Neurally Targeted Cognitive Training to Augment CBT Outcomes in Pediatric Anxiety

NCT04157296

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Principal Investigator*: Yanni Liu, Ph.D.

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.3, 4.1, 5.5, 8.1.3	An fMRI may be completed after 4 weeks of at home CCT for CBT+CCT group.	Completing 4 weeks of at-home CCT is important as demonstrated by previous Akili studies, and may collect brain indexes of cognitive control capacity.
8.1.3	NIH toolbox assessment/Millisecond cognitive test/BRIEF2 questionnaire may be administered at fMRI scan following completion of 4 weeks of at home CCT for the CBT+CCT group.	NIH toolbox assessment/Millisecond cognitive test/BRIEF2 questionnaire collect behavioral indexes of cognitive control capacity at same time as MRI.

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

1 CONTENTS

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: Yanni Liu Date: 9/24/2019

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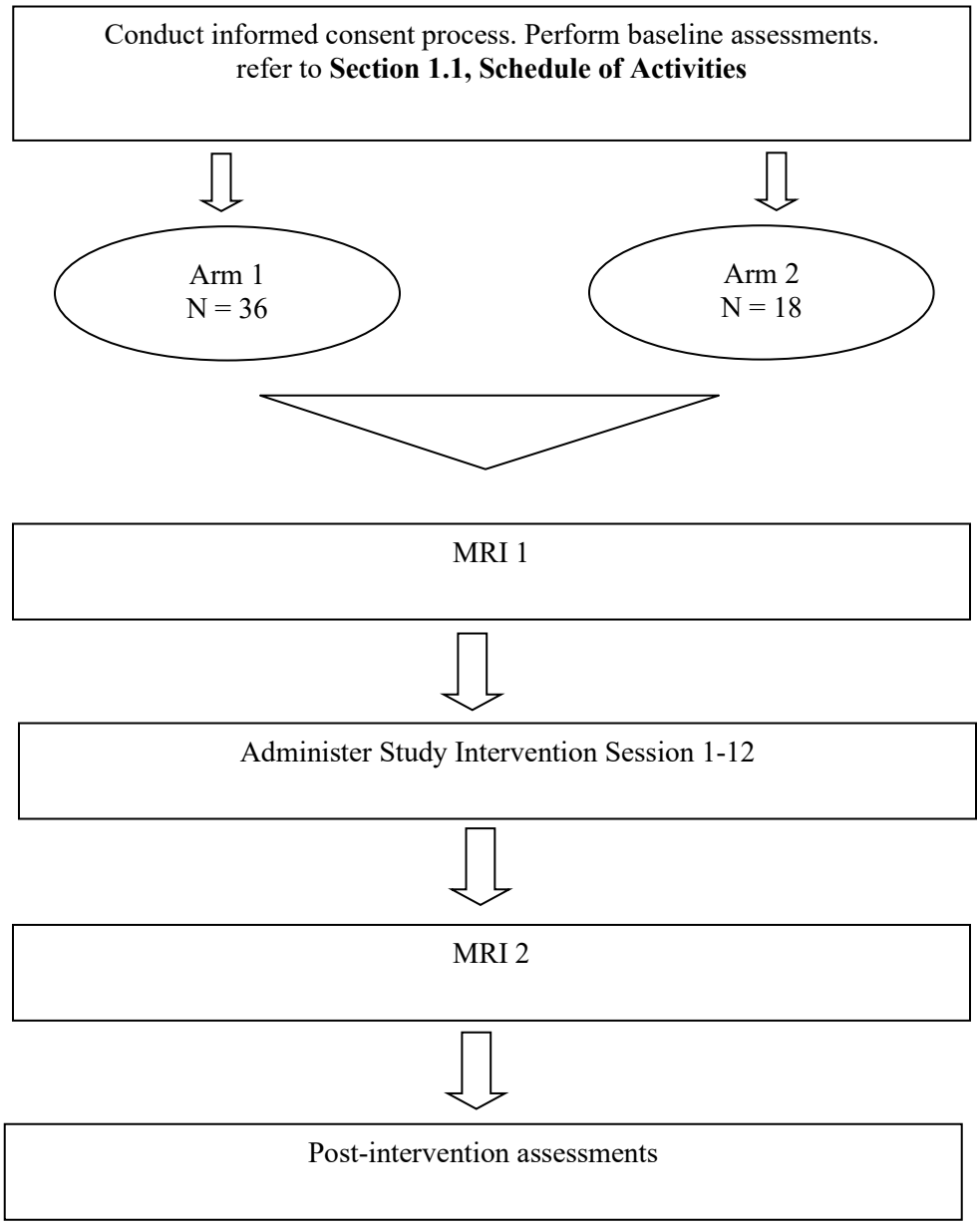
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Neurally Targeted Cognitive Training to Augment CBT Outcomes in Pediatric Anxiety
Grant Number:	MICHR Pathway to Independence AWD003558
Study Description:	Anxious youth (ages 7-17) will be recruited and assigned to cognitive behavioral therapy (CBT) only or computerized cognitive training (CCT) plus CBT groups. Multilevel data (clinical measures of anxiety, behavioral and brain indexes of cognitive control capacity) will be collected before and after treatment, to examine the extent to which CBT+CCT may engage brain and behavior targets related to cognitive control, and reduce anxiety symptoms.
Objectives*:	Primary Objective: Examine whether CBT+CCT will further engage the task control network (TCN). Secondary Objectives: (1) Examine whether CBT+CCT will further improve cognitive control capacity; (2) Examine whether CCT will augment the CBT outcome
Endpoints*:	Primary Endpoint: Brain activation and connectivity in the task-control network Secondary Endpoints: (1) Behavioral performance in cognitive interference task and tasks testing cognitive control capacity such as in the NIH toolbox; (2) Anxiety severity and treatment response rate
Study Population:	Anxious youth (AY) between the ages of 7 to 17.99
Phase* or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	University of Michigan
Description of Study Intervention/Experimental Manipulation:	Participants will be recruited to either CBT or CBT+CCT. In the CBT group, participants will be offered cognitive behavioral therapy (CBT), about one hour per week for up to 12 weeks with a therapist targeting anxiety symptoms; in the CBT+CCT group, participants will be offered additional cognitive training (about half an hour) before each of the CBT session for up to 12 weeks. They may also receive up to 4 weeks of at home CCT which may be completed for up to two weeks immediately prior to beginning CBT and up to the first four weeks of CBT (~30 minutes x 5 days per week).
Study Duration*:	1 year
Participant Duration:	4- 6 months

1.2 SCHEMA

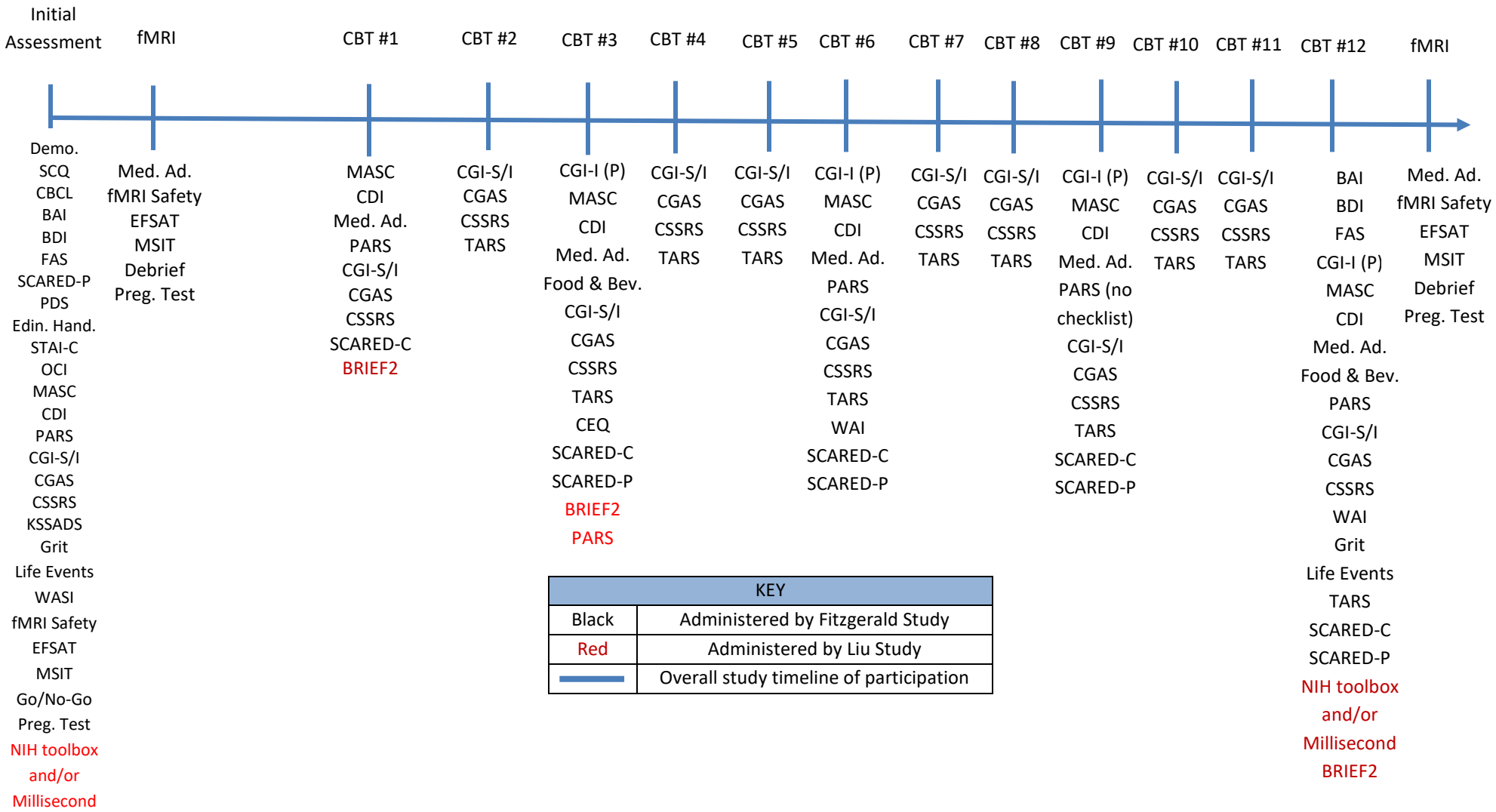
Flow Diagram


Conduct informed consent process. Perform baseline assessments.
refer to **Section 1.1, Schedule of Activities**
Arm 1
N = 36
Arm 2
N = 18
MRI 1
Administer Study Intervention Session 1-12
MRI 2
Post-intervention assessments

