HRP-503B – BIOMEDICAL RESEARCH
PROTOCOL (2017-1)

Protocol Title: Brain response associated with parent-based treatment for childhood anxiety disorders

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Version Date: Click or tap here to enter text.

(*If applicable*) **Clinicaltrials.gov Registration #:** NCT03585010

INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.

2. If a section or question does not apply to your research study, type "Not Applicable" underneath.

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SECTION I:

1. Statement of Purpose:

Anxiety disorders impact up to one-third of children, cause tremendous suffering, increase risk for psychiatric and medical morbidity, impair school and social functioning, and cost billions of dollars each year. Data consistently show that child anxiety is characterized by amygdala hyperactivity and deficits in prefrontal control of the amygdala. Emerging data link these disruptions to anxious children's over-reliance on parents for amygdala- medial prefrontal cortex (mPFC) engagement and anxiety reduction. This study aims to test whether an entirely parent-based psychosocial treatment with no child involvement, Supportive Parenting for Anxious Childhood Emotions (SPACE), engages an amygdala-mPFC target in anxious children, lessening child reliance on parents to reduce amygdala reactivity.

Offspring's natural reliance on parents for anxiety reduction is magnified in clinically anxious children. Parents become deeply enmeshed in their child's symptoms through the process of family accommodation, defined as change in parents' behavior to help the child avoid or alleviate anxiety. In clinically anxious children, 90% report depending on parents to reduce their anxiety, and 97% of parents report accommodating their anxious child's symptoms. Anxious children's reliance on parents for anxiety reduction may disrupt the child's ability to independently reduce amygdala reactivity and anxiety.

The study will examine clinically anxious children's amygdala-mPFC response to fear faces when (A) the child's parent is beside them holding their hand during the fMRI scan (Parent-Present), and (B) the child is alone during the scan (Parent-Absent) (within-subjects design). Children with primary anxiety disorder diagnoses will serve as participants. Children will complete Parent-Present and Parent-Absent scans PRE- and POST-SPACE, or PRE- and POST-CBT (Cognitive-behavioral therapy), an established treatment of equal duration and therapist-parent contact.

> **Aim 1:** Demonstrate SPACE lessens children's reliance on parents to reduce amygdala reactivity (i.e., target engagement).
> **Aim 2:** Demonstrate associations between target engagement and anxiety outcomes.
> **Aim 3:** Establish feasibility and acceptability of SPACE, as well as patient satisfaction.

2. Probable Duration of Project: 5 years.

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientificdata.
Anxiety disorders comprise the most prevalent disorders of childhood and adolescence. If not treated successfully, anxiety disorders cause significant short and long-term impairment and pose huge financial and societal costs (Costello, Egger, & Angold, 2005) through factors such as increased school dropout, teenage childbearing, and lost productivity in the workplace (Compton et al., 2004; Greenberg et al., 1999). Despite strong evidence for the efficacy of cognitive-behavior therapy (CBT), up to 50% of children remain symptomatic after treatment

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and many continue to meet diagnostic criteria (Compton et al., 2004; Rapee, Schniering, & Hudson, 2009). A significant proportion of children remain symptomatic even after combined CBT and psychopharmacological treatment (Walkup et al., 2008). Evidence for parental influences in the etiology and maintenance of anxiety in children (Ginsburg, Silverman, & Kurtines, 1995; Hudson & Rapee, 2002; Rapee et al., 2009) has often led to the reasonable assumption that including parents in treatment would enhance effects relative to individual CBT (CBT). However, involvement of parents in the therapeutic process has not always yielded superior effects compared to CBT alone (Bodden et al., 2008; Heyne et al., 2002; Nauta, Scholing, Emmelkamp, & Minderaa, 2001; Spence, 2000; Wood, Piacentini, Southam-Gerow, Chu, & Sigman, 2006), as a number of meta- analytic and comprehensive reviews also have shown (Barmish & Kendall, 2005; Breinholst,

Esbjorn, Reinholdt-Dunne, & Stallard, 2012; Reynolds, Wilson, Austin, & Hooper, 2012; Silverman, Pina, & Viswesvaran, 2008). This study shifts away from past conceptual treatment models, which emphasized training parents in specific behavioral skills (e.g., problem solving) and instead emphasizes the ways in which parents become enmeshed and entangled in their child's anxiety. Family Accommodation (FA)(Calvocoressi et al., 1995) describes the ways in which parents are drawn into their child's anxiety through participation in the child's symptoms and modification of schedules and routines intended to reduce or prevent the anxiety. Children's reliance on parents for protection and regulation of negative affect states can contribute to parental entanglement in these symptom-driven dynamics, which may perpetuate rather than alleviate child anxiety. FA is highly prevalent among parents of anxious children and associated with more severe anxiety symptoms (E. R. Lebowitz et al., 2013). The SPACE Program (Supportive Parenting for Anxious Childhood Emotions) (Eli R. Lebowitz & Omer, 2013) translates the modification of these patterns of enmeshment and entanglement into a series of concrete steps in a manualized treatment protocol aimed to reduce FA and in turn, to bring about improvement in child symptoms.

Cross-species neurobiological evidence indicates that parental presence reduces amygdala reactivity and activates the mPFC to reduce offspring anxiety. In humans we recently demonstrated parental presence increases functional connectivity between their child's mPFC and amygdala, reducing the child's amygdala reactivity and anxiety. In a healthy sample, parental engagement of child amygdala-mPFC connectivity was linked to the child's reliance on parents for help with anxiety. Data from clinically anxious children likewise show parental presence engages child mPFC, and data we collected since our previous submission demonstrate that parental presence reduces amygdala reactivity in clinically anxious children. Parental reduction of child anxiety via amygdala-mPFC circuitry serves an important function for children, but can go awry in childhood anxiety disorders. Evidence suggests that in typically developing children normative changes during frontoamygdala development correspond to a natural shift from child dependence on parents for anxiety reduction toward increased independent engagement of amygdala-mPFC circuitry and reduced amygdala reactivity. This shift toward independent anxiety reduction is impeded in clinically anxious children, whose symptoms are linked to a clear pattern of amygdala hyperactivity and deficits in prefrontal control of the amygdala.

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Neurobiological and clinical research support this model, whereby clinically anxious children are more dependent on parents for amygdala-mPFC engagement and anxiety reduction. Data from clinically anxious children who requested their parent be in the scan room show significant impact of parental presence on the mPFC. Clinically, children with anxiety disorders rely heavily on parents, who are deeply embroiled and enmeshed in their child's anxiety symptoms through the process of family accommodation, defined as changes in parental behavior to help their child to avoid or alleviate anxiety.

