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Electrophysiological predictors and indicators of contingency management treatment response: Rationale and design for the ways of rewarding abstinence project (WRAP)

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ABSTRACT

Background: Electrophysiological measures can predict and reflect substance use treatment response. Veterans are disproportionately affected by disorders of addiction; cocaine use disorder (CUD) being particularly problematic due to high relapse rates and the absence of approved pharmacotherapies. Prize-based Contingency Management (PBCM) is an evidence-based behavioral intervention for CUD, involving incentives for cocaine abstinence but treatment response is variable. Measurement-based adaptation of PBCM has promise to improve effectiveness but remains to be usefully developed.

Methods: This trial aims to determine if individuals with distinct neurocognitive profiles differentially benefit from one of two existing versions of PBCM. CUD patients will be randomized into treatment-as-usual or 12-weeks of PBCM using either monetary or tangible prize incentives. Prior to randomization, EEG will be used to assess response to monetary versus tangible reward; EEG and cognitive-behavioral measures of working memory, cognitive control, and episodic future thinking will also be acquired. Substance use and treatment engagement will be monitored throughout the treatment interval and assessments will be repeated at post-treatment.

Discussion: Results of this trial may elucidate individual differences contributing to PBCM treatment response and reveal predictors of differential benefits from existing treatment variants. The design also affords the opportunity to evaluate treatment-related changes in neurocognitive functioning over the course of PBCM. Our model posits that PBCM scaffolds future-oriented goal representation and self-control to support abstinence. Individuals with poorer functioning may be less responsive to abstract monetary reward and will therefore achieve better outcomes with respect to abstinence and treatment engagement when tangible incentives are utilized.

1. Introduction

Electrophysiological methods, including event-related potential and functional connectivity approaches, have potential to clarify mechanisms of substance use treatment response and characterize individual differences therein. Veterans are disproportionately affected by substance use disorders [1,2] – with cocaine use disorder (CUD) being particularly problematic due to high relapse rates [3] and the absence of approved pharmacotherapy options [4]. Behavioral interventions for CUD have therefore become an important focus of treatment and Contingency Management (CM) has emerged as the best-supported approach [5–7]. CM involves reinforcing objectively-verified cocaine abstinence with reliable, short-term reward, such as chances to win prizes, i.e., Prize-Based CM (PBCM). However, individual responses to PBCM are variable [8] and long-term benefits are limited [5] – limitations magnified by costs of implementation with respect to staffing and prizes.

Measurement-based approaches to PBCM implementation have promise to improve the effectiveness and efficiency of CM programming but have not yet been investigated in relation to promising

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neuromarkers. Importantly, two versions of PBCM are currently utilized in the largest CM implementation effort to date, across 131 sites within the Veterans Health Administration [9,10]. Because these versions differ with respect to the psychological proximity of reward, individuals with distinct neurocognitive profiles may differentially benefit from one version or the other. Specifically, VA PBCM programs employ either abstract (vouchers) or concrete (tangible prize) incentives, the latter being potentially more effective in Veterans with poor future-oriented thinking and planning ability. While selection between existing PBCM variants currently reflects practical considerations only, pretreatment neurocognitive functioning could meaningfully and realistically inform clinical decision-making in this regard [8].

This study aims to advance measurement-based implementation of CM by testing a novel neurocognitive model with immediate implications for understanding and predicting inter-individual variation in CM treatment response. Specifically, the future-minded decision-making (FMDM) model posits that CM scaffolds future-oriented goal representation and self-control to support abstinence during use-related decision-making [11,12]. For individuals with greater FMDM impairment, concrete, readily accessible incentives may be more effective than abstract voucher-based rewards that require increased future-oriented thinking and planning to acquire value.

To test this model, neurocognitive substrates of FMDM will be examined as predictors of differential treatment response in voucher (VoucherPBCM) versus tangible prize (TangiblePBCM) versions of PBCM. Treatment-related change in neural and cognitive-behavioral correlates of FMDM will also be evaluated in PBCM relative to treatment-as-usual (TAU) care. Veterans with CUD will be allocated to receive 12 weeks of VoucherPBCM, TangiblePBCM, or TAU. Pre- and post-treatment electroencephalography (EEG) and cognitive-behavioral assessments will be used to measure FMDM-related constructs: working memory, self-control, future-oriented decision-making, future reward representation, and related neuromarkers. These measures will be investigated as predictors of differential treatment response in VoucherPBCM versus TangiblePBCM, as well as maintenance of benefits during a post-treatment follow-up period. Change in FMDM-related neural and cognitive measures over the course of treatment will also be evaluated for evidence of neuroadaptation, e.g., changes in functional connectivity and remediation of FMDM-related functioning through PBCM. Taken together, results of the current project will represent an important step toward precision implementation of PBCM.

2. Methods

The Institutional Review Board of the Veterans Affairs Pittsburgh Healthcare System (VAPHS) approved this study and conducts ongoing monitoring. This study is funded by VA CSR&D project ID CX001807-01A1 and is registered on clinicaltrials.gov (ID: NCT03799341). This study is currently in its third of 5 years and recruits on a rolling basis (although an administrative hold on in-person research activities resulted in a temporary pause in recruitment during the COVID-19 pandemic).

Specific Aims and Hypotheses. See Fig. 1 for an infographic depicting the study design vis-à-vis Specific Aims 1 and 2. A summary of research assessments and relevant outcome measures is additionally provided in Tables 1 and 2.

Specific Aim 1: Evaluate the utility of EEG and cognitive-behavioral measures of FMDM as predictors of differential treatment outcomes in TangiblePBCM versus VoucherPBCM.

Hypothesis 1a. FMDM-related measures will predict differential outcomes in TangiblePBCM relative to VoucherPBCM, with more FMDM-impaired individuals demonstrating improved treatment response in the former relative to the latter.

