OFFICIAL TITLE OF STUDY: Attention Bias Modification Training for Child Anxiety CBT Nonresponders

NCT NUMBER: 01819311

DATE: 7-31-2017

Significance

Anxious Youth Who Do Not Respond to Cognitive Behavior Therapy (CBT)

Despite the strong efficacy evidence for CBT, for up to 50% of youth, symptoms of anxiety persist after a full course of treatment[1-3]. Many of these youth continue to meet diagnostic criteria for an anxiety disorder[1-3], and suffer concomitant emotional distress and impairment[1]. They also are likely to experience frustration and demoralization by perceived "failure," especially if CBT was pitched as a "treatment that works." Given that *untreated* anxiety disorders pose a huge financial burden on the health care system[4], as well as additional societal costs through "…higher rates of school dropout, teenage childbearing, marital instability, and poor career choices…"[5], unsuccessfully treated youth anxiety disorders likely pose similar burden. There is not a single empirical study that has examined what might be beneficial clinical next steps to allay persistent anxiety disorders and symptoms of youths who did not respond to CBT.

There are a number of reasonable choices to pursue as next steps, as discussed later in the application. In the subsequent sections, we discuss the reasons why Attention Bias Modification Training (ABMT) represents a promising option for youth CBT nonresponders**.** We begin first by summarizing the strong empirical evidence for threat related attention bias in anxious individuals, followed by the evidence for ABMT as frontline treatment for anxious individuals. We next provide the rationale for leveraging our current R01 (MH079943; Silverman, PI) to collect data on the potential utility of ABMT as a treatment augment for CBT nonresponders.

Threat Related Attention Bias in Anxious Youth and Adults. There is substantial convergent evidence of threat related attention bias in anxiety from behavioral and neuroscience research[6-8]. A common paradigm for assessing threat related attention bias is the visual probe-detection task. In the most widely used form of the task, a pair of threatening and neutral stimuli (e.g., facial expressions) is presented simultaneously and then followed immediately by a visual probe (e.g., a dot). The probe replaces the threatening stimulus on some trials and the neutral stimulus on others. An individual's difference in average response times when identifying the location of the probe following threatening stimuli versus neutral stimuli provides an index of attention bias.

Anxious individuals typically display faster response times on trials in which the probe replaces the threatening stimuli, which reflects an attention bias toward threat[7]. This pattern has been replicated among children[9-15], adolescents[16], and adults[17-19], including youth and adult patients with Social Phobia (SOP)[12,14,18] and Generalized Anxiety Disorder (GAD)[12-14,17,20], youth patients with Separation Anxiety Disorder (SAD)[12,14], and youth and adults with subclinical anxiety symptoms[9,16,21]. Cortical-subcortical circuitry findings from brain imaging studies correspond to these behavioral findings: Researchers have evoked an amygdala–ventrolateral prefrontal cortex (LPFC) circuit involved in attention to threat[16,22-27]. The amygdala is believed to facilitate vigilance through immediate, reflexive threat processing that occurs below awareness; the LPFC is believed to facilitate later strategic processes related to emotion regulation[22,24,25,28,29]. These findings suggest LPFC activation compensates for amygdala hyperactivation.

Anxiety is unique relative to other psychiatry symptoms in that there is marked cross-species conservation of brain-behavior associations. Specifically, across a range of mammalian species, similar changes in neural circuitry engagement and information processing occur when an organism confronts a threat[30]. This is also true for referred and nonreferred children, adolescents, and adults[31], suggesting developmental continuity in the neural circuitry underlying response to threat.

Given the strong evidence for attention bias to threat in anxious individuals, investigators' efforts turned toward developing novel translational treatments to address this bias, with the expectation that modifying attention bias would lead to reductions in anxiety symptoms. These efforts are summarized next.

ABMT for Anxious Youth and Adults. The direct translational treatment implication of attention bias to threat has been referred to as ABMT[32], Attention Training[33,34], or Attention Modification Program[35,36]. ABMT is based on the premise that the attention bias of anxious individuals can be shaped and modified via repetitive, computer based training that affects both subcortical (i.e., amygdala) and frontal-cortical (i.e., LPFC) neural networks[25]. In ABMT, patients complete the visual-probe detection task described above, with the critical exception that the probe always replaces the neutral stimulus and never replaces the threatening stimulus.

ABMT is an efficacious front line treatment among adults with primary diagnoses of SOP[33,37] or GAD[35], and adults with subthreshold anxiety symptoms[34,38-40]. ABMT results in decreases in attention biases (large effect sizes) and anxiety symptoms (medium to large effect sizes)[32]. The ABMT research literature with children and adolescents is similarly positive in showing reductions in anxiety and its disorders in both nonreferred[41,42] and referred samples[36,43,44]. For example, in an open trial of ABMT among 16 referred youth ages 10-17 with primary diagnoses of SOP, GAD, or SAD, youth showed statistically significant reductions in youth, parent, and clinician ratings. Additionally, 75% of the youth no longer met diagnostic criteria for any anxiety disorder[36].

Since our initial submission of this R34, the first randomized controlled trial of ABMT in youth was

published[44]. This trial demonstrated ABMT's efficacy as a frontline treatment among 40 clinic referred youth ages 9-14 with primary diagnoses of SOP, GAD, SAD, or specific phobia. Compared to a placebo control (PC) task, ABMT led to significantly larger reductions in youths' ratings of anxiety symptoms and independent evaluators' (IE) ratings of anxiety severity.

[In the next section, and in response to the previous critiques, we elaborate on the theoretical and empirical connections between attention bias to threat and CBT nonresponse, as well as the basis for our addition of attention control in this resubmission to investigate its potential role as a moderator. This is followed by a subsequent section, also in response to the previous critiques, in which we detail the rationale for ABMT as a treatment augment for youth who follow this path to nonresponse.**]**

[Attention Bias' Connection with CBT Anxiety Nonresponse and ABMT as a Potential Treatment Augment. CBT aims to change behaviors (e.g., avoidance, interpersonal patterns) and cognitions (e.g., beliefs, attributions) using top down intervention strategies[45,46] that correspond to LPFC activation[46-48]. Although CBT is helpful for many youth with anxiety disorders, much of information processing including attention bias to threat reflects bottom up, automatic processes that correspond to subcortical (e.g., amygdala) activation[23,24]. There is empirical evidence that attention bias, a bottom up process, prospectively predicts youth CBT anxiety nonresponse. Specifically, in a relatively large sample (N=131; ages 8-16) of youth with primary diagnoses of SOP, GAD, SAD, or specific phobia who were randomized to either group CBT or individual CBT, attention bias to threatening stimuli significantly predicted CBT nonresponse[49]. Youth who displayed an attention bias to severely threatening stimuli at pretreatment were significantly more likely to be classified as CBT nonresponders at posttreatment[49]. Demographic factors and treatment condition (group, individual) did not significantly predict nonresponse. Although not focusing specifically on attention biases, a recent study conducted by Vasey and colleagues in an adult clinical anxious sample found that another bottom up process (i.e., implicit attitudes) interfered with exposure based anxiety treatment response[50].

