OFFICIAL TITLE OF STUDY: Targeting Attention Orienting to Social Threat to Reduce Social Anxiety in Youth

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PROTOCOL

The primary goal of this 2-site (Florida International U; Yale U) R01 project is to confirm attention bias modification treatment (ABMT) as an efficacious treatment for social anxiety disorder (SAD) in children and adolescents (i.e., "youth") ages 10 to 14 years. We will randomize N=260 youths (130 each site) to 8 sessions of either ABMT or Neutral Control Task (NCT) delivered twice weekly for 4 weeks, with 160 trials per session. At pre-treatment (PRE), post-treatment (POST), and 6-month Follow-Up, we will assess the target, specifically, P1 amplitudes for socially threatening stimuli, and social anxiety symptom severity rated by independent evaluators (IEs), youths, and parents.

Aim 1: Demonstrate target engagement. Hypothesis 1: P1 amplitudes for socially threatening stimuli in the dot-probe task will be significantly lower at POST in the ABMT arm compared with the NCT arm.

Aim 2: Demonstrate effects of ABMT on social anxiety symptom severity. Hypothesis 2a. Social anxiety symptom severity rated by IEs, youths, and parents at POST will be significantly lower in the ABMT arm compared with the NCT arm. **Hypothesis 2b.** Youth ratings of state anxiety measured during a social evaluative stress task at POST will be significantly lower in the ABMT arm compared with the NCT arm.

Aim 3: Demonstrate target validation. Hypothesis 3: P1 amplitudes for socially threatening stimuli in the dot-probe task will mediate reductions in social anxiety symptom severity.

Aim 4: Evaluate maintenance of target engagement, effects on social anxiety symptom severity, and target validation. Hypothesis 4: Target engagement, effects on social anxiety symptom severity, and target validation will be maintained at 6-month Follow-Up evaluation.

APPROACH

See Figure 1 for the randomized controlled design and Table 1 for the measures administered at each assessment. Following parental consent and child assent, youths and parents will be administered interviews and questionnaires (see Measures) and youths will complete the dot-probe task while EEG/ERP data are collected (PRE). Youths will also be administered a measure of state anxiety immediately before a social stress task at PRE.

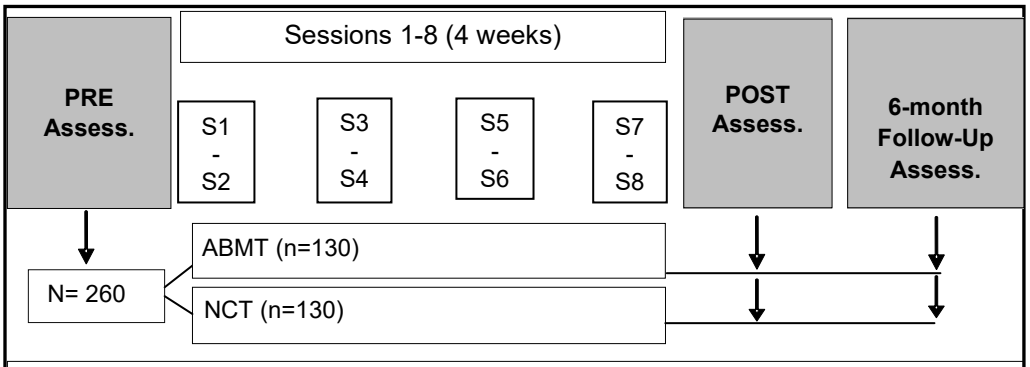

Figure 1. Study Design and Assessment Waves. (S = session)

Subjects will be randomized 1:1 to two study arms: ABMT or NCT. Subjects in each arm will complete 8 sessions over 4 weeks. Number and duration of sessions will be identical in both arms. We will collect data on the target variable (P1 amplitudes) and the outcomes (social anxiety symptom severity) from the youths and parents one week after treatment ends (POST). At POST, youths will also be re-administered a measure of state anxiety immediately before a social stress task. Six months after the POST assessment, youths and parents will once again be administered all measures including the dot-probe task while EEG/ERP data are collected and a social stress task (Follow-Up).

Subjects

Two-hundred sixty youths ages 10 to 14 years with SAD will be admitted to the study (n=130 at each site). **Inclusion Criteria.** (A) Be between ages 10 and 14 years; (B) meet DSM5 criteria for a diagnosis of SAD; (C) cease other psychosocial treatment; (D) presence of any coexisting psychiatric diagnoses must be of lesser severity than SAD; and (E) have no current psychotropic medication other than a stable dose of stimulant or non-stimulant medication for coexisting ADHD.

