Testing Reinforcer Pathology: Mechanisms and Interventions to Change Alcohol Valuation

Statistical Analysis Plan

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Acronyms and Definitions of Terms

ANOVA	Analysis of variance
AR(1)	Autoregressive model of order 1
ARRS	Alcohol Relative Reinforcement Schedule
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorders Identification Test
AUQ	Alcohol Urges Questionnaire
AWSC	Alcohol Withdrawal Symptoms Checklist
BrAC	Breath Alcohol Concentration
CET	Control Episodic Thinking
DD	Delay Discounting
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EFT	Episodic Future Thinking
fMRI	Functional Magnetic Resonance Imaging
PACS	Penn Alcohol Craving Scale

RP	Reinforcer Pathology
TLFB	Timeline Follow Back

Document History

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Introduction

Alcohol use disorder (AUD) is a major contributor to disability, morbidity, and mortality. Although existing alcohol services are efficacious and replicable, only 1 in 9 individuals with AUD benefit from treatment with medication, and only small reductions in alcohol consumption result from brief psychotherapeutic interventions[1–4]. Therefore, the scientific premise of this project is that existing treatments are less than optimally robust. The understanding of AUD and the factors leading to alcohol's overwhelming valuation is incomplete.

Our knowledge of AUD can be improved with application of a novel reinforcer pathology framework[5–8] derived from behavioral and neuroeconomic research that can identify factors affecting alcohol's valuation and provide a novel context for advancing interventions. Thus, the scientific goal for this project is to mechanistically test reinforcer pathology to increase our understanding of AUD. In the proposed research, we will evaluate the utility of reinforcer pathology in modulating alcohol valuation in rigorous behavioral, functional magnetic resonance imaging (fMRI), and field conditions, while explaining results using neuro-computational modeling.

Reinforcer pathology provides a conceptual framework for understanding why alcohol is highly valued in AUD and in turn suggests targets that if shown to be mechanistically related to alcohol consumption and valuation may later suggest novel interventions. Central to this iteration of reinforcer pathology is the idea that the value of reinforcers is integrated over a temporal window. Reinforcer pathology specifies that the temporal window over which reinforcers are integrated systematically interacts with alcohol and prosocial reinforcers to determine their relative value. Consider that alcohol reinforcers are intense, reliable, brief, and immediate, while prosocial reinforcers (e.g., employment, relationships) are less intense, more variable (e.g., a good, bad, or okay day at work), and accrue value over a longer time frame (e.g., a long, fulfilling career). Short temporal windows increase the value of alcohol and decrease the value of prosocial reinforcers. Conversely, long temporal windows would reverse the valuation of both alcohol and prosocial reinforcers.

The temporal window can be measured behaviorally and neurally with delay discounting (DD). DD measures the reduction in the value of a reinforcer as a function of delay. The extant data suggests that excessive DD is ubiquitous in substance use disorders[8–10]. Moreover, DD has been suggested to serve as a behavioral marker at all stages of the addiction process[11] and has been predictive of therapeutic outcomes[12–14]. Yet reinforcer pathology is the only contemporary theory of addiction that includes DD as a determinant of the addiction process[15].

Alcohol valuation is measured by a variety of methods including behavioral economic demand (i.e., the quantitative relationship between consumption of alcohol and its cost), drinking behavior, and other measures (e.g., craving). One way of measuring alcohol valuation is the alcohol purchase task which assesses motivation for consumption during escalating levels of response cost using simulated marketplace survey techniques[16–18]. Like DD, the alcohol purchase task predicts therapeutic outcomes[14,19,20].