Because of this evidence linking bottom up processes to anxiety treatment nonresponse, and specifically showing attention bias' connection with CBT anxiety nonresponse, it is plausible that youth with anxiety disorders who do not respond to top down LPFC based compensation strategies such as CBT will benefit from an intervention that targets directly bottom up, amygdala based attention bias to threat: ABMT[13,49,51]. Neuroimaging studies and behavioral paradigms indicate attention bias manifests very rapidly and below awareness[23,24]. Such automatic behaviors may thus be responsive to constrained, intensive, and repeated practice of a narrow skill[52], the type of practice ABMT provides to disengage attention from threatening stimuli and thereby correct attentional threat bias. Thus, the primary purpose of this R34 project is to test preliminarily whether ABMT leads to significant reductions in anxiety among CBT nonresponders (Aim 1) and whether this effect is maintained over an eight week followup (Aim 2).

Proposed Theoretical Working Model. In thinking carefully through the previous critiques, which requested that we develop our theorizing about the circumstances under which bottom up processes such as attention bias to threat may interfere with some youths' ability to benefit from CBT, we reviewed the literature extensively and thus gained insights about the potential importance of attention control. Attention control, a subdomain of executive control, is a top down (i.e., effortful) regulatory ability that allows youths to disengage attention from one stimulus and engage with another stimulus[43,53,54]. Research supports a model in which attention bias is significantly associated with anxiety symptoms among youth who possess poor attention control, that is, among youth who are unable to use top down strategies to override bottom up attention bias[55-58]. Likewise, evidence indicates that adults who are high in trait anxiety and possess good attention control are able to disengage attention from threatening stimuli, whereas those who possess poor attention control are unable to do so[53]. Findings with adult patients further show impaired components of executive control interfere with patients' abilities to benefit from CBT (e.g., executive functioning deficits in older adults with GAD[59,60]).

Guided by the findings that attention bias to threat predicts CBT anxiety nonresponse[49] and the role of attention control as a potential moderator[55-58], we asked Dr. Michael Vasey to join our investigative team as a consultant. We are grateful he agreed, as he has studied and written extensively about the interaction between attention control and attention bias[55,56,58]. Dr. Vasey worked with us to refine our model for this resubmission, which now draws more sharply the conceptual connections between attention bias to threat and CBT nonresponse depending on youths' levels of attention control (see Figure 1). As shown in Figure 1, our model proposes the bottom up process of attention bias to threat as likely to interfere with youths' ability to benefit from CBT when they are unable to strategically modulate attention bias through attention control. That is, amygdala based attention bias to threat is posited to have a negative impact on CBT response in the absence of LPFC based compensation strategies. We recognize Figure 1 represents just

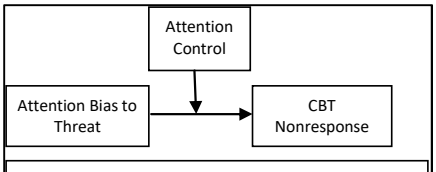

Figure 1.Theoretical model of the relations between attention bias, attention control, and CBT nonresponse.

one of multiple potential paths to CBT anxiety nonresponse. We elaborate on this point in the subsequent section, "Why Modify Attention Bias in this R34 rather than Other Variables?"

Also in response to previous critiques, we further refined our theoretical working model about how ABMT may lead to anxiety symptom reduction among CBT nonresponders. As shown in Figure 2, ABMT directly reduces attention bias to threatening stimuli[32,44]. Attention bias may have a direct effect and an indirect effect through interpretation bias on anxiety symptoms[61,62]. These effects are expected to be moderated by attention control: Youth with lower attention control may be benefit more from an intervention that targets a bottom up process such as attention bias to threat than youth with higher attention control[53,55].

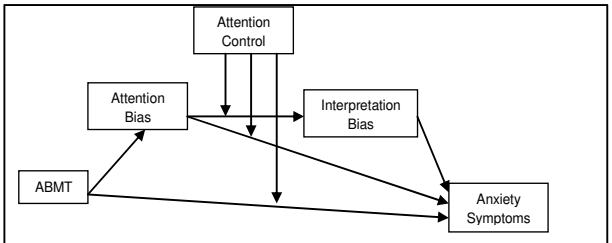

Figure 2. Theoretical working model of ABMT's anxiety symptoms reduction effect.

The model may be more complex than depicted in Figure 2 because it does not consider bidirectional effects and other potential moderator variables. We further note that a couple of researchers have speculated ABMT may reduce anxiety indirectly by improving attention control[43,63]. However, there exist no empirical data to support attention control as a mediator of ABMT outcome. Along similar lines, there is a possibility attention bias may moderate ABMT outcome, but this possibility is based on a single adult study with SOP only[64]. Our entire investigative team gave careful thought to these issues via lengthy email and Skype discussions. We reached a consensus that the model in Figure 2 accurately represents the empirical literature. We believe our proposal to gain preliminary insights on this model within the context of a R34 represents a promising initial effort (in the field as a whole) to begin to learn about the viability of variables that are likely to be involved in ABMT's anxiety reducing effects. Nevertheless, we will have the data available to explore the other possibilities mentioned above. Thus, consistent with Specific Aim 3, our intent in this R34 is to assess the variables in Figure 2 and use the data to inform decisions about whether they are worth pursuing in future research.

Why Modify Attention Bias in this R34 rather than Other Variables? We hope it is apparent from the above material that we worked hard in this revision to respond to the previous request to elaborate on the rationale for using ABMT as a treatment augment for CBT nonresponders and to further develop our theoretical model. As noted above, in our extensive review of the literature that led us to attention control, we also read carefully through the literature on predictors and moderators of youth anxiety CBT nonresponse, including research on the following predictor variables: sex and socioeconomic status[65-69], age[65,68-71], race[65,68,72], comorbid psychopathology[65,67,73-76], parent behavior[77-79], parent psychopathology[65,67,68,70,71,77,78,80-82], and therapeutic alliance[83,84]. Null effects were consistently found for some of these variables, whereas other variables were significant predictors of CBT nonresponse in some but not all studies. Low treatment involvement prior to exposure sessions[85] and use of safety seeking behaviors during exposure sessions[86] were identified as significant predictors of CBT nonresponse in single studies only. Fewer studies have examined moderators of CBT nonresponse and the general pattern of findings is the same[70,87,88].

