OFFICIAL TITLE OF STUDY: Attention Bias Modification Training in Youth With Subthreshold Impairing Anxiety

NCT NUMBER: 02410967

DATE: 04-05-2018

PROTOCOL

Over the past three decades, substantial advances have been made in knowledge about treating children and adolescents who suffer from diagnosable anxiety disorders[1]. The knowledge landscape is bleaker when it comes to youth who do not have diagnosable anxiety disorders but instead experience subthreshold impairing anxiety (SubImpAnx). There is a critical need to develop evidence based interventions for youth with SubImpAnx given its high prevalence[2], the significant concurrent impairment and distress associated with SubImpAnx[2,3] and the high risk of escalation from SubImpAnx to diagnosable anxiety disorders[4,5].]

The small number of intervention studies that have addressed SubImpAnx have not focused exclusively on SubImpAnx. Further, the interventions examined were traditional, resource intensive approaches (e.g., CBT)[6-8]. Even when it comes to diagnosable disorders, traditional approaches to mental health service delivery for youth cannot meet current demand[9-12]. The inadequacies of traditional service delivery are magnified for impaired but undiagnosed youth. The economic challenges the U.S. faces render even more urgent the need to move beyond traditional service delivery toward developing and evaluating 'least restrictive' interventions to address SubImpAnx in terms of impact on patients (i.e., cost and personal investment) and therapists (i.e., training and treatment delivery)[13]. Efforts such as computer assisted and web based cognitive behavioral therapy for anxiety disorders represent promising directions[14-17]. It is an unaddressed empirical question whether a least restrictive treatment can reduce SubImpAnx in youth.

This application represents an initial step to address this question by collecting pilot data on a novel least restrictive treatment rooted in neuroscience among youth with SubImpAnx: Attention Bias Modification Training (ABMT). Substantial evidence from behavioral and neuroscience research documents a threat related attention bias in anxiety[18-20], including subthreshold anxiety in youth[21-24]. Attention bias to threat occurs in response to stimuli presented very rapidly and corresponds to perturbations in amygdala-prefrontal circuitry[24-30]. ABMT is the direct translational treatment implication of attention bias to threat. ABMT targets attentional threat bias via computer based training that affects subcortically based and frontal-cortical networks[28].

No research has examined ABMT among youth with SubImpAnx. Given evidence of consistent attention bias across youth with subthreshold anxiety[21-24] and youth with anxiety disorders[31-33], it is reasonable to hypothesize an anxiety reduction effect of ABMT among youth with SubImpAnx. If effective, ABMT would represent a least restrictive treatment option for youth with SubImpAnx with respect to patient impact in that it is low-cost, brief, and portable, and with respect to therapist impact in that it does not require skilled clinicians.

This UH2 study will enroll [66] clinic referred youth ages 8-16 years who do not meet DSM-IV diagnostic criteria for anxiety disorders but instead have SubImpAnx. [50 youth will be enrolled at the FIU Child Anxiety & Phobia Program and an additional 16 youth will be enrolled at the Yale Child Study Center]. These youth will be randomly assigned to 8 sessions of either ABMT or a placebo control (PC) task over 4 weeks. Clinician ratings on youth anxiety symptoms and impairment will be evaluated as the primary outcome. Parent ratings and youth self ratings on anxiety symptoms and impairment will be evaluated as secondary outcomes. Measures will be collected at pretreatment, immediate posttreatment (post), and 8 week followup. The following aims will be addressed:

Aim 1: Collect pilot data on the effects of ABMT and a PC task on levels of anxiety and impairment at post. A multisource assessment approach will be used to preliminarily examine anxiety and impairment reduction among youth in the ABMT condition as compared to youth in the PC task condition at post.

Aim 2: Collect pilot data on the effects of ABMT and a PC task on levels of anxiety and impairment at a follow up evaluation 8 weeks after the post evaluation. This will provide initial data regarding the maintenance of ABMT effects 8 weeks after treatment ends. A multisource assessment approach will be used to preliminarily examine anxiety and impairment reduction among youth in the ABMT condition as compared to youth in the PC task condition at the 8 week follow up.

Aim 3: Preliminarily examine whether ABMT leads to lower levels of attention bias toward threatening stimuli as compared to a PC task at a post evaluation and at a follow up evaluation 8 weeks after post. Reductions in attention bias to threat have been theorized to mediate ABMT's anxiety reduction effect[34,35]. Data from this UH2 will allow us to gain perspective on the theoretical underpinning of ABMT and will inform decisions about whether to pursue attention bias as a mediator in a subsequent R01.