Hypothesis 1b. Inclusion of predictors from the FMDM account will significantly improve performance of predictive models forecasting short- and long-term outcomes in CM and these predictors will be favored for inclusion even when penalties are introduced to capture measurement cost (e.g., EEG-based measures being more expensive to acquire than questionnaire-based measures).

Specific Aim 2: Evaluate treatment-related change in EEG and cognitive-behavioral correlates of FMDM-related cognitive functioning during CM versus TAU.

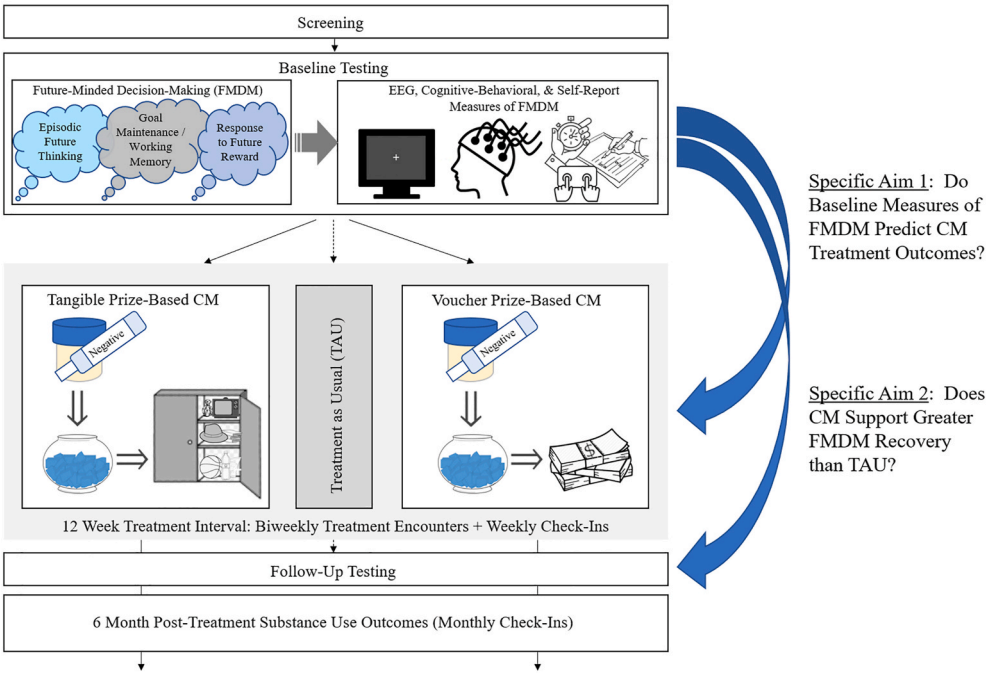

Fig. 1. The current precision mental health clinical trial evaluates whether future-minded decision-making (FMDM) capacity (measured using EEG, cognitive-behavioral paradigms, and self-report assessments) predicts differential benefits of Prize-Based Contingency Management (PBCM) utilizing either voucher or tangible prize-based reinforcement. Treatment-related change in FMDM-related measures will also be investigated in PBCM conditions relative to treatment-as-usual.

Table 1
Summary of experimental paradigms used in cognitive-behavioral and EEG-based assessments.

Experimental Paradigm	Description
Personalized Delay Discounting Task	• Participants are interviewed about upcoming positive and neutral life events (e.g., birthdays, holidays, vacations), occurring at latencies from one week to one year. • Events rated with respect to personal relevance, valence, and arousal/excitement. • Participants subsequently complete delay discounting trials with and without inclusion of event tags referencing personally-meaningful future events from the interview. • Allows concurrent assessment of standard delay discounting behavior (i.e., without event tags) and discounting in the context of episodic future thinking (with event tags). • The difference in delay discounting slopes estimated for each condition will be used as a measure of future-minded decision-making.
Auditory Consonant Trigrams Test	• Participants maintain letter sequences in working memory while performing a distractor task for 0, 9, 18, or 36 s. • On each trial, participants receive a letter sequence and starting number, count backwards by threes for the duration of the delay period, and attempt to recall the letter sequence. • Scores index maintenance and decay of working memory contents of potential relevance to maintenance of goal representations.
Concrete-Abstract Incentive Delay Task	• A modified version of the Monetary Incentive Delay will be used to assess response to voucher versus tangible-prize rewards. • Each trial consists of a cue signaling reward magnitude, an imperative stimulus, and a feedback presentation. • Block-wise presentation of voucher and tangible-prize reward trials enables measurement of differential suppression of alpha frequency brain waves (indicating greater engagement) during anticipation of abstract (voucher) versus concrete (tangible-prize) rewards. • Voucher and tangible-prize wins will be banked separately; a performance-based bonus will be awarded to support naturalistic reward processing.
Parametric Conflict Flankers Task	• A modified flankers task will be used to measure cognitive control-related ERPs (conflict N2 and ERN) and functional connectivity between mediofrontal and lateral-frontal electrode sites measures (e.g., theta frequency synchronization). • Trial-to-trial response conflict will be parametrically manipulated through different levels of flanker-target incongruity (i.e., Congruent, Incongruent-Low, Incongruent-Medium, and Incongruent-High). • Enables concurrent assessment of electrophysiological and cognitive-behavioral metrics of performance-monitoring, conflict detection, and control adaptation.

Hypothesis 2a. Individuals in TangiblePBCM and VoucherPBCM will demonstrate greater treatment-related change in functional connectivity networks underlying goal-informed cognitive control processes, as well as behavioral measures of working memory and future-oriented decision-making, relative to TAU.

Exploratory Sub-Aim. Longitudinal change in FMDM-related measures will be investigated in relation to patterns of abstinence during PBCM and will reflect distinct treatment response trajectories.