As research on predictors and moderators of CBT nonresponse grows and replicates, we and other researchers will likely forge conceptual connections linking the above mentioned variables in efforts to develop alternative treatments for anxiety disorders – similar to the conceptual connections forged here between attention bias, anxiety disorders, CBT nonresponse, and ABMT as an augment. Within this frame, in response to a reviewer's question about why we are not studying medication as a treatment for nonresponders in this R34, we have been working on forging a connection in this area and we soon will resubmit a separate grant application to explore sertraline augmentation for some CBT nonresponders. Similarly, upon completion of our current R01 MH079943 we may find youth nonresponse is related to specific types of parental behaviors for certain subgroups of patients. If so, then we would be positioned to examine treatments that involve parenting strategies for these subgroups of nonresponders. As these examples indicate, there are several treatment choices that could be pursued for youth CBT nonresponders, once conceptual connections are forged. We hope we have made clearer in this revision why it would be useful to test ABMT in this preliminary way.**]**

Research Overview and Future Plans

[We now clarify in this resubmission that treatment nonresponse is operationalized as meeting criteria for a primary diagnosis of GAD, SOP, or SAD at posttreatment (post) and one year follow up (FU) in R01MH079943 (target N=70, see Approach). This operational definition ensures all ABMT participants show clinically meaningful anxiety and associated impairment due directly to a primary diagnosis of an anxiety disorder.**]**

All youth in R01 MH079943 received the same individual CBT protocol involving 12 to 14 weekly gradual exposure tasks (starting session 3) coupled with cognitive therapy, with some variation in parental roles. By participating in this intensive CBT, youth had ample opportunities to experience fear/anxiety activation via exposure tasks *and* to process their emotional and cognitive responses in a therapeutic context. All cases were

supervised by Dr. Silverman (co-PI), who has 25 years' experience conducting NIMH funded CBT trials with youth with anxiety disorders. Because the plan in this R34 is to test ABMT *only* among CBT nonresponders and because of random assignment to conditions, the specific CBT condition of the nonresponders will have no impact on R34 findings and conclusion. Further, we will include R01 MH079943 condition as a covariate in R34 analyses if appropriate (see Data Analysis).

We are fortunate in that as we write this application, R01 MH079943 (Silverman, PI) is in progress with just under one year of data collection to go, not including a likely one year no cost extension. The R01 is a large single site study testing hypothesized mediators of change in CBT. In this application, we request funding to leverage our current R01 (before this window of opportunity closes) in order to conduct this R34 project. If this R34 is funded, we will be in a relatively unique position to collect critical data on acceptability, feasibility and preliminary effects relating to the project's experimental condition, ABMT, as well as the project's control condition, PC Task, when delivered as an augment for anxious youth who did not respond to CBT. Additionally, if funded, the data will provide us with an opportunity to examine the viability of the variables included in our theoretical working model, allowing us to further develop and refine the conceptual connections we have forged preliminarily within the context of this R34 application (Figure 2).

[We see this R34 as a springboard to an R01 in that it will provide essential data regarding the potential application of ABMT as an augment to CBT. Importantly the R01 would not require a resource intensive randomized CBT trial where nonresponders are identified and then given ABMT. Instead, we will consider examining ABMT versus PC Task as an augment concurrently, or sequentially; plus the R34 will inform decisions for the R01 about using participants' baseline variables (e.g. attention control, attention bias) to inform which treatment for whom (i.e., which patients will likely need more than CBT and would thus be assigned to augmentation with either ABMT or PC Task). This would position us to test hypotheses regarding who might benefit from augmentation with ABMT before failure in the full CBT course.**]**

We recognize the avenues we pursue for our next ABMT R01 would be modified if the R34 data do not support ABMT's efficacy. One reason this is possible is because we are conducting a stringent test of ABMT; that is, with patients who 'failed' CBT. We will draw conclusions accordingly if the R34 results are not positive.

Given the state of the literature, our most important purpose is thus to collect data on the feasibility of ABMT and PC Task and to test preliminarily the effects of ABMT among anxiety disordered youth who do not respond to CBT (**Specific Aim 1**) and whether an effect of ABMT is maintained over an eight week FU period (**Specific Aim 2**). Having said this, treatment development and theory development ought to go hand in hand, in an iterative process[89-92]. As such, an additional purpose of this R34 is to gain perspective on our theoretical working model (Figure 2) to inform decisions about which variables to pursue in a future R01 (**Specific Aim 3**).

The Study Hypotheses. We propose to gather preliminary efficacy data on ABMT using a randomized placebo controlled design to address the following three specific aims.

Aim 1: Test whether ABMT produces significantly lower levels of anxiety at post as compared to PC Task.

Hypothesis 1a (Primary Outcome): Levels of IE ratings on youth anxiety severity for patients in the intervention condition will be significantly lower after eight sessions of ABMT as compared to IE ratings for patients in the control condition who participate in eight sessions of a PC Task.

Hypothesis 1b (Secondary Outcome): Levels of parent ratings on youth anxiety symptoms for patients in the intervention condition will be significantly lower after eight sessions of ABMT compared to parent ratings for patients in the control condition who participate in eight sessions of a PC Task.

Hypothesis 1c (Secondary Outcome): Levels of youth self ratings on anxiety symptoms for patients in the intervention condition will be significantly lower after eight sessions of ABMT as compared to youth self ratings for patients in the control condition who participate in eight sessions of a PC Task.

Aim 2: Examine whether ABMT leads to significantly lower levels of anxiety as compared to a PC Task at a FU evaluation eight weeks after the post evaluation. This would suggest the maintenance of ABMT effects eight weeks after treatment ends.

Hypothesis 2a (Primary): Levels of IE ratings on youth anxiety severity in the intervention condition will be significantly lower at FU compared to IE ratings in the control condition.

Hypothesis 2b (Secondary): Levels of parent ratings on youth anxiety symptoms in the intervention condition will be significantly lower at FU compared to parent ratings in the control condition.

Hypothesis 2c (Secondary): Levels of youth self ratings on anxiety symptoms in the intervention condition will be significantly lower at FU compared to self ratings in the control condition.

Aim 3: Gain perspective on the viability of variables as potential moderator and mediators of ABMT to inform decisions about whether to pursue them in a future R01. The variables we wish to gain perspective on are attention bias toward threat, **[**attention control**]**, and threat-related interpretation bias (Figure 2).

[Specifically, we propose to examine all mediation paths in Figure 2 and only one moderation path due to

power constraints: Attention control as a moderator of the association between condition and anxiety symptoms. The other two moderation effects in Figure 2 will be pursued in a R01 if initial support for the primary moderation hypothesis is obtained in this R34. They are presented in Figure 2 so we can share with reviewers our larger conceptual frame regarding the potential interrelations among the model's variables.**]**

PRELIMINARY STUDIES

This proposed study builds on different facets of each of the investigative team's (Silverman, Pettit, Bar-Haim, Pine, **[**Vasey**]**, Jaccard, Castellanos) past research. Generally, all members of the team have some history of collaboration. If funded, this study will provide the team with the critical and fairly minimal resources to allow for a careful execution of a much needed pilot controlled experiment on ABMT among CBMT nonresponders. NIMH's call for innovative and translational research such as the one represented by this study requires the assembling of an investigative team in which each member is expert in an area needed to move ABMT to the next level of theoretical and empirical inquiry. We elaborate briefly below how we have such a team (see also biosketches). We also discuss below how the R34 project is coordinated with R01 MH079943.

Dr. Silverman directs the Childhood Anxiety and Phobia Program (CAPP) at FIU and has conducted NIMH funded research since 1989 to develop and evaluate youth anxiety psychosocial treatments[93-95]. Dr. Silverman also has developed and evaluated assessment approaches[96-98]. Dr. Silverman is PI of the current CBT clinical trial (R01 MH079943) for youth who meet DSM-IV criteria for SOP, GAD, or SAD. Dr. Castellanos is the onsite psychiatrist and Dr. Pettit is co-I of this trial. **[**Dr. Pettit brings to the site unique expertise and experience in using computer-based performance tasks in research including set up, administration, and data acquisition, reduction, and analysis, as well as advanced quantitative modeling.**]** Dr. Pettit has studied extensively the course and etiology of internalizing disorders[99-107], including cognitive and information processing styles among youth with internalizing disorders[99,102,108,109]. Dr. Jaccard will provide additional guidance on and assistance with the optimal approach to data analysis. He has worked as a lead data analyst in NIH funded research for over 30 years, including Dr. Silverman's entire NIMH funded clinical trials.