4. Research Plan:

The study is a clinical trial involving children with primary anxiety disorders. Children will randomly be assigned to one of two treatment conditions.. One condition is Supportive Parenting for Anxious Childhood Emotions (SPACE) which focuses on reducing family accommodation of child anxiety symptoms. The comparator condition is cognitive-behavioral therapy (CBT) an established and evidence-based treatment for childhood anxiety disorders, of known efficacy.In CBT children will be introduced to and discuss the presenting problem, review treatment rationale and goals, work with the therapist to devise an anxiety hierarchy, and participate in in-session and out-of-session exposure tasks. Additionally, children will be introduced to the cognitive component of treatment by identifying faulty cognitions and generating incompatible self-statements, and exploring alternatives. . Families will be randomly assigned to one of the aforementioned conditions. After initial screening, children will first participate in a pre-treatment assessment (PRE). The PRE assessment will include: a structured interview with child and parent covering anxiety symptoms and related conditions, questionnaires completed by child and parent, a brief parent-child interaction which is video-taped, collection of blood and saliva (see procedures below). Following the PRE assessment, eligible patients will be randomized into either SPACE or CBT and will undergo a neuroimaging scan using fMRI to examine behavioral and brain processes associated with anxiety and fear processing.

In the SPACE treatment condition parents participate in 12 weekly parent-only sessions. In the CBT treatment condition children participate in 12 weekly child-only sessions. Parents of children assigned to CBT will meet with the child's therapist three times over the course of the treatment study, to be kept informed about their child's progress and provide helpful information to the therapist. Sessions can take place in person at the Yale Child Study Center or over secure video-link using the HIPAA approved Zoom software provided by Yale University. Participants will choose whether to have the sessions in person or over zoom and can elect to have some in person and some over Zoom. Youth and parents will be re-assessed after 6 treatment sessions (MID) and after the 12th session (POST). These assessments include the same procedures done at the first assessment, except the MID assessment does not include clinical interviews. After the 12th treatment session children will also undergo a second neuroimaging scan using fMRI. In both treatment conditions participants will be invited back for a follow-up visit 6-months from their initial appointment. At this appointment, these assessment procedures are the same as the MID assessment, but does not include a video-taped interaction or saliva sample.

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Participants who are already enrolled will be invited to electronically complete an optional set of questionnaires related to their experiences during the COVID-19 pandemic (Please see Measures for list of questionnaires). This part of the study is completely optional. The questionnaires will be administered via the HIPAA-secure REDCap platform. Participants will receive $15 when they submit the completed questionnaires.

Assessment Procedures:
Each of these three assessments (PRE, MID, POST) will be conducted in single sessions at our clinic by carefully trained independent evaluators (IE). Each assessment session will include collection of biological samples, behavioral observation, and self-report measures. During the youth interview, the parent will be administered the questionnaires and vice versa. Questionnaires will be completed using iPads via the HIPAA- compliant REDCap/Qualtrics app. In specific circumstances, participants may have the option to complete the questionnaires via HIPAA-compliant REDCap/Qualtrics web link outside of the laboratory. For example, during an initial visit, if a parent and child have each completed their interview and the child has already completed their questionnaires and cognitive testing, a parent may prefer to complete their parent-report questionnaires at home to reduce the visit length and reduce burden on the child.

Measures:
Interviews
Anxiety Disorders Interview Schedule (ADIS (Silverman, Saavedra, & Pina, 2001). The ADIS is the gold standard in assessing the presence and severity of anxiety disorders in youth and will be used to establish the presence of a primary anxiety disorder in potential study participants.
Clinical Global Impressions Scale (CGI (Guy W Editor, 1985). Youth outcome will be assessed on a global level using the 7-point CGI Severity Scale, ranging from 1 (not at all) to 7 (among the most extremely ill patients). The 7-point CGI Improvement Scale ranges from 1 (very much improved) to 7 (very much worse). A CGI Improvement Scale rating of 1 or 2 indicates clinically meaningful improvements in anxiety symptom severity. This measure is included because it is widely used as an indicator or treatment response.
Pediatric Anxiety Rating Scale (PARS (RUPP Anxiety Study Group, 2002). Using information obtained from interviews with parents and youths, an IE scores each of 50 anxiety symptoms as either present or absent during the past week. Endorsed symptoms are rated by the IE on 7 dimensions and each dimension is rated from 0 to 5; total scores range from 0 to 35. The PARS has adequate internal consistency (αs .64-.91) and interrater reliability (ICCs .78-.97), sensitivity to change in treatment studies, and convergent validity (Walkup et al., 2008). This measure is included along with the CGI as recent research has shown it can detect response and remission in child anxiety (Caporino et al., 2012). At the pre assessment, the interviewer who conducts the ADIS – C/P will conduct the CGI and the PARS rating. At post assessments, an IE will complete the ratings.

Child
Self-Reports
The measures listed below will be administered to parents and/or children as indicated in the table.

Parent Completes	Child Completes

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Multidimensional Anxiety Scale for Children	Multidimensional Anxiety Scale for Children
Family Accommodation Scale Anxiety	Family Accommodation Scale Anxiety
Parent Phobia Questionnaire	Child Spider Phobia Questionnaire
Couple's Satisfaction Inventory	Anxiety Sensitivity Index – CASI
Experience in Close Relationships Scale	Kern Attachment Scale
Mood and Feelings Questionnaire – MFQ	Mood and Feelings Questionnaire – MFQ
Child Anxiety Impairment Scale (CAIS)	Child Anxiety Impairment Scale (CAIS)
Client Credibility Questionnaire (CCQ)	Client Credibility Questionnaire (CCQ)
	Difficulties in Emotion Regulation Scale
Affective Reactivity Index	Affective Reactivity Index
Intolerance of Uncertainty Scale	Intolerance of Uncertainty Scale
Responses to Uncertainty and Low Environmental Structure questionnaire	Responses to Uncertainty and Low Environmental Structure questionnaire
Beck Anxiety Inventory	Attention Control Scale
Beck Depression Inventory	
Behavioral Inhibition & Activation Scale	Behavioral Inhibition & Activation Scale
Child Behavior Checklist	
Parenting Stress Index	
Parent Report of Parental Behavior Inventory	Child Report of Parental Behavior Inventory
Perceived Stress Scale	Perceived Stress Scale
Petersen Pubertal Development Scale	
Screen for Child Anxiety Related Disorders	Screen for Child Anxiety Related Disorders
Alphabetical Index of Occupations and Industry	
MacArthur Scale of Subjective Social Status	
Edinburgh Handedness Inventory	
Treatment Utilization	
Parenting Beliefs about Anxiety Questionnaire (PBA-Q)	
Supportive Parenting Questionnaire	

In order to assess comprehension of the task completed in the MRI scanner, participants will complete two study-specific questionnaires: a brief Noise Rating as well as a Shapes Task Questionnaire, both of which were designed specifically for this protocol.

