Protocol #: 17-0464
Project Title: Neurocognitive Targets of Hostile Interpretation Bias Training to Treat Irritability

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I. Hypotheses and Specific Aims:

Chronic irritability is a prominent dimension of pediatric psychopathology for which evidence-based treatments are scarce, have limited efficacy, or adverse side effects. There is a need to develop novel treatments, especially those that target the neurocognitive basis of irritability. One candidate is Interpretation Bias Training (IBT), a computer-based training designed to target rapid, automatic processing of social information. In a small open trial, IBT showed promise as an acceptable, feasible treatment for irritability. However, its underlying neurocognitive targets have not been established. In order to translate IBT for clinical use, we propose to examine two promising neurocognitive targets of IBT.

Specific Aim 1: Establish hostile interpretation bias as a treatment target for irritability and engage it through interpretation bias training. One hundred adolescents, drawn from an outpatient psychiatric clinic with varying degrees of clinically significant irritability, will be randomized to a session of active (n=50) or sham (n=50) IBT.

Hypothesis 1.1: The degree of hostile interpretation bias is positively associated with clinical irritability
Hypothesis 1.2: Active but not sham interpretation bias training will reduce hostile interpretation bias.

Specific Aim 2: Establish the ability to learn benign judgments of ambiguously hostile social information as a treatment target for irritability and engage it through interpretation bias training. A subsample of 50 participants (n=25 in each active and sham group) will train during fMRI.

Hypothesis 2.1: Learning rates during active IBT will be associated with baseline irritability.
Hypotheses 2.2, 2.3: In neural systems underlying threat learning, response while learning new associations during active IBT will be related to clinical irritability in terms of both neural activity (2.2) and functional connectivity (2.3).

Exploratory Aim 3: Provide preliminary evidence that changes in treatment targets are related to changes in irritability. To better establish the mechanism of target engagement and gather preliminary evidence for an efficacy trial, we will measure any changes in irritability after IBT. Therefore, we hypothesize that changes in irritability following active IBT will be associated with changes in hostile interpretation bias (hypothesis 3.1) and threat system response (hypothesis 3.2).

II. Background and Significance:

Significance. Severe, chronic irritability currently affects approximately 3% of youth in the U.S. and is one of the most common presenting complaints to psychiatrists.[1-5,14,15] Across 24 studies, chronic irritability in youth predicts later development of adult psychopathology, particularly depressive and anxiety disorders.[6] It ranks among the strongest predictors of suicidality across the life span.[16-19] The impairing nature and long-lasting adverse effects of chronic irritability[20-22] underscore a critical need for effective treatments. Preliminary evidence suggests that interpretation bias training (IBT) may reduce irritability,[13] yet this treatment remains undeveloped. To further develop this treatment, we propose to first establish its neurocognitive targets: hostile interpretation bias and learning circuitry response. The successful completion of this proposed research will establish the neurocognitive basis for a randomized controlled trial of the efficacy of IBT for clinical irritability. This contribution would be significant because it will further develop an evidence based, nonpharmacologic, and inexpensive treatment for irritability that targets specific neurocognitive mechanisms.

Irritability and Hostile Interpretation Bias. Prior work suggests, but has not established, that pathologic irritability is associated with hostile interpretation bias. Here, we use 'hostile interpretation bias' as an atheoretical, general term describing a tendency towards interpreting ambiguous social stimuli as threatening.[23] It is also known as 'hostile attribution bias' and 'hostile attribution of intent.' Biased interpretations are automatic, that is occur rapidly and without awareness,[24,25] and influence subsequent cognitive processes to promote a threat response.[24,26-28] Hostile interpretation bias is a well-established cognitive correlate to two irritability-associated constructs: [29,30] trait anger[23,31,32] and a tendency towards aggression (association with aggression *r*=.17 across 41 studies[33]). In particular, the association between hostile interpretation bias and aggression increases with increasing severity of aggression.[33] Hostile interpretation bias may be measured by a number of methods, often by biased judgments of complex social scenarios.[33] However, to elucidate its neurocognitive underpinnings, recent work has measured hostile interpretation bias during judgments of ambiguous face-emotions.[34,35] Using ambiguous face emotions, hostile interpretation bias was associated with a tendency towards expressing one's anger and low anger control in N=101 undergraduates.[36] I led a study reporting that, relative to youth without psychopathology, hostile interpretation bias was associated with disruptive mood dysregulation disorder (DMDD), a mental disorder characterized by severe, chronic irritability (N=89, Cohen's *d*=0.51, equivalent to *r*=.25).[13] Considering work in anger and aggression, this prior work converges to strongly suggest that irritability, across disorders, is positively associated with hostile interpretation bias (hypothesis 1.1).

