Project IMPACT: In-the-Moment Protection From Automatic Capture by Trigger

NCT02579317

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Statistical Analysis Plan

Distributional properties of all variables will be examined and data will be transformed as indicated. Our broad approach to hypothesis testing of differences in baseline status between groups, within-person changes over time due to intervention effects, and moderation by patient characteristics is consistent with the recommended analysis of clinical trial data. Importantly, the analysis approach proceeds from full information covariance matrices with missing data assumed to be missing at random, consistent with the intention to treat (ITT).

Aim 1: To determine whether strategic manipulation of the BAR mechanism bolsters treatment gains, alcohol and drug use data as well as anxiety, depression, and craving ratings from VAS assessments will be compared across the BAR (TAU+RB) and placebo (TAU+CON) manipulation groups. It is hypothesized that the TAU+RB compared to the TAU+CON group will show better alcohol and drug use outcomes, and reduced anxiety, depression, and craving. We will use a randomized, controlled, repeated measures design to assess the utility of resonance breathing as an adjunct intervention to TAU. We will compare this intervention to placebo. Our primary outcomes will be changes in alcohol (e.g., % drinking days, % heavy drinking days, drinks per drinking day) and other drug use, as well as anxiety, depression, and craving as measured from the VAS.

Building on the standard generalized linear model (GLM) approach to RCT data analysis, we will use piecewise growth curve modeling (GCM) to test the effects of resonance breathing on growth (recovery) rates of regulatory dysfunction (craving, anxiety, depression) across a 6 mo period during and following treatment. Like GLM, GCM analysis allows us to parsimoniously model these outcomes in terms of both initial level and change, and to model app use (frequency, duration, quality of use) as a time varying covariate to account for how stable or fast growth may be. Both analytic approaches assume that change is a continuous process and that an individual's underlying growth trajectory determines her status at any point in time. However, applied to the present study design and intervention assessment, we hypothesize the operation of three distinct trajectories associated with naturalistic change in response to TAU, associated with the intervention period added to TAU, and associated with post-treatment functioning. Specifically, in our design, Period 1 spans 4 baseline assessments prior to intervention during which IOP treatment is expected to initiate modest improvements in outcomes. Period 2 spans the 8 week intervention period (4^{th}-11^{th} wks of treatment) is predicted to show escalated recovery for the TAU+RB group compared to the active placebo group. The trajectory underlying the extended recovery process during Period 2 will be operationalized by intercept, linear, and quadratic trends separately for each group. Period 3, post treatment, will capture sustained, increasing, or decreasing gains following treatment and modeled by these 3 trends. Consistent with this conceptual model, dependent variables will be deconstructed into trends separately for these three time periods. Piecewise GCM provides conceptually and analytically appropriate specification and flexibility in incorporating transitional periods in studying changes across time. This analysis is robust with incomplete or missing data (i.e., missed assessment, dropout) assuming data are missing at random. BIC and penalties for model complexity will be used to identify the most parsimonious model. We expect a larger average linear trend for Period 2 than Periods 1 and 3. The variance in slope is expected to be larger during Periods 2 and 3 when individual differences in app usage and benefit will increase. A significant, negative quadratic slope indicating a leveling off in recovery over time is expected in Period 3. We will model each outcome as a function of intervention group, time of assessment, and baseline values of the outcome prior to entry into the RCT. Models may include race/ethnicity, age, education, and AUD and drug diagnosis. We will also explore analyses that are modeled in relation to the frequency and average duration of 'app' use. Interactions of baseline levels, time, and intervention group will be assessed.