Participants. A total of 180 Veterans with CUD will be recruited into the study. Participants will be recruited at the time of outpatient substance use treatment engagement through the Center for Treatment of Addictive Disorders (CTAD) at VAPHS. All participants will be military Veterans between the ages of 18 and 70 and will have normal or corrected-to-normal vision and hearing. Veterans will be excluded due to: (1) history of severe traumatic brain injury, seizure disorder, or other neurological illness, (2) severe of unstable medical or psychiatric condition, (3) moderate-to-severe neurocognitive impairment (Saint Louis University Mental Status (SLUMS) $\leq$ 20), or (4) current pregnancy or lactation. All participants will be required to meet DSM-5 criteria for mild-to-severe CUD, have used cocaine within the past 45 days (or during the past 60 days if living in a controlled environment for part of this time), and have a stated goal of cocaine abstinence. Patients currently living in a controlled environment will additionally be excluded. Selection criteria for CUD participants were chosen to identify Veterans for whom CM is clinically indicated. In addition, criteria specify exclusion of individuals for whom brain-based data may be aberrant due to organic factors, as well as those whose medical or psychiatric status may preclude full participation in a longitudinal study. In order to capture a representative clinical sample, CUD patients with comorbid substance use and/or other mental health conditions will not be excluded.

Study Procedures: Individuals with CUD (n = 180) will be recruited upon engagement with outpatient substance use services and assigned to 12 weeks of TangiblePBCM (n = 70), VoucherPBCM (n = 70), or TAU (n = 40). Participants in all conditions will complete EEG and cognitive-behavioral assessments of core FMDM constructs (i.e., goal-informed cognitive control processes, executive working memory, episodic future thinking, and reward anticipation) before and after the 12-week treatment interval. Self-report measures of other clinically-relevant indicators (e.g., addiction propensity and severity, self-efficacy, motivation for change) also will be evaluated and outcomes (treatment engagement, subjective and objective measures of substance use) will additionally be followed throughout the 12-week treatment interval and for 6 months post-treatment in both CM groups.

Screening Procedures. Preliminary eligibility for the study will be assessed during a telephone interview with study staff. Veterans meeting general criteria will be invited to schedule an initial study visit involving informed consent, cognitive screening (i.e., Saint Louis University Mental Status (SLUMS) exam), and diagnostic interview procedures (i.e., Mini International Neuropsychiatric Interview (MINI) 7.0.2, and the Addiction Severity Index-Lite (ASI-Lite)). The MINI will be used to identify comorbid psychiatric and substance use diagnoses, as well as CUD severity. The SLUMS will be administered to screen for moderate-to severe cognitive impairment. Participants determined to be eligible following participation in diagnostic interview and neuropsychological screening procedures will be scheduled for a Baseline Assessment.

Baseline Assessment. Participants will be asked to abstain from drug use for 72 h before the baseline assessment visit and will be required to pass breathalyzer (BAC = 0.000%), as well as urine and/or oral saliva drug screens (negative for all common illicit substances excluding marijuana) in order to proceed with baseline testing. A timeline follow-back procedure will also be used to assess past-month drug use. Participants will complete self-report measures of several constructs relevant to FMDM and clinical status, including the following: measures of craving (Drug Craving Questionnaire, Alcohol Craving Questionnaire [13]), sensation seeking (Sensation Seeking Scale [14]), avoidance and inflexibility in response to cocaine triggers (Avoidance and Inflexibility Scale [15]), motivation for change (Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) [16]), previous relapse experiences (Time to Relapse Questionnaire [17]), sensitivity to reward and punishment (Sensitivity to Punishment/Sensitivity to Reward Questionnaire-20 (SPSRQ-20) [18]), subjective experience of retrospective and prospective memory proficiency (Prospective-Retrospective Memory Questionnaire [19]), self-efficacy (Drug Taking Confidence Questionnaire [20]), future mindedness (Consideration of Future Consequences Scale [21]), nicotine dependence (Fagerström Test for Nicotine Dependence [22]), and adverse

Table 2
Summary of assessments and outcome measures by study timepoint.

		Screening	Baseline Testing	12-Week Treatment Interval	Follow-Up Testing	Post-PBCM Check-Ins
Primary & Secondary Outcome Measures	PBCM Session Attendance			PBCM		
	Point-of-Care PBCM Urine Results			PBCM		
	Laboratory-based Urinalysis Results			X		(PBCM)
	Non-CM Treatment Encounters			X		PBCM
	Self-Reported Cocaine Use		X	X	X	PBCM
	Self-Reported Drug & Alcohol Use		X	X	X	PBCM
Eligibility Assessment	SLUMS	X				
	Point-of-Care Drug & Alcohol Screening		X		X	
Psychodiagnostic Assessment	MINI for Psychotic Disorders Studies	X				
	Addiction Severity Index-Lite	X			X	
EEG Assessments	Concrete-Abstract Incentive Delay		X		X	
	Parametric Conflict Eriksen Flanker		X		X	
	Resting State/Spontaneous Blink Rate		X		X	
Cognitive-Behavioral Assessments	Personalized Delay Discounting		X		X	
	Auditory Consonant Trigrams Test		X		X	
Self-Report Assessments	Drug Craving Questionnaire		X		X	
	Alcohol Craving Questionnaire		X		X	
	Fagerstrom Test for Nicotine Dependence		X		X	
	Consideration of Future Consequences Scale		X		X	
	Avoidance and Inflexibility Scale		X		X	
	Time to Relapse Questionnaire		X		X	
	Prospective-Retrospective Memory Questionnaire		X		X	
	Sensation Seeking Scale		X			
	SOCRATES		X			
	SPSRQ-20		X			
	Drug Taking Confidence Questionnaire		X			
	Adverse Childhood Experiences Questionnaire		X			

