Statistical Analysis Plan

Study Title: Neural Mechanisms of Enhancing Emotion Regulation in Bereaved Spouses
ClinicalTrial.gov Identifier: NCT04822194
Sponser: The National Institute on Aging
Intervention: Cognitive Emotion Regulation Training
Protocol Number: 1
Phase: Phase 1
Statistical Analysis Plan Version: 1.0
May 21, 2025

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Statistical Analysis Plan

Introduction:

The objective of this research study is to examine the efficacy and behavioral and neural mechanisms of a cognitive emotion regulation training intervention in bereaved spouses. The primary endpoints are the assessments of the psychological, psychophysiological, and neural mechanisms mediating behavior change as a function of the cognitive emotion regulation intervention. Psychological mechanisms will be assessed by emotion regulation task-based self-reported negative affect. Psychophysiological mechanisms will be investigated by analysis of respiratory sinus arrhythmia data, a measure of heart rate variability reflecting adaptive cardiac vagal tone. Neural mechanisms will be assessed via analysis of fMRI data. The secondary endpoint is testing the efficacy of the intervention via assessment of psychological outcomes (i.e., the behavior change, as represented in changes in depressive symptoms, stress, and grief rumination).

Objectives:

This study represents a Phase I, Stage I clinical trial. The project builds upon promising preliminary work to investigate the effectiveness and underlying neurobiological mechanisms of a novel, five-session cognitive reappraisal intervention in bereaved spouses. The study aims to mechanistically relate changes in psychological, psychophysiological, and neural function during a novel emotion regulation intervention never before implemented in this stressed, high risk group. The goal is to inform future interventions that can reduce negative psychological outcomes in bereaved spouses.

Specific Aims:

(1) To determine if a relatively brief, focused intervention in reappraisal-by-distancing in bereaved spouses engages the targeted mechanisms. Hypotheses: Distancing training is expected to result in longitudinal reductions in self-reported negative affect, increases in RSA, and changes in neural activity in a priori ROI's above (i.e., reductions in amygdala activity, increases in DLPFC activity) that are greater than those for reinterpretation training.
(2) To examine the impact of changes in the targeted mechanisms in changing health-relevant behavior. Hypotheses: Across time and participants, reductions in self-reported negative affect, increases in RSA, and changes in neural activity are expected to lead to reductions in depressive symptoms and grief rumination.
(3) As an exploratory aim, to mechanistically relate intervention effects to behavior change as a function of changes in the targeted processes. Crucially, this aim will also include assessment of interactions with age and gender of the bereaved spouse and initial depression and grief severity.

Hypotheses: Distancing training will lead to reductions in grief rumination and depression that are mediated by changes in the targeted neurobiological and behavioral mechanisms.

Sample Size::

84 bereaved participants will be recruited (i.e., N=42 per each intervention cell) and randomly assigned to receive either Distancing Training or Reinterpretation Training.

Power Analyses:

Outcome: Self-reported negative affect

Sufficient power to assess self-reported negative affect outcomes will be achieved by recruiting 42 participants per training cell. This sample size estimate is based upon a power analysis using an approximate effect size (d=.70) previously reported for within and between-subjects behavioral analyses of longitudinal reappraisal training data[1]. Power analyses using this approximate effect size indicate over 95% power (α=.05) to detect within-group effects and 90% power (α=.05) to detect between-group effects should be achieved with 36 participants per cell. Assuming all-cause attrition of 15% (which reflects a liberal upper bound given past participant attrition rates of approximately 10%), the proposed sample size should provide sufficient power to assess this outcome. Post-attrition, we expect to have analyzable complete data for approximately 36 participants per cell.

Outcome: Respiratory sinus arrhythmia (RSA)

Sufficient power to assess respiratory sinus arrhythmia outcomes will be achieved by recruiting 42 participants per training cell. This sample size estimate is based upon a power analysis using an approximate effect size (d=.70) previously obtained for within and between-subjects analyses of RSA data[2]. Power analyses using this approximate effect size indicate over 95% power (α=.05) to detect within-group effects and 90% power (α=.05) to detect between-group effects should be achieved with 36 participants per cell. Assuming all-cause attrition of 15% (which reflects a liberal upper bound given past participation attrition rates of approximately 10%), the proposed sample size should provide sufficient power to assess this outcome. Post- attrition, we expect to have analyzable complete data for approximately 36 participants per cell.

Outcome: Neural activity (fMRI)

Sufficient power to assess neural activity outcomes will be achieved by recruiting 42 participants per training cell. This sample size estimate is based upon a power analysis using a within-subject fMRI effect size estimate for right amygdala affective reactivity from a recent large-scale meta-analysis of fMRI effect sizes using Human Connectome Project data[3] of approximately d=.70. This effect size estimate is also appropriate for between-subjects neural effects[4]. Power analyses using this approximate effect size indicate over 95% power (α=.05) to detect within-group

effects and 90% power (α=0.05) to detect between-group effects should be achieved with 36 participants per cell. Assuming all-cause attrition of 15% (which reflects a liberal upper bound given past participation attrition rates of approximately 10%), the proposed sample size should provide sufficient power to assess this outcome. Importantly, this sample size will also account for any participant data loss due to excessive scanner motion (despite mitigation efforts to avoid this), task non-response in the scanner, and poor signal-to-noise in MR signal, in addition to participants dropping out of the study. Each of these classes of participant attrition is expected to be rare. Thus, post-attrition from all causes, we expect to have analyzable complete data for approximately 36 participants per cell.