Because of the novelty of reinforcer pathology, we will conduct mechanistic tests of it by increasing the temporal window (decrease DD) using episodic future thinking (EFT)**.** Episodic future thinking (EFT) is based on the new science of prospection first identified in a Science publication in 2007[21] and refers to pre-experiencing the future by simulation. Considerable evidence suggests that prospection is important for understanding human cognition, affect, motivation, and action[22]. Individuals with damaged frontal areas, as well as individuals with AUD, show deficits in planning prospectively.[23–25] One systematic method to engender prospection is EFT. EFT, as applied in our prior studies, and in this proposal, consists of having participants develop potential future events that correspond to several future time frames (e.g., 1 week, 1 month, 3 months etc.). For each of these time frames participants are asked to concretize the events (e.g., What are you doing? Who will be there? What will you see, hear, smell, and feel?). Participants are instructed not to refer to alcohol use or the goals of cessation. As such, we note that EFT is different from a variety of other approaches including brief motivational interviewing, cognitive behavior therapy, and implementation intentions. We and others have used EFT, compared to the control condition (control episodic thinking; CET), to decrease DD in individuals with AUD[26,27], smokers[28–30], overweight/obesity, and controls[31–34]. Supporting reinforcer pathology, EFT also reduces valuation of alcohol, cigarettes, and food in the purchase task among individuals with AUD[26,27](Fig. 2), smokers[30], and the obese[35], respectively. EFT also decreases self-administration of cigarettes[28] among smokers, and of highly palatable snacks[31,32,36] among the obese. Therefore, consistent with reinforcer pathology, EFT robustly reduces DD and self-administration and valuation of substances and food. Specifically, by lengthening the temporal window, the perceived value of brief, intense reinforcers decreased. However, examination of the effects of EFT on alcohol self-administration, in the laboratory or the natural environment, is limited. For example, [37] showed decreases in DD and daily drinking following EFT in a sample of individuals with AUD. However, measures of demand or the neural correlates of EFT in AUD were not investigated in that study.

In the present study, we hypothesize that EFT will decrease reinforcer pathology measures in the real world over a longer time frame than has been done previously; that

is, EFT will decrease delay discounting, as well as alcohol consumption in the real world, demand, and craving compared to a control episodic thinking (CET) condition. Moreover, we hypothesize EFT will enhance activation in brain regions associated with prospection (e.g., hippocampus and amygdala) and the executive decision system (e.g., DLPFC). These analyses will help demonstrate the mechanisms by which EFT operates and contribute to the understanding of EFT as a potential therapeutic behavioral intervention.

Aims and Objectives

This SAP presents planned analysis tailored to the following three research aims:

Objective 1: We hypothesize that an intervention involving EFT will increase the temporal window, as measured through delay discounting, and decrease alcohol valuation (consumption, demand, and craving).

Objective 2: We hypothesize that an intervention involving EFT will show associated neural functional connectivity differences compared to the control condition.

Objective 3: We hypothesize that an intervention involving EFT will change the cognitive process involved in valuation and consequently the mathematical model that best describes delay discounting.

Study Design and Setting

Protocol Registration

We pre-registered this project on Clinical Trials.gov on October 14, 2019. The latest updates were made to the protocol on July 14, 2023, based on changes in recruitment criteria. The project can be located using the identifier NCT04125238.

Study design

Participants will be enrolled into the study and undergo the informed consent process (including signing of the informed consent) during Session 1. Session 2 will be baseline

assessments; this may be on the same day as Session 1; the baseline monitoring phase will follow Session 2. During the baseline monitoring phase, participants will provide breath samples to assess for recent alcohol use and report their drinks per day and report their alcohol withdrawal symptoms per day. Following the baseline period, participants will return for Session 3, where they will undergo fMRI procedures and then be randomized to either the EFT or control group (Control Episodic Thinking, CET). Participants will complete 2 weeks of monitoring (Monitoring Phase 1) where they will provide three breath samples per day and report the number of drinks they consumed per day. Participants will then come back to the lab to generate new EFT/CET cues at Session 4, and then complete Monitoring Phase 2 for two more weeks. After conclusion of the second monitoring phase, participants will complete Session 5 which is composed of assessments and an fMRI scan. A one-month follow-up will be conducted as Session 6.

Episodic Future Thinking (EFT): Participants will generate positive future events they are looking forward to at a number of time points in the future (e.g., 1 day, 2 weeks, 1 month, 3 months, 1 year, 5 years, and 25 years).

Control Episodic Thinking (CET): Participants will generate positive recent past events that have happened to them at a number of time points (last night from 7pm-10pm, yesterday between 4pm-7pm, yesterday between 1pm-4pm, yesterday from 10am-12pm, yesterday between 7am-10am, the night before last between 7pm-10pm, and evening before last between 4pm-7pm).

Session 1	Session 2	Remote 7 days	Group Assignment	Session 3 fMRI	Remote 14 days	Session 4	Remote 14 days	Session 5 fMRI	Session 6 1 month later

Inclusion/exclusion

Inclusion criteria for signing consent will require that participants: (1) demonstrate high-risk or harmful drinking (AUDIT>15; i.e., 16 or higher), (2) be between 21-65 years old, and (3) have a desire to quit or cut down on their drinking, but do not have proximate plans to enroll in treatment for AUD during the study period.

Exclusion criteria include: (1) meeting moderate to severe DSM-5 criteria for substance-use disorders other than alcohol, nicotine, or marijuana, (2) having a current diagnosis of any psychotic disorder, (3) having a history of seizure disorders or traumatic brain injury, (4) having any contraindication for participation in the fMRI session, or (5) reporting current pregnancy or lactation.