Drs. Bar-Haim and Pine are leading experts on attention biases among anxious youth. Dr. Bar-Haim developed the attention modification task that will be used in this project and published two of only four studies to date on the use of ABMT with youth, summarized in the Significance section[41,42]. His work has been groundbreaking in demonstrating feasibility, acceptability, and initial efficacy of ABMT among youth[42]. Dr. Pine has published extensively on the neural circuitry involved in attention processes in child and adolescent anxiety[16,23,24,26,27,110-114] including in Dr. Silverman's 2nd edition of her co-edited volume[115]. Dr. Pine also collaborates with Dr. Bar-Haim on work examining attention biases in anxiety[61,116-119], including work on ABMT. **[**In the resubmission, we added Dr. Michael Vasey as a consultant. Dr. Vasey is a pioneer on attention processes in anxiety. He conducted seminal studies documenting an attention bias to threat in anxious children[10,11,120], and subsequently proposed and tested a model in which attention control moderates the relation between attention bias to threat and anxiety among youth[55,56,58]. Thus, Dr. Vasey brings to the team expertise in the interaction between top-down and bottom-up attention processes in youth anxiety.**]**

As noted, Dr. Silverman is PI of the current clinical trial (R01 MH079943) for approximately 300 youth who meet DSM-IV criteria for SOP, GAD, or SAD. Participants who complete this trial and continue to meet criteria for a primary diagnosis of SOP, GAD, or SAD at post and one year FU will be recruited for the proposed project. As of July 2012, 190 participants have completed R01 MH079943. Table 1 shows the number of participants who have completed R01 MH079943 and the projected number who will complete R01 MH079943 during each 12 month period through the end of the study (including a likely one year no cost extension). Based on preliminary findings from the R01 MH079943 sample and findings from past youth anxiety CBT trials including Silverman et al. trials[1-3], we expect 60 to 80% of participants will meet criteria for treatment response. The current response rate among participants who completed R01 MH079943 is 70.4%. Thus, consistent with past work, about 30% of participants who complete R01 MH079943 will meet our operational definition of nonresponder, leading to a total of 90 youth who will be eligible for the R34. Based on our past studies and pilot data (described below), we project that 70 (~77%) families of these 90 youth will provide their consent to participate in the R34. Based on pilot data and attrition rates in ABMT studies with clinical samples[33,35,37,42], we estimate about 90% of the 70 youth who enroll in the

Table 1. Schedule of projected R34 enrollment in relation to R01 MH079943 activities.

	2009	2010	2011	2012	2013	2014	2015	Mar 2016
R01 MH079943								
Cumulative n completed trial	22	81	150	210	270	300 (end June)	--	--
R34								
Cumulative n enrolled in study	--	--	--	--	20 (start April)	45	70	70
Cumulative n completed study	--	--	--	--	12	35	60	63

R34 will complete the study, leading to a final estimated sample of 63 study completers (final column in Table 1; also see Approach section for details about R34 selection, recruitment, and attrition). The amount of time from R01 MH079943 completion to R34 condition assignment (assuming April 2013 start date) will range from about four years to one month. As described in Data Analysis, we will examine length of time since R01 MH079943 completion and any intervening treatment as covariates, as appropriate.

In summer 2011, Drs. Silverman and Pettit received training in the computer administered ABMT protocol. Dr. Silverman also visited Dr. Bar-Haim's laboratory in Israel and observed ABMT administrations. Drs. Silverman and Pettit then submitted an IRB protocol to allow for gathering preliminary data relating to acceptability, feasibility, and pre to post ABMT response on youth anxiety symptom self ratings in an open trial. Upon receiving IRB approval, eight families where the youth met the proposed inclusion criteria were randomly selected and contacted for participation in this open trial. It was explained to the families that they were being invited to participate in a new treatment that has some promising evidence for reducing anxiety. Families were asked if they would be willing to come back to FIU for eight meetings to participate in a pilot study on ABMT. Six of the eight families agreed to come in for ABMT. The two families who expressed reluctance to coming in live in nearby Broward County (18 miles north of Miami-Dade County, where our main clinic is located). Although the number of our R01 families who live in Broward County is small (6%), if this R34 is funded, we intend to collect ABMT data on this small proportion of families. There will be no difficulty in collecting data from these families because we already have a satellite clinic in the FIU Pines Center Campus.

The six pilot study participants included four girls (66.7%) and ranged in age from 10 to 13 years (mean=11.17). All six met diagnostic criteria for GAD, SOP, or SAD. All six families completed all eight ABMT sessions in four weeks. Indeed, we only needed to reschedule 1 out of 48 appointments across the six participant families! We also administered a youth anxiety symptom measure, the Multidimensional Anxiety Scale for Children (MASC)[121]. Mean self ratings on the MASC significantly decreased from 42.17 to 33.50, $t(5) = 3.57$, $p = .02$. All six participants showed declines on the MASC and there was no indication that the mean decreases were driven by outliers. We are encouraged by these initial data because they show (1) acceptability and feasibility of ABMT and (2) youth anxiety symptom reduction.

[These Preliminary Studies' data were noted by a couple of the reviewers as 'Approach Strengths' (e.g., "a thoughtful and sequential series of pilot testing of ABMT at their site and with the proposed sample."). In this revision, we have strengthened the pilot data on feasibility further. Specifically, since the prior submission, we received IRB approval to gather pilot data on the randomized controlled trial protocol, not just an open trial. We thus identified and contacted five families and invited them back to CAPP to learn more about this project. Four families agreed to come in and also agreed to random assignment to either ABMT or PC Task. At the time of this submission, two of the youths have completed a pre assessment, eight sessions of PC Task, and a post assessment. One youth has completed a pre assessment, eight sessions of ABMT, and a post assessment. The other case is currently still receiving ABMT. These data lend further support to our ability to successfully carry out the proposed R34 protocol, including random assignment to conditions and participants' full completion of conditions.**]**

APPROACH

Design

See Figure 3 for the randomized, double blind, placebo controlled design. After a pretreatment (pre) assessment, patients will be assigned randomly to one of two conditions: ABMT or PC Task. In ABMT, patients will complete eight biweekly sessions of ABMT followed by a post assessment. In PC Task, patients will complete eight biweekly sessions of a PC Task followed by a post assessment. After post assessment, no training or assessment will be administered for eight weeks. At that time, patients will come back to our clinic for a FU assessment. **[**After the FU assessment, patients in the PC Task condition will be offered ABMT (see Human Subjects).**]** Total duration of patients' involvement from pre to FU will be about 12-14 weeks. Number and duration of sessions will be identical in both conditions.