Questionnaires related to stress and coping during the COVID-19 pandemic: The following questionnaires will be used to assess circumstances, stress, and coping related to the COVID-19 pandemic. The Emotion Regulation Questionnaire, Difficulties in Emotion Regulation Scale, Emotion Regulation Checklist, Parenting Stress Index, Intolerance of Uncertainty Scale, Screening for Child Anxiety and Related Emotional Disorders, Beck Depression Inventory, Children's Depression Inventory, Perceived Stress Scale, Positive and Negative Affect Schedule, Kerns Security Scale, and Benevolent Childhood Experiences Scale.

The Difficulties in Emotion Regulation Scale, Parenting Stress Index, Intolerance of Uncertainty Scale, Screening for Child Anxiety and Related Emotional Disorders, Beck Depression Inventory, Perceived Stress Scale and Kerns Security Scale are all approved on the current protocol and may be re-administered to assess functioning during COVID-19. Questions will also be asked from the following measures that have been developed within the research community in response to the COVID-19 pandemic: Fear of Illness and Viral Evaluation (FIVE), Coronavirus Impact Scale, Coronavirus Health Impact Survey (CRISIS),

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Epidemic-Pandemic Impacts Inventory, and COVID-19 and Perinatal Experiences (COPE) survey. We have also modified the items on the Parental Trauma Response Questionnaire to be specific to the COVID-19 pandemic.

Parent-Child Interaction

Child and mother will engage in a brief video-recorded behavioral interaction, lasting only a few minutes, during which they will be asked to solve a puzzle together. The interaction will be systematically coded using a well-established, valid and reliable coding system.

Cognitive and Behavioral Task:

Participants will complete several tasks administered by research personnel or on a computer to provide measures of cognitive (e.g., intelligence) and behavioral functioning (e.g., associative learning).

Wechsler Abbreviated Scale of Intelligence (WASI). We will collect measures of cognitive functioning using the WASI (Wechsler, 1999). This is an abbreviated assessment of cognitive functioning that is standardized and has been validated for use with children. It consists of four subtests: vocabulary, block design, similarities and matrix reasoning.

The computerized tasks will take place inside the MRI scanner. For any children who do not complete the MRI scan, they will be offered the opportunity to complete the tasks outside of the scanner to obtain behavioral measures. The stimuli will be visual or auditory and may vary in emotional valence from positive (e.g., pleasant noise, happy faces) to neutral (e.g., shapes, neutral faces) to negative (e.g., metallic noise, fearful faces). Examples of visual stimuli include geometric shapes, faces, objects, letters, or places. Examples of auditory stimuli include musical instruments (e.g., a chime or gong), metallic sounds, animal sounds, human sounds (e.g., baby cooing), or white noise. Participants may be instructed to press different buttons depending on the pictures they see on the screen. Participants will be provided with sample stimuli comparable in content before the tasks begin. This way, participants will have the opportunity to evaluate their comfort level with the stimuli beforehand. Participants will be reminded that they may withdraw their participation at any time if they are not comfortable with any of the stimuli. There is little risk involved in these tasks other than boredom or some frustration. One

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of the tasks involves a well-established protocol in which the parent enters the scanner environment to test the effect of parental presence on child's processing of emotion (e.g., Coan et al., 2006; Conner et al., 2012). Thus, all parents who will be invited to enter the scanner environment will complete the same thorough metal screening. For children whose parents have contraindications for entering the scanning environment, children can complete this task outside of the scanner instead.

Yale Interactive Kinect Environment Software (YIKES). YIKES is a software package developed at the Yale Child Study Center (Lebowitz et al., 2015) to allow for more accurate and sensitive measurement and study of anxious avoidance. The software creates a game-like environment in which a participant attempts to catch target items falling on screen by moving in to the right and left and presents pre-programmed stimuli designed to engage avoidance behavior on the sides of the screen. The software interacts with the Microsoft Kinect sensor to chart a subject's motion in real time and records their location with high spatial and temporal resolution and accuracy. The sensor does not record the video and no images of the participant are stored.

Attention Bias to Threat. Attention bias to threat will be assessed with a probe-detection task using the computer software Eprime. Participants (both mother and child) will complete tasks using a provided laptop computer and mouse. A centered fixation cross will appear first and will be followed immediately by two faces of the same actor expressing different emotions, one above the other. Participants will be told that a probe (< or >) will appear on the screen and that their task is to push the corresponding mouse button

Blood Samples:
Subjects will be asked to provide us with a small blood sample for our research during the initial appointment, and again at the 6-month follow up appointment. The total amount drawn will be less than one ounce each time. An experienced and qualified professional will draw the blood from a vein near the elbow.

We will also ask for permission to store blood samples for future research projects. If the subject agrees, the blood will be stored in a safe place without personal identification and retained for future research purposes.

Saliva Sample
To collect a sample of saliva we will subjects to chew on a small cotton swab for about one minute, then spit it out into a special sterile container.

MRI:
All participants will be scanned using a 3T scanner located at the Yale Magnetic Resonance Research Center or Yale's Brain Imaging Center. We train children on the tasks in a simulator so that they can acclimate to the scanning environment. Prerecorded scanner sounds will be played as the participant is in the simulator. We will describe and answer any questions the child or parent has about the MRI procedure. The simulator is a replica of the 3T scanner and includes speakers for simulating sounds, a screen to simulate visual stimuli, and a motorized table for simulating experiences the participant will have in the actual scanner. The participant

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will watch videos and practice the computer tasks while in the simulator. Only after acclimating the child to the scanner environment so that both the child and parent are comfortable with the procedure, will the child be scheduled for the actual scan. Otherwise the study will be terminated.