experiences in childhood (Adverse Childhood Experiences questionnaire [23]). These instruments were chosen to measure clinically-relevant factors in substance use treatment (e.g., motivation, craving, and impulsivity), as well as factors previously associated with CM treatment outcomes specifically [8]. Participants will also complete a series of cognitive-behavioral tasks including an Auditory Consonant Trigrams working memory test [24] and a personalized delay discounting task [25,26]. Additional experimental paradigms will be administered during acquisition of EEG data using a 32-channel Brain Products actiCHamp active electrode recording system. EOG data will additionally be acquired from three passive electrodes via a bipolar-to-auxiliary adapter throughout the EEG recording session. The EEG recording session will consist of a 5-min resting state acquisition period, followed by administration of two cognitive-behavioral tasks: (1) a modified monetary incentive delay task and (2) a modified Eriksen flankers task [27]. Additional details of EEG and cognitive-behavioral paradigms and measures of interest are included in Table 1.

Randomization. A minimization approach was selected to allow for stratification on an expanded set of potentially-relevant clinical and demographic factors. Specifically, participants will be stratified by age (18–50, >50), sex (male/female), involvement in medication-assisted treatment for opioid use disorder (yes/no), and a category representing potentially interrelated factors: working memory function and serious mental illness (SMI) comorbidity (impaired working memory with SMI, impaired working memory without SMI, intact working memory with SMI, intact working memory without SMI). For the combined stratification category, impaired working memory is defined as an Auditory Consonant Trigrams score below the age-specific norm and the presence of SMI is defined as a current diagnosis of bipolar or psychotic illness. Working memory ability was identified as a focus of stratification due to the expected relationship between this aspect of cognitive functioning and other FMDM-related constructs of interest. Veteran- and age-specific norms are also available for the Auditory Consonant Trigrams test, thus providing the basis for a norm-referenced cut-off [24,28]. Our minimization algorithm uses a marginal balance measure of imbalance and a biased-coin minimization approach, as recommended for designs with unequal treatment allocation [29]. A p-value of 0.7 and group ratio of 7:7:4 were employed to achieve sufficient randomness in allocations while also approximating 20% of allocations to TAU and 40% to each PBCM treatment condition using a biased-coin approach. All our prognostic factors were weighted equally. Veterans will be informed of their group assignment at the conclusion of baseline testing, whenever possible.

Validation of Randomization Approach. While minimization-assigned treatment groups are expected to be well-matched with respect to means and proportions of prognostic variables of interest, it is not yet known if this method provides for comparable variance in continuous prognostic variables across treatment conditions. Because we are specifically assessing differential treatment response in relation to patient-level characteristics, variability in FMDM-related functioning should also be comparable within each treatment condition under study. Our approach to this issue was two-fold: (1) we employed norm-referenced performance on the Auditory Consonant Trigrams task as a proxy for FMDM in our minimization approach and (2) we conducted a series of simulations to evaluate how minimization impacts the overall distribution of continuous prognostic variables. For the latter, we specifically considered variability in age within and between treatment conditions due to the availability of data on age from our target population and possible impact of age on FMDM [30]. We first generated a mock dataset of N = 180 samples representing our four prognostic variables of interest (i.e., age, sex, involvement in medication-assisted treatment, working memory/SMI diagnosis) based on data from an earlier pilot study and clinic records. We then conducted 20 simulations of the minimization procedure. Our results confirmed that our approach preserves means

and proportions of our prognostic variables. Additionally, Brown-Forsythe tests for the equality of group variance in age between treatment conditions demonstrated no significant difference in variance between treatment conditions in all 20 simulations, even without correcting for multiple comparisons (See Fig. 2).

Interventions. Participants will be randomly assigned to receive Prize-based Contingency Management (PBCM) with either voucher or tangible prize rewards or treatment-as-usual alone. For participants assigned to either PBCM condition, PBCM will be used as an adjunct to treatment-as-usual (TAU) outpatient care. To wit, all participants will receive TAU throughout the 12-week treatment interval, with approximately 78% additionally receiving PBCM. For all participants, TAU will entail twice-weekly urinalysis and recommended participation in at least two outpatient group and/or individual psychotherapy encounters per week; participants will additionally continue pharmacotherapy for substance use and/or other mental health conditions, if applicable. For those assigned to PBCM, treatment will additionally involve twice-weekly sessions with a PBCM provider, each lasting approximately 15 min. During each PBCM session, a urine specimen provided by the patient is tested for cocaine using a point-of-care immunoassay drug test. Results of point-of-care testing are then shared with the patient and negative results are reinforced with draws from a fish bowl containing 500 paper slips, 250 of which award 'small', 'large', or 'jumbo' prizes (remaining slips include words of encouragement).

Patients are reinforced with a single prize draw for their first negative specimen; an additional prize draw is added for each consecutive negative result, up to 8 prize draws per session. Abstinence-contingent prize draws are reset to one upon either a positive test result or unexcused absence. We will systematically evaluate two PBCM variants that are already used within the VA and vary with respect to the psychological proximity of reward. The probability of each reward magnitude will be the same in both treatment conditions. Specifically, 41.8% of paper slips will award a 'small' prize, 8% will award a 'large' prize, and 0.2% will award a 'jumbo' prize. Participant outcomes (outpatient treatment engagement, % cocaine-negative urines, self-reported days of use) will be followed throughout the 12-week treatment interval via weekly check-ins by phone or in-person. Outpatient substance use treatment engagement and urinalysis results will additionally be monitored through review of participant medical records.

