Smartphone Training for Attention Regulation for IBS

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Data Analysis Strategy.

Overview of Data Analyses. Our study team specializes in statistical analysis and measurement models related to those described in this proposal. Dr. Creswell and our team biostatistician (co-I Dr. Branson) will coordinate the data analytic aspects of the project, and carry out the proposed mixed effect linear models (MLMs). A secure de-identified database will be maintained by the PI and project coordinator (see Budget Justification). A CONSORT flowchart will be generated in Year 1 that tracks participants through the study. Descriptive statistics will be used to characterize the sample, and chi- square and one-way ANOVAs will be used to evaluate success of randomization on primary variables of interest. In addition to the MLMs presented below, as a sensitivity analysis we will also consider MLMs that adjust for baseline variables of interest. To help explain study attrition, chi-square and independent-sample t-tests will compare dropouts to non-dropouts. We are defining successful treatment completion as having completed 11 out of the 14 available lessons. While our primary analyses follow intention-to-treat principles, we will also assess how sensitive results are to excluding subjects who do not successfully complete their respective treatment.

Treatment groups will be dummy coded with CC (coping control) used as the reference group. We will test for treatment condition effects on the stress and symptom outcome measures using MLMs as we did in our publications in the R21 feasibility trial[18]. MLMs provide an optimal analytic strategy because they model all available data (following intent-to-treat principles in RCTs) and allow us to flexibly evaluate the nested nature of this data structure. Specifically, we will create (for EMA) 3-level MLMs (levels: individual participants; day; within-day time) using restricted maximum likelihood estimation. The 3-level EMA MLMs testing each aim will compare the 3 treatment intervention groups on each dependent variable (e.g., daily stress) from the pre, post, and follow-up training measurement occasion. The 3-level models will include a random intercept for day nested within participant. Measurement occasion (pre, post intervention, follow-up), group condition, day-specific factors (e.g., day-of-week or weekday versus weekend), and within-day time will be modeled as fixed effects. All models will be fit with compound symmetric variance-covariance data structure but other structures (e.g., autoregressive covariance structure, ARH(1), spectral power) will be evaluated using Akaike's Information Criterion (AIC). We have specified this initial approach for modeling random and fixed effects, but we will evaluate whether this approach best fits the data using likelihood ratio tests and AIC. In testing each aim, each measurement occasion × treatment interaction will be evaluated with a decision rule that a significant effect is observed when the measurement occasion × treatment interaction statistic and corresponding p-value is less than .05 (two-tailed). When a significant interaction is observed, follow-up planned contrasts in each MLM will compare specific groups at post-training. To help with benchmarking we will provide effect size statistics corresponding to the magnitude of change over time, and between groups at each post-treatment time point. One strength of our approach here is that it extends an established MLM data analytic pipeline we used in our three-arm EMA R21 trial publications with success[18,76], along with MLM mediation analyses in other MBSR RCT publications[98].

Testing our Hypotheses. We are specifying a priori predictions about the effects of MA-MBSR intervention, relative to MO-MBSR and CC. Thus no statistical corrections for multiple comparisons will be made for our primary study hypotheses or specified pair-wise comparisons. When additional exploratory analyses are conducted, a Holm's correction will be made for multiple comparisons. We have previously published our MLM approach evaluating MA-MBSR effects relative to these two control groups (see Chin et al., 2019 or Lindsay et al., 2018 publications)—so here we highlight our equations and approach. In previous work we have focused on stress, so below we apply this approach to evaluating hypothesis #2, specifying that MA-MBSR will reduce symptoms relative to MO-MBSR and CC. This hypothesis will be tested separately for clinician assessed, physician assessed or patient self-reported symptoms (using the IBS-SS). The general form of the model to be tested, exclusive of covariates, is as follows, in mixed model

notation:

$IBS\ symptoms_{it} = \gamma_{00} + \gamma_{01}*(txgroup_i) + \gamma_{10}*(time_{it}) + \gamma_{11}*(txgroup_i)*(time_{it}) + u_{0i} + e_{it}$ where IBS $symptoms_{it}$ is the composite symptoms score for individual *i* at time-point *t*, $time_{it}$ is the measurement occasion (pre, post intervention, or follow-up) assessment time of year, $txgroup_i$ is the treatment group a participant is assigned to. In multilevel notation:

Level 1: $Symptoms_{it} = \beta_{0i} + \beta_{1i}*(time_{it}) + e_{it}$
Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}*(txgroup_i) + u_{0i}$
$\beta_{1i} = \gamma_{10} + \gamma_{11}*(txgroup_i)$

The primary test of hypothesis is the F-test of the null hypothesis H_0: $\gamma_{11}= 0$. Note that this general model will be used, with different outcomes (e.g., stress) and for subsequent aims below but will not be repeated.

For hypothesis #3, we will use EMA-sampled IBS symptom severity to test whether EMA-sampled stress reduction will statistically mediate symptom improvements. We will test for concurrent relations between EMA-sampled stress and IBS symptom severity (within the same moment) and also test lagged relations (stress at time *t* predicting IBS symptom severity at time *t+1*). To conduct this mediation analysis, we will compare two MLMs that use IBS symptom severity as the outcome and group condition as a fixed effect: one MLM will include stress as an additional fixed effect, and another will not. If the fixed effect for group condition is statistically significant in the latter but not the former, stress reduction will be declared to act as a mediator for symptom improvements.

For hypothesis testing, we will first run unadjusted models without covariates, as described above. Then, as a sensitivity analysis, we will run adjusted models that incorporate baseline characteristics related to sociodemographic covariates (sex, gender, age, race), clinical covariates (IBS subtype, baseline IBS symptom severity, baseline perceived stress), and other time-related covariates such as day-of-week when appropriate (e.g., for analyses involving EMA samples where we observe repeated measures across and within days).

Attrition and Missing Data. We expect minimal participant attrition (<15%) during the study period across conditions. Dropouts are not expected to be a function of the missing outcome data given the observed. Our unadjusted analyses assume data are missing completely at random, while our adjusted analyses loosen this assumption to allow for data to be missing at random. We will also assess the sensitivity of our results to violations of the missing-at-random assumption (e.g., via pattern-mixture models). Additionally, we will evaluate whether adherence to the program and EMA vary across groups. To evaluate attrition, we will compare study dropouts to study completers based on observed participant characteristics.