A member of the research team will accompany the child to the Yale Magnetic Resonance Research Center or Yale's Brain Imaging Center and stay for the duration of the scanning session. All participants will undergo a metal/MRI screening prior to entering the MRI environment. This will include measuring height, weight, and waist-to-hip ratio. All participants will walk through a detector designed to detect metal objects as part of the metal screening. For females who indicate on the screening that they may be pregnant, the MRI portion of the visit will be stopped (the participant may still complete the behavioral task on the computer outside of the scanner). This procedure is in accordance with the MRRC's policy on pregnancy (please see attached policy: "Risks of MR Procedures during Pregnancy"). No pregnancy test will be administered. In the scanner, the participant will be positioned using foam padding to minimize motion and maximize comfort. A head coil will be used to acquire all images. The participant's choice of video will be displayed immediately upon being placed in the scanner and will remain on during the acquisition of anatomical scans (10-15 minutes). Immediately following these scans, the participant will be asked to play the computer tasks during the fMRI scans (30-45 minutes). Then resting-state and diffusion tensor imaging scans will be acquired (20-30 minutes). The participant can also view a video of their choice during the diffusion tensor imaging scans. In the MR scanner we can communicate with the participant via a microphone so the participant can hear the experimenter as the instructions aregiven. Participants wear earplugs to reduce noise from the scanner and earphones to allow the experimenter to communicate with them. The entire MRI procedure including positioning in the scanner will take approximately 60-90 minutes. As stated in the consents, the scan will be stopped, and the participant removed from the scanner immediately at any time the participant requests to end the scan.

Anatomical MRI will be acquired for localizing the subject's brain in the scanner and to identify standard anatomical landmarks for prescribing the other scans. **Diffusion Tensor Imaging** (DTI) will be performed to examine the development of white matter tracts, specifically those involving the frontal cortex and amygdala. During acquisition of anatomical and DTI scans the participant will be able to watch a video of his/her choice. **Resting-state Functional MRI** will be performed to investigate functional connectivity of hippocampal- frontoamygdala networks at rest. Subjects will be asked to keep their eyes open during the image acquisition. **Task-based Functional MRI** will be used to examine brain activation during emotion processing and associative learning. For the functional studies, stimulus presentation and response collection will be controlled using E-Prime software on a computer located in the MR Center control room. Computer images will be projected onto an LCD panel for the participant to see. A fiber optics response box will be used for recording behavioral responses (e.g., accuracy, reaction time). A typical session will include: collection of anatomical images (10-15 min); task-based fMRI including instructions to subject, behavioral task, and functional scan acquisition during

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computer tasks (25-40 minutes); resting-state fMRI (5-10 minutes); and collection of DTI (5-10 minutes).

Parameters for the pulse sequences are as follows:

- Localizer: Voxel size 0.5x0.5x7.0, FoV=250mm, TR=7.5ms, TE=3.69ms, flip angle = 20 degrees, slice thickness=7.0mm, base resolution=256
- Scout: Voxel size 1.6x1.6x1.6 mm, FoV=260mm, slice thickness=1.6mm, TR=3.15ms, TE=1.37ms, flip angle=8 degrees, base resolution=160, PAT mode = GRAPPA, accel factor=3
- T1 navigator: Voxel size: 8.0x8.0x8.0, FoV=256mm, slice thickness=8.0mm, TR=9.9ms, TE-4.6ms, flip angle=2 degrees, base resolution=32
- T2 navigator: Voxel size: 1.0x1.0x1.0, FoV=256mm, slice thickness=1.0mm, TR=3200ms, TE=564ms, base resolution=256mm
- DTI: Voxel size:1.7x1.7x1.7mm, FoV=240mm, slice thickness=1.7mm, TR=4100ms, TE=88ms, flip angle 1=90 degrees, flip angle 2 = 180 degrees, echo spacing-0.69ms
- Resting-state fMRI: Voxel size: 2.4x2.4x2.4mm, FoV=230mm, slice thickness=2.4mm, TR=809ms, TE=32ms, flip angle=54 degrees, base resolution=96, measurements=375, echo spacing=0.52ms, SMS factor=6, SMS shift=3
- Task-based fMRI: Voxel size: 2.4x2.4x2.4mm, FoV=230mm, slice thickness=2.4mm, TR=809ms, TE=32.0ms, flip angle=54 degrees, measurements=410, base resolution=96, echo spacing=0.52ms, SMS factor=6, SMS shift=3

Galvanic Skin Response. While the subjects are performing the tasks we will also take physiological measures of learning, which are reflected by changes in a subjects' sweat response (a measure of the galvanic skin response, GSR). Galvanic Skin Response will be collected with electrodes on the subject's hand or foot. During the MRI scan, we will also assess physiological measures including heart rate and respiration. These measures are commonly used as covariates that index physiological noise in analyses of resting-state fMRI data. All of the materials (including the electrodes for the GSR) are non-ferrous (i.e., do not contain iron) and can be used safely during testing both in and out of the MRI scanner. They are non-invasive and do not cause discomfort to the participant.

5. Genetic Testing N/A ☐

A. A portion of blood drawn and saliva collected will be saved for genetic testing looking at single nucleotide polymorphisms on the oxytocin receptor gene OXTR. These variations have been associated with the function of oxytocin system, various aspects of social behavior, and have linked parental behavior to the presence of anxiety in children at risk for the development of anxiety disorders.

i. the plan for the collection of material or the conditions under which material will be received: Samples will be collected together with the plasma collected for Oxytocin level analysis, by the department of laboratory medicine

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ii. the types of information about the donor/individual contributors that will be entered into a database: Information will include personal and demographic variables including geographical location of residence, age, and the variables assessed in this study.
iii. the methods to uphold confidentiality: Samples will be de-identified and stored without any personal identifying information. The personal information will be stored separately from samples on encrypted computers stored in secure locked facilities.

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? Only the PI and research team will have access to the database and will decide on any future use of the genetic samples for research.
C. Is widespread sharing of materials planned? NO
D. When and under what conditions will materials be stripped of all identifiers? If participants request that their samples be completely de-identified we will remove all identifying information including the subject number key from the samples.
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? Donor-subjects can withdraw their materials at any time or request that the identifiers be removed completely.

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? If participants request that the material be withdrawn completely, we will destroy all the material relating to them. If they request that it be de- identified, we will remove all identifying information.

F. Describe the provisions for protection of participant privacy Samples will be de-identified and stored without any personal identifying information. The personal information will be stored separately from samples on encrypted computers stored in secure locked facilities. Only the research team will have access to the data or the samples.
G. Describe the methods for the security of storage and sharing of materials: Material will be kept securely in refrigeration in locked office/laboratories in secure and locked buildings. The electronic information will be kept on encrypted computers in locked cabinets in locked offices.

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.
The population will include children aged 6-12 with anxiety disorders along with their parents. No special groups are being targeted for inclusion apart from the children with anxiety.