Tangible Prize-Based CM. For participants assigned to TangiblePBCM, prize draws resulting in one or more 'small', 'large', or 'jumbo' wins will result in immediate access to a prize cabinet stocked with small (approximately $1 in value), medium (approximately $4 in value), large (approximately $20 in value), and jumbo (approximately $100 in value) incentive items. Medium incentive items are included for selection in the event that a patient wishes to redeem several small prize slips on the same day and are considered equivalent to 4 small prizes. Selection of specific prize items will be informed by patient preference and items will be restocked regularly. The prize cabinet will be open during TangiblePBCM sessions such that prize items are readily visible. Selection of

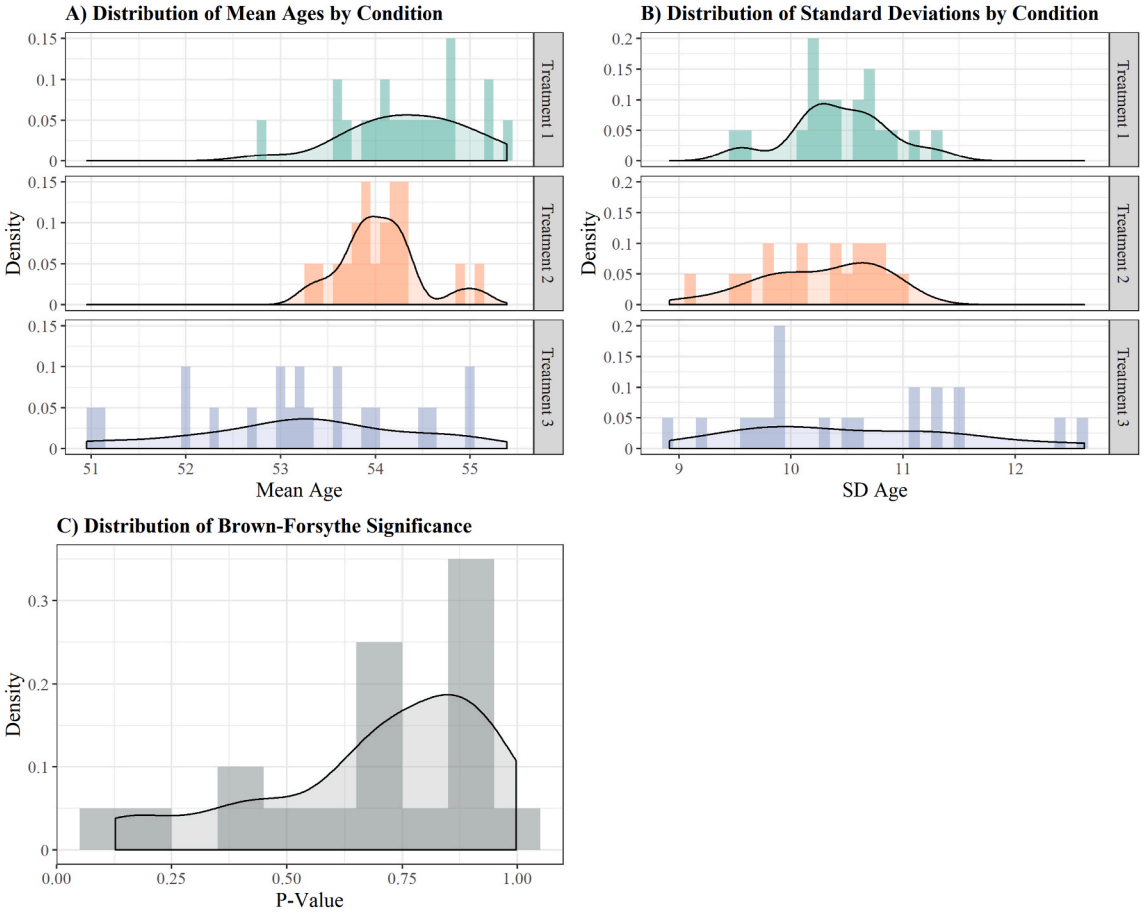

Fig. 2. We generated a dataset of N = 180, comparable to our pilot population in age, gender, working memory, and serious mental illness status. We conducted 20 simulations in which we assigned these observations to treatment groups based on these 4 prognostic variables, using the same minimization procedure specified in our protocol. While age was treated as a categorical variable with two levels for the purpose of minimization (i.e., 18–50, >50), both the mean (Panel A) and standard deviation (Panel B) of age were comparable across treatment conditions. As would be expected, simulation results were somewhat more variable for Treatment 3, which was set to include ~22.2% of participants to model our TAU condition. Importantly, none of our simulations yielded a significant difference in variability in age across the 3 treatment groups, as indicated by the Brown-Forsythe test statistic (Panel C). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

prizes, maintenance of the prize cabinet, and policies regarding prize redemption will follow guidance on administration of TangiblePBCM within the context of research protocols [31].

Voucher Prize-Based CM. For participants assigned to VoucherPBCM, prize draws resulting in one or more 'small', 'large', or 'jumbo' wins will be reinforced with Veterans Canteen Service vouchers in the specified amount (i.e., $1, $20, or $100, respectively). Veterans Canteen Service vouchers can be redeemed for goods and services through Veterans Canteen Service vendors (e.g., Patriot Store retail locations, Patriot Café food courts) at VA facilities. Participants in this condition will additionally be asked to provide information on voucher redemption during PBCM sessions and/or weekly check-ins.

Post-Treatment Follow-Up. A subset of pre-treatment assessment procedures will be repeated at the conclusion of the 12-week treatment interval for all participants. Procedures will generally involve repetition of the EEG session, as well as re-administration of cognitive-behavioral testing and state-dependent self-report questionnaire measures. The timeline follow-back procedure will be completed again at the time of the follow-up visit and a subset of items from the Addiction Severity Index-Lite will also be readministered. Participants assigned to PBCM will also be asked to engage in brief monthly assessments for 6 months following the conclusion of the 12-week treatment period. Timeline follow-back data will be the primary outcome measure and will be collected by phone or in-person. Participants assigned to TAU will not be subject to longer term follow-up. We will also continue to monitor outpatient substance use treatment engagement and urinalysis results (when available) through review of participant medical records during this time period. See Table 2 for an overview of data collected by study timepoint.