IBT to Treat Irritability. Prior work suggests, but has not established, that irritability may be reduced by training against hostile interpretation bias. Interpretive biases are well-established targets of training programs to treat anxiety and depression,[37] two phenomena with which irritability shares genetic,[38,39] concurrent,[40-42] and longitudinal associations.[15,20-22,39] Indeed, irritability and anxiety share similar cognitive biases towards facial expressions signifying social threat.[43,44] Following prior work in depression,[45] an IBT program was developed to reduce anger and aggression with the presumptive target being hostile interpretation bias.[12] IBT uses face emotions, mixtures of happy and angry expressions, as social stimuli (Figure 1). In two randomized controlled trials,[12] two daily sessions of sham versus active computer-based training shifted participants' judgments of ambiguous facial expressions from ''angry'' to ''happy.'' Active training was associated with decreased anger in healthy young adults and aggression in youth with conduct problems. In a small, open trial (N=14),[13] colleagues and I showed that four daily sessions of IBT was associated with reduced irritability in youths with DMDD. Both trials demonstrated a robust change in interpretation bias as measured by the same face-set stimuli used in training. However, there is no evidence that IBT results in generalized changes of hostile interpretation bias, i.e.

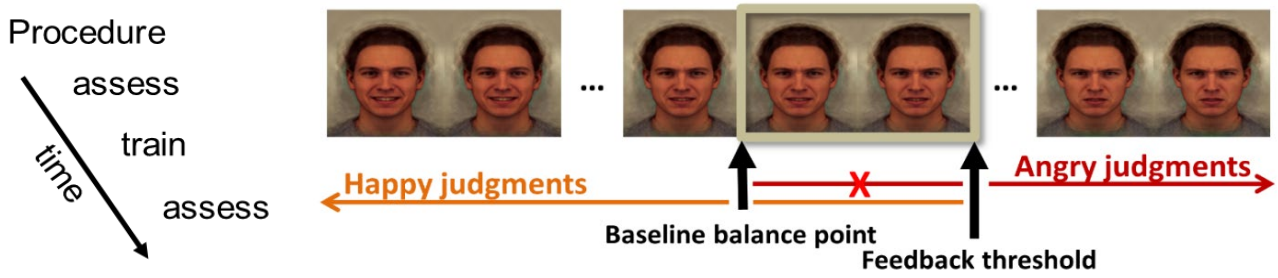

Figure 1. An interpretation bias training session. First the balance point is assessed. It is the point on a continuum of happy to angry faces where a person's judgments of them switch from predominantly happy to angry. Training sessions provide feedback on judgments that encourage happy judgments of two ambiguous faces previously judged as angry. Training effects are measured by another balance point assessment.

changes in interpretation bias to other face-set stimuli or other measures of hostile interpretation bias. Still, the effect of the training on symptoms related to hostile interpretation bias is compelling and supports further investigation to determine whether IBT reduces its intended target, hostile interpretation bias (hypothesis 1.2), under the NIMH plan for treatment development (Strategy #3.1).[46]