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☒ Children ☐ Healthy ☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking ☐ Prisoners ☐ Economically disadvantaged persons
☐ Decisionally Impaired ☐ Employees ☐ Pregnant women and/or fetuses
☐ Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion? Inclusion Criteria: Children must be a) 6-12 years old; and b) score below 2 on the Petersen Pubertal Development Scale; and c) meet DSM-5 diagnostic criteria for a primary anxiety disorder; and d) not have
another mental illness more impairing than their most impairing anxiety disorder; and e) have an IQ of >80 to minimize neurobiological heterogeneity.
Exclusion Criteria: Children will be excluded for any of the following: a) neurological disorders (including seizures), organic mental disorders, psychotic disorders, or pervasive developmental disorders; or b) show high likelihood of hurting themselves or others; or c) current psychosocial or psychopharmacological treatment. Stable doses of stimulant medications for ADHD will be permitted if parent and child, in consultation with the prescriber, agree to not make changes to dosage during the study period and to not administer the medication in the 24-hour period prior to pre-treatment and post-treatment MRI scans (MRI scans will be arranged on dates the child would not be taking a stimulant medication, in consultation with the prescriber and with agreement from the parent); or d) history of neurological illness or head injury with loss of consciousness > 5 minutes; or e) vision or physical disability that interferes with seeing stimuli presented briefly on computer screen and/or clicking a mouse button rapidly and repeatedly; or f) have contraindications for MRI scanning (e.g., metal implants, pacemakers, braces, claustrophobia, pregnancy, weight > 250 pounds).

Exclusion Criteria – Parent: Parents will be excluded for any of the following: a) pervasive developmental disorders, mental retardation, selective mutism, organic mental disorders, bipolar disorder, psychotic disorders, drug/alcohol abuse/dependence; b) <1 year living with the child prior to admittance; c) suicidal attempt in past 6 months. When a child is excluded, the parent is also excluded (unless as parent of another child); when a parent is excluded, the child will not participate.

9. How will **eligibility** be determined, and by whom?
All parents who are interested in participating in this study will be administered a standardized telephone screen to ensure their child is experiencing anxiety problems and is eligible for MRI (including current psychiatric medications). The brief telephone screen will be completed by trained research assistants. If their child is experiencing anxiety problems and is eligible for MRI, the family will be scheduled for the Pre Assessment. After signing informed consent/assent forms, parents and youth will complete the ADIS: C/P. The purpose of the interview is to determine DSM-5 anxiety diagnoses and to rule out exclusionary diagnoses. The ADIS: C/P will be completed by one of the study's personnel. Cognitive testing administered by trained research personnel during the evaluation visit will be used to determine eligibility based on IQ. Eligibility will be determined after reviewing results of the ADIS: C/P and Pre Assessment with key study personnel at a staff meeting.

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At the MRI visit, participants will again be given a thorough metal screening (Yale-MRRC MRI Safety Questionnaire) by trained research personnel to ensure that they are still eligible for the MRI (e.g., to rule out participants with a change in status of metal in the body, such as a child who recently got braces). At any time (during the phone screening prior to enrollment, or after enrollment in the study), the research personnel and the PI may determine that a participant is not fit to enroll in or continue in the study should they judge that it is in the participant's best interest to do so, if the participant begins a new medication or treatment that would change their eligibility, if they (or their parent) do not comply with the study plan, if they repeatedly miss appointments, if there is concern about their (or their parent's) ability to complete the interview and/or questionnaires validly and reliably, or for various other administrative reasons.

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
Interviews and questionnaires: Feeling upset when talking about anxiety or attending to anxious thoughts.
Behavioral Interactions: Temporary discomfort when discussing an issue on which child and mother disagree.
Blood Draw: Minor discomfort, redness or ecchymosis; Bleeding: Rarely: Phlebitis, infection, fainting. The blood draw is an optional component of the study.
Risk to personal information: There is always a risk to confidentiality when personal information is collected. See data protection section.
Treatment – SPACE: Not getting better; Getting worse during treatment; Child responding with elevated anxiety, distress, or aggression to parents not accommodating the child's symptoms; strain on marital relationship; parent-exacerbated anxiety.
Treatment – CBT: Not getting better; Getting worse during treatment; temporary elevated anxiety (e.g. during exposure tasks).
MRI – Magnetic resonance imaging is considered to be a medically safe procedure, and the procedure is painless. There is no evidence for long-term effects of MRI procedures on the body. The Food and Drug Administration (FDA) has set recommendations for exposure in MRI studies and this study satisfies those criteria. MRI acquisition involves exposure to a strong magnet. Thus, the primary risk associated with MRI is risk of injury associated with metal objects being drawn into the magnet. These objects could be internal (e.g., metal implants in the participant's body) or external items. In addition, some participants may experience transient peripheral nerve stimulation or nausea in the bore of the magnet. Nausea is minimized by stabilizing the head. There is minimal risk involved in the collection of physiological data (e.g., galvanic skin response) during the MRI. The adhesive on the GSR attachments may cause itching or a sticky feeling on participants' skin in the small area on which the electrodes are attached.

The MRI procedure does require participants to lie still with the head and part of the body confined in a tunnel-like device for a considerable length of time (60-90 minutes including several breaks between the collection of images). Some participants may find the confinement in the MRI machine to be claustrophobic, physically uncomfortable, or noisy.

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11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

To minimize risk relating to questionnaire and interview assessments: It is possible that some children and adolescents and parents may become slightly anxious or upset when asked to attend to their anxious thoughts or feelings as required by these procedures. We anticipate such reactions will be short-lived in nature and typically have no significant long-term consequences. In fact, many children and parents are likely to benefit from an improved self-understanding derived from the completion of these measures. These measures are standard and widely used in this age range, and there have been no reports of negative iatrogenic effects. Participants and their parents are not required to answer questions during interviews or on questionnaires that they find too sensitive.

To minimize risk relating to blood draw: Venipuncture will be performed by qualified and experienced personnel in an approved location at the Yale University Department of Laboratory Medicine. Trained, qualified and experienced personnel reduce the risk of pain, bleeding, redness, inflammation, ecchymosis, phlebitis and infection. Qualified locations reduce risks that accompany fainting. The amount of blood to be drawn, not more than 15ml, is well within what is permissible and should not present risk. Participants will be able to decline to have the blood draw at any time until it is completed.

To minimize risk relating to behavioral interactions: Parent and child will each be able to terminate the entire interaction, or part of it at any time. Children and parents will be given instructions that they may stop whenever they want. The graduate research associates also have been carefully and thoroughly trained in the providing of reassurance. Similar procedures have been widely used for many years without report of negative results. In addition, the research associate will spend some time with the participants following each assessment procedure and discuss the participants' reactions to the procedure.