Analytic Strategy. The current trial aims to examine candidate predictors of differential treatment response in TangiblePBCM versus VoucherPBCM (i.e., alpha suppression during reward anticipation, change in delay discounting with inclusion of future event tags), as well as brain-based predictors of more general potential relevance to PBCM treatment response (i.e., electrophysiological signals related to cognitive control). Specifically, we will consider event-related potential (ERP) components that signal the need for additional control resources when there is conflict between competing response options (i.e., the conflict N2) and/or an erroneous response has been made (i.e., the error-related negativity (ERN)). Both the N2 and ERN have previously been localized to the anterior cingulate cortex [32,33] and amplitude of the ERN has previously been identified as a predictor of treatment outcome in patients with cocaine use disorder [34]. Treatment-related change in (1) EEG theta synchronization between mediofrontal and lateral-frontal electrode sites and (2) delay discounting behavior will also be examined for evidence of enhanced control- and episodic future thinking-related neurocognitive adaptation in PBCM versus TAU conditions. Individual differences in delayed reward representation and/or inhibitory control may additionally reflect variability in executive working memory function, of relevance to context and goal maintenance. Consequently, this aspect of FMDM is also measured at pre- and post-treatment and considered with respect to both predictive modeling and neuroadaptive aims. The predictive utility of several standard self-report and psychodiagnostic (e.g., presence of SMI, psychiatric symptom severity based on ASI-Lite) measures will also be evaluated.

Specific Aim 1: Predictive models of PBCM treatment response and long-term outcomes will be developed separately. Candidate predictors will include pretreatment FMDM-related EEG (concrete versus abstract alpha suppression, ERN amplitude, parametric conflict N2 amplitude effect) and cognitive-behavioral measures (Auditory Consonant Trigrams score, change in delay discounting slope with event tags (i.e., episodic future thinking effect on discounting)), as well as clinical indicators and self-report scores. In order to examine the interaction between candidate predictors and PBCM reward parameters, PBCM condition will also be considered as an explanatory variable in predictive models. Analogous exploratory analyses will also be conducted to identify predictors specific to PBCM treatment response versus TAU in order to clarify the relevance of FMDM-related constructs to treatment response in CM specifically, versus substance use treatment more generally.

Predictive Modeling. Regression trees will be grown to examine the predictive structure of explanatory variables, including PBCM treatment condition, with respect to the following continuous outcomes: (1) % cocaine-negative urines during PBCM, (2) % PBCM sessions attended, (3) % days of any self-reported substance use during PBCM, and (4) % days of self-reported stimulant use during the 6 months following PBCM. Classification and Regression Trees (CART) involves partitioning observations into more homogenous subgroups with respect to the outcome of interest by identifying cut points along predictor variables. For each CART, cost-complexity pruning will be conducted using five-fold cross validation to limit overfitting. A Random Forest (RF) approach will subsequently be implemented with each set of predictors and outcomes to objectively evaluate the relative importance of each predictor and optimize overall model performance. RF involves growing an ensemble of decision trees based on bootstrapped samples of observations and predictors to increase tree diversity. This method includes internal cross-validation using out-of-bag error rates (based on observations not included in the bootstrap sample) to limit overfitting during model training and performs well without excessive tuning of model parameters. Taken together these data mining approaches will provide deep insight into interrelationships between predictors and outcomes of interest. Top predictors will subsequently be entered into a resource-constrained Tabu regression search procedure [35] to develop multiple regression models forecasting treatment response (% cocaine-negative urines) in each PBCM variant, while penalizing individual predictors based on measurement cost. Resource-constrained Tabu search has not previously been used to analyze the predictive utility of neuromarkers in view of the increased cost of measuring these signals but is ideally suited to this issue in measurement-based care.

Specific Aim 2: We additionally hypothesize that PBCM will be associated with differential enhancement of control-related EEG theta synchronization between mediofrontal and lateral-frontal electrode sites during high conflict events in the Parametric Conflict Flankers task, relative to TAU and will foster greater improvement in working memory and episodic future thinking effects on delay discounting (Hypothesis 2a). Increased functional connectivity within control-related brain networks in conjunction with PBCM, as compared with TAU, would reflect important mechanisms of neural recovery facilitated by this intervention. Theta frequency synchronization likelihood between mediofrontal and lateral-frontal electrode sites will be computed to quantify transient network dynamics related to control modulation. Treatment-related change in executive working memory and delay discounting behavior will also be evaluated as cognitive-behavioral indicators of FMDM-related function.

Longitudinal Analysis. Repeated measures analysis of covariance (ANCOVA) will be conducted to evaluate treatment-related change in the following indices of FMDM between PBCM and TAU: (1) control-related theta synchrony between mediofrontal and lateral-frontal electrode sites, (2) Auditory Consonant Trigrams working memory score, and (3) change in the episodic future thinking effect in delay discounting slopes). A 3×2 general linear model design will be utilized, including treatment condition during the 12-Week treatment interval as the between-subjects factor and assessment latency as a within-subjects factor. Tukey's HSD will be used for post hoc evaluation of marginal means to clarify main and interaction effects. In order to account for differences in substance use and treatment engagement between PBCM and TAU, these factors will be considered as covariates in all comparisons. Adjusted marginal means will subsequently be used to investigate these covariates as moderators of the treatment-by-time interaction. Given the previously identified relationship between control-related theta phase synchrony and amplitude of the ERN [36] and conflict N2 [37], treatment-related change in these ERPs will be evaluated using the

same approach. Correlations between ERN/N2 amplitudes and control-related theta synchrony, as well between EEG and cognitive-behavioral measures, will also be computed for each time-point to identify significant linear relationships between dependent measures.