Learning and its Neural Correlates During IBT. Impairments in learning during IBT may hinder an individual's ability to benefit from it. As part of our open trial of IBT on DMDD,[13] we gathered preliminary evidence suggesting that the clinician-rated degree of improvement in irritability in youths with DMDD trended towards an association with the overall change towards more positive, i.e. "happy," judgments over the course of IBT (r=.49, p=.08). Thus, the effect of IBT on irritability may be moderated or mediated by a patient's ability to learn new valence associations to ambiguous facial expressions, i.e. capacity to train against their hostile interpretation bias. As described in the preliminary studies section below, we have evidence that youths with severe irritability are slower learners during IBT. As a first step towards investigating the role of the threat-learning system as a mediator of IBT treatment effect on irritability, we will test the hypothesis that pre-IBT irritability is associated with deficits in a person's ability to learn benign associations (hypothesis 2.1).

Learning during IBT should involve the neural threat-learning system, which includes the amygdala, anterior cingulate, and orbitofrontal cortex.[47] Hostile interpretation bias is likely mediated by amygdala-enhanced detection of threat cues in ambiguous social information.[27,29,35,48] To reverse these associations, IBT uses reinforcement learning against the biased judgments of social threat in ambiguous cues. Notably, we hypothesize that this would engage the orbitofrontal cortex to update the valence-associations of ambiguous information[47] as well as the anterior cingulate cortex during unexpected feedback to perceived threat.[49,50]

My colleagues and I recently published preliminary evidence suggesting that the lateral orbitofrontal cortex response to ambiguous expressions of happiness and anger changes after IBT in youths with DMDD (Figure 2). By combining computational modeling with functional magnetic resonance imaging (fMRI), we propose to directly test the involvement of the threat-learning circuit during training (hypotheses 2.2 and 2.3). If IBT's effect on irritability is mediated by learning, it follows that the degree of change in irritability is associated with the degree of change in hostile interpretation bias (exploratory hypothesis 3.1) and the threat-learning system response (exploratory hypothesis 3.2).

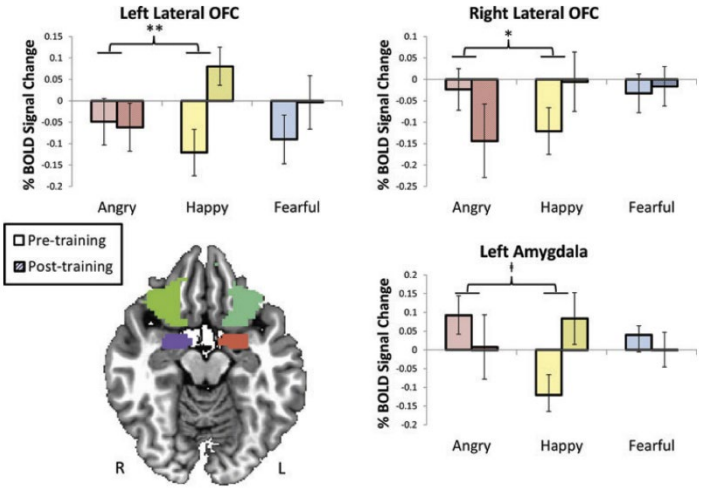

Figure 2. IBT is associated with increased neural activity in response to subtle expressions of happiness, relative to anger, in the bilateral orbitofrontal cortex (OFC) p's<.05 and left amygdala (p<.1). Activation during implicit processing of 50% emotion-neutral facial morph, relative to a fixation cross, measured before and after four sessions of daily training. *p < 0.05, **p < 0.01.

Summary
Prior work strongly suggests an association between irritability and hostile interpretation bias (hypotheses 1.1). Earlier work also suggests IBT may reduce hostile interpretation bias, but only when hostile interpretation bias is measured by the same stimuli used in IBT. This study will assess whether a reduction in hostile interpretation bias generalizes (hypothesis 1.2). Prior work suggests, but has not proven that that irritable youth are slow to learn benign interpretations (hypothesis 2.1) and this is mediated by neural response (hypotheses 2.2 and 2.3).