Exclusion Criteria. (A) meet for Autism Spectrum Disorder, Intellectual Disability, Bipolar Disorder, Tourette's Disorder, Psychotic Disorders, or Substance Use Disorders; (B) show high likelihood of hurting themselves or others; (C) be a victim of undisclosed abuse requiring investigation/supervision by Social Services; (D) have a history of neurological illness, including seizures/epilepsy, or head injury with loss of consciousness $\geq$ 5 minutes; or (E) have an uncorrected vision or physical disability that interferes with their ability to see stimuli presented briefly on a computer screen or click a mouse button rapidly.

Interventions

ABMT. Subjects assigned to the ABMT arm will complete 2 ABMT sessions a week for 4 weeks, for a total of 8 sessions. At each session, subjects complete 160 ABMT trials. In each ABMT trial (see Figure 5 for an example trial of ABMT), following a fixation cross, 2 faces of the same actor (one angry, one neutral), one above the other, are presented for 500ms. Next, a probe (< or >) appears in the location of the neutral face. Subjects press the left or right mouse button to indicate the orientation of the probe (< or >). The probe remains on the screen until subjects respond. Neutral face location, actor, and probe type will be fully counterbalanced.

NCT. Subjects assigned to the NCT arm will complete 2 NCT sessions a week for 4 weeks, for a total of 8 sessions. At each session, subjects will complete 160 NCT trials. In each NCT trial, following a fixation cross, 2 faces of the same actor (both neutral), one above the other, are presented for 500ms. Subjects press the left mouse button to proceed to the next trial.

Measures

I. Measure of Target: P1 amplitude elicited in the dot-probe task

Subjects will complete the dot-probe task. In the task, a pair of facial expressions (threatening-neutral or neutral-neutral) from the same actor is presented vertically for 500ms and then followed by a visual probe for 1000ms. The probe appears in the location of the previously viewed threatening face (i.e., congruent trials) or neutral face (i.e., incongruent trials for threatening-neutral trials). Subjects press the left mouse or right mouse button to indicate the orientation of the probe (< or >). Subjects complete 240 trials: 80 congruent, 80 incongruent, and 80 neutral. As in past studies, a different set of faces will be used in the dot-probe assessment task (i.e., not the same faces as in the training protocol). EEG/ERG data will be collected during completion of the dot-probe task.

a. Electrophysiological Recording. Subjects will be fitted with a 128-channel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). Raw signal EEG will be collected continuously using NetStation 5.3. The raw signal will be amplified and sampled at 1 KHz with a band-pass filter of 0.1-100 Hz. Once impedance values are below 50 kΩ, EEG will be recorded continuously and referenced to Cz. After collection, data will stored until offline processing. After acquisition, data will be re-referenced offline using an average reference.

b. Event-Related Potentials. EEG data will be analyzed offline using NetStation ERP Analysis Tools (5.3). In post-processing, EEG data will be re-filtered with a lowpass filter of 30 Hz. Ocular and motor artifacts exceeding ±75 μV will be rejected. Data will be segmented and visually inspected for additional ocular and motion artifact. Epochs containing blink activity will be removed as EOG contamination. Bad channels will be identified and interpolated. The entire trial will be excluded if more than 15 sensors are rejected or if other significant movement artifact occurs. Data will be re-referenced to average reference and baseline-corrected. Trials will consist of a 100 ms baseline period and 500 ms period following onset of facial stimuli. Exhaustive windows will be shaped by minima and maxima of peak onset ranges recorded per subject, and group-wise grand averages will be inspected to confirm the latency windows included all subjects' P1 component. Mean amplitude within the determined time window will be computed for Neutral-Threat stimuli.

II. Anxiety Outcome Measures

a. Independent Evaluator Ratings: Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA). The LSAS-CA is a widely used, psychometrically sound clinician-administered measure of social anxiety in youth.

b. Youth Self-Ratings and Parent Ratings: Screen for Child Anxiety Related Emotional Disorders (SCARED-C/P). The SCARED is a widely used, psychometrically sound measure of youth anxiety.

c. Youth State Anxiety Self-Rating before Trier Social Stress Task (TSST). We will use the State-Trait Anxiety Inventory for Children – State Subscale (STAIC-S) administered before the TSST to assess subjects' levels of state anxiety. The TSST is a widely used social stress task wherein subjects are told that they will give a video-recorded speech about their strengths and weaknesses and then are given three minutes to prepare for the speech. At the end of the three-minute preparation period, subjects will be administered the STAIC-S and will then complete the speech task.