Aim 4: Describe the course of anxiety symptoms and impairment during treatment among youth in the ABMT condition. Youth anxiety symptoms and impairment will be assessed at pre and every other session (i.e., sessions 2, 4, 6, 8), and post. We will explore the trajectory of anxiety symptoms and impairment across these six assessment waves in an effort to gain initial insight into 'dosage' related issues of ABMT.

APPROACH

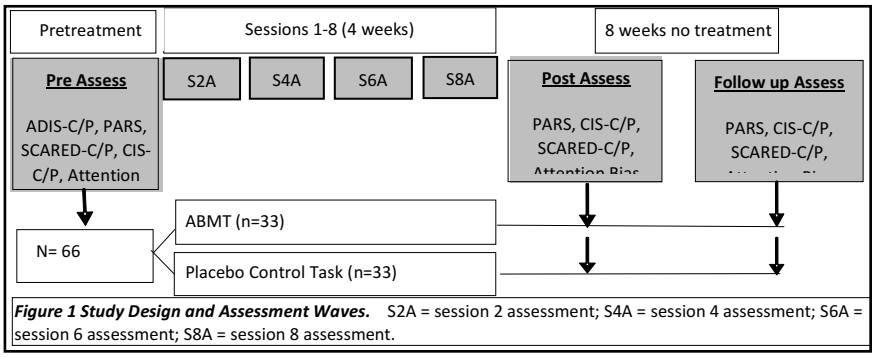

Figure 1 Study Design and Assessment Waves. S2A = session 2 assessment; S4A = session 4 assessment; S6A = session 6 assessment; S8A = session 8 assessment.

See Figure 1 for the randomized, double blind, placebo controlled design. After a pre assessment, participants will be randomly assigned to either ABMT or Placebo Control (PC) Task.

In ABMT, participants will complete 8 sessions of ABMT. In PC, participants will complete 8 sessions of a PC task. Number and duration of sessions will be identical in both conditions. All participants will complete the Columbia Impairment Scale and Screen for Child Anxiety Related Emotional Disorders after even numbered sessions. A week after session 8, all participants will complete a post assessment. After post, no training or assessment will be administered for 8 weeks. Participants then will complete a follow up assessment. After the follow up, participants in the PC condition will be offered ABMT. All participants will be offered further treatment resources as needed (see Human Subjects). Total duration from pre to follow up will be ~12-14 weeks.

Participants. [66] youth (8-16 years) will be admitted.

Inclusion Criteria. (A) Youth and parents must endorse youth SubImpAnx; and (B) if youth have ADHD, mood disorders, tics, or impulse control problems, those disorders must be treated with medication and be stabilized.

Exclusion Criteria. For youth to be excluded, they must (A) meet diagnostic criteria for Organic Mental Disorders, Psychotic Disorders, Pervasive Developmental Disorders, or Mental Retardation; (B) show high likelihood of hurting themselves or others; (C) not be living with a primary caregiver who is legally able to give consent for participation; (D) be a victim of previously undisclosed abuse requiring investigation by Department of Social Services; (E) be involved currently in a psychosocial treatment; (F) have a serious vision problem that is not corrected with prescription lenses; or (G) have a physical disability that interferes with their ability to click a mouse button rapidly and repeatedly.

Treatment Conditions. Consistent with past ABMT trials[76,77], participants will complete 15-minute ABMT or PC task sessions 2X a week for 4 weeks. At each session, participants will complete 160 trials of either the ABMT task or the PC task. In both tasks, a fixation cross will appear first, followed by 2 faces of the same actor, one above the other. One face will depict the actor emoting an angry expression and the other will depict the actor emoting no expression. After presentation of the faces for 500ms, a probe (< or >) will appear in the location of one of the faces. Participants will indicate the type of probe (< or >) by pressing either the left or the right mouse button. The probe will remain on the screen until participants respond. After responding, the next trial will begin. **ABMT Task:** In this task, the probe will replace the neutral face on 100% of trials. On 80% of trials, angry face location will predict probe location (i.e., in the location opposite the angry face). On these trials, angry face location and actor will be fully counterbalanced. Probe type will appear with equal probability for angry face location and actor. On the other 20% of trials, participants will see neutral-neutral face pairs. **Placebo Control (PC) Task:** The PC task will be identical to the ABMT task except for the frequency with which the probe replaces the neutral face. 80% of trials include one neutral face and one angry face. On these trials, angry face location, probe location, and actor are fully counterbalanced. Probe type appears with equal probability for angry face location, probe location, and actor. The other 20% of trials include neutral-neutral face pairs. The PC task is an ideal control condition because it is robust to differential expectancy effects[84].