Recruitment

Participants will be recruited from the community via posted flyers, word of mouth referrals, and electronic advertisements (e.g., Craigslist, Facebook). Participants may contact the lab directly via email, Facebook, phone, walk-in, face-to-face at tabling events, or completing the online pre-screening questionnaire. Participants will also be contacted directly if they have given prior permission (through previous informed consent form) or by completion of a confidential pre-screening questionnaire.

We have developed and are currently using a separate pre-screening protocol, which occurs prior to enrolling participants into our intervention protocols, to effectively decrease attrition in our studies by ensuring that participants meet most inclusion/exclusion criteria (e.g., MRI scanner eligibility) prior to enrolling into the randomized study. Given that this separate screening protocol is used for all currently on-going studies in the lab, we cannot accurately estimate the total number of potential participants we expect to screen. However, as described above, we expect enrolling 170 participants to complete 54. We plan to enroll more than our average attrition rate because of the increased screening procedures and the time demands of the study. Additionally, the first few participants enrolled into the study may be pilots.

Participant Retention

We will evaluate continuation in our study after a baseline period of drinking has been completed. We expect to retain 75% of our participants at this time point. Specifically, 75% of our participants will present with at least 4 out of 7 drinking days, and at least 4 days with 4 or more drinks or an average higher than 4 drinks per day on drinking days.

Once participants reach this study phase , we expect a 70% retention for the rest of the study.

Randomization

Participants will be randomly assigned to experimental or control groups, balanced by number of drinks per day (square root transformed) and baseline DD rates.

Sample size

Although we have observed large effect sizes of EFT on DD in AUD participants in prior pilot studies (pre-post d=1.6; post-only d = 0.68), we used a more conservative medium effect size (f=0.25) to inform sample sizes and increase our power to detect effect on the broader range of measures proposed here (e.g., intensity of demand). Using a repeated measure correlation of 0.5, 52 total participants would be needed to complete this study (26 participants per group), assuming a Type I error rate of 0.01 and 80% statistical power, based on repeated measures within- between interaction ANOVA with 2 groups and 2 measurements.

Data Measures

Demographics

Demographic measures collected include age, sex, gender, ethnicity, and race.

SES

Education level, income, occupation/working status, household members

Delay discounting

To measure DD, the hyperbolic discounting model[38] will be fit to participants' indifference points across delays: $V=A/(1+kD)$ in which V is the immediate subjective value of the delayed option, A is its objective amount, D is its delay, and k is the only free parameter, indexing rate of discounting (larger k implies greater delay discounting, and a shorter temporal window). The discounting rate k will be log transformed to approach normality and stabilize the variance. Analysis will proceed by fitting the above equation to individual

subject data, then comparing values of discount rate *ln*(*k*) between experimental groups, as described above. We will compare fit to the hyperbolic model in comparison to alternative models as part of our third Objective.

Demand measures

To obtain dependent measures of demand, participants' data from the alcohol purchase task will be fit to a modified[39] exponential equation of the demand function[18] to quantify the relationship between the price of alcohol and consumption: $Q=Q_0 \times 10^{k(\exp(-\alpha Q_0 C)-1)}$ where Q is consumption of the commodity, C is the price, Q_0 is the derived initial consumption without cost constraints (demand intensity), k is the span of the function in logarithmic units, and α is the demand elasticity. Values of k are set to a constant determined empirically by the actual data, leaving Q_0 and α as free parameters to be fit. Note that although the delay discounting model and the demand equations use k, they refer to different variables. Dependent measures will be compared between experimental groups, as described above.

Resting state fMRI

We will use a 3T Siemens MAGNETOM Prisma^{fit} scanner (Siemens, Erlangen, Germany) with a 20-channel head/neck coil. T1-weighted images will be acquired at 1×1×1 mm^3 resolution using 3D MPRAGE, FOV = 256×256×176 mm^3, TR/TE/TI = 1950/4.44/950 ms, FA = 12°, phase partial Fourier 7/8, slice partial Fourier 6/8, GRAPPA factor = 4 with 33 reference lines, and bandwidth = 140 Hz/pixel. Functional BOLD data will be acquired using EPI with thirty-three 4 mm interleaved slices with a 10% slice gap, TR/TE = 2000/30 ms, FA = 10°, in-plane resolution of 3.4 × 3.4 mm^2, anterior-to-posterior phase encoding and a bandwidth = 2442 Hz/pixel. Participants will be instructed to keep their eyes open during the scan and direct their gaze on a white plus (+) sign centered on a black background.