Power Analysis. In analyses of baseline predictors of treatment response in PBCM recipients (estimated n = 119–140) and long-term (i.e., six month) outcomes (estimated n = 105–140), using the statistical rule of thumb of needing 10 observation per predictor, there will be adequate power to include 10–14 variables in regression-based analyses. Assuming 15% attrition, the estimate of the detectable effect size (β = 0.20, alpha = 0.05) for the treatment by time interaction for a total sample size of 153 is f = 0.13. The anticipated effect size of treatment-related change in functional connectivity measures is not known. However, previous work has established a medium-to-large effect size for treatment-related change in the ERN and N2 [38,39].

Exploratory Analyses. Additional exploratory analyses will be conducted to examine distinct treatment response trajectories vis-à-vis longitudinal change in global measures of functional connectivity derived from EEG datasets. Cross-sectional analyses will also be conducted to investigate potential differences in cognitive-behavioral and EEG-based measures of FMDM between subgroups defined on the basis of comorbid mental health conditions, as well as medication-assisted treatment status.

3. Discussion

In the absence of FDA-approved pharmacotherapy options for CUD patients, providers have increasingly embraced specialized behavioral interventions – of which Contingency Management has emerged as the leading treatment option. CM has accumulated substantial empirical support over the past 25 years and has been consistently associated with reduced use and improved treatment retention in individuals with CUD [3–5]. Despite these favorable outcomes, the long-term sustainability of CM within both VA and community settings rests upon the cost-effectiveness of this treatment option. VA has already sought to address this fundamental issue by adopting a prize-based variant of CM [9,40] which utilizes a lower-cost reinforcement schedule with comparable effectiveness [41].

Precision implementation of CM represents another promising approach to minimizing the cost of incentive-based treatment, while also enhancing overall effectiveness. Importantly, previous efforts to improve CM effectiveness have highlighted opportunities to adapt CM treatment parameters in response to individual difference factors. Both increased magnitude [42] and probability [43] of contingent reward, for example, have been demonstrated to increase cocaine abstinence in CM and may be specifically indicated for patients with greater CUD severity. Given evidence of variable treatment response and poor retention of benefits following CM treatment, personalization of CM treatment protocols may also enhance and extend overall effectivenesss [8]. However, in order to pursue this direction, it will first be necessary to clarify *mechanisms and predictors underlying CM treatment response*.

The alternative reinforcement model of CM conceptualizes substance use as a conditioned response to drug-related positive reinforcement that can be systematically shaped by environmental contingencies. Under this model, abstinence-contingent alternative reinforcement works to increase the frequency of abstinence-consistent behaviors and to decrease use-related behaviors by manipulating opportunity costs. Basic tenets of this account are robustly supported within the scientific literature and have framed a preponderance of CM research to date. Under this model, inter-individual variation in CM treatment response is dependent on magnitude and frequency of reward. In practice, however, alternative rewards offered in CM are not immediately available; rather they occur at a delay of hours to days following use-related decision making. Recent critiques have thus highlighted that the potency of CM treatment depends – not only on the magnitude and probability of future reward – but also on its robust mental representation at the time of use-related decision-making [11,12]. Thus, individual differences in future reward valuation provide a promising new opportunity for adaptive intervention delivery. Accordingly, a novel future-minded decision--making (FMDM) model has been proposed to advance scientific inquiry into heretofore overlooked, cognitive components of this important intervention. FMDM constitutes a promising avenue for informing precision implementation of CM, offering both theoretical and practical strengths.

The FMDM model posits that CM treatment functions by scaffolding both recovery-oriented goal setting and goal-oriented decision-making. Specifically, by presenting reliable, short-term reward to reinforce abstinence, CM provides frequent opportunities for mental representation of delayed reward and related contingencies (See Fig. 3). CM can therefore be understood to engage executive working memory processes related to goal maintenance, as well as episodic future thinking, which involves mental simulation of future events. Through these processes, positive outcomes of abstinence can be robustly represented at the time of use-related decision-making and abstinence goals can be more readily accessed to capacitate both proactive and reactive control of behavior.

While recent work has highlighted the potential predictive utility of FMDM-related constructs [11,12], such predictors have not yet been studied in the context of FMDM-informed CM variants. This trial specifically tests two existing versions of Prize-Based CM (PBCM) that may differentially benefit individuals based on baseline FMDM ability. Specifically, the two treatment conditions under study differ with respect to the psychological proximity of rewards offered – with TangiblePBCM offering more psychologically proximal, concrete reward and VoucherPBCM offering abstract, monetary rewards. Viewing precision implementation of CM through an FMDM-informed lens may also offer considerable practical benefits over models that manipulate the frequency or magnitude of reward. Efforts to increase the psychological proximity of CM reward need not entail additional costs or potentially inequitable distribution of reward based on patient characteristics. Indeed, ethical considerations with respect to the latter makes measurement-based adjustment of CM parameters affecting subjective (rather than objective) reward value a preferred direction for this work [8].

Results of the current trial will (1) determine if FMDM-related cognitive abilities predict differential success in concrete (Tangible PBCM) versus abstract (VoucherPBCM) reward variants of CM and (2) reveal the degree to which cognitive abilities underlying FMDM are remediated through participation in CM programming. Predictive models of CM treatment response, to be developed through this work, may have strong and immediate translational relevance. As summarized in Table 3, results may inform future use of PBCM – either by establishing a basis for measurement-based implementation of TangiblePBCM versus VoucherPBCM, or by demonstrating that individually-informed implementation is not indicated. If our hypotheses are confirmed, our results will yield a predictive model that utilizes low-cost measures to assign appropriate treatment to patients with different levels of future-minded decision-making ability at pretreatment. Neurocognitive markers associated with PBCM response, either prospectively or longitudinally, will also provide the foundation for future directions of this work. Such markers represent proxy indicators of PBCM-related mechanisms of change and experimental treatments targeting these neurocognitive processes (e.g., cognitive training, neurofeedback, or noninvasive brain stimulation) may also have promise to enhance CM benefits.