Measures. See Figure 1 for the assessment schedule. Each assessment will be conducted in single sessions at our clinics by carefully trained graduate research assistants.

I. Primary Outcome: Pediatric Anxiety Rating Scale (PARS)[93]. The PARS is a widely used, reliable, and valid measure of global anxiety symptoms and impairment in youth ages 6-17. At the pre assessment, the interviewer who conducts the ADIS-C/P and PARS interviews will complete the rating. At post and follow up, an independent evaluator blinded to the patient's treatment condition will complete the PARS.

II. Secondary Outcomes: Youth Impairment, Youth Anxiety Symptoms. Youth impairment and anxiety symptoms will be assessed from the youth and parent perspectives using the respective versions of the **Columbia Impairment Scale (CIS-C/P)**[94] and the **Screen for Child Anxiety Related Emotional Disorders (SCARED-C/P)**[95,96]. The CIS is a reliable and valid global impairment scale for youth[94,97]. The SCARED is a widely used, psychometrically sound measure of youth anxiety[95,96,98,99].

III. Attention Bias to Threat will be assessed with a probe-detection task identical to the PC task, except that a unique set of faces will appear in this task[73]. Scores are calculated by subtracting response times when the probe appears at neutral face location from response times when the probe appears at angry face location.

IV. Maintenance of Blind. We will determine maintenance of the blind by asking youth participants and their parents at follow up whether they believed the youth was in either the ABMT or PC condition.

V. Inclusionary Measures. a. ADIS-C/P[92]. Youths and parents will be administered the ADIS-C/P to determine SubImpAnx status as described in Inclusion Criteria. **b. Treatment Utilization**[100]**.** Medication and psychosocial treatment utilization will be assessed at pre, post, and follow up to identify new treatment families may start during their participation in the UH2 (we will request they not alter treatment during the study).

STATISTICAL ANALYSIS PLAN

Data management protocols will be used to ensure data integrity. Missing values will be estimated using Markov chain Monte Carlo multiple imputation algorithms based on the Gibbs sampler. Analyses will focus on least squares test (OLS) of means and modern robust estimation procedures[101] that rely on Wilcox's R routines[102]. We will examine associations between condition and baseline variables to ensure successful randomization and will use a Holm adjusted Bonferroni method to control experimentwise error rates[103].

Aim 1: Preliminarily examine whether levels of anxiety and impairment at post are lower for youth in ABMT as compared to youth in PC. The OLS analysis is a 2 group single degree of freedom contrast between the ABMT and the PC conditions using pre scores as a covariate to increase statistical power. The contrast focuses on the comparison of adjusted means at post. Of interest is whether the contrast between conditions is statistically significant for independent evaluator rated anxiety symptoms and impairment (PARS; **Primary Outcome**), parent ratings on youths' anxiety symptoms (SCARED-P) and impairment (CIS-P) (**Secondary Outcome**), and youth self ratings on anxiety symptoms (SCARED-C) and impairment (CIS-C) (**Secondary Outcome**).

Aim 2: Preliminarily examine whether levels of anxiety and impairment at 8 week follow up are lower for youth in ABMT as compared to youth in PC. The analytic approach will be identical to Aim 1, except that contrasts will focus on scores at the follow up evaluation instead of the post evaluation.

Aim 3: Preliminarily examine whether ABMT, as compared to PC Task, leads to lower levels of attention bias to threat at post and follow up. The analytic approach will be identical to Aims 1 and 2, except that contrasts will focus on scores on the attention bias task instead of scores on anxiety symptoms and impairment.

Aim 4: Describe the course of anxiety symptoms and impairment during treatment among youth in the ABMT condition. Youth anxiety symptoms and youth impairment will be assessed at pre, ABMT sessions 2, 4, 6, 8, and post. These 6 assessments waves can be used to gain insight into the timing of ABMT response. This analysis will be approached from a latent growth modeling framework. In separate analyses, we will model the trajectory of anxiety symptoms (SCARED-C/P) and impairment (CIS-C/P). Models of no growth, linear change, and quadratic change will be explored in an effort to identify the best fitting trajectory. We will use growth modeling variants that are amenable to small sample sizes[108].