III. Preliminary Studies/Progress Report:

I have developed this paradigm at the NIMH with Dr. Ellen Leibenluft and have recently published results supporting Aim 1, the association between hostile interpretation bias and irritability, and Aim 2, the association between interpretation bias training and neural response in the threat system, reviewed above. Using these

datasets, we completed further, unpublished work to demonstrate that we may feasibly investigate Aim 2 by applying computational models, adapting IBT to fMRI, and collecting data at the University of Colorado Brain Imaging Center. Feasibility of investigating Aims 1 and 2 are sufficient for investigating Aim 3.

Learning Rate on Active Faces During IBT Differs between Youths with DMDD and Healthy Youths.
With support from the NIMH Unit on Learning and Decision Making Drs. Averbeck and Costa, we fit a Rescorla-Wagner model filtered through a Softmax equation to measure the learning rate of 13 adolescents with DMDD and 9 youths without psychopathology during four training sessions of IBT. The model detected a between-group difference in learning rate during the first session of IBT (Figure 3). This work provides the foundation for the development of computational models to measure learning and the real-time change in hostile interpretation bias (Aims 1 and 2) and neural correlates (Aim 2) during IBT. It also supports the study design which depends on measuring irritability-associated learning effects during a single session of IBT.

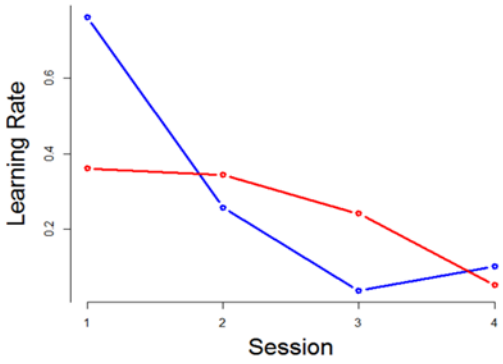

Figure 3. The trajectory of learning benign interpretations of angry faces differs between patients with DMDD (red) and healthy youth (blue), suggesting irritable youth are slower learners than nonirritable youth in IBT. Plotted values are the fixed effects estimates of learning from the mixed-effects ANOVA (Group by Session effect, p=0.03). The largest difference was within the first session (t(20)=1.88, p=.08., Cohen's *d*=0.84, a large effect).

Neural Activity During Judgments of Ambiguous Face-Emotions.
In Dr. Leibenluft's lab, we adapted the hostile interpretation bias assessment portion of IBT to fMRI. We tested the feasibility of using this adaptation with 16 patients, ages 8-17, with diverse mental disorders at the NIMH. These patients tolerated making judgments of these faces sets in sessions lasting at least 28 minutes. We then successfully tested this task on a 24-year-old young adult on the CU Denver MRI scanner. Robust activation in networks of face emotion processing were detected. The work demonstrates that blood oxygen-level dependent (BOLD) signal during judgments of ambiguous faces may be measured in adolescent patients.

IV. Research Methods

A. Outcome Measure(s):

Hostile Interpretation Bias. Hostile interpretation bias is measured by the tendency of individuals to judge ambiguous face-emotions as angry. The "balance point" is a common measure of hostile interpretation bias (Figure 1). It is the point along a happy-angry continuum of face-emotions where judgments switch from predominantly happy to angry.[13]

Learning Rate. Learning rate is parameter in the Rescorla-Wagner model that estimates how quickly an individual learns to switch their responses.

Neural Activity. Neural activity is measured by the amplitude of the blood-oxygenation level dependent (BOLD) signal during functional magnetic resonance imaging (fMRI).

Neural Connectivity. Neural connectivity refers to the coordinated activity between cortical and subcortical neurons. It is measured by the covariance of BOLD signal during fMRI. Specifically, the amplitude of covariation by task condition in linear models.