1.3 SCHEDULE OF ACTIVITIES

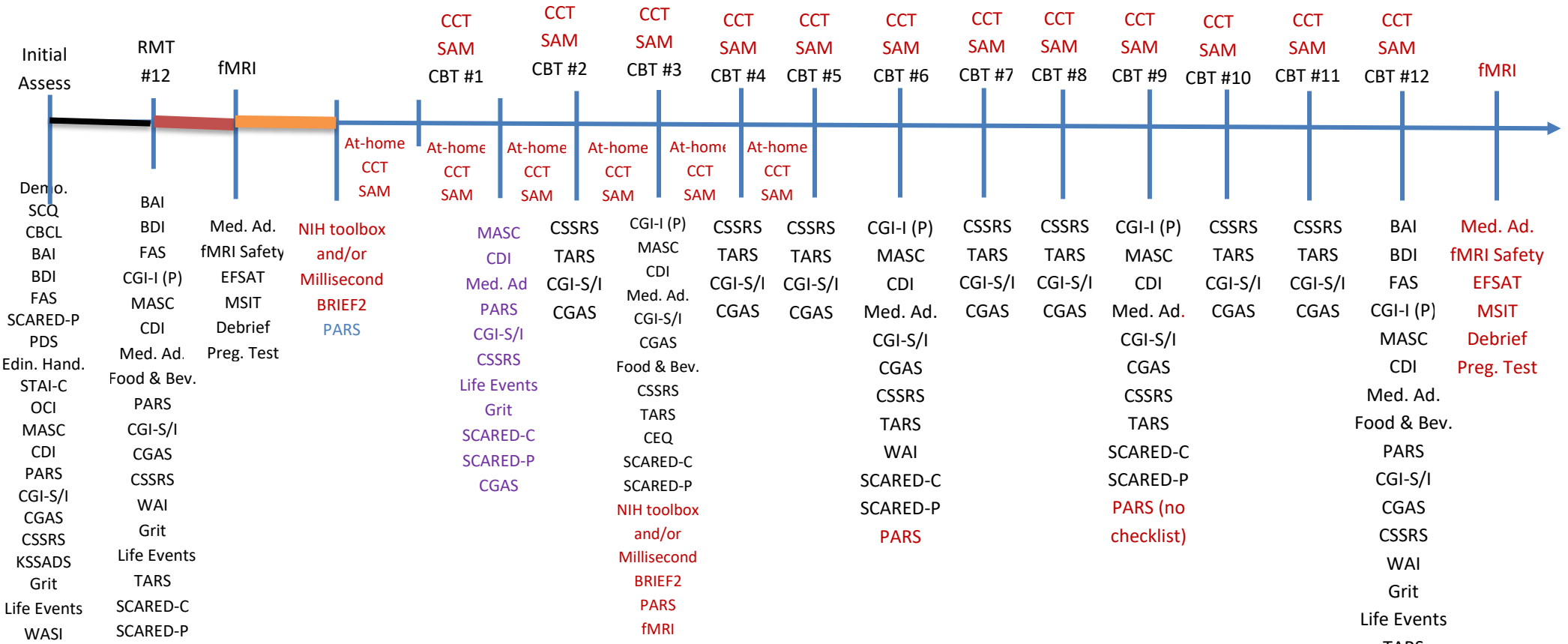
The following assessments and study activities may be done at each time point. For NIH Toolbox and PARS assessments, some variability in administration may occur based on subject's schedule. All assessments completed as part of Dr. Fitzgerald's study *Dimensional Brain Behavior Predictors of CBT Outcomes in Pediatric Anxiety (HUM00118950)* will not be repeated for this protocol and previously collected data will be used. At P.I. discretion, participants may also not be required to complete an fMRI.

CBT-Only Timeline of Events (Primary Arm, Fitzgerald HUM00118950)



KEY	
Black	Administered by Fitzgerald Study
Red	Administered by Liu Study
▬	Overall study timeline of participation

CBT+CCT Timeline of Events (Primary Arm, Liu HUM00169730)



KEY	
Black	Administered by Fitzgerald Study
Red	Administered by Liu Study
Blue	Administered by Liu Study if more than about 6 weeks since collected at RMT #12
Purple	Administered by Fitzgerald Study if >3 weeks since collected at RMT #12
	Overall study timeline of participation
	RMT course of treatment
	Time between RMT #12 and fMRI #2
	Time between fMRI #2 and beginning at-home CCT

2 INTRODUCTION

2.1 STUDY RATIONALE

Clinically significant anxiety is the most common mental health disorder in early life, affecting 33% of youth by adolescence (Merikangas et al., 2010); if not treated effectively, anxiety can impair function at school, at home and with friends, and increase risk for psychopathology in later life. Cognitive behavioral therapy (CBT) is the first-line treatment for childhood anxiety, but response is heterogeneous, with 40%-60% of anxious youth continuing to experience impairment from symptoms after treatment (Walkup et al., 2008). Anxiety has been associated with deficits in capacity for cognitive control, which enables directed attention to regulate behavior and emotion. Poor CBT response may relate to disruptions of brain processes supporting cognitive control, hindering the ability to cognitively restructure and expose oneself to feared situations, as CBT requires. Promoting cognitive control, through activating associated neural circuits, may facilitate ability to engage in CBT and pave the way for greater benefit from treatment.

Cognitive control is mediated by a network of superior parietal, lateral and medial prefrontal cortex (i.e., task-control network, TCN) (Menon, 2011) and impaired function in this network characterizes anxious compared to healthy youth. Specifically, we have shown hypo-activity of lateral prefrontal cortex during cognitive interference in patients with pediatric anxiety disorders compared to healthy youth (Fitzgerald et al., 2013); it has also been reported that hypo-connectivity within the task control network may contribute to the development of anxiety (Geiger, Domschke, Ipser, Hattingh, Baldwin, Lochner, Stein, 2015). Moreover, our preliminary CBT treatment data suggests that an increase in superior parietal cortex activity during cognitive interference associates with a decrease in anxiety severity (Liu, Morrison, Hanna, Phan, Monk, Fitzgerald, 2019). These neuroimaging findings from our lab align with an accumulating body of evidence that impaired cognitive control capacity, indexed by performance on cognitively demanding tasks, associates with increased anxiety symptoms across children and adolescents (Han, Helm, Iucha, Zahn-Waxler, and Hastings, Klimes-Dougan, 2016; Hopkins, Lavigne, Gouze, LeBailly, and Bryant, 2013; Muris, van der Pennen, Sigmond, and Mayer, 2008). Given these findings, behavioral capacity for cognitive control and underlying TCN function may serve as targets for improving anxiety through augmentation of CBT effect. However, no available treatments for anxiety specifically target cognitive control. **We propose that computerized cognitive training (CCT), through increasing cognitive control capacity and engaging the TCN, may augment CBT response**. Recent work has shown CCT increased cognitive control capacity in children and adults with neurocognitive deficits (Marusic et al., 2018; Boivin, Nakasujja, Sikorskii, Opoka, and Giordani, 2016; Giordani et al., 2015); other researchers found CCT improved school-administered test performance through priming cognitive control function before tests (Wexler et al., 2016). We believe that children who may not respond to CBT alone, will benefit from CBT *plus* CCT, based on the central hypothesis that CCT, delivered immediately prior to CBT sessions, will exercise task-control network and thereby facilitate the receipt of CBT.

2.2 BACKGROUND

2.2.1 ANXIETY IS PREVALENT IN CHILDREN, CAN CAUSE LIFE-LONG IMPAIRMENT AND BETTER TREATMENTS ARE NEEDED.

Anxiety emerges early in life and affects 33% of youth by adolescence (Merikangas et al., 2010). If not treated, anxious symptoms often persist and increase risk of depression, school dropout, substance abuse and even suicide in adolescence and adulthood (Achenbach, Howell, McConaughy, and Stanger, 1995; Zimmermann, Wittchen, Hofler, Pfister, Kessler, and Lieb, 2003; Pine, Cohen, Gurley, Brook, and Ma, 1998). CBT is the most widely used therapy to treat childhood anxiety, but less than 60% of affected youth respond and many of those treated continue to experience residual symptoms (Walkup et al., 2008). Treatment failure may occur when children are unable to mobilize cognitive control to persevere in fearful situations, particularly since the most "active ingredient" of CBT is repeated exposure to situations that may *seem* scary, but do not involve actual danger (e.g., starting a new school) (Peris et al., 2015). Increasing cognitive control may be an important target for augmenting CBT outcome and reducing anxiety in youth.

2.2.2 ANXIETY IS ASSOCIATED WITH DEFICITS IN COGNITIVE CONTROL, AND ITS UNDERLYING TASK-CONTROL NETWORK.

Cognitive control is the ability to direct attention and cognitive resources to regulate behavior and emotion. Behavioral and neuropsychological data have consistently shown increased anxiety symptoms associated with lower levels of cognitive control in children and adolescents (Han, Helm, Iucha, Zahn-Waxler, Hastings, and Klimes-Dougan, 2016; Hopkins, Lavigne, Gouze, LeBailly, and Bryant, 2013; Muris, van der Pennen, Sigmond, and Mayer, 2008). At the neural level, cognitive control can be measured by functional magnetic resonance imaging (fMRI) in a network encompassing superior parietal, dorsal lateral (dlPFC) and medial (mPFC) prefrontal cortex (Menon, 2011). This network is called the task-control network (TCN), activated during a variety of cognitive tasks. In adults, increased anxiety has been associated with reduced dlPFC activation in cognitive tasks with or without threat stimuli in community samples (Bishop, Duncan, Brett, and Lawrence, 2004; Bishop, 2009), interpreted as impoverished recruitment of TCN in regulating attention for high-anxious individuals, even when threat is absent. Our own study of pediatric anxiety disorders, showed dlPFC hypoactivation in error processing during a cognitive interference task in pediatric anxiety, suggesting insufficient engagement of TCN may contribute to a deficient capacity for adjusting repetitive anxious thoughts and behavior during an error (Fitzgerald et al., 2013). Given these findings, increasing TCN functions may help to reduce the anxiety symptoms.

2.2.3 NEURALLY TARGETED COGNITIVE TRAINING TO INCREASE COGNITIVE CONTROL MAY AUGMENT TREATMENT OUTCOME IN PEDIATRIC ANXIETY.

Increased TCN engagement has been reported to associate with decreased symptoms after CBT in pediatric obsessive-compulsive disorder (OCD) (Huyser, Veltman, Wolters, de Haan, and Boer, 2011), and we are currently conducting an R01 funded study to determine whether changes in TCN function associate with CBT outcome in pediatric patients with non-OCD anxiety disorders. Our preliminary data suggests that, as with OCD, increased TCN activation (specifically in superior parietal cortex) associates with decreased anxiety from pre- to post-CBT in young patients (Liu, Morrison, Hanna, Phan, Monk, and Fitzgerald, 2019). Given the evidence linking cognitive control deficits to anxiety and linking TCN engagement to CBT response, the immediate next step is to determine whether strategies to boost TCN engagement might facilitate CBT response in young patients.

Cognitive training has been applied to a variety of populations across different ages, but it is most effective for children when the brain is highly plastic (Diamond and Ling, 2015). In a recent study, computerized cognitive training (CCT) games designed to engage TCN showed improved school-administered test performance in second-grade children through priming cognitive control function before tests, and increased academic achievement by enhancing cognitive control over a training period of four months (Wexler et al., 2016). Emerging work from our lab shows cognitive training in clinically anxious preschoolers, delivered through training camp, has reduced anxiety symptoms, increased cognitive control and increased TCN engagement (Hruschak et al., 2019). Guided by these converging lines of evidence, in this proposal we will examine whether cognitive training will prime and engage the TCN to augment the CBT outcome and reduce childhood anxiety.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 RISK ASSOCIATED WITH SCREENING AND ASSESSMENTS:

1) Risk of boredom or fatigue (likely, not serious). Participants may become tired or bored during the assessments and computerized cognitive testing.