To minimize risk relating to treatment: Changes in parents' behavior (e.g., reducing their accommodation of the child's anxiety) involves some risk of children feeling upset, becoming angry, or parents' experiencing anxiety. Every treatment session includes a review of the past week and query for any uncomfortable events. Any description of extreme exacerbation in parent or child anxiety; suicidal or self-injurious behavior; or other potentially harmful or dangerous event will be reviewed clinically and addressed. The therapists will report any such event immediately to the PI. Co-investigator Dr. Silverman has many years of experience working with anxious children and their parents, including in multiple large scale clinical trials and will oversee the project closely. Upon consultation, a determination will be made about the most appropriate manner in which to intervene (e.g., alternative treatment, hospitalization, etc.), and the child or parent will be excluded from the study, as necessary.

To minimize risk relating to cognitive and behavioral tasks: Participants can stop the tasks at any time and are reminded of this prior to beginning them.

To minimize risk relating to MRI: All FDA guidelines for MRI scanning are carefully observed at the Yale MRRC and Yale BIC. All of the scans will be performed using an MRI scanner employing pulse sequences and hardware that have been approved by the FDA. The field strength is 3 Tesla and all relevant operating characteristics (RF power deposition, rate of change of the field gradients, coil design) fall within the limits of FDA guidelines.

Participants will be carefully screened to exclude those who may have metal in or on their bodies that cannot be removed. We conduct a thorough metal screening at both the phone screening and again at the beginning of the MRI visit to ensure that the participant's status is still safe for MRI scanning. Yale MRRC and Yale BIC rules strictly forbid staff from entering the magnet room carrying metal objects.

Because the MRI procedure requires participants to lie still in a tunnel-like device for a considerable length of time, some participants can find the confinement or noise uncomfortable. We provide ear protection to soften the noise level for participants. We also use an extensive simulation procedure at the mock MRI scanner during the first visit to help participants acclimate to the MRI environment. Especially for children and adolescents, this is helpful to get used to the feeling of staying still in the tunnel and hearing the types of sounds that the scanner makes. Participants who experience claustrophobia during the mock MRI scan or who endorse claustrophobia on the screening will not be scheduled for the MRI scan. Based on our prior publications that have used this procedure, we are confident that the mock scan will be helpful for acclimating to the MRI environment (e.g., Gee et al., 2012; Gee et al., 2013a; Gee et al., 2013b; Gee et al., 2014; Gee et al., 2016). All participants are given a button to signal distress so that they can stop the scan at any time. Participants also use an intercom to communicate with the experimenter during the scan.

At all times, participants will have the option to discontinue the scan if they find it to be objectionable in any way. We can allow them to take additional breaks, if desired, in between image sets, but if that is not acceptable, they are free to discontinue at any time. Participants will be paid for their participation in the MRI visit regardless, without any worry of bias because of their level of participation.

In accordance with Yale MRRC policy, the MRI scan is for research purposes only. As specified in the consent form, participants are explicitly told that the scans are not designed to find abnormalities. If a worrisome finding is seen on a scan, a radiologist or other physician will be asked to review the relevant images. Based on his/her recommendation (if any), the PI or consulting physician will contact the participant, inform the participant of the finding, and recommend that the participant seek medical advice as a precautionary measure. However, the decision for additional examination or treatment would lie only with the participant and their physician.

There is minimal risk involved in the collection of physiological data. Participants can choose not to participate at any time if they experience discomfort (e.g., stickiness) from the adhesive and can remove the adhesive and wash the skin off at any time.

In the opinion of the PI, scheduling MRI scans on days the child is not taking stimulant medication will not increase risks.

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Consent and Assent documents will review all relevant risks and protections, including risk to confidentiality, as detailed in the appropriate sections below.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk.
b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? Minimal risk.
c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are availablehere http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

i. Minimal risk
ii. Greater than minimal

The data and safety monitoring plan for this study will follow the guidelines developed by the Yale University Biomedical Institutional Review Board and are based on the requirements of the NIH and the NIMH guidance on Risk-Based Monitoring (https://www.nimh.nih.gov/funding/clinical- research/nimh-guidance-on-risk-based-monitoring.shtml). The plan provides a description of the procedure for monitoring and evaluating the progress of the intervention trial, and the mechanism for reporting adverse events.

Drs. Eli Lebowitz, Ph.D. (PI), Dylan Gee, Ph.D. (Co-I), Wendy Silverman, Ph.D. (Co-I), and Hilary Blumberg M.D. (Co-I) will monitor the safety of study participants to ensure that they do not incur undue risk. The safety monitoring will focus on clinical functioning of the participants as well as the assessment and intervention procedures including fMRI assessments. Drs. Lebowitz, Gee, Silverman and Blumberg will also continually reassess risks versus benefits throughout the study period.

The level of risk for this study is low. In general, no serious adverse risks are seen associated with either the assessment, intervention, or MRI procedures. The assessment procedures are widely used, and non-invasive and parent-based treatment has been used in many clinical trials and has not been found to carry any significant risk. SPACE is a novel intervention but has been piloted in multiple clinical trials and has not been found to carry any significant risk.
Dr. Silverman has decades of experience conducting clinical trials for childhood anxiety disorders, including of parent-based interventions. Dr. Lebowitz has implemented SPACE with many families directly and supervised other clinicians in this approach and has served as PI of a randomized clinical trial of SPACE. During the project, as part of the safety monitoring procedures, PI Lebowitz and Co-I Silverman will conduct weekly supervision meetings with therapists for purposes of monitoring child clinical

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functioning. This will include reviewing therapist notes etc. for monitoring participant safety. Dr. Blumberg has decades of experience studying brain response using fMRI in children and adults. Dr. Gee has experience using fMRI to study brain response and anxiety including in young children and serves as PI on another study utilizing fMRI to study brain response and anxiety in childhood. The study team including Drs. Lebowitz, Gee, Silverman, and Blumberg will meet weekly to discuss study progress including any concerns that arise.

As in any therapeutic endeavor it is possible that some children could react adversely during the assessment and/or intervention procedures. All adverse events will be carefully monitored by the Co-PIs. The occurrence of any serious unexpected adverse event (e.g., threats to one's life and/or others, suicidal attempts, etc.) will be reported by the Co-PIs to the university IRB within 5 days. The Co-PIs, Yale University IRB, Yale Magnetic Resonance Research Center (MRRC), Yale Brain Imaging Center (BIC), and Yale Pediatric Protocol Review Committee (PPRC) have the authority to stop or suspend the study or require modifications. The Co-PIs and Co-Is will also make biannual reviews of safety and adverse events.