Irritability. Within this study, irritability will be analyzed as a dimensional construct along the Affective Reactivity Index (ARI). Several prior reports of ARI scores and variance in different cohorts of youths with anxiety disorders, attention-deficit hyperactivity disorder, and DMDD strongly suggests that our recruitment strategy will guarantee a broad variability in ARI scores.[42,51-53]

B. Description of Population to be Enrolled:

We request a pilot group of up to 10 participants to establish the procedure and ensure the fMRI IBT training work wells at the UC Denver Brain Imaging Center in irritable youth. This study will target the total accrual of 100 youths, ages 13-17 years, drawn from a clinical sample, with at least mild, clinically significant irritability, typical intellectual functioning (IQ>80), absence of major medical problems, including head trauma. We anticipate 126 individuals may be enrolled allowing for 21% attrition and/or data loss. The total accrual target of 136 probands, who each require at least one caregiver to be involved, but we will not prevent another parent from participating. We will encourage one caregiver to fill out measures, as they are repeated measures. Based on prior experience, about 1.5 caregivers will be involved, yielding about 340 individuals on whom we will have collected information and 250 (100 probands plus 150 caregivers) who will be enrolled to generate sufficient data.

Additionally, we will recruit a small subsample from the same clinical population but with low irritable mood youth defined as parent-report ARI<3 and self-report ARI<2. Three volunteers will be uniformly assigned to each arm of the study at random.

Exclusionary diagnoses include current posttraumatic stress as well as lifetime bipolar I, II, cyclothymic, psychotic, and autism spectrum disorders. The rationale for these exclusions are to minimize confounds due to disorder-specific, face-emotion processing impairments or traumatic events. Exclusion criteria include clinical judgement of psychiatric instability and clinical high-risk status for danger to self or others. Exclusionary criteria include pregnancy. To operationalize some instability, any mental health treatment changes, new prescriptions of psychoactive medications, or substance use within 4 weeks of trial start will be considered exclusionary. Participants will be informed of these requirements during scheduling. A focus on adolescents maximizes comparison to prior work, ensures a more homogenous developmental level of face-emotion processing ability, and reduces age-related motion during fMRI or inattention to task.

Recruitment will take place through an established recruitment network across several clinical sites within the Children's Hospital Colorado Network of Care (CHCO NOC), University email and social media announcement(s), postings on our lab website and childrenscolorado.org, and ResearchMatch (Materials Attached).

BuildClinical, a platform for academic researchers to accelerate clinical research recruitment, will also be used to distribute approved advertisements on their website and affiliated social media accounts.

Participants may contact study personnel via email or telephone call. Then, a telephone screen by Drs. Stoddard or Penner with the adolescent's parent or guardian will address standard MRI, study-specific exclusions, and likelihood of having clinical irritability (Attached). This screen has been designed to reduce the chance that an adolescent participant will be ineligible for randomization to a study arm after Assessment.

If Dr. Penner or Stoddard do not identify an exclusion and clinically significant irritability is likely, they schedule two study visits with the family, at their convenience, to ensure clinic and scanner availability.

B. Study Design and Research Methods

Participants will complete two study visits and one online assessment, with procedures listed in this table and described below.

Clinical Assessment	Training	Post training Assessment
Day 1	Up to Day 7	1 week ± 3 days after training
Clinic	Clinic	Online
Consent ARI WASI KSADS C-SSR Scales	IBT	ARI Scales

Assessment, Visit 1, Day 1

This visit will occur at the Pediatric Mental Health Institute (PMHI) outpatient clinic in a private laboratory room (see COMIRB Application, Section Q, for facilities description).

Adolescents and their parent will begin with a session to obtained informed consent and assent with study personnel (see COMIRB Application, Section L, for procedure). Clinical assessment will begin with the parent and adolescent will each complete their respective versions of the Affective Reactivity Index (ARI) to

measure level of irritability. Adolescents with mild clinical irritability will be invited to continue (parent-report ARI ≥ 3 or self-report ARI ≥ 2; based on sensitivity analyses in Kircanski et al.[52]).