   To minimize risk: Participants will be allowed breaks in between testing sections.

2) Loss of confidentiality around sensitive information (rare, not serious).

   To minimize risk: All subjects are assigned research numbers, and all research information collected is linked to the subject only by this number. Great care is taken to remove all identifying information from research records. A single tracking file contains links to the research records and subject codes. Recruitment tracking files are kept only for the duration of recruitment. Paper records are kept in locked file drawers in a locked room, to which only authorized research personnel have access. Paper records with identifying information (consent form, payment records) are kept in locked file cabinets, physically separate from the research records. Computer records with identifying information are kept on secure, password protected servers. Staff members are trained to scrupulously protect the confidentiality of sensitive information, and take care to limit the printing of documents with identifying information and to avoid unnecessary discussion of subject names. Screening forms for subjects who do not qualify for the study will be destroyed, except for anonymous information unlinkable to the subjects (such as age, gender, and education).

   However, if a subject may become eligible in the near future, e.g. they need to wait 1 month after a recent medication change, we will retain certain records so as not to repeat the assessments, with the assent of the potential participant.

3) Risk of worsening of anxiety symptoms.

   To minimize this risk: Clinically trained study staff will be alert for the emergence of worsening anxiety symptoms, as well as suicidal thoughts amongst participants. Weekly assessments will monitor symptoms, including suicidality, as part of Dimensional Brain Behavior Predictors of CBT Outcomes in Pediatric Anxiety (HUM00118950). In the event of symptom worsening, consultation with Dr. Fitzgerald may lead to withdrawing the subject so they can receive treatment outside the protocol.

4) Suicide protocol

   For Dimensional Brain Behavior Predictors of CBT Outcomes in Pediatric Anxiety (HUM00118950), the suicide protocol begins with assessment of suicidal thoughts, plans, intentions and behaviors with the C-SSRS (at screening and at each treatment session). If assessment uncovers suicidal plans or intentions or recent behaviors, emergency evaluation will occur, and an appropriate plan of action will be followed, e. g. referral to psychiatric emergency room. Dr. Fitzgerald will be contacted and will join the decision making process about how to manage the suicidal thoughts or behaviors. See "DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION" below for criteria about when we will withdraw a patient from the study for suicidality.

2.3.1.2 RISKS ASSOCIATED WITH FMRI SCANNING:

1) Discomfort or anxiety (occasional, not serious). There is a minor risk of discomfort or anxiety/panic from being in the confined space of the MRI scanner.

   To minimize risk: The risks of discomfort and anxiety will be minimized by custom pads and pillows to make the subject as comfortable as possible. The subject is allowed to communicate with the machine operator via an intercom and may trigger an audible alarm at any time. Before the subject rolls into the bore of the magnetic, he or she is always reminded that they are free to stop the study at any time if they become uncomfortable.

2) Peripheral nerve stimulation (rare, not serious). Fast imaging sequences, such as those employed in this study, have the potential to induce peripheral nerve stimulation (PNS). PNS can be described as a light touching sensation on the skin surface and may cause mild discomfort, but is not harmful to the subject.

   To minimize risk: The MRI machine is operated within FDA guidelines so the potential for inducing PNS is low.

3) Slight dizziness, light-headedness or nausea (rare, not serious). Sometimes subjects report these symptoms during or immediately after the scanning session.

   To minimize risk: If a subject feels light-headed, we will have them get up from the scanner bed very slowly, resting with feet dangling for several seconds or more before attempting to stand.

4) Magnetic resonance image will reveal a minor or significant lesion in the brain, e. g. a tumor, previously unknown to the subject, and requiring additional follow-up. (rare, serious).

   To minimize risk: Subjects will be made aware of the risk of learning about an anomalous finding in the study that might require further evaluation with a clinical MRI study. We will also inform the subject that many abnormalities will not be picked up in this study, since the scanning sequences we use are not sensitive to many forms of brain pathology. However, in the event that we find something that is very obvious, such as a large tumor, Dr. Liu or Dr. Fitzgerald will personally inform the subject by phone call, or in person. No diagnosis will be offered, but the P.I. will recommend that the subject pursue a follow-up study with their primary care clinician.

5) Hearing damage - from loud, vibrating noises made by the scanner (very rare, serious).

   To minimize risk: all subjects will wear earplugs and/or earphones throughout the procedure, which attenuate high decibel sounds, but still enable a subject to hear the intercom and respond to questions from the investigator while they are in the scanner.

6) Injury (very rare, serious). Because the strong electromagnetic fields can move metal objects and cause heating, there is a risk that loose objects (jewelry, keys) outside the body could be accelerated by the magnetic field, striking and injuring a subject. There is also a risk that the magnetic fields could disturb a metal fragment in the body, interfere with an implanted device, such as a pacemaker or neurostimulator, or cause metal (including foil-backed medication patches) on or in the body to heat up, causing harm.

   To minimize risk: The MRI suite is kept clear of all objects that could be picked up by the magnetic field, and all subjects complete a comprehensive MRI screening form prior to entering the scanner, which is reviewed by the MRI technologist (trained in clinical MRI) before scanning begins.

2.3.2 KNOWN POTENTIAL BENEFITS

For all patients, there is a potential benefit from the CBT treatment; for the CBT+CCT group, there is a potential additional benefit from the cognitive training.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The proposed experiment should reveal important information about the nature of mental processes involved in the pathophysiology of anxiety. It is expected that this information will indirectly lead to the development of better forms of treatment for this disorder. There is no other, safer or less-invasive means of answering the questions posed by the experiment described above. Strategy has been made to minimize each risk, respectively.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Examine whether CBT+CCT will further engage the TCN.	Brain activation and connectivity in the task-control network	We anticipate that CBT+CCT relative to CBT alone will result in greater engagement of the TCN.
Secondary		
Examine whether CCT will further improve cognitive control capacity	Behavioral performance in cognitive interference task and tasks testing cognitive control capacity in the NIH toolbox	We anticipate that CBT+CCT relative to CBT alone will result in increased cognitive control capacity.
Examine whether CCT will augment the CBT outcome.	Anxiety severity and treatment response rate	We anticipate that CBT+CCT relative to CBT alone will lead to more reduction on anxiety severity and higher treatment response rate
Tertiary/Exploratory		
Explore the associations between changes in TCN, behavioral and CBT outcome	Change of TCN activation, change of behavior, change of CBT outcome	Not applicable

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesized that computerized cognitive training (CCT), through engaging the task-control network and increasing cognitive control capacity, may augment the CBT response. In this study, eighteen clinically anxious children ages 7 to 17 will be recruited and assigned to CBT+CCT for up to 12 weeks; thirty-six age- and gender-matched anxious children will be recruited and assigned to CBT only for up to 12 weeks. Before and after therapy, all participants may complete structured clinical assessment of anxiety, a computerized evaluation of cognitive control capacity (e.g., NIH Toolbox; Zelazo, Anderson, Richler, Wallner-Allen, and Beaumont, 2013) and MRI scanning during a cognitive interference task and resting-state to assess brain activation and functional connectivity in the TCN. However, at P.I. discretion, participants may not be required to complete an fMRI. Participants may also complete structured clinical assessment of anxiety, computerized evaluation of cognitive control capacity, and MRI scanning during therapy.

This study will be incorporated into an ongoing fMRI study (HUM00118950, PI Fitzgerald) investigating dimensional brain-behavioral predictors of CBT outcomes in pediatric anxiety. In the parent R01 (HUM00118950), 210 youths (7-17 years) with impairing anxiety are being recruited and randomized 2:1 to receive 12-week CBT or a non-active control therapy, “relaxation and mentorship therapy” (RMT);

multilevel data including fMRI, DTI and clinical measures are collected before and after treatment. As part of the parent study, RMT completers are offered study CBT (at no cost), without additional scanning.

Study activities that may be completed remotely (i.e., Millisecond behavioral assessment, clinical measures and assessments, CCT, and CBT through the parent study) will be conducted via an encrypted HIPAA-compliant video conferencing platform (e.g., BlueJeans, Zoom), phone call, and/or Millisecond/Qualtrics links. It will be standard practice to conduct as many procedures remotely as possible to better protect subject(s)/parent(s) and staff against the risk of COVID-19. However, when remote visits are not possible (e.g., NIH toolbox behavioral assessments, fMRI), in-person visits will be allowed and the study will follow all U-M safety guidelines for entering and being in U-M buildings (e.g., COVID screenings, PPE, social distancing, etc.).

Eighteen RMT subjects in the parent study will be recruited to our CBT+CCT group, and thirty-six age- and gender-matched CBT subjects in the parent study will be recruited to our CBT control group. The proposed study may add:

1) For all fifty-four subjects recruited from parent study:
    a. NIH Toolbox and/or Millisecond behavioral assessment before and after the CBT course of therapy as well as once before the RMT course of treatment and once at about 3 weeks of CBT and another time if completing the fMRI following 4 weeks of at home CCT for the CBT+CCT group
    b. BRIEF2 questionnaire before, after, and at about week 3 of the CBT course of treatment, as well as once before the RMT course of treatment and at the fMRI following 4 weeks of at home CCT for the CBT+CCT group
    c. Clinical assessment of anxiety at week 3 of CBT treatment.
2) For patients originally randomized to RMT in the parent study who wish to enroll in the current study during their Optional CBT participation:
    a. augmentation of the CBT offered by the parent R01 study with CCT games delivered prior to each CBT session (CBT+CCT) along with a brief survey (the Self-Assessment Manikin) they may be asked to complete before and after CCT
    b. fMRI following 4 weeks of at home CCT, and fMRI following CBT+CCT completion
    c. Clinical measures and assessments before and throughout the course of CBT treatment
    d. at home CCT (~30 min/day), 5x per week, for up to 4 weeks, for up to two weeks before starting CBT and for up to 4 weeks after starting CBT, along with a brief survey (the Self-Assessment Manikin) they may complete before and after CCT

Data analyses will compare pre- and post-CBT data from the parent study with pre- and post-CBT+CCT data collected for the proposed study. These data will include NIH Toolbox and/or Millisecond measures of behavioral capacity for cognitive control; multi-modal assessment of TCN with fMRI, resting state and DTI; and, detailed assessment of anxiety symptoms using both clinician-interview and self-report. Pre- to post-therapy change in anxiety severity (clinician-measured) will serve as the primary outcome variable; regression analyses will be used to test for associations of anxiety change with changes in brain-behavioral indices of cognitive control following CBT compared to CBT+CCT. To increase clinical relevance of study results, analyses will also consider responder status, a common end point for clinical trials.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We hypothesize that CCT, delivered immediately prior to CBT sessions, will exercise task-control network and thereby facilitate the receipt of CBT. So in the control group, age- and gender-matched anxious youth received CBT only; their behavioral, brain and clinical data will serve as comparison, to evaluate whether CCT will augment the CBT effect.

The aims of this project are to:

(1) Examine whether CBT+CCT will further engage the TCN. We hypothesize that (a) both groups will have increased activation and functional connectivity in task-control network after therapy vs. before therapy; however, (b) the increase will be greater in CBT+CCT vs. CBT only group.

(2) Examine whether CBT+CCT will further improve cognitive control capacity. We hypothesize that (a) both groups will have improved behavioral performance on the conflict interference task and tasks testing cognitive control capacity included in the NIH Toolbox; however, (b) these effects will be greater in CBT+CCT vs. CBT group.

