Reward Re-Training: A New Treatment to Address Reward Imbalance During the COVID-19 Pandemic

Statistical Analysis Plan

NCT04661410

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STATISTICAL DESIGN AND POWER

Descriptive statistics and exploratory graphing will be generated for all variables of interest measured at all time points (i.e., baseline, mid-treatment, post-treatment, 3-month follow-ups). Data summaries will be produced both for the combined sample, and separately by treatment condition. Variables will be transformed if necessary using Box-cox power transformation. Baseline characteristics will be compared between treatment conditions using ANOVA (or non-parametric Kruskal Wallis test, as appropriate) for continuous variables and a chi-square test for categorical variables. Key baseline variables that differ by condition will be considered for use as covariates in the analyses described below.

Primary Aim 1. To assess feasibility and acceptability, we will use the following benchmarks: (a) recruitment success: enrollment of 60 patients; (b) attrition: retention of >75% of patients through all assessments; (c) study retention: patients attend at least 90% of all treatment groups; (d) satisfaction: patients express high satisfaction with RRT based on feedback questionnaires.

Primary Aim 2. To evaluate the effect of each treatment condition on hypothesized targets, we will model the pattern of change in reward response to palatable food, reward response to day-to-day life activities, social isolation, and loneliness separately over time using multilevel models (PROC MIXED in SAS).[1] The first level will model individual participant's score on the relevant target over time with baseline as time 0. At the second level, the individual intercept and slope will be entered as outcomes with treatment condition as a predictor. We will examine each treatment condition separately. The cross-level interaction between time and treatment condition will be used to determine the effect of treatment condition on the pattern of change in the hypothesized targets. Restricted maximum likelihood will be used to estimate model parameters and to test the significance of random effects. Both linear and higher-order time effects will be examined based on model selection criterion such as Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). With the fitted multilevel model structure, statistical contrasts will be performed at mid-treatment, post-treatment, and 3-month follow-up.

We will conduct mediation analysis to determine whether temporally-precedent changes in the hypothesized targets mediate differences in the primary outcomes between the two treatment conditions. In particular, we will examine improvement in each hypothesized target from baseline to mid-treatment assessment predicting post-treatment outcomes and improvement at post-treatment predicting 3-month follow-up outcomes. We will use the mediation model outlined by Preacher and Hayes to estimate the total and specific indirect effects of each hypothesized mediator individually.[2, 3] The bias-corrected bootstrap test will be applied to test the joint significance of the indirect pathways. This approach expands on Baron and Kenny's methods by providing additional guidelines and techniques that allow for the most robust and accurate interpretation of these mediating effects.[4, 5] Should these mediation analyses prove promising, we will explore how the entire pattern of changes in the mediators from baseline to later time periods (mid-treatment and post-treatment assessments) influences the corresponding pattern of outcomes over time using the parallel process growth models.[6]

Primary Aim 3. Analyses will be conducted via linear mixed effects models for longitudinal data, which increase power by fully exploiting the strong correlation in treatment outcomes of interests (i.e., percent binge frequency reduction and percent change in EDE global eating pathology) across time. Patterned covariance matrices as implemented in (PROC MIXED in SAS)[1] and will be used to evaluate between group differences for percent binge reduction and percent change in EDE global eating pathology across the study as a whole, and at each assessment post-baseline. Separate variance components will be used to capture therapist and participant-within-therapist variation. The within-subject covariance matrix will be assumed common across study arms, with an exponential variance function to deal with heteroscedasticity and a continuous-time AR(1) correlation matrix to accommodate residual autocorrelation over the unequal–size time intervals between follow-ups. Outcomes at all four time points will be estimated jointly for maximum statistical efficiency in the presence of intermittent missingness and loss to follow-up. The model will include random effects for subject and time (with higher-order effects if needed to capture nonlinear change), and fixed effects for treatment arm, time by treatment interaction, demographic information, and baseline values of binge frequency and global eating pathology. Time-specific covariate-adjusted contrasts will be used to compare outcome between groups.

Secondary Aim 1. We will use the same analytic approach described above for Primary Aim 3 but will test the impact of treatment condition on secondary outcomes including depression, substance abuse, and quality of

life.

Attrition. Patterns of missing data will be examined. Likelihood-based estimation methods and multiple imputation models will be used to handle missing data.[7] In addition, we will use Hedeker and Gibbons' procedure[8, 9] to examine if dropouts influence the multilevel model results. If the missingness mechanism is related to the missing outcome itself, we will use sensitivity analyses to explore how robust our findings are with respect to a range of assumptions regarding missing data.

Power analyses. Using the method described by Raudenbush[10-12] and implemented with the software Optimal Design, power calculations were made for mixed effects models. A sample size of 154 (77 for each condition) is required for 80% power to detect a medium effect with the significant level of 0.05 and four assessment points, assuming the ratio of the variability of level-1 coefficient to the variability of level-1 residual is one. Fritz and MacKinnon[13] documented sample size requirements to guarantee 80% power at the significance level of 0.05 for mediation models. Under the assumption of a medium effect for intervention with the mediator and a medium effect for the mediator on outcome controlled for intervention, the required sample size is 72 in total with 36 per intervention arm to achieve 80% power in simple mediation models. Given our relatively small sample size (*n*=60), our study is powered to detect large effect sizes. While we observed large effect sizes in our pilot trial of RRT compared to a wait list control, we anticipate that the effect sizes may be smaller in the current trial as supportive therapy is an active treatment condition. It is likely that we may be underpowered for formal tests of statistical significance in this preliminary study. We will rely on effect sizes for interpretation when underpowered.

References

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