Finally, we would like to highlight unique aspects of our study design that could potentially inform other similar work targeting precision mental health. As described under Methods, we chose a minimization approach to allocate participants into the three conditions under study (i.e., TAU, TangiblePBCM, VoucherPBCM). This adaptive stratified sampling method is particularly advantageous when the number and anticipated importance of prognostic factors is relatively high in

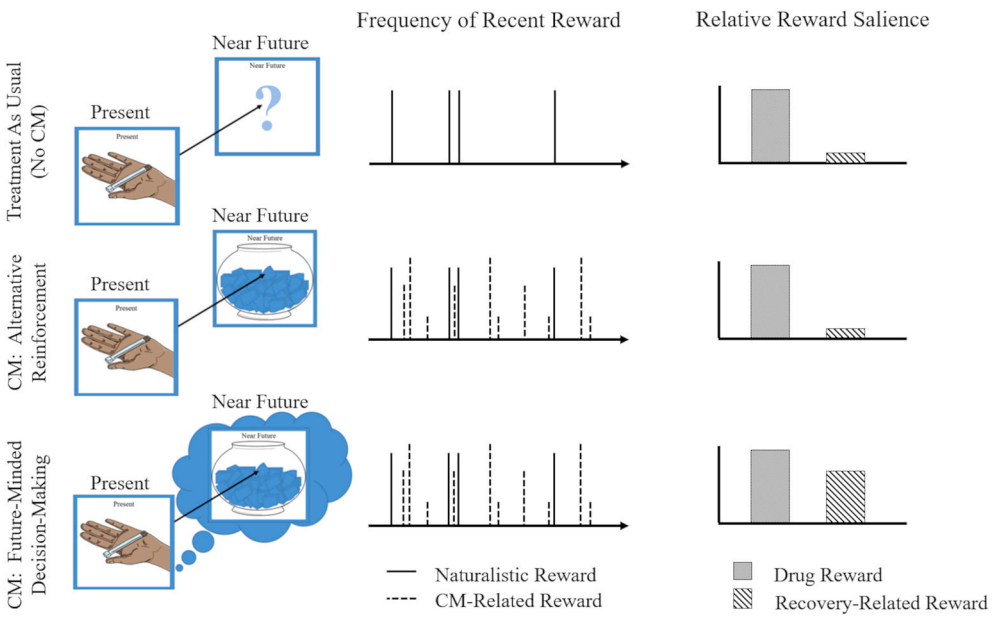

Fig. 3. In standard care (TAU; top panel), recovery-related reward can be infrequent and uncertain. CM provides reliable, near future opportunities for non-drug reward, increasing reward frequency in conjunction with abstinence to reinforce recovery-related behavior change (Alternative Reinforcement; middle panel). However, the motivational salience of drug reward remains high due to its magnitude and proximity. During *in the moment* decisions to use the FMDM model of CM (bottom panel) suggests robust mental representation of abstinence-contingent CM reward increases its motivational salience to support recovery-oriented decision-making and self-control.

Table 3
Summary of possible outcomes and implications for clinical implementation of PBCM.

	Finding from the Proposed Research	Recommendation
Hypothesis	Patients with greater FMDM impairment (as indexed by neurocognitive markers) will demonstrate improved treatment outcomes in TangiblePBCM relative to VoucherPBCM.	TangiblePBCM is recommended for patients with greater FMDM impairment.
	Patients with less FMDM impairment (as indexed by neurocognitive markers) will demonstrate improved treatment outcomes in VoucherPBCM relative to TangiblePBCM.	VoucherPBCM is recommended for patients with less FMDM impairment.
Alternative Outcomes	Treatment outcomes are comparable in TangiblePBCM and VoucherPBCM, regardless of level of FMDM impairment.	TangiblePBCM and VoucherPBCM are equally appropriate for all patients.
	Treatment outcomes are improved in TangiblePBCM relative to VoucherPBCM, regardless of level of FMDM impairment.	TangiblePBCM is recommended for all patients.
	Treatment outcomes are improved in VoucherPBCM relative to TangiblePBCM, regardless of level of FMDM impairment.	VoucherPBCM is recommended for all patients.

comparison with the total sample size. While minimization is not yet widely used in precision mental health research, available technology has recently made this approach more accessible. Moreover, as we report herein, minimization not only works to reduce imbalance in the means and proportions of prognostic factors between groups but also appears to maintain comparable variance in underlying continuous variables, when applicable. This is particularly important in work examining patient-level predictors of differential treatment response, wherein insufficient predictor variability in one or more conditions could significantly distort results.

In addition to validating our minimization approach through simulations, we have also employed a norm-referenced cutoff to ensure a comparable proportion of participants with impaired versus intact working memory across treatment conditions. Under the assumption that working memory is a core ability underlying future-minded decision-making (FMDM), comparable variability in other FMDM-related measures (e.g., cognitive control-related electrophysiological signals, delay discounting behavior) is expected. We also believe this to be the first trial of its kind to employ resource-constrained Tabu regression to evaluate the added value of brain-based predictors in relation to measurement cost (e.g., the cost of computerized cognitive testing versus an EEG procedure). This approach has the benefit of prioritizing measures that can inform individualized selection and adaptation of mental health interventions while keeping the cost of assessment low. Weighting candidate predictors in accordance with measurement cost and procedure invasiveness can improve the translational impact of precision mental health research and should be considered for modeling undertaken in similar work.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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