Adolescents and their parents will complete a semi-structured diagnostic interview about the adolescent with Drs. Stoddard or Penner using the computerized Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version, (KSADS-PL)[54] updated for DSM-5 and the Columbia-Suicide Severity Rating Scale (C-SSR; PMC 3893686). This will allow for diagnostic characterization of the sample, and the evaluation of exclusionary diagnoses. Pubertal development will be assessed using Tanner's Sexual Maturation Scale.[55,56] Adolescents will also complete the Wechsler Abbreviated Scale of Intelligence- 2nd edition (WASI-II),[57] which provides a full-scale intelligence quotient (IQ) estimate based on the administration of two subtests: Vocabulary and Block Design. During the initial clinical assessment and in the post training assessment, clinical characteristics will also be assessed using self- and parent report scales of depression (Short Moods and Feelings Questionnaire),[58] anxiety (Screen for Child Anxiety Related Emotional Disorders),[59] ADHD symptoms (SNAP-IV, PMID 11211365), anger (State-Trait Anger Expression Inventory 2, Child and Adolescent Version), [60] and irritability (Brief Irritability Test (BITe). In response to the COVID-19 pandemic, we will also be assessing COVID-related stress using pediatric and parent reports via the Patient-Reported Outcomes Measurement Information System (PROMIS) Physical and Psychological Stress 8a and the Coronavirus Impact Scale (CIS).

During this visit, adolescents will complete the following self-report forms via RedCap:

1. Short Moods and Feelings Questionnaire (MFQ; 2 minutes)
2. Screen for Childhood Anxiety Related Emotional Disorders (SCARED; 8-10 minutes minutes)
3. Affective Reactivity Index (ARI; 2 minutes)
4. State-Trait Anger Expression Inventory-2 Child and Adolescent (STAXI-2 C/A; 5-8 minutes)
5. Brief Irritability Test (BITe; 2 minutes)
6. PROMIS Pediatric Short Form – Physical & Psychological Stress Experiences 8a (3-5 minutes)

During this visit, caregivers will complete the following parent-report forms via RedCap:

1. ARI (2 minutes)
2. SCARED (8-10 minutes)
3. MFQ (2 minutes)
4. SNAP-IV, items 1-40 only, (5-10 minutes)
5. PROMIS Parent Proxy Short Form – Physical & Psychological Stress Experiences 8a (3-5 minutes)
6. Coronavirus Impact Scale (2 minutes)

All forms are included in the Appendix. Based on our pilot, we estimate the total time for Visit 1 to take 3-3.5 hours.

While COVID-19 safety procedures are still in effect on the Anschutz Medical Campus, the following adaptations may be made to Assessment, Visit 1, Day 1:

The first study visit may be conducted completely over telehealth through a University-approved and CHCO-compliant audio/video application. Informed consent and assent will be obtained remotely using REDCap's eConsent framework. All measures will be administered virtually. Tanner and the STAXI-2 C/A will be omitted for individuals conducting Visit 1, Day 1 via telehealth as online copies of these measures are not available.

The first study visit may also be split between in clinic and telehealth appointments. The clinic and telehealth appointments will occur within 48 hours of each other. Staff, adolescents, and caregivers will maintain CHCO safety procedures at all times in the clinic.

Randomization

Within 48 hours of Visit 1, Drs. Penner or Stoddard will determine if any exclusion criteria are met. This time allows Drs. Stoddard and Penner to consult each other or clarify information with the participants to achieve consensus for any unclear exclusionary diagnosis. If so, Dr. Stoddard will call the participants to thank for their participation, inform them of their exclusion, and cancel their second visit. Some exclusionary criteria are not stable, and it is likely the participants will be eligible during the study period. In that case, participants will still be

marked as a “Screen Failure,” in the consented, but not enrolled, category. However, they will be offered the opportunity to reschedule in the future. In this case, the participants will need to repeat visit 1.