(3) Examine whether CCT will augment the CBT outcome. We hypothesize that relative to CBT group, anxiety severity will be reduced more and treatment response rate will be higher in CBT+CCT group.

(4) Explore the associations between changes in TCN, behavioral and CBT outcome. We hypothesize that increased TCN activation and functional connectivity, and improved behavioral performance on cognitive control tests will correlate with better treatment outcome in both groups.

4.3 JUSTIFICATION FOR INTERVENTION

The CBT intervention will consist of up to 12 weekly 60 minute sessions of the manualized therapy, adapted from the Coping Cat program, for the treatment of pediatric anxiety disorders. The CBT+CCT intervention will consist of ~30 minutes of CCT games prior to each CBT session, to engage cognitive control capacity prior to receipt of CBT. They may also receive up to 4 weeks of at home CCT to complete for up to two weeks before starting CBT and up to 4 weeks after starting CBT (~30 minutes per session). If assigned, this may be done at home 5 days per week. The CCT games will be designed to target focused attention, response inhibition, working memory and multiple simultaneous attention to constitute a general executive function training, and activate neural systems associated with executive function/cognitive control. Difficulty of the games will be titrated individually and by session to avoid boredom and progressively activate the functional systems underlying cognitive control, which we hypothesize will optimize participant's ability to engage in, and thus benefit from, in the CBT intervention. For both groups, participants will have to complete at least 8 intervention sessions.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, at least 8 intervention sessions of CBT (for CBT group) or CCT+CBT (for CBT+CCT group), pre and post fMRI scans, NIH toolbox and/or Millisecond assessments, and final independent evaluation. At P.I. discretion, participants may be considered to have completed the study even if they have not completed all of these activities.

5 STUDY POPULATION

Fifty-four clinically anxious youth will be studied (36 CBT, 18 CBT+CCT). All subjects will be between 7 and 17.99 years old at the time of initial consent. Subjects will be recruited from an existing R01 study at the University of Michigan (HUM00118950, PI Fitzgerald*)*, also referred to as parent study. The R01 parent study, at year 4 of the five-year period, has successfully recruited and retained over 100 anxious youth with moderate or greater levels of symptoms, e.g., PARS score > 10 and CGAS score < 60; it will recruit over 100 additional anxious youth randomized 2:1 to CBT and RMT through 05/31/2021. To date, nearly all participants randomized to RMT in the parent R01 study have chosen to continue the CBT sessions after RMT completion; thus we expect 44 youth to be eligible for the CBT+CCT, providing ample opportunity to recruit 36 CBT and 18 CBT+CCT over the one year period of the proposed study. Based on the retention rates of therapy (96.2%) and fMRI motion (89%) in the parent R01, we expect to have 32 CBT-treated and 14 CBT+CCT-treated anxiety youth with usable pre- and post-treatment data.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet the following criteria:

1. Parent or guardian willing to give informed consent, and children willing to give informed assent to participate in the study.
2. Must be actively enrolled and maintain eligibility in HUM00118950 to participate in the study.

5.2 EXCLUSION CRITERIA

An individual who meets the following criteria will be excluded from participation in this study:

1. Color blindness

5.3 LIFESTYLE CONSIDERATIONS

Patients will not be taking any psychotropic medications for 4 weeks prior to beginning the study with the exception of stimulants for ADHD. In such cases, patients will be required to maintain a stable dose of stimulant medication for 2 weeks prior to fMRI #1.

During the study, we will permit medication for 1) insomnia, e.g. trazodone, temazepam, melatonin, or non-benzodiazepine GABA-selective agents (at standard dosages) for as long as needed, and 2) agitation, e. g. lorazepam, clonazepam for up to 14 days. Initiation of allowable “rescue” medications will be considered AEs and data will be collected on them during the scheduled assessments and recorded in the Case Report Forms. NOTE: Initiation of other medications, prior to the end of the study, may be recommended by the study psychiatrist or requested by the patient. In this event, the patient will be withdrawn from the study and referred to clinical care.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful treatment of a previous affective disorder, and the lifting of physical activity restrictions previously in place. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited from anxious youth in parent study. All participants will be approached to consent to the current protocol after they consent to the parent study. Age and gender match will be attempted. The following **recruitment and retention strategy** is specified in the parent study:

Recruitment will be from the outpatient psychiatry programs at the University of Michigan Health System, from multi-media advertisements (UMClinicalStudies.org, passive advertisements on social media sites and Craigslist Ann Arbor, Google Adword campaigns, print and electronic media, radio ads and flyers) and by referral from community clinicians. The recruitment process is designed to limit interference with clinical care and assure the informed participation of patient subjects. By obtaining a waiver of consent for screening purposes, recruitment is facilitated by pre-review of computer-based medical records to identify potential research participants who have contacted the Department of Psychiatry. In addition, we will scan UMClinicalStudies.org, the UM registry of individuals who are interested in participating in clinical research. Some of this screening will occur through the structured recruitment activities of University of Michigan's psychiatric department—for example, best practices alert. Paid advertising (e.g., radio, newspaper ads, utilizing Survey Research Organization (SRO)) may also be employed, if needed to reach recruitment goals.

The study sample will represent the normal to abnormal range of anxiety severity when considered across AY and LAY subjects. Thus, we will use a stratified recruitment strategy in which phone screens include administration of the DSM-Oriented Scale for Anxiety from the Child Behavior Checklist (CBCL) to enhance sampling across this range. Using this data, the study coordinator will track recruitment and enrollment of subjects with "high" (i.e., clinically significant anxiety, t-score >60), mid- (t-score 50-60) and low- (t-score <50) levels of symptom severity. Note that stratification of high, middle and low anxiety severity is intended only to facilitate recruitment across the full range of symptom severity. By contrast, all analyses will use linear regression, considering anxiety scores as continuous measures.

Clinic recruitment of pediatric subjects with Anxiety: We may recruit from three sources: 1) patients seeking treatment at the UM's Child and Adolescent Anxiety Program (CAAP, directed by PI Fitzgerald); 2) primary pediatric UM outpatient clinics and community clinics; and 3) the community. Recruitment from this wide demographic will enable targeted enrollment of 210 CBT-eligible AY as well as 70 LAY with minimal to no anxiety. On average per year, we will enroll 47 subjects with high- to mid-range anxiety (i.e., CBT-eligible AY) and 16 with low-range anxiety. To achieve this goal, we will capitalize on high pediatric anxiety patient flow through CAAP (300/year) and an advertising campaign (Facebook, Twitter, Google AdWords, targeted flyering) modeled after Dr. Fitzgerald's ongoing recruitment efforts for her R01 study of CBT for OCD (successfully enrolling 4 patients per month).

Dr. Fitzgerald is a member of the UM Psychiatry clinical staff and co-directs the Child Anxiety Clinic. Her role in the clinic primarily involves supervision of trainees who deliver direct clinical care to child anxiety patients, although Dr. Fitzgerald does see a small number of anxiety patients herself. If a dual role exists in which she is the treating clinician-principal investigator of a patient-potential subject, she will disclose this dual role and possible conflict of interest to them. Moreover, she will emphasize that participation is voluntary, that they do not have to participate, and the decision not to participate will not affect their care, now or in the future. A study coordinator (not Dr. Fitzgerald) will reiterate these points as part of the formal consent process. Clinicians outside of the study team may be asked to inquire if patients are interested in research participation, and if so, for permission for study team members to contact them. In addition, should a physician discuss with the study team a patient they feel likely eligible for the study, a study team member will outreach to the patient to offer information on the study with the clinician's permission to do so.

Recruitment of clinic scheduled or wait-listed pediatric subjects with Anxiety: We will contact scheduled or wait-listed patients who look like they might have anxiety based on information from their electronic medical record. Then we will contact them by phone, [SECURE] email or MiChart patient portal, announcing our affiliation with the U-M Psychiatry Anxiety Disorders clinic, and ask them if they would be interested in hearing about a research study involving treatment. If they are, we will conduct our phone screen.

Recruitment of participants not being seen in the Department of Psychiatry: Through community advertisements, we will also screen, assess and enroll participants who are not followed in the Department of Psychiatry. Initial screening will occur in a telephone interview. In many cases, we will request records from outside providers to assess eligibility, using standard release of information forms. For potential participants who appear eligible, a face-to-face initial assessment will be scheduled. A similar process will occur with control subjects who respond to advertisements, although medical records will generally not be requested

Minimizing the potential for coercion of patients to participate: Because members of the research team are involved in clinical care and research, there is the potential that some patients of the study team may be recruited. It will be made clear to all potential subjects that participation is entirely optional and not a part of regular treatment. The bulk of the recruitment process will occur with the study coordinator, who does not treat patients in any of the clinical venues where recruitment will occur. Overall, the research team is experienced in clinical research and very mindful of the conflict between the dual roles of clinician and researcher. They firmly believe that the safety and desires of the patient take precedence over any research protocol, and work hard to assure their patients that research participation is not required for treatment. In the case where a patient of a study team member is recruited, the consent process and signature on the informed consent document and will be obtained by the study coordinator.

Payment of participants

Participants will receive payments for the initial assessment through the parent study. For the current protocol, they will receive $10 for each behavioral NIH toolbox and/or Millisecond assessment and BRIEF2 questionnaire before and after treatment as well as $10 each for the NIH toolbox and/or Millisecond assessment and BRIEF2 completed before the RMT course of treatment, and around week 3 of CBT for CBT+CCT group as well as when completing the fMRI after completing 4 weeks of at home CCT. Participants in the CBT-only group will receive $10 for the clinical assessment of anxiety and BRIEF2 they may complete at week 3 of CBT. Participants in the CBT+CCT group will receive $50 per fMRI scan (i.e., up to 3 scans - 1 before, 1 during, and 1 after CBT+CCT may be completed if the subject has not participated in the parent study; up to 2 scans may be completed if the subject has participated in the parent study and already received a pre-CBT+CCT scan). Participants in CBT+CCT group will also receive $15 for each CBT+CCT session (up to 12 sessions), $10 for each week of at home CCT training they may complete for two weeks before beginning CBT and during the first 4 weeks of CBT, if they complete at least 4 of the 5 daily trainings. If it is requested for a participant to come back for additional interviews or additional practice sessions in the scanner, we will offer the participant $15 for these visits as well. Additional $50 payment(s) will be provided if they are asked to come in again due to any possible technical difficulties with the MRI scanner (but not for repeated scans where participants choose to abort scan and try again at a later date). The parent/guardian will receive the incentive. Payment for all participants will be made in a single payment at the completion of their participation in the study.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Cognitive behavioral therapy: The CBT intervention is administered per the protocol of the parent study. It will consist of up to 12 weekly 60-minute sessions of the Coping Cat (ages 7-13) or Cat Project (ages 14-17) manualized programs that have demonstrated efficacy for the treatment of pediatric anxiety disorders (Kendall and Hedtke, 2006; Beidas, Benjamin, Puleo, Edmunds and Kendall, 2010). Session content includes: building rapport, identifying anxious feelings/somatic responses and relaxation skills (Sessions 1-2); identifying and challenging anxious thoughts, problem-solving, and self-evaluation/reward (i.e., cognitive restructuring, Sessions 3-5); and, progressive exposure to anxiety provoking situations (sessions 6-12). Parenting content is incorporated into two sessions prior to the initiation of cognitive restructuring and exposure. On some occasions, it may not be clinically appropriate to include a parent in the sessions. This will be determined on an as-needed basis through clinical consensus meeting. Recent research shows that cognitive restructuring and exposure (but not relaxation training, RT) are the "active ingredients" of Coping Cat CBT. Thus, the Cat protocols have been adjusted for the current trial with RT condensed into 2 sessions rather than being delivered over 3-4 sessions as in CAMS). This will maintain fidelity to Coping Cat content, while reducing the increased likelihood of attrition associated with longer treatment protocols. Delivery of CBT intervention over the course of up to 12 (rather than 16) sessions is intended to a) maintain fidelity to Coping Cat content and closely mimic its delivery in CAMS (outcomes assessed at week 12) and b) minimize boredom and the potential effect on anxiety that could be associated with a longer duration control treatment.

