sliding scale.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   This is a minimal risk trial with no foreseen injury risks. The participant's insurance carrier will be expected to pay the costs of medical care. No additional financial compensation for injury is available.

   a. Will medical treatment be available if research-related injury occurs? No
   b. Where and from whom may treatment be obtained? The emergency room or private provider
   c. Are there any limits to the treatment being provided? Yes
   d. Who will pay for this treatment? Patient insurance
   e. How will the medical treatment be accessed by subjects? By self- referral

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