Alcohol Consumption

Changes in drinks per day and the number of positive breath alcohol samples (BrAC) will be compared within subjects between pre-intervention and post-intervention. In

addition, differences in drinks per day and the number of positive BrAC samples will be compared between groups (EFT and CET). A Timeline Follow Back (TLFB[40]) will be conducted during Session 2 (pre-intervention) and Session 6 (1-month follow-up) to assess the number of alcoholic drinks consumed daily for the past 30 days. During the intervention period (from Session 2 to Session 5), participants will report daily the number of alcoholic drinks consumed.

Alcohol Urges Questionnaire (AUQ)

The Alcohol Urges Questionnaire [41] will be used to assess craving for alcohol. This 8-question measure of drinking urges is scored by summing responses to a 7-point Likert scale. The dependent measure of the summed score will be compared within subjects between pre-intervention and post-intervention. In addition, differences in alcohol craving will be compared between groups (EFT and CET).

Alcohol Use Disorders Identification Test (AUDIT)

The Alcohol Use Disorders Identification Test (AUDIT[42]) will be used to assess hazardous or harmful alcohol use. AUDIT is a 10-item screening tool that assesses alcohol consumption, drinking behaviors, and alcohol-related problems. Differences in alcohol AUDIT scores will be compared between groups (EFT and CET).

Alcohol Relative Reinforcement Schedule (ARRS)

The Alcohol Relative Reinforcement Schedule measures the extent to which alcohol serves as a reinforcer for an individual compared to other activities or substances[43]. Participants will be asked to rate the frequency with which they engage in activities with and without alcohol and how enjoyable those activities are. Changes in alcohol reinforcing value before and after the intervention will be compared between groups (EFT and CET).

Alcohol Withdrawal Symptoms

The Alcohol Withdrawal Scale (AWSC[44]) will be used to assess the severity of alcohol withdrawal symptoms. The AWS consists of a list of common withdrawal symptoms

associated with alcohol cessation, including physical and psychological manifestations. This is a 17-question where the withdrawal symptoms are scored by summing responses to a 5-point Likert scale. Severity of withdrawal symptoms will be compared between groups (EFT and CET).

Contemplation Ladder

The Contemplation Ladder is a 10-point scale that assesses readiness to change alcohol use. Changes in readiness to change alcohol before and after the intervention will be compared between groups (EFT and CET).

Penn Alcohol Craving Scale

The Penn Alcohol Craving Scale (PACS[45]) is a 5-item questionnaire that measures an individual's craving to drink alcohol in the past week. Changes in alcohol craving before and after the intervention will be compared between groups (EFT and CET).

Statistical Principles

Data preparation and analysis occurs in 3 steps: (1) assessment of data integrity; (2) descriptive analyses; and (3) longitudinal analyses. To assess data integrity, the distribution of all variables will be examined, appropriate methods will be used for handling missing data, and distributional transformations will be applied if needed to meet normality assumptions. We will also evaluate data for, and report the results of, overall consistency (e.g., between self-reported use and breath sample results). A significance level of $p<0.05$ will be used for all analyses. Multiple testing corrections will be used to control for false positives. Here we present our current analysis plan for the proposed tests. We recognize that upon completion of data collection, we may identify additional hypotheses to test. We will first implement the analysis plan proposed herein, followed by additional hypotheses and analyses as secondary/explorative thereafter.

Statistical Analyses

Objective 1: *We hypothesize that an intervention involving EFT will increase the temporal window and decrease alcohol valuation (consumption, demand, and craving).*

Our primary measure of alcohol use during the intervention period will be the daily self-reported number of drinks per day and the SOBERLINK breathalyzer screens. We will use generalized linear mixed models to compare the daily number of drinks between the EFT and CET groups. Mixed models is a method suited to the analysis of repeated measurement data. Here, the daily number of drinks will be modeled using a Poisson distribution. In the event the daily number of drinks exhibit over dispersion, other distributions, such as a negative binomial, will be considered. In a similar manner, dichotomous breathalyzer results data (positive or negative) throughout the 5-week field test will be analyzed as a function of intervention assignment, while accounting for time of day (morning, afternoon, evening) and repeated measures from each subject. Intrasubject correlation will be accounted for using an autoregressive correlation structure (AR(1)), since drinking days may be temporally related. In the event the AR(1) correlation structure is not representative of the data, other correlation structures will be considered. All missed assessments, although rare in our experience with similar field studies (approximately 5%), will be included as missing data. In the event of high rates of missing data, we will employ techniques consistent with the intention-to-treat paradigm, such as last observation carried forward methods or worst-case scenario (that all missing data is a positive BrAC measure).