Computerized cognitive training: The CCT games are designed to target executive functions such as focused attention, response inhibition, working memory and multiple simultaneous attention to constitute a general executive function training, and activate neural systems associated with executive function/cognitive control. Difficulty of the games will be titrated individually and by session to avoid boredom and progressively activate the functional systems underlying cognitive control, which we hypothesize will optimize participant's ability to engage in, and thus benefit from, the CBT intervention. These types of games are modelled after existing programs (Brain Powered Games, Giordani et al., 2015; Akili Interactive, Anguera, Gunning and Arean, 2017; Brain HQ www.brainhq.com) that help to improve executive functions and are well-tolerated by participants of varying ages.

6.1.2 ADMINISTRATION AND/OR DOSING

Cognitive behavioral therapy: CBT treatment will be delivered over the course of up to 12 weeks including 60 minutes of face-to-face meeting at the clinical setting. CBT may be delivered via remote video conference if social distancing policies prohibit this type of in-person interaction (e.g., COVID-19). If a remote video conference is not possible, therapy sessions may be scheduled as in-clinic remote visits in the Rachel Upjohn Building.
Computerized cognitive training: The CCT intervention will consist of ~30 minutes of CCT games that may be completed prior to CBT sessions 4-12, to engage cognitive control capacity prior to receipt of CBT. These sessions of CCT may be completed at home if social distancing policies prohibit this type of in-person study activity (e.g., COVID-19). Participants may also receive up to four weeks of at home CCT

(~30 min/day), 5 days per week, for up to two weeks prior to beginning CBT and up to 4 weeks after beginning the 12-week CBT protocol. Participants may complete CCT on an iPad provided by Akili Interactive, or they may complete CCT by downloading the application onto their own Akili-compatible personal device.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The CBT treatments will be delivered by masters or PhD level therapists trained in these modalities. Supervision will be provided by an expert in the study of CBT in anxiety disorders. Each therapist will treat patients who receive CBT and CBT+CCT. An evaluator, blind to treatment assignment, will assess the patients with the scales described below. The preference will be assessment in person, but, if required, assessment by telephone may be done. In-house form will be used by clinical psychology supervisor to rate therapist adherence to treatment manuals.

Video/audio recording: We are seeking permission to have some assessments and CBT sessions recorded to obtain reliability/fidelity measures. Not all participants will be recorded; this will be determined by needs of the study. The recordings will be done mainly for the K-SADS and/or PARS assessments and therapy sessions.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

There is no randomization in this pilot study. Participants are recruited from the parent study where assignment to the two treatment arms (CBT vs RMT) is stratified based on age and gender, using block randomization to ensure a 2:1 ratio of participants in CBT vs. RMT group (HUM00118950). In this study, we will recruit all possible participants in the RMT group in the parent study to participate in CBT+CCT, and recruit age- and gender-matched participants from CBT group. Efforts will be made to keep therapists blinded to participant group (i.e., CBT+CCT vs. OPT CBT).

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Assessments (or subsets of questions from these measures) will mainly be completed as part of the parent study and utilized for analysis in this protocol. At each time point, assessments may include:

Assessments Completed by Independent Evaluator– Weeks 0, 1, 3, 6, 9 & 12

a) PARS
b) Clinical Global Impressions-Severity and Improvement Scale (CGI); (*Guy and Bonato 1970*).

Assessments by Clinician – Weeks 1-12

a) CGI (S/I)
b) Treatment Adherence Rating Scale (TARS) A therapist-administered instrument to assess patient completion of assigned CBT or RMT homework.
c) C-SSRS (since last visit)
d) CGAS

Assessments Completed by Subjects – Weeks 1-12

a) Medication Adherence (also all fMRIs)
b) MASC – week 1, 3, 6, 912
c) CDI– week 1, 3, 6, 9, 12
d) CGI-I (parent report) – week 3, 6, 9, 12.
e) FAS (parent report) – week 12
f) BDI (parent report) – week 12
g) BAI (parent report) – week 12
h) Beverage and Food Questionnaire – week 3 and 12
i) GRIT Scale – week 12
j) SCARED (parent) – week 1, 3, 6, 9, 12
k) SCARED (child) – week 1, 3, 6, 9, 12
l) Life Events Checklist – week 12

Other Assessments

a) CGAS (Independent Evaluator, Week 0 and 12)
b) Credibility/Expectancy Questionnaire (CEQ; Subject, week 3) – A 6-item scale rating the patient's expectations for treatment success (Devilly & Borkovec, 2000)
c) Working Alliance Inventory (WAI; Subject, Weeks 6 & 12) -- A 12-item scale rating the patient's feelings about their relationship with the therapist (Horvath & Greenberg, 1989) – approximately 5 minutes.
d) Randomization "guess" form to be completed by Independent Evaluator at week 12 to assess blindedness (CBT-only).
e) Self-Assessment Manikin (SAM; Subject, may be completed before and after each session of CCT) – A 3-item scale rating the patient's feelings of pleasure, arousal, and dominance (Bradley & Lang, 1994) – approximately 2 minutes.
f) Behavior Rating Inventory of Executive Function, Second Edition (BRIEF2; Parent, pre-RMT course of treatment, pre- and post-CBT course of treatment as well as week 3 of CBT, and when completing fMRI after completion of 4 weeks at home CCT for the CBT+CCT group) – at 63-item parent-report scale assessing executive function of the patient (Gioia, Isquith, Guy, & Kenworthy, 2015) – approximately 10-15 minutes.

6.5 CONCOMITANT THERAPY

Patients will not be taking any psychotropic medications for 4 weeks prior to beginning the study with the exception of stimulants for ADHD. In such cases, patients will be required to maintain a stable dose of stimulant medication for 2 weeks prior to fMRI #1. Dr. Fitzgerald will manage patient stimulant medications for the duration of the study, meeting with medicated patients 2-4 times, as needed, during the up to12-week period of study therapy.

6.5.1 RESCUE THERAPY

To address participant crises or unusual needs/circumstances that arise, additional treatment sessions (i.e., ASAP sessions) can be provided to address these needs and facilitate participant retention. A maximum of 2 additional off-protocol sessions is allowed for each phase of the study (CBT or CBT+CCT). These could include psychotherapy or methods outside of prescribed protocol (e.g. motivational interviewing). Additionally, clinical assessment for urgent crisis may be offered and will be scheduled at therapist's behest, participant request or as needed to help reduce dropout. Participants who require more than this limited intervention will be withdrawn and clinical care recommended.

During the study, we will permit medication for 1) insomnia, e.g. trazodone, temazepam, melatonin, or non-benzodiazepine GABA-selective agents (at standard dosages) for as long as needed, and 2) agitation, e.g. lorazepam, clonazepam for up to 14 days. The study psychiatrist will manage initiation and ongoing treatment with these allowable medications during the study. Initiation of allowable "rescue" medications will be considered AEs and data will be collected on them during the scheduled assessments and recorded in the Case Report Forms. NOTE: Initiation of other medications, prior to the end of the study, may be recommended by the study psychiatrist or requested by the patient. In this event, the patient will be withdrawn from the study and referred to clinical care.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

CBT or CBT+CCT will be stopped in the event of any of the following:

- Suicidal thoughts with specific plans and intentions (Endorse item 4 or 5 on the C-SSRS and the judgment of the clinician that risk of suicide is high and imminent)
- Suicide behaviors during the study period (assessed by C-SSRS)
- Hospitalization required for any psychiatric symptoms
- Symptom worsening: > 25% increased PARS score (referenced to baseline) for more than 2 assessments in 1 week

Reasons for discontinuation will be documented, and all outcome assessments will proceed as scheduled, if possible.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, i.e. inability or unwillingness to complete study intervention or outcome assessments
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The study is suspended or canceled

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and

receive the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for four scheduled visits and study staff are unable to contact the participant after at least 3 attempts for each visit.

The following actions must be taken if a participant fails to return for a required study visit:

- The experimenter will attempt to contact the participant, reschedule the missed visit within four weeks, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the experimenter designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and emails). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

8.1.1 SCREENING AND INITIAL ASSESSMENTS

Participants will complete questionnaires in order to collect basic health and demographics information. The initial assessment is completed as part of the parent study and will occur in 1 – 3 sessions, depending upon subject convenience. Data collected from this assessment will be used for analysis for this protocol. The following evaluations and assessment tools (or subsets of questions from these measures) may be used to determine eligibility for the study and gather baseline information:

1) Demographics and medical history form. An in-house form for basic demographic information, medical and family history completed by study team or as self-report.
2) Social Communications Questionnaire (SCQ) (Rutter et al, 2003). A 40-item parent report to rule out diagnosis of Autism Spectrum Disorder.
3) Child Behavior Checklist (CBCL), (Achenbach and Rescorla 2001). A 126-item parent-completed checklist which provides DSM-IV oriented subscales for Depressive Problems, Anxiety Problems and Attention Deficit/Hyperactivity Problems (Inattention and Hyperactivity/Impulsivity subscales). Approximately 10 minutes.
4) Beck Anxiety Inventory (BAI; Beck & Steer, 1993). This 21-item self-report survey measures severity of anxiety symptoms in adolescents and adults. Approximately 5 minutes.
5) Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996). 21-item self-report measure assessing adult depression. Approximately 5 minutes.
6) Family Accommodation Scale (FAS; Lebowitz et al., 2012): 13-item parent report measure assessing family accommodation of child symptoms. Approximately 5 minutes.