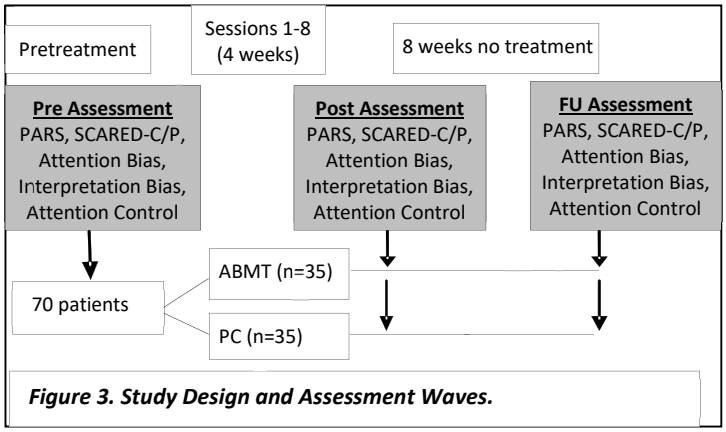

Figure 3. Study Design and Assessment Waves.

Participants

Approximately 70 youth (8-16 years) will be admitted to the study. Based on participant characteristics in R01 MH079943, we expect an even gender distribution. Based on attrition rates in ABMT studies with clinical samples[33,35,37,42], we estimate 5-15% attrition from pre to FU, which would yield 60-66 study completers. We

will follow all randomized participants so that we can perform per protocol analyses (PP; evaluating participants who complete the study) and intent to treat analyses (ITT; evaluating all participants enrolled regardless of whether they complete the study). ITT is widely used in randomized clinical trials, although some researchers have expressed concern it may underestimate treatment effects and be overly conservative for preliminary efficacy studies[122-124]. Conversely, PP may overestimate treatment effects[124]. In light of their advantages and limitations in a pilot study and consistent with guidelines of the International Conference on Harmonisation[125], we will analyze the data using both approaches and note differences in findings across the approaches.

Recruitment and Selection. All patients who have completed or who will complete the 12-14 week CBT trial in R01 MH079943 and still meet criteria for a primary diagnosis of SOP, GAD, or SAD at post and one year FU will be contacted. We note that among youth patients there is *no* evidence that attention bias differs across type of anxiety disorder[12,14]. Requirement of a diagnosis at both post and FU ensures the sample consists of youth who do not respond to CBT. If we required a diagnosis *only* at post (not FU), the sample might include youth who have a positive albeit slow response to CBT[126]. Waiting a full year allows sufficient time for beneficial CBT effects to manifest – or more relevant to the R34, *not* to manifest. Conversely, if we required a diagnosis *only* at FU, the sample might include youth who responded to CBT but subsequently relapsed or recurred in the year after CBT. It would be inaccurate to label such youth 'CBT nonresponders.' Thus, we view it important to require a primary diagnosis of SOP, GAD, or SAD at both post and one year FU so that we can draw conclusions accordingly with respect to ABMT effects for a clearly defined population.

Preliminary data from 190 youth who completed R01 MH079943 thus far indicate 30% meet this diagnostic requirement. This figure is consistent with past CBTs[1-3] including Silverman et al. trials[93]. Based on these data, we project 90 youth will have met eligibility criteria by the end of R01 MH079943 in June 2014 (see timeline in Table 1). These 90 youth will be recruited for the proposed project. Based on our past studies and initial pilot data collection, we project 70 (~77%) of these 90 youth will participate. To ascertain potential sample bias due to refusal to participate, we will compare youth who agree to participate to those who do not agree on socioeconomic status, ethnicity, age and gender, and clinicians' severity ratings at the R01 MH079943 FU. Further information relevant to patient selection is discussed in Human Subjects.

Inclusion Criteria. The inclusion criteria are the same used generally across past ABMT trials. The only main difference in this project's inclusion criteria is the requirement that all youth must have participated in our R01 MH079943 CBT trial and were deemed treatment nonresponders, as described above. All youth participants who are recruited will be between 8-16 years old. To be included in the project: **[**(A) they must still have a primary DSM-IV diagnosis of GAD, SOP, or SAD; (B) if they have comorbid ADHD or depressive disorders, those disorders must be treated with medication and stable; and (C) if they have tics or impulse control problems, those problems must be treated with medication and stable and cause minimal or no impairment. Youth on a stable dose of medication will be included so as not to limit generalizability. Stable medication is defined in Human Subjects, as well as how we will work with the project's onsite psychiatrist, Dr. Castellanos. Dr. Castellanos is the onsite psychiatrist for R01 MH079943, which has the same medication criteria proposed for the R34. As such, Dr. Castellanos is well aware of the medication issues involved in the trial. Medication treatment will be held constant so as not to jeopardize the study's internal validity. That is, because medication response is stable prior to R34 study enrollment and is held constant throughout the study, changes in outcome variables may be attributed to the intervention rather than to medications.**]**

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) have not been living with a primary caregiver for at least 6 months who is legally able to give consent for the child's participation; (D) be a victim of previously undisclosed abuse requiring investigation or ongoing supervision by the Department of Social Services; (E) be involved currently in another 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. See Human Subjects for more information on study's exclusion criteria, including the decision to exclude youth involved in another psychosocial treatment.

Treatment Conditions

Patients will be assigned randomly to the two conditions (i.e., ABMT or PC Task). The administration of each session is identical in both conditions and will follow the same standardized protocol. Because all participants who will be enrolled in this R34 participated in R01 MH079943, they already have experience in coming to our clinic. Further details on our clinic setting are provided under Facilities and Other Resources.

General Procedures. Following the prototype of past ABMT trials[33,35], patients will complete 15-minute ABMT or PC Task sessions twice a week. Consistent with the modal number and temporal spacing of sessions in past research[33,35,37], patients will complete eight sessions spaced over four weeks. In the event that patients

miss scheduled sessions (e.g., due to illness, travel), the length of the treatment period may be extended up to two weeks (for a total of six weeks). To maintain integrity of the study design and FU assessment, treatment will stop after six weeks regardless of how many sessions have been completed. Number of sessions and number of weeks needed to complete sessions will be considered in the analyses (see Data Analysis).

At each session, patients will be brought into a therapy room equipped with a table, chair, and computer. A 21-inch monitor and mouse will be on the table. Patients will sit facing the monitor and will be instructed to place their dominant hand on the mouse. Patients will be told that a probe (< or >) will appear on the screen and that their task is to push the left mouse button when < appears and to push the right mouse button when > appears. The importance of completing the task as quickly as possible without compromising accuracy will be emphasized. Patients then will complete 160 trials of the task. Trials will be presented in EPrime software. A centered fixation cross will appear first and will be followed immediately by two faces of the same actor against a white background, one above the other. One face will depict the actor emoting an angry expression and the other will depict the actor emoting no expression. Each face is 34mm in height and 47mm in width. After presentation of the faces for 500ms, a probe (< or >) will appear in the location of one of the faces. Patients will be instructed to indicate the type of probe (< or >) by pressing either the left or the right mouse button. The probe will remain on the screen until patients respond. After responding, the next trial will begin.