Confidentiality: All subject information will be de-identified and stored separately with only a subject identification number. The key to the ID numbers will be stored electronically on a secure encrypted computer accessible only with a password by the Co-PIs, Co-Is and IRB.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? Write here

ii. What provisions are in place for management of interim results? Write here

iii. What will the multi-site process be for protocol modifications? Write here

13. Statistical Considerations: Describe the statistical analyses that support the study design. General Overview. Data management protocols will be used to ensure data integrity. Missing values (including fMRI data) will be estimated using chained equation multiple imputation algorithms.108 Analyses will focus on least squares test (OLS) of means and modern robust estimation procedures94 that rely on Wilcox's R routines (which generally have more statistical power than traditional OLS)95. If non-normality or outliers appear problematic, we will use the Wilcox functions base on M estimation. We will examine associations between arm and baseline variables to ensure successful randomization. Our analytic approach follows NIH guidelines on rigor and reproducibility, including analysis of sex as a potential covariate. Aim 1: Demonstrate target engagement. Child reliance on parent for amygdala reactivity reduction (calculated as the difference between amygdala reactivity to fear faces in the parent-absent compared to parent-present scan, and from hereon referred to as 'child reliance on parent') will decrease significantly from PRE to POST treatment for children whose parents participate in SPACE, as compared with children whose parents participate in CBT. The assessments of interest for this question are PRE and POST. The additional time-point (MID) will be useful to gain preliminary insights relating to more complex questions of mediation. The OLS analysis is a

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2-group single degree of freedom contrast between SPACE and CBT using child reliance on parent at PRE as a covariate to increase statistical power. The single degree of freedom contrast focuses on the comparison of covariate-adjusted means at POST. Of interest is whether the contrast between arms is statistically significant for child reliance on parent; the direction of change will be determined by the sign of the parameter estimates. A dummy variable for the two arms (SPACE, CBT) will be included in the OLS analysis, with randomization to SPACE scored 1 and randomization to CBT scored 0. A statistically significant negative parameter estimate of the effect of treatment arm on child reliance on parent indicates that reduction in child reliance on parent at POST is significantly greater following SPACE compared with CBT. The same analysis will be conducted for mPFC activation and for amygdala-mPFC functional connectivity.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒ N/A
B. DRUGS/BIOLOGICS ☒ N/A
B. DEVICES ☒ N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: 226 children and their mothers, for a total of 452 participants

b. If this is a multi-site study, give the total number of subjects targeted across all sites:

Write here:

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers ☒ Internet/web postings ☐ Radio ☐Tabling
☐ Posters ☐ Mass email solicitation ☐ Telephone
☒ Letter (postcard)☒ Departmental/Center website ☐ Television
☐ X Blog posting with approved messaging/advertising
☐ Newsletter via email
☐ X messaging/advertising on music-listening platforms
☐ Medical record review* ☒ Departmental/Center research boards ☐x Newspaper
☒ Departmental/Center newsletters ☒ Web-based clinical trial registries☒ Clinicaltrails.gov
☒ YCCI Recruitment database
☒ Other: The Yale Child Study Center Anxiety & Mood Disorders Program sees children with anxiety disorders and those who meet study criteria will be offered the opportunity to

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participate in the study. ☒ Social Media (Twitter/Facebook):

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*** Requests for medical records should be made through JDAT as described at** http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. Children will be recruited through ongoing evaluations regularly conducted at the Yale Child Study Center. The YCSC has existed for over a century and is a major referral source for the community, treating children from all over Connecticut (as well as neighboring states). We therefore anticipate no difficulty in attaining the projected children and parents for this project. After a pre- treatment assessment (PRE), patients will be randomized into either parent-only treatment (SPACE) or child-only treatment (CBT).

b. Describe how potential subjects are contacted. Parents who are interested in enrolling their child in the study will make initial contact. A phone screen will be administered by a study personnel member to ensure their child is experiencing anxiety difficulties and is eligible for MRI.

c. Who is recruiting potential subjects? The study personnel including PI and research assistants will be responsible for recruiting potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No

If yes, describe the nature of this relationship. Some participants may have been assessed or treated by members of the research team in the past.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: It would be impractical to obtain the subject's

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authorization because the screening phase occurs over the telephone. That is because parents will make initial contact with us prior to enrolling their child in the study. During this initial phone contact, a standardized phone screen will be completed to ensure that their child is experiencing anxiety problems and is eligible for MRI. The following information will be collected: demographic information (including youth's home address, age, sex), referral source, a brief description of presenting problem, whether or not the youth is on medication (name and dosage), and contraindications for MRI contained on the Yale Magnetic Resonance Research Center's metal screening form or the Yale Brain Imaging Center's metal screening form. We will obtain verbal authorization from the parent by including the following language in the telephone script:

"We will keep the information we just talked about in our files until you come in to the Child Study Center to sign informed consent and complete the study's procedures. If you are eligible and choose to be part of the study, this information will become part of your study file. If you are not eligible or don't come in, we will keep this information until the study is over and then we will destroy it. We are required by law to keep this information confidential and we will not use it for any purpose other than to see if you qualify for this study and for research oversight."

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
For Parents: The PI or study personnel will explain the study to the participants. We will ensure that they have understood the terms of consent and their rights and privileges. The explanation will include a description of the randomization procedures. After that, if participants are willing they will sign the consent form. Separate consent will be requested for the videotaping of the parent-child interactions. Those who decline involvement will be offered alternative treatment at the Child Study Center Outpatient Clinic, as well as receive referral information for alternative appropriate treatment resources.

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For Children: Parental informed consent will be obtained prior to the child's assent. The PI or study personnel will explain the study to the participants and to the parents in developmentally appropriate terms. The explanation will include a description of the randomization procedures. We will ensure that parent and child understand the terms of consent and their rights and privileges. After that, if they are willing, parents will provide permission and children will sign the written assent. Separate consent will be obtained for the videotaping of the parent-child interactions.

The following documents will be used during the consent/assent process:

Compound Authorization and Parental Permission Form Child Assent Form (children 6-12 years of age) Videotaping consent form

The session will proceed only when the investigator, the participant, and (for children) his or her parent(s) or legal guardian(s) are in full agreement that the procedures are understood and the subject's assent (children) and consent (parents or legal guardians) has been obtained.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed. The minimal age for participation is six. To ensure that all children and parents have understood the consent and are capable of granting consent or assent, the member of the research team will briefly discuss those terms with him or her asking one or two pertinent questions in age appropriate language. Trained study
personnel are experienced with working with children, adolescents, and adults in a research setting, including clinical populations.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior touse.
This study will only enroll participants who are fluent in English because of the need for standardized measures of anxiety and related symptoms.
As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note***** If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ Not Requesting any consent waivers

☒ Requesting a waiver of signed consent:

☒ Recruitment/Screening only (if for recruitment, the questions in the box below will apply to recruitment activities only)

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? **YES ☒ NO ☐**
- Does a breach of confidentiality constitute the principal risk to subjects? **YES ☒ NO ☐**
  OR
- Does the research pose greater than minimal risk? **YES ☐ NO☐**
- Does the research include any activities that would require signed consent in a non-research context? **YES ☐ NO ☐**

☐ **Requesting a waiver of consent:**

☐ **<u>Recruitment/Screening</u>** only (if for recruitment, the questions in the box below will apply to recruitment activities only)

☐ **<u>Entire Study</u>**

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?