7) Screen for Child Anxiety Related Disorders (SCARED Parent and Child Versions): Developed by Boris Birmaher, M.D., Suneeta Khetarpal, M.D., Marlane Cully, M.Ed., David Brent, M.D., and Sandra McKenzie, Ph.D., Western Psychiatric Institute and Clinic, University of Pittsburgh (October, 1995). The SCARED consists of 41 items and 5 factors that parallel the DSM-IV classification of anxiety disorders.
8) Tanner stage will be determined by self-report on the Pubertal Development Scale (PDS) (Petersen, Crockett et al. 1998).
9) Edinburgh Handedness inventory (Oldfield, 1971). A 15-item self-report of hand use.
10) State-Trait Anxiety Inventory for Children (STAI-C); (Spielberger, 1973). A self-report, 20-item scale on anxiety symptoms (trait only) for child subjects. Approximately 5-10 minutes.
11) Obsessive-Compulsive Inventory (OCI) (Foa, Huppert et al. 2002). An 18-item self-report scale for OC behavior, from normal to pathological. Total scores on this scale range from 0 to 72, with scores above 21 indicating a likely OCD diagnosis. Approximately 10 minutes.
12) Multidimensional Anxiety Scale for Children (MASC); (March, Parker et al. 1997). Self-report assessing anxiety. Approximately 10-15 minutes.
13) Children's Depression Inventory (CDI); (Kovacs, 1992). Self-report, 28 item scale on depressive symptoms. Approximately 5 minutes.
14) Pediatric Anxiety Rating Scale (PARS). A clinician-administered assessment to rate the severity of anxiety symptoms associated with common DSM-V anxiety disorders (social phobia, separation anxiety disorder, and generalized anxiety disorder) in children. Total scores on this scale range from 0 to 30, with scores above 13 indicating clinically meaningful anxiety. Approximately 20–30 minutes.
15) Clinical Global Impressions-Severity and Improvement Scale (CGI-S/I); (Guy and Bonato 1970).
16) Children's Global Assessment Scale (CGAS); (Shaffer, Gould et al. 1983). A single-item scale, administered by the clinician.
17) Columbia Suicide Severity Rating Scale, present/lifetime version (Posner, Oquendo et al. 2007). A clinician-rated scale assessing suicidal ideation and behavior. Approximately 5 min.
18) Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS); (Kaufman, Birmaher et al., 1997). Standard assessment tool to obtain a diagnosis, may include parent interview. Approximately 3-4 hours.
19) Grit Scale: (Duckworth, 2007): 12 item measure. Add up all the points and divide by 12. The maximum score on this scale is 5 (extremely gritty), and the lowest scale on this scale is 1 (not at all gritty).
20) Life Events Checklist: Adapted from Child and Adolescent Survey of Experiences: Child Version (CASE) (Allen and Rapee, 2009). Assessing events people may find bad or upsetting, as well as events people may find good or enjoyable. Approximately 15 minutes.
21) Wechsler Abbreviated Scale of Intelligence (WASI). A short-form administration of two sub-tests of the WAIS (vocabulary and matrix design) to establish IQ. 15 min (can be completed at any time prior to fMRI #2).
22) fMRI Safety Screen form to ensure that there are no contraindications for fMRI. This form is provided by the fMRI lab and is not included within study documentation. The most current version of this screening form will be used at all times to ensure the safety of participants undergoing fMRI.

Electronic data capture:

Subjects may complete the self-report forms described above using Qualtrics or hardcopy forms. Qualtrics is an Application Service Provider (ASP) with a Software-as-a-Service (SaaS) platform for creating and distributing online surveys and related research services. The platform records response data, performs analysis, and reports on the data. All services are online and require no download software; only modern JavaScript-enabled browsers are required (no Java/JVM or Flash). Surveys are usually taken online within

a web browser, with optional SMS surveys and offline methods available for smartphones/tablets. Qualtrics has been approved for the University of Michigan research community, and individual investigators access the web interface through a University of Michigan Qualtrics portal. Subjects may receive a coded link via email which will take them to the required surveys. The emailed link contains no identifiable information about the subjects, and once activated, establishes an https encrypted link with the Qualtrics server. Once completed, each survey is locked so that re-access is not permitted. We can also adapt the process for each subject, e.g. provide access on computers or tablets in the Department of Psychiatry for subjects who do wish or cannot use email. Some subjects may request paper, and, if so, paper forms will be provided.

If desired, subjects can receive the initial assessments either in hard copy or an emailed link ahead of attending their initial assessment to limit their time on site. Subjects will be asked to complete the online Qualtrics survey prior to their initial evaluation. A copy of the consent form will be emailed to the subject, along with a secure web-link to the Qualtrics site or a copy of the consent form included in the hard copy packet. For this, a waiver of documentation of informed consent will be sought. If subjects who complete these online surveys screen out, their Qualtrics data will be deleted. Data will be downloaded from Qualtrics and secondarily stored in a REDCap database to be used for analysis.

Responses entered by subjects will be available to the clinicians working with the patient subjects in the study. Please note that the suicide assessment rating (C-SSRS) is administered by clinicians at every visit. Thus, any potentially dangerous clinical condition will be identified in a timely fashion and acted upon accordingly.

8.1.2 EXPERIMENTAL NEUROCOGNITIVE TASKS

During the initial screening visit, first fMRI, or first day of therapy, participants may be asked to complete an Inhibitory Control Task and NIH toolbox. Participants may also be asked to complete Millisecond.

- **Go/no-go task**: A typical approach to the study of inhibitory control is the use of neuropsychological tasks, such as the "go/no-go" paradigm (Durston, Thomas et al. 2002). This task engages individuals in responding to "go" (target) signals, and occasionally requires them to inhibit the response when a "no-go" (no target) signal occurs. Thus, it measures the ability to inhibit a prepotent tendency to respond. The participant is instructed to respond to target stimuli (e.g., any letter except "X") by pressing a button on a computer/iPad and to make no response to non-target stimuli (e.g, the letter "X"). Both misses and false alarms are used to assess accuracy – a measure of inhibitory control. Reaction times for correct trials are also recorded.

- **The NIH toolbox Cognition Battery of assessments**, if completed, will be administered electronically using an iPad, and may be completed before and after the CBT or CBT+CCT therapy, as well as before the RMT course of therapy, at week 3, and when completing the fMRI following completion of the 4 weeks of at home CCT for CBT+CCT. Tasks may include Flanker inhibitory control and attention, Dimensional Change Card Sort, List Sorting Working Memory Test, and Pattern Comparison Processing Speed Test; these tasks are not specifically trained in CCT to ensure that we measure transfer of training to general cognitive control capacity, rather than practice effect on specific tasks. Composite scores will be used to index cognitive control capacity. Please note that select NIH toolbox tasks may be conducted via HIPAA compliant videoconferencing or screensharing, such as BlueJeans or Zoom, when feasible or necessary (e.g., social distancing restrictions due to COVID-19).

- **The Millisecond cognitive tests** may be administered, before and after the CBT or CBT+CCT therapy as well as before the RMT course of the therapy, at week 3, and when completing the fMRI following completion of the 4 weeks of at home CCT for CBT+CCT. Tasks may include Flanker

inhibitory control and attention or Dimensional Change Card Sort; these tasks are not specifically trained in CCT to ensure that we measure transfer of training to general cognitive control capacity, rather than practice effect on specific tasks. Reaction times and accuracy will be used to index cognitive control capacity. These tasks are sent to participants as a link which can be completed on a personal device (e.g., computer, tablet).

8.1.3 FMRI SCANS

Staff and subjects/parents will follow the fMRI Lab COVID-19 safety guidelines at all times.

Overview: fMRI scans will be performed at two time points for the parent protocol – after the initial assessment and prior to the onset of the first course of treatment (~0 - 14 days prior for anxious participants), and after the completion of treatment (~0 - 30 days after the last therapy session. For the current protocol, an additional scan may be performed following completion of the 4 weeks of at home CCT and at the end of CBT+CCT. If more than about 6 weeks have elapsed since their second scan through the parent protocol, a repeat scan may be obtained prior to the onset of CBT+CCT. Immediately prior to the fMRI session, we will review the MRI protocol, repeat screening for contra-indications to MRI and have subjects remove all objects from their person that could be disturbed by the magnetic fields. They will then undergo the fMRI session (approximately 1-1.5 hours for setup and acquisition). The fMRI methods described below will be the same for each of the scans participants will undergo. Should a participant wish to receive an image of their brain, one will be provided. Please note that, at P.I. discretion, participants may not be required to complete an fMRI.

Assessments prior to each fMRI scan:
1) Review of fMRI safety form (copy to fMRI lab)
2) Urine pregnancy test for women who endorse possibility of pregnancy.

Placement in the Scanner:
When we position a subject in the scanner, head movement will be minimized through: (a) instructions to the participant; and (b) packing the head inside the head coil with a system of foam padding and pillows that we have found is well-tolerated by the participants, yet limits movement. Extra care will be taken to insure that the participant's head is positioned as straight as possible since that eases the task of identifying landmarks used in positioning slices to be acquired in the fMRI scans. A mirror or MR-compatible goggle system projects the computer display output into the bore of the scanner. Stimuli are controlled and responses recorded either by E-Prime (PST, Inc., Pittsburgh, PA) or similar lab software. Participants will wear a response claw on their hands with buttons in order to make button-press responses during cognitive tasks. The stimulus-presentation and response-collection systems have been tested to insure that no artifacts are introduced and that there has not been an increase in the image-level noise. The goggle system may contain an eye-tracking camera, which can permit the monitoring and possible analysis of eye movements during the scan. In addition, MR-compatible earphones may be used and physiological sensors may be attached. These sensors consist of a strain gauge, or strap that goes around the torso, to measure respiration, and plastic finger cuff, to measure heart rate by plethysmography (although latter may not be used if it is redundant with pulse oximeter). These non-invasive sensors are FDA-approved components of the scanner, and the fMRI laboratory has begun to incorporate the physiological information into the acquisition sequences in order to improve image reconstruction. Because this is an area of data analysis that remains under development, we may not employ these sensors in all scans. Once in the scanner, subjects can communicate via intercom with the technician running the scanner in the control room. A window separates the control room from scanner room, which is sealed off from the outside by a light vacuum seal. In addition to the intercom system, subjects are given a squeeze bulb. They are informed that should they need to exit

the scanner immediately or gain the attention of the technicians, they can trigger an alarm in the control room by squeezing the bulb.

Scan Acquisition:
Scanning will occur on a 3.0 T GE 750 scanner at the University of Michigan fMRI Laboratory. The scanning session is described below. While scanning parameters may change, power-monitoring software on the scanner will ensure total energy delivered to the subject will remain within FDA guidelines. Specifically, the specific absorption rate (SAR) will not be greater than: 1) 4 W/kg averaged over the whole body for any period of 15 minutes; 2) 3 W/kg averaged over the head for any period of 10 minutes; 3) 8 W/kg in any gram of tissue in the head or torso; 4) 12 W/kg in any gram of tissue in the extremities, for any period of 5 minutes. Also, in order to keep the time in the scanner to a reasonable length, some non-essential acquisitions may be dropped.

T2w 3-plane localizing images will be acquired followed by a 3D T1w MPRAGE image with 1.0-mm isotropic voxels (176 slices, FOV=256 mm, FA=8°, TI=1060 ms, TR=2500 ms, and TE=1.9 ms). Next, a 3D T2w image (3D CUBE) will be acquired with 1.0-mm isotropic voxels (176 slices, FOV=256 mm, TR=3200 ms, and TE=60 ms, and ETL=140). Prospective motion correction (PROMO) will be enabled in both T1w and T2w structural scans to reduce the motion artifacts. Multiband DTI images will be acquired with 96 gradient directions (including 6 for b=500s/mm2, 15 for b=1000s/mm2, 15 for b=2000s/mm2, and 60 for b=3000s/mm2) and 6 T2w (b=0) images. This DTI sequence uses a multiband acceleration factor of 3, with no inplane acceleration (1.7-mm isotropic voxels, 81 slices, FOV=240 mm, FA=77°, TR=4100 ms, TE=82 ms). Functional multiband EPI T2*-weighted images will be acquired for the fMRI task (below) and for two 5-minute eyes-open-with fixation resting-state sequences. Task performance, motion, and eye closure will be monitored and recorded by a trained RA throughout the session. These images will use a multiband acceleration factor of 6, with no in-plane acceleration (2.4-mm isotropic voxels, 60 slices, FOV=216 mm, FA=52°, TR=800 ms, TE=30 ms).
In the event of technical difficulties with the fMRI scanner, subjects may be asked to complete additional fMRI sessions.