During the pilot phase, eligible adolescents will not be randomized to a study arm, but will be invited to follow procedures for any arm. After pilot, eligible adolescents will be randomized for a 2 x 2 factorial, single blinded, randomized controlled trial, eligible adolescents will be assigned to one of four arms representing TRAINING (active or sham IBT) and SCANNING (in- or out-of-scanner IBT). First, scan ineligible patients will be assigned to out-of-scanner training. Second, randomization will use established minimization procedures[64] (R packages randPack and/or *randomizeR*) to ensure the four arms are similar in terms of sex, age, socioeconomic status (SES), and IQ. The single blind is required so I may track adolescents with acceptable data. Acceptable behavioral data are at least 70% accuracy on extreme morphs (see Stoddard et al.[13] for the development of this threshold) and, if applicable, scans of acceptable quality (see below). Allocation to any arm will end when the accrual goal of 25 adolescents with acceptable data have been reached for a total N=100. Since this is a small trial that is not intended to assess clinical efficacy, promoting power and ensuring balance across confounds outweigh the potential for allocation bias due to single-blinding or minimization procedures.[62]

Training, Visit 2, Up to Day 7

For those randomized to out-of-scanner conditions, this visit will occur at the Anschutz Medical Campus Gary Pavilion outpatient psychiatric clinic in a private laboratory room. For those randomized for in-scanner conditions, this visit will occur at the Anschutz Medical Campus Brain Imaging Center (BIC). See COMIRB Application, Section Q, for facilities description. See COMIRB Application, Section J, for MRI safety screening procedures.

At the start of the second visit, adolescents will complete an out-of-scanner interpretation bias assessment on a laptop approximately 3 minutes. Adolescents will then complete an in- or out-of-scanner session of active or sham IBT depending on their allocation (approximately 18 minutes). Immediately after IBT, all adolescents will complete an out-of-scanner interpretation bias assessment presented on a laptop. To assess whether training on the ‘prototypical’ male face-set generalizes to other face-sets, adolescents will complete another interpretation bias assessment designed by Dr. Bar-Haim and colleagues.[44] It has nearly identical trial structure, but uses four NimStim[63] face-identities that differ in gender and race along the same 15-morph continuum and takes 7.5 minutes to complete. Details of these cognitive tasks and image acquisition are provided below.

At the end of this session, we will give participants a RedCap link and log on instructions. We will ask them to complete an online assessment via RedCap in one week. For those who opt against completing their assessment online, we will give them a packet of assessment measures.

Based on pilot experience at the NIMH, I anticipate the visit length for each out-of-scanner arm to be one hour long and the visit length for each in-scanner arm to be two hours.

While COVID-19 safety procedures are still in effect on the Anschutz Medical Campus, the following adaptations will be made to Training, Visit 2, Up to Day 7:

Adolescents and their caregivers will be screened for COVID-19 symptoms the day before their scheduled Visit 2 in accordance with CHCO site standards or BIC standards, depending on randomization.

Visit 2 appointments occurring at the Gary Pavilion outpatient clinic will adhere to all CHCO site safety procedures. Staff, adolescents, and caregivers will maintain CHCO safety measures at all times in the clinic. Alternatively, Visit 2 appointments at the Brain Imaging Center will adhere to all BIC/University COVID safety procedures. Staff, adolescents, and caregivers will maintain BIC safety measures at all times in the building.

Assessment, Online, About one Week after IBT

The day before it is due, Drs. Penner or Stoddard will call the family to remind them to complete their follow up assessment. Drs. Penner or Stoddard will ask parents, “Do you have new concerns about your child since the training session?” The scales included in this assessment are the same as in the first visit, excluding the Tanner Scale. In addition, during the post-training assessment, adolescents will complete the Intent Attributions

Questionnaire, another measure of interpretive bias (10 minutes).[64] Because this scale can only be administered every six months, we are limited to a post-training assessment only. Though we cannot assess IBT-associated changes in ratings on this scale, we can assess for both associations with irritability as well as differences in hostile attribution bias between those in the sham vs. active IBT groups.