Secondary analyses. In addition to the primary hypotheses listed above, we propose several additional analyses that will more fully characterize the behavior of our research participants and potentially lead to future research questions related to EFT in AUD. To this end, we hypothesize that EFT will result in changes (baseline versus post-intervention) in secondary outcome measures (e.g., Alcohol Withdrawal Symptoms Checklist). All these secondary hypotheses will be analyzed analogous to the primary hypothesis.

Covariate Plan:

We will test for individual differences in outcome measures for the intervention for each of these stratified variables. Therefore, we will include AUDIT score, SES, age, and gender in the analyses testing for an interaction between these variables and the intervention.

Sensitivity Analyses:

Due to the longitudinal nature of the experimental design, some participant drop-out is expected. We will perform sensitivity analyses to identify and document any potential biases that may arise due to participant drop out.

- Attrition prior to randomization: We will evaluate if any demographics and assessment values from S1 are associated with participant drop-out at S2.
- Attrition between Session 3 and Session 4: We will evaluate if differences in the attrition rates between EFT and CET exist during the first 2-week field test. Moreover, we will evaluate if demographics and assessment values are associated with participant drop-out prior to S4.
- Attrition between Session 4 and Session 5: We will evaluate if differences in the attrition rates between EFT and CET exist during the second 2-week field test. Moreover, we will evaluate if demographics and assessment values are associated with participant drop-out prior to S5.
- Missing daily reports/BrAC during 4-week intervention: We will evaluate if there is an association between the percentage of missing data points during the 4-week intervention and average daily drinks to assess if missing data is missing at random. For example, a negative correlation between the average daily drinks and percentage missing data may suggest missing daily values are not random. In addition, we will evaluate if missing BrAC values are associated with time of day.
- Attrition at 1-month follow-up: We will evaluate if there are differences in the 1-month follow-up rates between the EFT and CET groups. We will evaluate if average daily consumption is associated with 1-month follow-up rates. We will evaluate if participant demographics and assessment values are associated with 1-month follow-up rates.

We will report the results of all germane sensitivity analyses in all publications and discuss potential biases that may result from participant drop-out.

Exploratory Analyses:

In addition, we will perform an exploratory mediation analysis evaluating if AUDIT score, SES, age, gender, psychiatric comorbidities, executive function, family history, impulsivity, and reward sensitivity mediate the relationship between intervention and the primary outcomes. This analysis will be completed using bootstrap-based approaches, as described in Preacher and Hayes.

Objective 2: *We hypothesize that an intervention involving EFT will show associated neural functional connectivity differences compared to the control condition.*

fMRI resting state analysis

Resting state seed-based analyses will be conducted with the CONN Toolbox[46]. Preprocessing will include slice-timing correction, outlier detection, motion realignment, normalization to the MNI template, and spatial smoothing at 6 mm2. Following this, the data will be bandpass filtered (0.008 to 0.09 Hz) and despiked. Finally, the data will be linearly detrended using CompCor with five principal components to remove white matter and cerebrospinal fluid signal. We will compute seed-based correlations to all voxels in the brain using a pre-specified set of seeds. Anatomical specification of seeds will be defined by the Harvard-Oxford atlas in the CONN toolbox. The pre-specified set will consist of nodes of the DMN (posterior cingulate cortex, medial prefrontal cortex, left angular gyrus, right angular gyrus), salience network (anterior cingulate cortex, left insula, right insula), and the left and right hippocampus. Group analyses will use a general linear model to determine connectivity differences between EFT and CET participants.

Objective 3: We hypothesize that EFT will change the cognitive process involved in valuation and consequently the mathematical model that best describes delay discounting.

The hyperbolic model, described above, is the most common cognitive model used to explain the change in discounting (D) as a function of time (D(t)). However, other mathematical models have been developed to explain additional neurocognitive processes in DD. We hypothesize that EFT will change either (1) the parameters in neurocognitive models fit to D(t), (2) which neurocognitive model best fits D(t), or (3) both which model and the value of the parameters that produce best fits to D(t). We will perform hierarchical Bayesian model fits to the exponential, hyperbolic, generalize hyperbolic, quasi-hyperbolic, and double exponential models of DD. Model comparison and qualitative analysis of best fitting model parameters will be performed to evaluate the effect of EFT on neurocognitive processes underlying DD.

Software

All software, packages and their respective versions will be reported in publications.

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