Title: Threat Interpretation Bias as Cognitive Marker and Treatment Target in Pediatric Anxiety: R61 Phase

NCT NUMBER: NCT04245501

Revised document date: 02/20/2020

PROJECT SUMMARY AND SPECIFIC AIMS:

Anxiety is the most common mental health problem in youth, affecting one in four children and adolescents. Unfortunately, evidence-based interventions (pharmacotherapy, cognitive-behavioral therapy) are costly, not widely available, and ineffective for a substantial proportion (~50%) of youth. In response, experts have called for novel ***treatments that directly target mechanisms underlying youth anxiety*** while simultaneously addressing barriers to care (i.e., cost, accessibility). One such promising mechanism is interpretation bias - the inaccurate interpretation of threat from ambiguity. We have previously demonstrated that interpretation bias occurs in over 90% of anxious youth, accounts for 46% of variance in anxiety severity above and beyond demographic and clinical characteristics, and differentiates between anxious and non-anxious youth. These data indicate that ***interpretation bias is a ubiquitous phenomenon underlying anxiety expression in children and adolescents*** and therefore may be an ***ideal intervention target.*** Cognitive bias modification for *interpretation bias* (CBM-I) is a computerized intervention that attempts to reduce anxiety symptoms by directly modifying interpretation bias; participants are provided with real-time corrective feedback when they select threat-relevant interpretations of ambiguity. CBM-I has demonstrated preliminary efficacy for reducing anxiety symptoms in adults. Yet extant CBM-I data in youth are sparse, and several critical questions have not been answered: 1) is the targeted mechanism (interpretation bias) modified by CBM-I in youth?; 2) what dose reflects meaningful interpretation bias change?; and 3) is interpretation bias reduction the mechanism underlying anxiety symptom reduction? Consistent with NIMH strategies to "define mechanisms" and "accelerate therapeutics", we propose to test interpretation bias as a putative intervention target. This proposal includes a two-phased study of *personalized* CBM-I in youth ages 10 to 17 who meet diagnostic criteria for anxiety disorder (generalized, social, separation). In the R61 Phase (N=46), an RCT examines whether CBM-I personalized to youth anxiety symptoms engages the interpretation bias target, compared to a computerized interpretation control condition (ICC). Our Go/No-Go Milestones reflects a significant difference in interpretation bias reduction between groups (CBM-I outperforms ICC). The interpretation target will be measured at multiple time points (4, 8, 12, 16 sessions) to identify the optimal dose for target engagement.

Aim 1: Directly engage and modify interpretation bias. *We predict that, compared to ICC, personalized CBM-I will result in significantly greater reduction of interpretation bias on at least two of three measures: objective linguistic interpretation bias via a word-sentence association paradigm*[6,7]*, objective visual interpretation bias via an ambiguous faces task*[12]*, subjective questionnaire of threat attributions.*[13]

Aim 2: Determine CBM-I dose for R33 Phase and subsequent trials. *Dosing is a critical issue relevant to target validation. Interpretation bias will be assessed at four CBM-I doses (4, 8, 12, 16 sessions) in order to identify the optimal dose at which bias reduction occurs.*

Aim 3: Ascertain feasibility and acceptability of approach. *We predict that CBM-I will be feasible with youth, and acceptable to youth and parents.*

R61 GO/NO-GO MILESTONES FOR R33 PHASE:

To proceed to the R33 Phase, CBM-I in the R61 Phase must meet the following criteria:

1) **target engagement** on at least two of three interpretation bias outcomes (described above) as reflected by a significant medium effect (d=0.50) between groups from pre-to-post-intervention.
2) be **feasible** in regards to administration (average of 90% training sessions completed) and rated as **acceptable** (average score of 30 out of 50 on self-reported exit interview[14]) to youth and parents.

STATISTICAL ANALYSIS PLAN:

Aims 1 and 2. Multilevel modeling (using Mplus 8.4 [Muthén & Muthén, 2022] software) will examine changes in interpretation bias assessed via both objective (word-sentence association paradigm [WSAP], ambiguous face task [FACES]) and subjective (CATS) measures. Given that some enrolled participants may be siblings, we will adjust all analyses for within-family correlations. In order to estimate the importance of modeling the family-level variance separately from the person-level variance, we will first estimate the Intraclass Correlation Coefficient (ICC) for the three-level model of each target outcome as the proportion of the between-person variability that is between families = (Level 3 variance)/(Level 3 + Level 2 variance). Three-level models will be utilized for outcomes where ICC is high, and two-level model (i.e., observations at level 1 clustered within individuals at level 2) for low ICC that adjust standard errors chi-square statistics for the family-level clustering, using TYPE=TWOLEVEL COMPLEX analysis in Mplus (Muthén & Satorra, 1995).

For each target outcome, multilevel models will test the effects of CBM-I vs ICC group on changes in the outcome. Given that bias change over time may not occur in a linear fashion, we will compare several alternative models for change over time. For the interpretation bias outcomes (assessed at training sessions 1, 5, 9, 13, and one-week post session 16), we will test a *linear model* of change, a *quadrative model*, a *piecewise model that estimates change with two slopes* – one specifying the early rate of changes in the outcome (between training sessions 1 and 9) and the second specifying the rate of change that occurs during later sessions (starting from session 9 to one-week post session 16), and a *piecewise model that estimates changes with three slopes* – one specifying early rate of changes in outcome (between training sessions 1 and 5), the second specifying rate of change that occurs during middle sessions (between sessions 5 and 13, and the third specifying rate of change that occurs during later sessions (starting from session 13 to one-week post session 16). Once the best-fitting model is identified for each outcome, the treatment group will be used to predict between-individual differences in slopes.

Aim 3. In regards to treatment completion and feasibility, we will examine the percentage of youth who completed all 16 trainings, and the proportion of trainings completed by youth who did not complete all 16 trainings. In regard to acceptability, youth and caregivers will complete the Participant/Parent Acceptability Questionnaire and Exit Interview (PAQ). The PAQ assesses how much computer tasks (i.e., bias assessments and trainings) made participants feel tired or bored, whether the computer trainings helped the youth feel less worried, nervous, scared or stressed, whether it was difficult to remember to complete at-home trainings, barriers to participation (i.e., travel, time off work/school, etc.), an overall/global rating for their experience with the study, and whether they would recommend the study to a friend. PAQ total scores range from 0 to 50, with higher scores indicating higher acceptability of the computerized intervention and related training session procedures. Scores of 30-39 indicate at least moderate acceptability, with scores of 40-50 indicating high acceptability. Given that CBM-I and ICC may be associated with differential acceptability, we will also compare acceptability ratings for youth and caregivers between randomized groups with t-tests.