STATISTICAL ANALYSIS PLAN

We will conduct a full missing values analysis (MVA) in order to identify variables that are related to missingness; these variables will be included as auxiliary variables in any analysis models to reduce bias due to missingness. The proposed analysis methods (i.e., multilevel regression with maximum likelihood estimation) are robust to MAR (missing at random) or MCAR (missing completely at random) mechanisms, which will minimize impact of missingness and attrition. If there is evidence of MNAR (missing not at random) patterns, we will use appropriate methods. We will assess whether data meet all assumptions of analysis (multivariate normality, outliers) prior to analyses. We will adjust for any violations using robust methods (such

as using bootstrap standard errors). We will evaluate group differences in potential covariates (e.g., sex, pubertal status, race/ethnicity, P1 amplitudes, social anxiety severity, comorbid diagnoses, treatment utilization) prior to analyses to assess randomization and will include these variables in models as needed. Analyses will use the combined dataset from the two sites. Site will be included as a covariate to adjust for any clustering effects. In general, mixed models (also called multi-level or growth models) will be used to assess change in outcome variables over time within each treatment arm. Preliminary models will include time, group, and the time x group interaction, which indicates whether the groups differ in their change over time (on average). We will evaluate modesl with random intercepts (allowing individuals to vary in their mean levels of the outcome) and random slopes (allowing individuals to vary in their change over time) and choose the best model using likelihood ratio (LR) tests. We will also evaluate models with non-linear change with respect to time (e.g., ln[time]) and choose the best model using LR tests. We will use a Holm adjusted modified Bonferroni method for controlling experimentwise error rates; it is more powerful than traditional Bonferroni or Scheffe methods.[171]

Aim 1: Demonstrate target engagement. The effect of treatment group on P1 amplitudes will be assessed using a mixed model with P1 amplitudes as the (repeated) outcome =; group, time, and the group x time interaction will be included as predictors. The “time” variable will be centered at POST assessment, allowing us to evaluate group differences at that wave. The group effect represents the difference between groups at the POST assessment; significantly lower scores in the ABMT arm compared with the NCT arm would confirm target engagement.

Aim 2: Demonstrate effects of ABMT on social anxiety symptom severity. The same general procedures described in Aim 1 will be applied to Aim 2 data analysis. The effect of treatment group on social anxiety symptom severity will be assessed using a mixed model with social anxiety symptom severity as the repeated measure; group, time, and the group x time interaction will be included as predictors. The “time” variable will be centered at POST assessment, allowing us to evaluate group differences at that wave. Of interest is whether the contrast between study arms is statistically significant. The group effect represents the difference between groups at the POST assessment; significantly lower scores in the ABMT arm compared with the NCT arm would demonstrate the efficacy of ABMT. We will use the same analytic approach when examining subjects’ levels of state anxiety (STAIC-S) before the TSST.

Aim 3: Demonstrate target validation. We will examine changes in P1 amplitudes as a mediator of the social anxiety reduction effect of ABMT using an extension of the approach described in Aims 1 and 2, within a larger structural equation modeling (SEM) framework. Within a single model, change in P1 amplitudes will be modeled as in Aim 1 and change in social anxiety symptom severity will be modeled as in Aim 2. In addition, the effect of the P1 amplitudes slope on both (a) the group effect on social anxiety symptom severity and (b) the group x time interaction on social anxiety symptom severity will be included. These additional effects (“paths”) will allow us to evaluate how change in P1 amplitudes relates to group differences in change in social anxiety symptom severity across the assessment waves, including at POST. Statistical significance of the mediated effect will be assessed using Monte Carlo methods.

Aim 4: Evaluate maintenance of target engagement, effects on social anxiety symptom severity, and target validation. This aim represents a test of the maintenance of ABMT effects over 6 months. The analysis is a variant on the approach used in Aims 1 and 2. The effect of treatment group on each outcome at 6-month Follow-Up will be assessed using a mixed model with the outcome as the repeated measures at 4 waves (3 waves for state social anxiety before performance on the TSST); group, time, and the group x time interaction will be included as predictors. The “time” variable will be centered at the final wave (Follow-up), so group effects will reflect group differences at the 6-month Follow-Up. Maintenance of effects will be demonstrated by significantly lower scores in the ABMT arm compared with the NCT arm. Using a variant on the approach used in Aim 3, we also will examine how change in P1 amplitudes relates to group differences in social anxiety symptom severity at Follow-Up.