Aim 2: To assess differences in the BAR and placebo manipulation groups in relation to improved physiological and neurobiological control systems, we will use neurocardiac data collected during the pre- and post-intervention laboratory sessions. Neurocardiac data include HRV indices, BP variability indices, and BAR sensitivity from cross-spectral analyses. We will test for differences in change between the TAU+RB and TAU+CON groups. We hypothesize that both groups will show improvement from pre- to post-intervention, but that the TAU+RB group will show significantly greater improvement compared to TAU+CON. Separate analyses will also be performed on the subset of women who complete the neuroimaging laboratory sessions. Repeated measures ANOVA will be used to capture pre- to post-intervention change in each separate physiological and neurobiological outcome. Moreover, because hypotheses associated with Aim 1 and Aim 2 embed questions about inter-related, within-individual changes in BAR and drinking behavior over time, as well as differences between individuals in change we will use SAS9.3 to construct descriptive person-period data set to examine empirical growth plots, i.e., temporally sequenced graphs of BAR sensitivity and drinking outcomes. Each participant's empirical growth plots will be summarized using two standardized approaches: nonparametric and a parametric regression-based approach that yields a fitted trajectory. These individual level plots will be used to describe change in absolute and relative terms across individuals, and will add to the literature as there are currently no

developmental norms for BAR physiological functions due to lack of longitudinal data and large variability within age groups. These heuristic approaches to grouping participants will not be used to determine subpopulations of BAR change for hypothesis testing, however, because they are limited by the lack of statistical fit measures and other weaknesses. Thus, we will also use piecewise GCM to capture the pattern of change across time, as described above.

Brain Analysis. A whole-brain GLM analysis of the Blood Oxygenation Level Dependent (BOLD) data will be performed using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The BOLD scans will be motion corrected and spatial smoothing (Gaussian kernel FWHM 5 mm) will be applied. BOLD scans for each participant will be registered first to her high resolution anatomical scan (magnetization prepared rapid gradient echo, mprage) and then registered to standard space using the FSL's MNI template. In the first stage of analysis, activation patterns for each participant during rest and in response to resonance breathing will be obtained. Contrasts between resonance breathing versus resting states will then be computed. GLM results will identify suprathresholded voxels from which time series information will be extracted and used in the modeling of the connectivity of the regions of interest (ROIs).

Aim 3: To characterize change holistically within an individual, we will build on our existing physiological model of the BAR mechanism. We predict that the physiological data sample obtained at the first lab session can be used to predict individual client's treatment success in terms of drinking and other drug use outcomes as well as in co-occurring conditions (anxiety). Modeling will begin with parameterization, wherein the overall functionality of the system was deconstructed into its component parts (parameters) and their capacity for changing and interacting (states). Our initial model was built on over 100 cardiovascular parameters as well as 21 pressure, flow, volume, resistance, and elastance states, represented in a system of differential equations. In this application, we will build this model to include neural parameters and genetic moderators. The second step of the modeling process will be data reduction, accomplished through sensitivity analysis. The figure shows a heat map of global derivative sensitivity for one individual who was previously modeled. Twelve model parameters (lighter colored cells) captured system changes to a substantially greater degree than the other parameters (columns depict that this is true across multiple outputs, e.g., HRV, systolic BP). The present application will seek to replicate this result in a treatment sample, build on our critical observation that there was a large distribution of change in unobservable biological processes in response to resonance breathing, and better understand how these physiological changes affect changes in drinking behavior. A major emphasis of Aim 3 will be to explore in greater detail how behavior change arises from such individual-level changes in cardiovascular processes and thus determine for whom a resonance breathing intervention may be most useful. In collaboration with Dr. Mezic, the second stage of multivariate predictive modeling and integration of cardiovascular, neural, genetic, and behavioral data will employ specialized GoSUM software (Aimdyn Inc., Santa Barbara, CA). Very briefly, a nonlinear analytical model will be built that maps physiological parameters to outputs (e.g., indicators of drinking behavior, craving). Genetic variables will be used as moderators of outcome. The nonlinear model is built to maximize predictive power or minimize prediction error. Sensitivities, wherein good convergence is imperative, are computed from the model and from the learned distribution of parameters in the 175 participants, from which we will produce thousands of artificial samples. These methods ensure that the sensitivities produced by GoSUM are 100% accurate and do not depend on the initial number of participants. Of course, not all variance in the outputs can be explained by the predictors included in our proposed model. GoSUM will then be used to identify the amount of variance explained and show how that variance is sensitive with respect to predictors.

Fig 14. Only a subset of unobservable cardiovascular parameters influence system response to resonance breathing.