In each session, patients will see 160 trials, 40 of which will include only neutral faces. The purpose of these 40 trials is to decrease the contingency ratio of neutral face: probe, which may reduce the chances that patients will identify the mechanism underlying the training paradigm. The remaining 120 trials will include one neutral face and one angry face. The faces to be used in the probe detection task were selected from a standardized set of emotional expressions used in previous ABMT trials[41,44] with youth. The set includes 10 actors (5 male, all Caucasian) selected from the NimStim set of facial expressions[127] displaying angry or neutral expressions. We decided to use faces as task stimuli rather than words for three reasons. First, it avoids confounds between developmental aspects of emotional and linguistic processing. Second, research indicates that emotional faces generate larger and more consistent attention bias than threatening words[17,128]. Third, face-based dot-probe tasks have been administered to non-human primates. Thus, the use of faces facilitates cross-species comparisons. **[**We decided to use these 10 faces because (1) they tap into threat-processing neural circuitry[23], (2) they are the identical stimuli used in the only published clinical trial of ABMT with referred anxious children[44], (3) they are being used in ongoing research in the UK, Netherlands, Germany, Israel, Brazil, and US and similar findings are emerging at all sites, and (4) there is no evidence of advantage for disorder specific stimuli faces[32]. Use of different faces, including faces of different emotions and faces of actors from different racial backgrounds, will be important for replication studies, but may introduce a confound in this first test of ABMT among CBT nonresponders.**]**

ABMT Task. In this task, the probe will replace the neutral face on 100% of trials. On 80% of trials, the location of the angry face will predict the location of the probe (i.e., in the location opposite the angry face). On these trials, angry face location (top or bottom) and actor will be fully counterbalanced. Probe type (< or >) will not be factorially counterbalanced but will appear with equal probability for angry-face location and actor. On the other 20% of the trials in this task, patients 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 will be fully counterbalanced. Probe type will appear 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 should be robust to differential expectancy effects, in contrast to other possible control conditions such as medication or behavior treatment.**]**

Task Administration. All sessions will be conducted by doctoral level graduate research assistants, who are blind to experimental condition and not involved in assessment procedures. Numeric codes representing experimental condition will be used to maintain the double blind (see Human Subjects). All research assistants will undergo thorough training in study procedures, which include (1) being trained in task protocol by Dr. Pettit, (2) administering practice sessions to Dr. Pettit, (3) administering one supervised session to a patient while being observed by Dr. Pettit through the clinic's one way mirrors and (4) completing a session summary form jointly with Dr. Pettit (see Measures). The ABMT and PC protocols are essentially contained on the computer software program. Graduate research assistants will be instructed to bring each patient to a therapy room and will start the software program. All instructions for the task appear on the computer screen and the investigative team's experience has been that youth readily understand the task. Additional details on task administration are provided in Human Subjects. This includes rationale for administering tasks in our clinic instead of having youth self-administer tasks at home.

Measures

See Figure 3 for the study's assessment schedule. Each of the three assessments (pre, post, FU) will be conducted in single sessions at our clinic by carefully trained IEs (graduate research assistants who are not conducting treatment sessions). At each assessment session, youth and their parents will be administered the PARS in a randomly determined order. During the youth interview, the parent will be administered the questionnaires. Following the youth interview, the parent will be interviewed and the youth will be administered the attention bias task, the interpretation task, and the questionnaires. Following suggestions by Vasey, Dalgleish, and Silverman[120], ABMT and PC Task training sessions will not occur on the same day as the assessment sessions. Training sessions will begin the week following the pre assessment, and the post assessment will occur during the week following the final training session.

[I. Primary Outcome: IE Rated Anxiety Reduction

Pediatric Anxiety Rating Scale (PARS)[129]. The primary outcome has been modified to be IE rated anxiety severity as measured by the PARS. The PARS assesses global anxiety severity across SOP, SAD, and GAD in youth ages 6-17. Using information obtained from interviews with parents and youths, an IE scores each of 50 anxiety symptoms as either present or absent during the past week. Endorsed symptoms are rated by the IE on 7 dimensions (i.e., number of symptoms, severity of distress, severity of physical symptoms, frequency, avoidance, interference at home, and interference out of home). Each dimension is rated from 0 to 5; total scores range from 0 to 35. The PARS has adequate internal consistency (αs .64-.91) and interrater reliability (ICCs .78-.97), sensitivity to change in treatment studies, and convergent validity through significant correlations with parent ratings and youth self ratings on anxiety scales[129,130].**]**

At the pre assessment, the interviewer who conducts the ADIS-C/P and PARS interviews will complete the rating. At post and FU assessments, an IE blinded to the patient's treatment condition will complete the PARS. At each assessment wave, interrater reliability will be calculated on a random 25% of interviews that are re-rated by a third IE who is also blinded to treatment condition.

[We will use dimensional PARS scores as the primary outcome not dichotomous diagnostic status because the sample size needed to achieve adequate statistical power to detect an intervention effect on a dichotomous variable would not be feasible in this R34.. For example, the minimum sample size needed to achieve statistical power of .80 to detect a medium effect (odds ratio = 2.50) on diagnostic status would be 75 per group[131]. **]**

II. Secondary Outcomes: Youth Rated and Parent Rated Anxiety Reduction

a. Screen for Child Anxiety Related Emotional Disorders – Child Version (SCARED-C)[132,133]. It is important to assess specific anxiety symptoms in this controlled experimental study to determine whether ABMT has an effect at this level. We used the MASC in our small pilot summarized under Preliminary Studies. Based on the recommendation of our investigative team (Pine, Bar-Haim) we propose to use the SCARED in this project. The basis for the SCARED recommendation is because this anxiety symptom scale has been used in previous youth ABMT studies including the recent open trial[36] and randomized controlled trial[44]; significant SCARED reductions have been found. The SCARED also is being used in other ABMT trials being conducted in other countries (Israel, England, Australia, Brazil, Netherlands). The data we obtain in this study will thereby afford us the opportunity to make cross validation comparisons (other samples, other trials), if we elect to do so. The MASC and SCARED are significantly and highly correlated (e.g., r=.81)[134]. The SCARED consists of 41 items which youth rate on a 3-point scale. Test-retest reliability is satisfactory to excellent (ranging from .70 to .90). The SCARED is internally reliable (e.g., α=.90), sensitive to change, and has demonstrated good convergent and divergent validity compared with formal psychiatric diagnoses and/or structured psychiatric interview and with other widely used screening scales[132-135]. As in past ABMT research[36,42,44], the SCARED total score will be used in analyses.

b. Screen for Child Anxiety Related Emotional Disorders – Parent Version (SCARED-P)[132,133]. Parent ratings represent important additional outcomes in all youth anxiety randomized trials[136,137]. There is scant controlled parent data following youth participation in ABMT. We will address this gap in the literature by assessing outcome from parents' perspectives using the parent version of the SCARED. The reliability and validity of the SCARED-P have been demonstrated repeatedly and mirror those of the SCARED-C[132,133,135].

III. Potential Mediators and Moderator

We will assess each of the potential mediators and the hypothesized moderator shown in Figure 2 at each assessment session (Figure 3) to inform decisions about our future R01.

a. Attention Bias to Threat. As in prior research[36,41], attention bias to threat will be assessed with a probe-detection task identical to the one used in the PC Task, with the exception that unique faces will appear in this task (i.e., a different set of 10 faces will be used). Inaccurate responses when the probe appears on one side of the screen but patients select the other side will be excluded, as will trials with response latencies <50ms and >1200ms. Similar criteria have led to the exclusion of <5% of trials among adults[37] and children[36,42].