Experimental tasks which may be completed at each MRI:

- fMRI Task 1 – Emotional Faces Shifting Attention Task: The EF-SAT is a validated, effective probe of AT and CC-AT processing, previously reported from our lab. In this block-related design, participants view two 'types' of stimuli on each trial aggregated in blocks according to task instruction (a screen that precedes each block): 1) 'Match Faces' – a trio of faces and instructions to match one of the two faces (bottom) that expressed the same emotion as the target face flanked by a trio of shapes in the same field of view; 2) 'Match Shapes' – same instructions but with a trio of shapes flanked by a trio of faces in the same field of view. The target and congruent probe face display one of four expressions (angry, fearful, happy, neutral) and the other (incongruent) probe face always display a neutral (or happy if the target is neutral) expression. Faces will be selected from Gur/Upenn stimulus set. The Match Faces instruction requires subjects to attend to angry and fearful (relative to happy and neutral) facial expressions to probe AT, while the Match Shapes instruction requires subjects to ignore emotional faces in order to attend to shapes to assess CC-AT. EF-SAT data collection occurs over approximately 12 minutes.
- fMRI Task 2 – Multisource Interference Task: The MSIT probes cognitive control (CC) by eliciting interference between task-relevant and prepotent, but task-irrelevant response tendencies. It was originally developed to activate dACC but also engages vlPFC and dlPFC, including in pediatric samples. The MSIT requires subjects to identify the unique number among three digits, "1," "2," or "3" (e.g., for "311," the target is "3") by making a key press with one of three fingers, corresponding to the ordinal value of the target number: "1" → index finger, "2" → middle finger,

"3" ring finger. Interference occurs when the target number position is incongruent with its ordinal value (e.g., "3" presented at the 1st position) and with different, flanking numbers (e.g., "11"). In the control condition, the target number is always presented in a position compatible with its ordinal value (e.g., "1" presented in the first position) and flanked by zeroes (e.g., "100"). Our event-related version of the MSIT allows for separation of fMRI BOLD signal associated with correct incongruent, correct congruent and error trials. We have extensive experience with this task, as demonstrated by our preliminary data, and have shown that it reliably activates the dACC, as well as vlPFC in children and adolescents with and without anxiety symptoms. MSIT data collection occurs over approximately 15 minutes.

Post-scan debriefing: Subjects may answer several questions about how much they were frustrated/flustered with the task. Subject will also be asked to complete a Medication Adherence.

8.2 SAFETY ASSESSMENTS

- **fMRI Safety Screen form** in order to ensure that there are no contraindications for fMRI. This form is provided by the fMRI lab and is not included within study documentation. The most current version of this screening form will be used at all times to ensure the safety of participants undergoing fMRI.
- **Columbia Suicide Severity Rating Scale**, present/lifetime version (Posner, Oquendo et al. 2007). A clinician-rated scale assessing suicidal ideation and behavior.
- **Pediatric Anxiety Rating Scale (PARS)**. A clinician-administered assessment to rate the severity of anxiety symptoms associated with common DSM-V anxiety disorders (social phobia, separation anxiety disorder, and generalized anxiety disorder) in children. Total scores on this scale range from 0 to 30, with scores above 13 indicating clinically meaningful anxiety. Approximately 20–30 minutes. Symptom worsening: > 25% increased PARS score (referenced to baseline) for more than 2 assessments in 1 week

Any safety-related assessments (C-SSRS administered through the parent study, fMRI screening) or primary outcome measure (PARS– independent assessor may administer at weeks 0, 1, 3, 6, 9, and 12; missed week 9 will not be reported as a deviation) that are missed for a study visit/week of therapy a participant completed will be reported to the IRB as a protocol deviation. For the independent assessments, we will accept a window of ± 1 week. For CBT+CCT group, the 3-week, 6-week, and 9-week PARS assessments are completed under this protocol only, and a PARS assessment may be completed under this protocol prior to beginning at-home CCT treatment if there have been more than about 6 weeks since the RMT week 12 PARS. For the CBT-only group, the 3-week PARS assessment is completed under this protocol only. However, for the other assessments, missing or late assessments will not be reported as protocol deviations unless they constitute > 10% of the total assessments. In order to accommodate inevitable scheduling conflicts, holidays, etc., participants will be allowed to miss up to 4 sessions of therapy, and the sessions must be completed within 16 weeks. These allowances should affect neither the scientific integrity nor the safety monitoring provisions of the protocol.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

Any unfavorable or unintended symptom, sign, or disease associated with a medical treatment or procedure that may or may not be related to the treatment or procedure. Adverse events can be related to the treatment or to the disorder being treated (e.g. anxiety), as well as to a concurrent disorder or treatment (e.g. MDD or its treatment), or they could be entirely unrelated to any of these (e.g., motor vehicle accident).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol-defined surveillance
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse/overdose or cancer.

All SAEs will be:

- recorded on the appropriate SAE Report Form
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician.

The study will comply with IRB reporting requirements and guidelines for SAEs.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All Aes will have their relationship to study intervention or study participation assessed with a level of specificity appropriate to the study design.
All adverse events (Aes) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "potentially related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in treating anxiety will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All Aes, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All Aes occurring while on study will be documented appropriately regardless of relationship. All Aes will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for Aes characterized as intermittent.

A study team member will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious Aes) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. At each treatment session subjects will be questioned about putative Aes. Information to be collected includes event description, time of onset, clinician's assessment of severity (mild, moderate, or severe), relationship to study (assessed by the study PI and clinical team), expected versus unexpected, local versus systemic, and time of resolution/stabilization of the event. All Aes occurring while in the study will be documented appropriately regardless of relationship. All Aes will be followed to adequate resolution. Adverse event reporting will occur on the standard IRBMED timetable.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH/MICHR and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The only anticipated abnormal laboratory values will be the incidental findings from the MRI scan.

Discovery of a finding: If an incidental finding on a scan is detected by fMRI technologists and/or study personnel, the finding will be reviewed by a neuroradiologist. Any potentially serious abnormalities will be brought to the immediate attention of the PI and the clinical team.

Informing the subject: PI will then review the finding with the neuroradiologist before bringing it to the attention of the subject. The intention here is to control the circumstances by which the subject is informed of the anomaly, making sure that PI Liu is the person who talks to the subject, can answer questions based on the neuroradiologist's reading of the scan, and can gauge the emotional reaction of the subject to the news. The subject will be informed by Dr. Liu personally, either through a phone call or a face-to-face

meeting. While a face-to-face meeting is preferred, this may not be immediately convenient for the subject, and we must weigh the relative benefits of the more personal setting versus anxiety engendered by anticipating a meeting to discuss something the subject did not expect to hear.

Informing the subject's health care provider: Arrangements will be made to provide a summary of the finding to the subject's personal physician, with the patient's permission. In most cases, a follow-up, clinical MRI will be recommended, unless the consulting neuroradiologist advises an alternate course.

8.3.8 REPORTING OF PREGNANCY

We will inform the consenting parents of minor participants at the beginning of the process that we will respect the confidentiality of our teenage participants. It is important for us to let teenage participants know that they can be honest about sensitive topics without fear of reprisal from their parents. However, participants will also be informed about limits to confidentiality. If we learn that a subject has potential to harm him or herself, or another individual, we will break confidentiality and take steps to prevent harm. Similarly, any evidence of potential child abuse will be reported to Child Protective Services.

8.3.9 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.10 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (Ups) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, Ups will be reported using the following timeline:

- Ups that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor/funding agency within 10 days of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to study sponsor/funding agency within 30 days of the investigator becoming aware of the problem
- All Ups should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s): Change in Brain activation and connectivity in the task-control network (TCN)

  We hypothesize that **(a)** both groups will have increased activation and functional connectivity in task-control network after therapy vs. before therapy; however, **(b)** the increase will be greater in CBT+CCT vs. CBT only group. Baseline and week 12 assessment will evaluate pre- to post-CBT changes in brain activation and function connectivity in the task-control network including fronto-parietal and cingulo-opercular regions mediating cognitive control. Functional activation and connectivity of these brain regions are assessed using a conflict interference computer task performed during MRI scanning.

- Secondary Endpoint(s):

(1) Change in behavioral performance on the conflict interference task and tasks testing cognitive control capacity included in the NIH Toolbox: We hypothesize that **(a)** both groups will have improved behavioral performance on the conflict interference task and tasks testing cognitive control capacity included in the NIH Toolbox; however, **(b)** these effects will be greater in CBT+CCT vs. CBT group. This will be evaluated using two measures of the same construct at baseline and week 12. Pre- to post-CBT changes in the behavioral performance in a conflict interference task will be collected, as well as composite score from tasks included in the NIH toolbox.

(2) Change in Pediatric Anxiety Rating Score (PARS): We hypothesize that relative to CBT group, anxiety severity will be reduced more and treatment response rate will be higher in CBT+CCT group. This will be evaluated at baseline and week 12 through the PARS, a 50 question interview-based tool used to assess for the presence and severity of anxiety symptoms in children and adolescents utilizing parental and youth input to guide clinician ratings. The total scores on this scale range from 0 to 30, with scores above 13 indicating clinically meaningful anxiety.

9.2 SAMPLE SIZE DETERMINATION

No pilot data is currently available to enable a power analysis, but the proposed study will generate effect sizes for an R01 or R61/R33 application that will build from this pilot study.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Data will be analyzed using statistics software such as MATLAB, SPSS and R software. For descriptive statistics, means with standard deviation and range will be computed for continuous data (all brain and behavioral data and some of the clinical data). In general, statistical significance is reported based on $p<0.05$ two-tailed; for the fMRI data, $p<0.005$ uncorrected or $p<0.05$ corrected for family-wise error or false discovery rate where applicable.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

We hypothesize that CCT will further increase TCN activation and connectivity. The hypothesis will be tested using 2 (within-subject: pre vs. post) x 2 (between-subject: CBT vs. CBT+CCT) repeated-measures ANOVAs on brain activation and connectivity in TCN.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

(1) We hypothesize that CCT will increase cognitive control capacity (measured by NIH toolbox CC composite scores and behavioral performance on the MSIT task and/or Millisecond scores). The hypothesis will be tested using 2 (within-subject: pre vs. post) x 2 (between-subject: CBT vs. CBT+CCT) repeated-measures ANOVAs on behavioral performance.
(2) Repeated-measure ANOVAs will be conducted to examine effect of CCT on CBT. We hypothesize that anxiety severity (i.e., continuous PARS score) will be reduced more in CBT+CCT group, relative to CBT group. Chi-square tests will be used to test for differences in the ratio of CBT responders: non-responders between CBT+CCT and CBT group. We hypothesize that CBT+CCT will have more responders than the CBT.

9.3.4 TABULATION OF INDIVIDUAL PARTICIPANT DATA

All clinical, behavioral and neuroimaging measures will be listed by time point when applicable.