  ☐ **Yes** ***If you answered yes, stop. A waiver cannot be granted.***

  ☐ **No**
- Will the waiver adversely affect subjects' rights and welfare? **YES ☐ NO☐**
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? Protected health information will include psychiatric diagnoses, parents' and youth's ratings on measures of anxiety and related symptoms, medical history including history of anxiety disorders, and personal demographic information.

2. How will the research data be collected, recorded and stored? All research data will be collected by trained research personnel. Data will be collected in hard copy for some measures (e.g., semi-structured interview) and computerized form for other measures (e.g., Qualtrics-collected self-report and parent-report questionnaires, behavioral tasks administered on a computer, MRI scans that are collected via computer and stored on a secure server). Telephone screening paper forms will be stored under lock and key and/or on the HIPAA-compliant Qualtrics server. Participants who enroll in the study will be assigned a study ID code. Data collection will be conducted using the participant's unique study ID code. Behavioral and MRI data with participants' study ID codes data will be stored on a secure Yale-ITS server that only authorized trained study personnel can access; hard copies will be stored under lock and key in the secure research-dedicated space at Yale (Yale Child Study Center and Kirtland Hall). Only authorized Yale personnel will have access to the linking code/PHI files, which will be kept separate from the research data in locked files within secure research-dedicated space at Yale (Yale Child Study Center and Kirtland Hall), on a secure Yale-ITS server. Subject identifiers and linking code will be stored in separate locations within the database and have distinct access controls (e.g., different passwords).

3. How will the digital data be stored? ☐ CD ☐ DVD ☒ Flash Drive ☒ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? Confidentiality will be maintained by assigning each subject a number ID to be used on all data collected. PHI will not be kept on portable devices. Any data stored on portable devices will only contain the participant's study ID code (e.g., behavioral data collected on a laptop at the MRI scanner, backup copies of MRI scans on a portable hard drive or secured server). All computers and databases will be password-protected. Hard copies of all collected data (i.e., surveys and questionnaires) will be stored in locked file cabinets. Thus all data will be de-identified, coded, and stored in locked cabinets or password protected computer or server in an office that is locked. Information that will break subject confidentiality will not be shared. Data will only be released upon written consent of youth's parent and will be available for review by the Yale Human Investigation Committee. Only members of the

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research team will have access to participants' protected health information. Consistent with recent data-sharing efforts (e.g., 1000 Functional Connectomes Project), data from this study may be shared in repositories including those supported by the NIH (e.g., NITRC). All data will be anonymized prior to sharing. Genetic data will not be shared.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. Research data will be retained in accordance with Yale and HIPAA guidelines. De- identified data will be stored indefinitely (as noted above, archived computer files will not have any identifying information); any PHI and linking code with identifiers will be destroyed seven years following the end of the study. We will store paper files for seven years at which point they will be destroyed by study personnel or professional Yale affiliated service.

6. If appropriate, has a Certificate of Confidentiality been obtained? COC is automatic with NIH funded studies

SECTION V: POTENTIAL

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
The proposed study has the potential to benefit participants directly and to benefit others who currently suffer from anxiety or will in the future.
Direct Benefit: Anxiety disorders cause great distress and carry short and long term negative consequences if not successfully treated. Children participating in this study will either receive parent-or child-based treatment aimed at improving their symptoms and they can benefit from having less anxiety through participation in the study. As such, there is the potential for the child to benefit. Parents too can benefit from participation in the study. Child improvement is one of the potential benefits to parents. Parents may also benefit from learning how to better respond to their child's symptoms and from being able to actively help their child overcome anxiety.
Benefits to others with anxiety: The aim of this study is to enhance outcomes for treatment of childhood anxiety.
Societal Benefits: Anxiety disorders are exceedingly common and carry huge societal costs through multiple consequences such as decreased work productivity, school dropout, and teenage childbearing. Given the limits on the efficacy of current treatment, the investigation of a novel intervention, distinct from what is done in current treatment, has the potential for large societal benefit. This study will also provide novel and important information on the

neurobiology of child anxiety and treatment response and may provide the first evidence that parent-based treatment can impact a child's brain functioning, with potential benefits for children with anxiety and other problems.
Risk to Benefit: The study has very low risk but the potential to benefit the participants directly, other future potential patients, and society at large. Therefore, the low risks to the subjects are justified by the potential knowledge to be gained.

1. Alternatives: What other alternatives are available to the study subjects outside of the research? CBT or parent training may be provided as standard of care to youth not participating in this study.
2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation. Participants will be compensated $50 for the first MRI visit (which is expected to take approximately 2-2.5 hours) or a tablet of equal value. Participants will be compensated $100 for the second MRI visit (which is expected to take approximately 2-2.5 hours) or tablets of equal value. Participants can choose whether to receive the cash or the tablet(s) of equal value. Participants are compensated regardless whether they finish the MRI scan so that participants who feel uncomfortable with the scan can discontinue without concern about compensation. Participants who complete all components of the appointment will receive an additional
   $50 at each visit. The payment will be given to the parent participant who will provide it to the child participant at their discretion. Participants who return for their 6-month follow up appointment will be compensated an additional $100 or tablet(s) of equal value. There are no other payments to participants.
3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects. There are no costs to subjects for participation in this study, apart from the cost of time and resources involved in arriving for treatment and evaluation sessions.
4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).
   a. Will medical treatment be available if research-related injury occurs? Write here
   b. Where and from whom may treatment be obtained? Write here
   c. Are there any limits to the treatment being provided? Write here
   d. Who will pay for this treatment? Write here
   e. How will the medical treatment be accessed by subjects? Write here

N/A –the present study does not involve greater than minimal risk.
In the event that an incidental finding occurs from the MRI scan, the decision as to proceed with further examination or treatment lies solely with the participant and their physician. The investigators and Yale University are not responsible for any examination and treatment expenses that result from the participant's decision to seek further investigation based upon these findings.

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IMPORTANT REMINDERS

Will this study have a billable service?Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No☐
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐
c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at

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