Attention bias scores will be calculated by subtracting the mean response time on trials in which the probe appears at the neutral face location from the mean response time on trials in which the probe appears at the angry face location. Only the 120 trials that present angry-neutral face pairs will be used to calculate scores (the 40 neutral-neutral trials will be excluded). Positive values reflect an attention bias towards angry faces.

b. Threat-Related Interpretation Bias. Youths' interpretations of ambiguous situations will be assessed with the Children's Opinions of Everyday Life Events (COELE[138]). The COELE includes six hypothetical ambiguous situations in six areas identified as being of predominant concern in young people as found by Silverman et al (1995)[139]. Each of the six items will be read aloud to youths, followed by the open-ended question "What do you think happened in this situation?" Youths' spontaneous responses will be coded as threatening (1; explanations involving negative outcomes) or nonthreatening (0; explanations involving neutral or positive outcomes). Scores on the six items will be summed to derive a total threat interpretation score (range: 0 to 6). The COELE yields scores that have internal consistency (e.g., α=.80). Concurrent validity has been established via significant correlations with self-report measures of worry and trait anxiety[138,140]. As in past research[138,140], two coders blind to condition and study hypotheses will be trained to code responses on the six items. Interrater reliability has been excellent in past research (e.g., kappa > .85 for each item)[140].

[c. Attentional Control Scale for Children (ACSC)[141]. Youth's attention control will be assessed with the ACSC, a 20 item scale that assesses the youth's ability to focus and shift attention. Items are scored on a 4-point scale; higher total scores represent better capacity for attention control. The ACSC has been used with children as young as 8 years. Internal consistency is acceptable (α's from .72-.87)[57,141-144]. Convergent validity has been established via significant correlations with anxiety symptom severity, perceived control, and teacher ratings of school performance[57,141-143].**]**

IV. Acceptability, Feasibility and Maintenance of Blind. Feasibility will be ascertained by recording the number of eligible families who do not enroll their child in the study. Across both ABMT and PC, we will record number of enrolled patients who did not complete the study. We also will record (a) cancelled and missed sessions and (b) weeks needed to complete eight sessions. (A) and (B) will be recorded using the project's session summary forms, which will be completed by the PC and ABMT graduate assistant task administrators at each scheduled session. Dr. Pettit will review the session summary forms weekly to ensure their full completion. We also will determine maintenance of the blind by asking youth patients and their parents at FU whether they believed the youth was in either the ABMT or PC condition. Research on ABMT has found that most patients believed they were in the PC Task condition[33].

V. Additional Measures

a. Anxiety Disorders Interview Schedule – Child/Parent-IV (ADIS-C/P-IV)[145]. As in most youth anxiety CBT trials, youths' anxiety disorder diagnoses will be made using the ADIS-C/P. All youths and their parents (usually mothers, see Human Subjects) will be administered the ADIS-C/P at a pre evaluation to obtain current Axis I diagnoses and determine eligibility for study participation. The ADIS-C/P will be re-administered at post and FU evaluations. **[**Although diagnostic status is not an outcome variable due to low statistical power given its dichotomous nature, we will report rates of anxiety diagnoses across conditions for descriptive purposes.**]**

b. Treatment History and Utilization. There are two participant scenarios with respect to treatment history. One scenario is youth may have received subsequent psychosocial or medication treatment following their failure in the CBT protocol in R01 MH079943. The second scenario is youth may be currently receiving a medication treatment (youth currently involved in other psychosocial treatments will be excluded). Each scenario will be assessed carefully via questions[146] to be completed by parents at each of the three assessment sessions. This will ensure we identify past treatment, current additional treatment, and new additional treatment families may start during their participation in the R34. Responses will be collapsed to reflect three treatment variables: past medication, past psychotherapy, and current medication. If any of these treatment history and utilization variables are significantly associated with R34 condition, we will include them as covariates in analyses and will draw our conclusions accordingly.

INNOVATION

[As noted in the critiques of our initial submission, the proposed project is innovative in the following ways:

- ABMT is a theoretically-grounded intervention that targets subcortical, automatic processing of anxiety that may address brain regions and processes that are less directly impacted by CBT.
- This is the first trial of this brief intervention for an impacted population that at present has few evidence-based alternatives for their anxiety disorders should they fail to respond to CBT.
- ABMT is potentially more cost-efficient (shorter, requires less skilled therapists) and more disseminable (can be conducted at home, provide access where experts are not available) than traditional talk therapies. It may also be acceptable to those who find medication or talk therapy unacceptable.
- Addressing CBT nonresponse with a non-linguistic computer-based intervention is innovative compared to

the "more of the same" approach (booster sessions, augmented by medication).
We appreciate these positive comments about how the project is innovative. In addition, in response to reviewers' request that we further develop a theory-treatment link, in this resubmission we have further developed this link regarding why some patients do not respond to CBT and why ABMT is likely to help those patients. The innovation of the project has been further enhanced by including attention control as a potential moderator of ABMT's anxiety reduction effect. This project moves beyond past ABMT studies by collecting data not just on outcome, but also potentially promising mediator and moderator variables contained in our model.**]**

DATA ANALYSIS

Data management protocols will be used to ensure integrity of the data. Data will be checked for out of range and missing values. Missing data should be minimal. Missing values will be estimated using Markov chain Monte Carlo multiple imputation algorithms based on the Gibbs sampler in the Mplus program[147]. Space constraints do not permit us to describe all the details of our analytic approach. We highlight major issues focusing on the Specific Aims. Primary methods of analysis will focus on traditional least squares tests of means as well as modern robust estimation procedures[148] that are outlier resistant, make minimal assumptions about population distributions, and are more powerful than traditional methods[148-150]. The latter techniques rely on Wilcox's R routines[149]. Initial analyses will examine associations between condition and baseline variables (i.e., diagnosis, treatment history, demographics, and time since R01 MH079943 FU) to ensure randomization was successful. Table 2 provides a summary of planned analyses. We will compare the robustness of our conclusions with and without statistical corrections for multiple tests[151]. We will use a Holm adjusted modified Bonferroni method for controlling experimentwise error rates; it is more powerful than traditional Bonferroni or Scheffe methods[152].

Aim	Contrast	Outcomes
Aim 1: Efficacy	ABMT vs. PC Task at Posttreatment	PARS, SCARED-C/P
Aim 2: Maintenance	ABMT vs. PC Task at Follow up	PARS, SCARED-C/P
Aim 3: Potential Moderator & Mediators	1. ABMT vs. PC Task at Posttreatment (immediate effect) 2. ABMT vs. PC Task at Follow up (maintenance effect)	Attention Bias & Interpretation Bias (mediators), Attention Control (moderator)

Table 2. Planned Analyses.

Findings on acceptability, feasibility, and maintenance of blind variables will be reported separately for ABMT and PC, as well as the total sample. We will test for differences between ABMT and PC on these variables using independent sample t-tests.