9.3.5 EXPLORATORY ANALYSES

Linear regression models will be built to test whether change in cognitive control indices (behavioral, brain activations and functional connectivity) will associate with change on clinical outcomes (PARS scores). The standardized parameter estimates in each model will be examined. Secondary logistic regression will be conducted on CBT responder status.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written or electronic documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The protocol will begin by having the subject (or their parent[s] for adolescent subjects) provide assent and written informed consent. In the case that social distancing policies prohibit this type of in-person study activity (e.g., during COVID-19), informed consent will be obtained at the beginning of a remote visit. This remote visit will include a review of an oral assent script, assent from the minor subject, and signed electronic consent from the subject and their parent/guardian. Electronic informed consent signatures will be collected using SignNow. All procedures will adhere to the IRBMED Guidance for use of SignNow for Electronic Informed Consent Procedures. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subject/parents. Consent forms (written in non-technical language, understandable by the youngest subject to be enrolled in the study) describing in detail the study interventions/products, study procedures, and risks will be given to the subject/parent. Participants may also be presented with a visual timeline of the tasks that may be involved in participating in this study, during the consenting process or at another time during the study, to aid their understanding of the process. Upon reviewing the document, one of the investigators (or their designee) will explain the research study to the subject/parent and answer any questions that may arise. The subject/parent will sign the informed consent document prior to any procedures being done specifically for the study. Adolescent subjects will be asked to sign in the assent box on the main consent. The subjects may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subjects will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study. As some of the patients may also be treated by members of the study team, we will take special care to emphasize the voluntary nature of participation. NOTE: older teens may become legal adults (i.e., reach the age of 18 years) during the course of the study. If the teen is still actively involved in the study (i.e., data collection ongoing), then a new consent form, signed by the teen, will be obtained. However, if the teen reaches 18 years of age *after* their data collection has been completed, we will *not* re-contact to re-consent. This approach is intended to avoid burdening study participants and their parents.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, funding agency, and regulatory authorities. If the

study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight body.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by investigator, research staff, and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Research team will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

All paper and computer research records will be identified by subject ID number rather than name or other personally identifying information. Paper records are stored in a double-locked environment to which only authorized study team members have access. The link between subject ID and subject name will be kept in a separate password protected database. Consent documents and any other forms with identifying information will be maintained separately from research data files (identified by subject ID only).

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be

traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

The assessments in this protocol will ask participants about sensitive topics, such as mental illness, possible pregnancy and substance use. We will inform the consenting parents of minor participants at the beginning of the process that we will respect the confidentiality of our teenage participants. It is important for us to let teenage participants know that they can be honest about sensitive topics without fear of reprisal from their parents. However, participants will also be informed about limits to confidentiality. If we learn that a subject has potential to harm him or herself, or another individual, we will break confidentiality and take steps to prevent harm. Similarly, any evidence of potential child abuse will be reported to Child Protective Services. Since the assessment will occur along with clinical feedback to the minor participant and parents, we will need to discuss clinical situations that require an intervention, such as substance use disorders and substance use that interferes with treatment. If we become aware of imminent risk of harm to a parent, steps will be taken to ensure safety (e.g. referral to psychiatric emergency services or contacting appropriate authorities).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

The value of this research is significantly enhanced by making the data available for the widest possible use, and because of the rapidly changing world of data analysis, it is impossible to predict what future research will do with data collected for any particular project in the present. By keeping the data indefinitely, it will become available for projects, yet to be determined. These include projects run by the investigators, as well as those outside the institution through data sharing plans or central repositories. Increasingly, the NIH is requiring investigators to include data sharing plans as a part of the overall research plan, in order to maximize the benefit from the research.

When data are transferred to co-investigators and data repositories, de-identification will be performed, removing all HIPAA identifiers from the files. To prevent reconstruction of facial likenesses from structural image datasets, we will blur/obscure/strip the information from the MRI image around the face.

Subjects will be informed in the consent document that the data will be stored and that it may be shared with other investigators, both at the University and outside the University, through central databanks. The risk posed to subjects will be very, very small. Storing the data for an indefinite amount of time will follow strict protocols, outlined above, that will ensure the safety of the data and minimize the risk of accidental disclosure. Data that is shared or uploaded to central databanks will be de-identified and will be effectively anonymized, since investigators using these central databases will not have access to the keys linking

individual subjects to the data. Furthermore, no data will be shared without an agreement by stewards of the central databank to require data use agreements and prevent investigators from even attempting to identify subjects. It is extremely unlikely that an investigator would even be able identify subjects from shared data, without already having access to a subject's identifiers.

We have chosen not to provide an 'opt-out' option in the ICD, which is the practice in some studies collecting genetic information. Having some subjects 'opt out' of data sharing presents data tracking challenges (making sure that a few datasets among many are not to be shared), and introduces a very real risk of accidentally not honoring the desire of a subject to not permit data sharing. The imaging data in this project is different from genetics data, which is also placed in large databanks, because the imaging data is significantly less sensitive and has a far lower likelihood of identification, should somebody try to extract identity from public databanks. For example, the data does not contain information about ancestry, disease risk or genetic 'fingerprints' that can uniquely identify subjects. Therefore, we feel that with this lower risk, it is ethically permissible to not provide an 'opt-out' clause. If subjects object to data sharing, they have the option of not participating in the research. Although our project does provide a potential direct benefit in the form of CBT therapy, this treatment is readily available outside of the research protocol.

In some cases, participants may either be ineligible for the current protocol or be eligible for an additional study protocol. In these cases, if participant has indicated in the consent that they would like to be contacted for future studies, we will share their contact information with other research teams at the University of Michigan for screening purposes, and if eligible, can share some of our data with these investigators to assist in their screening and assessment process (per consent form).

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
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10.1.6 SAFETY OVERSIGHT

The investigators and study team will meet weekly (as close to that as permitted by travel and holidays) to monitor the study activities in order to ensure that the human subject protection, study procedures, administration, and data collection processes are of high quality and meet the appropriate, regulatory guidelines. No regular monitoring by an external monitor is planned.

10.1.7 CLINICAL MONITORING

No additional monitoring is required – the nature, size, and complexity of this study does not require additional safety monitoring to that provided by the IRB.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Research staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy, research staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

PI and research team will review data collection and entry periodically to evaluate compliance with the protocol and for accuracy; PI and investigators responsible for clinical evaluations will participate in routine inter-rater reliability sessions.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff under the supervision of the investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, the original entry will be crossed with a single

line, and initial and date the change. For some assessments, subjects may enter information directly onto a computer, rather than a paper form. Only research ID numbers will link these data with the subjects, and data will be stored in encrypted form on password-protected, secure computers. Systems that are only used to collect data, such as laptop or tablet computers, will also have research files securely deleted after upload to the central database. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (Aes), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Michigan Medicine servers in REDCap and/or statistical datasets. Clinical data will be entered directly from the source documents. Research data will be maintained on password protected computers, on a secure linux cluster maintained in the Psychiatry Affective Neuroimaging Laboratory (PANLab) or on secure UMHS-administered servers. Backup procedures include RAID drives with mirroring, and off-site backup.

10.1.9.2 STUDY RECORDS RETENTION

Files will be stored in a double-locked environment and access-limited under the purview of the PI. All research records will be identified by subject ID; pre-screening records will be scrubbed of identifiers and date shifted to preserve confidentiality.

Study database records will be identified by subject ID, and the link between identifiers and subject ID will be maintained by the PI and lab manager. The link will be destroyed after submission of the NIH final report or publication of the primary outcomes manuscript, whichever is later.

These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or research staff. As a result of deviations, corrective actions will be developed and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the investigator to use continuous vigilance to identify and report deviations. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
2.0	12/06/2019	Changed at-home administration of CCT from first 4 weeks of CBT to two weeks prior to and the two weeks after the first session of CBT. Remove all eligibility criteria except: must be enrolled and maintain eligibility in parent study; must be willing to give informed consent/assent; and must not be color blind. Updated fMRI scan acquisition methods.	Allows for ending of at-home CCT to align with week 3 to minimize overburdening of assessments. As parent study eligibility criteria may change, streamlines process of consenting to the present protocol; CCT graphic have signaling colors, so cannot be color blind. Wanted to provide most up-to-date scan techniques.
3.0	03/10/2020	Allows study to approach participants to consent after have consented to parent study rather than at the same time. Study may administer the SAM before and after each CCT session. Introduces timeline that may be shown to participants.	Allows flexibility around participant and staff schedules. SAM may assess participant feelings of arousal, pleasure, and dominance as related to CCT. Participant timeline may aid understanding of flow of study events.
4.0	05/28/2020	Participants may download the CCT game as an application on their own Akili-compatible personal device. NIH toolbox may be conducted via HIPAA compliant videoconferencing/ screensharing (e.g., BlueJeans or Zoom). Participants may not be asked to complete pre- and/or post-CBT fMRI. Participants may be asked to complete BRIEF2 before and/or after the CBT course of treatment.	Allows for flexibility regarding administration of CCT game rather than restricting to Akili-provided iPads. Allows more flexibility regarding administration of NIH toolbox, rather than only administering in-person. Ensures safety of participants during times of social distancing restrictions. Provides additional measure of cognition/executive functioning.
5.0	07/16/2020	All study activities that may be completed remotely will be, and study activities that must be done in-person will follow U-M safety guidelines. Participants may be asked to complete Millisecond behavioral assessment before and after CBT or CBT+CCT as well as at week 3 for CBT+CCT. CBT may be delivered via remote video-conference. CCT prior to CBT sessions 4-12 may be completed at home. Staff and subjects will follow the fMRI Lab safety guidelines. Participants may be asked to consent remotely, using SignNow to obtain electronic signatures.	Ensures safety of participants and staff during times of social distancing restrictions (e.g., COVID-19). Millisecond provides another platform to measure cognitive control capacity that can be completed remotely.
6.0		CBT+CCT participants may complete NIH toolbox/Millisecond before RMT and be paid $10 for this additional task.	It is preferable to administer NIH toolbox at an in-person visit already required by the parent study to

		CBT+CCT participants may complete BRIEF before RMT as well as at week 3 of CBT. CBT-only participants may complete PARS and BRIEF at week 3 of CBT.	reduce in-person contact, so we are administering NIH toolbox/Millisecond at the mock scan for all participants, pre-randomization. The BRIEF is paired with NIH toolbox/Millisecond collection. To better compare CBT-only and CBT+CCT, want to add PARS and BRIEF at week 3 for CBT-only.
7.0	03/15/2021	All study activities under the current protocol may be administered and at P.I. discretion participants may be considered complete without doing all study activities. The investigator may discontinue a participant's participation in the study if it is suspended or canceled.	Because study funding ends on 07/31/2021 and completion of all study activities takes between 12-28 weeks, some participants enrolled may not be able to complete all activities before funding runs out.
8.0	04/01/2021	At-home CCT may be completed for up to 4 weeks for up to 2 weeks before and up to 4 weeks after the first session of CBT. Participants may be asked to complete each MRI task. PARS may be completed before at-home CCT if more that 6 weeks between RMT week 12 IE and beginning at-home CCT.	Provide more flexibility for completion of 4 weeks of at-home CCT. Trying to keep scan times under 1 hour. Want to get accurate measurement of anxiety symptoms within reasonable amount of time before beginning at-home CCT.

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