Outcome: Depressive symptoms, grief rumination, perceived stress, and reappraisal usage frequency.

Sufficient power to assess questionnaire outcomes (i.e., depressive symptoms, grief rumination, perceived stress, and reappraisal usage frequency) will be achieved by recruiting 42 participants per training cell. This sample size estimate is based upon a power analysis using an approximate effect size (d=.70) previously reported for within and between-subjects analyses of questionnaire reports measuring these variables (e.g., depressive symptoms[2]; perceived stress[1]). Power analyses using this approximate effect size indicate over 95% power (α=.05) to detect within-group effects and 90% power (α=0.05) to detect between-group effects should be achieved with 36 participants per cell. Assuming all-cause attrition of 15% (which reflects a liberal upper bound given past participant attrition rates of approximately 10%), the proposed sample size should provide sufficient power to assess this outcome. Post-attrition, we expect to have analyzable complete data for approximately 36 participants per cell.

Definitions of Populations to be Analyzed:

Conditions or Focus of Study

- Bereavement
- Emotions
- Emotion Regulation
- Psychophysiology
- Social Affective Neuroscience

Eligibility Criteria

Inclusion Criteria:

- Recent bereavement of loved one (i.e. loss of romantic partner within the past 5-7 months)
- At least 18 years of age, with no maximum age, provided all other inclusion and exclusion criteria are met.
- Minimum score of 25 on the Inventory for Complicated Grief

- Must be able to speak, read, and write in English
- Must be eligible to safely complete MRI scanning

Exclusion Criteria:

- Death of a second close family member/friend in the past year
- If they are currently receiving psychotherapy
- If they have obstructive pulmonary and/or heart disease, diabetes, liver failure, or kidney failure
- If they have a significant visual, auditory, or cognitive impairment that compromises their ability to understand and complete the task
- If they've gotten divorced within the past year
- Prior participation in similar emotion regulation training protocol in Dr. Denny's lab
- If they have any contraindication to MRI scanning (i.e. pregnancy, presence of any non-removable metal on or in the body, implanted medical devices, tattoos, medication patches, orthodontic braces or permanent retainers, hearing aids, and history of claustrophobia or breathing disorders)

Data Analysis:

<u>All Outcomes</u>

Data analysis will primarily use linear mixed models, incorporating fixed effects for Training Group (Distancing and Reinterpretation), Session (T1-T5), and Trial Type (for analyses involving the reappraisal task; Look Neutral, Look Negative, and Reappraise Negative), and their interactions, as well as a random effect consisting of an intercept for each participant. In each analysis, statistically significant and near-significant intercept variance reflects reliable differences between participants. We will examine additional models that incorporate and estimate random-effects slope variance across participants on the time effect (i.e., Session). Outcome variables will be repeated measures in self-reported negative affect, RSA[5], and neural activity (Aim 1) and changes in health-relevant behavioral outcomes (e.g., depressive symptoms and grief rumination; Aims 2 and 3). In these analyses, gender, age, baseline depressive symptoms, expectedness of the loss, and current (non-excluded) medication use will be incorporated as covariates. Importantly, given that we anticipate enrolling an approximately equal number of men and women, we also anticipate having sufficient power to conduct exploratory analyses on the effect of gender (and age) on the hypothesized effects (all Aims). Further, Aim 3 will be investigated using multilevel mediation modeling[6,7] involving training group assignment as the higher-level predictor (X); self-reported negative affect, RSA data, and neural activity as potential individual-level mediators (M); and health-relevant behavior (i.e., depressive symptoms and grief rumination) as individual-level outcome variables (Y). Note that this will model mediation as a time-dependent and experimental process, both of which help

to rule out alternative explanations. Other exploratory model paths will also be tested. Appropriate covariates indicated above will be incorporated in all mediation models.

Data and Safety Monitoring Plan:

The monitoring for this project will include the Contact PI monitoring of participant safety, adverse event (AE) reporting in compliance with IRB, NIH, and FDA guidelines, and participation in the Continuing Review process with the IRB. The outcomes of IRB reviews are conveyed to the Contact PI via the administrative support staff in the Rice University Office of Sponsored Projects and Research Compliance (SPARC). Given the non-invasive, minimal risk nature of the proposed research, we anticipate that the types of Adverse Events that may occur, if any, will focus on possible distress associated with self-report of grief symptoms or with viewing of grief-related images during the psychological task. The study includes procedures to minimize these risks. All procedures and questionnaires used in this study have been widely and safely used. The Contact PI will assign all research participants a subject identification number for identification purposes. The master list of identifying information (e.g. name, address) will be maintained separately from the other individual-and area-level data, in a firewall and password-protected, encrypted file, on a Rice University institutional server. All data will be coded by number, and numbered codes will be disassociated from subject names and other identifying information. All research staff members are required to respect the confidentiality of participants and to complete rigorous data confidentiality and security training per procedures required by the Rice University IRB.

References

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