Aim 1: Test whether ABMT produces significantly lower levels of anxiety at post as compared to PC Task. This aim represents the efficacy test of the proposed project. The traditional ordinary least squares (OLS) analysis is a two group single degree of freedom contrast between patients in the ABMT condition (n=35) and patients in the PC Task condition (n=35) using pre scores as a covariate to increase statistical power. The single degree of freedom contrast focuses on the comparison of adjusted means at post. Of interest is whether the contrast between conditions is statistically significant for IE ratings of youth anxiety severity (PARS; **Hypothesis 1a**), parent ratings on youth's anxiety symptoms (SCARED-P; **Hypothesis 1b**), and youth self ratings on anxiety symptoms (SCARED-C; **Hypothesis 1c**). Significantly lower scores in the ABMT condition as compared to the PC Task would support the efficacy of ABMT for CBT nonresponders. The robust counterparts of these contrasts are described in Wilcox[149]. The two recommended methods focus on either medians or 20% trimmed means in conjunction with smoothers to model the regression surface for the covariates. We thus will pursue traditional analyses of means as well as robust analyses of medians and trimmed means, giving analytic preference to the latter methods over the more traditional OLS estimates, based on the simulation results of Wilcox[149].

Aim 2: Examine whether ABMT, as compared to PC Task, leads to significantly lower levels of anxiety at an eight week FU. This aim represents a test of the maintenance of ABMT effects over eight weeks. The analysis will focus on the between-groups contrast between patients in the ABMT condition (n=35) and patients in the PC Task condition (n=35). Patients' mean scores on the FU measures will be contrasted using a single degree of freedom contrast as a function of condition (ABMT, PC Task) in a between-groups design with the pre scores as a covariate. The single degree of freedom contrast focuses on the comparison of adjusted means at FU. Of interest is whether the contrast between conditions is statistically significant for IE ratings of youth anxiety severity (PARS; **Hypothesis 2a**), parent ratings on youth's anxiety symptoms (SCARED-P; **Hypothesis 2b**), and youth self ratings on anxiety symptoms (SCARED-C; **Hypothesis 2c**). Significantly lower scores in the ABMT condition as compared to the PC Task would demonstrate that ABMT produces reductions in anxiety at least eight weeks after treatment has ended. The robust counterparts of these contrasts are those described for Aim 1[149].

Aim 3: Gain perspective on the viability of variables as potential mediators and moderator of ABMT (Figure 2). This aim represents an exploratory aspect of this R34 application that will lay the groundwork for a larger R01, which may include testing of the mediators and moderator of ABMT's anxiety reduction effect. As

described earlier, reduction in attention bias toward threat and threat-related interpretation bias represent proposed potential mediators of ABMT[61,62], and **[**attention control is expected to moderate the effects of ABMT on anxiety symptom severity[55-58].**]** Although it is premature given the current state of the field to pursue tests for the full moderated mediation chain depicted in Figure 2 in this R34, it is reasonable to use the data to gain some perspectives on the viability of proposed moderator and mediators so as to inform decisions to pursue them in the larger R01. **[**The traditional moderation analysis relies on least squares regression with a focus on the statistical significance of the product term of the independent variable (condition) and the moderator (attention control) in predicting the dependent variable (anxiety symptom severity)[153]. In this R34 pilot study, and given our desire to balance risk of Type I and Type II errors, we will only test attention control as a moderator of the association between condition and anxiety symptom severity. The other two moderation effects depicted in Figure 2 will be tested in a larger R01 if initial support for the primary moderation hypothesis is obtained in this R34.

Mediation paths (Figure 2) can be explored in several ways. One strategy tests the joint significance of the path from the treatment to the mediator and the path from the mediator to the outcome. This follows the logic of the joint significance test of mediation by MacKinnon[154], but we will use the newer, more powerful partial posterior p value method by Biesanz[155]. This latter approach fares better than the asymmetric confidence interval approach for testing statistical significance[155]. A robust analog to the joint significance test will use Theil-Senn regression as applied to the target paths and then apply the logic of MacKinnon's joint significance to them. The magnitude of each indirect effect can be subjected to decompositional analyses through multiplicative and summation rules for mediation and the proportion of the total effect that each mediator accounts for can be documented (using the algorithms from the Mplus computer package[156]). Confidence intervals around these decomposed effects can be formed using percentile bootstrapping, which perform better than bias-corrected bootstraps in the context of such mediation analysis – see Biesanz[155].**]**

Statistical Power

Past research on ABMT with adult clinical samples has reported medium to large effect sizes for reductions in anxiety symptoms (Hedge's d=.78) and large effect sizes for reductions in attention bias toward threatening stimuli (Hedge's d=1.16)[32]. The extent to which similar effect sizes would be found in the proposed sample of youth who did not respond well to CBT is unknown. In this project, we would like to be able to detect effects of medium size (Cohen's d=.50) or larger. For a single degree of freedom contrast between two independent groups, the approximate sample size needed to achieve power of 0.80 for a mean difference of d=.50 is 64 per group, a number that exceeds our projected n=35 per group.

Approaches to increasing statistical power in randomized clinical trials generally focus on increasing sample size, but an alternative strategy is to introduce covariates that reduce within-subject error and thereby increase the precision of estimated between-group differences. The latter approach leads to a more sensitive significance test for the treatment effect[157]. In the proposed R34, our sample size will be constrained by the number of youth who do not respond to CBT in the current R01 MH079943 study. Thus, we will increase the statistical power available by adjusting for relevant covariates measured at pre. Covariate adjustment for the pre score on each outcome measure will substantially increase statistical power[158]. For example, if pre and post scores correlate at r=.65 (which seems reasonable based on the test-retest reliability estimates for our outcome measures and preliminary pre to post data from R01 MH079943), then power of 0.80 to detect a mean difference of d=.50 is available with a sample size of approximately 36 per group. Our projected sample size of 35 per group maps closely onto this estimate. To increase statistical power further, we will covary **[**pre attention bias scores**]** and examine other characteristics measured at pre (e.g., age, gender, diagnosis, R01 MH079943 condition, past treatment, current medication use, number of comorbid diagnoses) to determine whether they differ across conditions. If they vary across conditions, we will include them as covariates which will reduce the "noise" in the estimated treatment effect and thereby increase power. In general, the robust methods of analysis will be as powerful or more powerful than the least squares regression methods, so the power estimates above apply, conservatively, to the robust methods of analysis as well.

[For a test of moderation in Aim 3 that uses multiple regression, we will have power > .80 for a two tailed test (α=0.05) of the interaction term based on an N of 70 for a medium effect size (f^2=.15).**]** For tests of mediation in Aim 3 that use bivariate or multiple regression, we will have power of about 0.80 for a two tailed test (α=0.05) of a bivariate coefficient based on an N of 70 (i.e., pooling treatment & control groups) for an effect size that represents 10% explained variance, which seems reasonable for a mediator that is assumed to be relatively influential. For a multiple regression with two predictors, a two tailed test (α=0.05), and an overall squared R of 0.20, the power is 0.80 to detect a coefficient that represents 10% unique explained variance. These levels of power seem reasonable given the preliminary nature of this facet of the research and the presumed role of the moderator and mediators based on substantive considerations.