For online assessments, adolescents will complete the following self-report forms:

1. Short Moods and Feelings Questionnaire (MFQ; 2 minutes)
2. Screen for Childhood Anxiety Related Emotional Disorders (SCARED; 8-10 minutes minutes)
3. Affective Reactivity Index (ARI; 2 minutes)
4. State-Trait Anger Expression Inventory-2 Child and Adolescent (STAXI-2 C/A; 5-8 minutes)
5. Intent Attributions Scale (10 minutes)

During this visit, caregivers will complete the following parent-report forms:

1. ARI (2 minutes)
2. SCARED (8-10 minutes)
3. MFQ (2 minutes)
4. SNAP-IV, items 1-40 only, (5-10 minutes)

Based on conducting similar online assessments at the NIMH, I anticipate this assessment to take approximately ½ hour for the adolescent and 15 minutes for their caregiver.

Interpretation Bias Training Session. The interpretation bias training session consists of an assessment of interpretation bias followed by trainings to shift the bias. A training session is depicted in Figure 1.

The assessment uses “prototypical” male happy or angry expressions. These were created combining twenty males from the Karolinska Directed Emotional Faces set.[65] Thirteen linear morphs between these expressions generated a set of 15 stimuli, or “morphs,” on a continuum from happy (morph 1) to angry (morph 15). All trials consist of a fixation cross (1000ms plus 500-6000ms jitter, mean 1500 ms), morph presentation (150 ms), visual noise mask (250 ms), and response screen with a question mark (until response). Participants respond via keypress with ‘‘angry’’ or ‘‘happy.’’ Each morph of the full set is presented three times in random order. Data from this assessment is used to estimate each participant’s balance point, or the point along the morph continuum where the participant’s judgments change from predominantly happy to angry.

The training is divided into six blocks. Timing and stimulus presentation are the same as in the assessment block except that feedback was provided after each response. Because some will train during fMRI, which does not allow indefinite timing, the response screen timing is 1500 ms plus 500-6000 ms jitter, mean 2000 ms. Feedback will be presented for 1500 ms. Active training is designed to shift the balance point (measured by a pretraining assessment) toward happy judgments of ambiguous faces. Participants receive positive feedback for rating as happy (and negative feedback for rating as angry) two ambiguous morphs nearest to the balance point and had been rated as angry by the participant during the assessment. Patients will receive encouragement to attend for nonresponses, which are anticipated to be rare. Similarly, sham training provided feedback based on the balance point measured at the beginning of each session during the pretraining assessment block. In the case of sham training, the feedback is designed to reinforce, rather than shift, the current balance point. Regardless of what the baseline balance point is, feedback never encourages incongruent judgments of the three extremes on each end of the morph continuum. Both conditions present each morph twice in random order during each training block. There are six training blocks, consisting of 30 trials each lasing 2.7 minutes. In the scanner, each block will begin with an additional 9.2s of fixation for pre-magnetization and end with an additional 12s of fixation to measure BOLD return to baseline.

Acquisition and Processing of Neuroimaging Data. Adolescents will be scanned at the Brain Imaging Center at the University of Colorado Denver, using a 3.0 T Siemens Trio MR system with a 12-channel head coil. All adolescents will undergo either a real-scanner or mock-scanner acclimation procedure to orient them to the scanner and minimize loss due to motion artifact. BOLD sensitive echoplanar images with axial slices (3mm thick) encompassing the cerebrum and part of the cerebellum (TR/TE=2300/30msec FA=70 FOV=24cm, matrix=96x96). A T1-weighted MPRAGE structural image will be collected to assist with co-registration and normalization of functional images. All fMRI data will be pre-processed and analyzed using the Analyses of

Functional NeuroImages software (AFNI). Each adolescent's echoplanar images will be aligned using the first slice as a reference. Images will undergo diffeomorphic registration to the MNI template, resampled to 2.5mm^3 voxels, and spatially smoothed using a Gaussian kernel of 5mm full-width at half-maximum. Movement parameters from the realignment stage will be entered as covariates of no interest to control for movement and for censoring or 'scrubbing' at a threshold 1 mm Euclidean distance. Task events will be modeled using a using a gamma variate hemodynamic response function with duration modulation via AFNI's 3dDeconvolve. Adolescents with average motion per TR of >1 mm Euclidean distance before censoring or a nonresponse rate of >20% will be excluded.

C. Description, Risks and Justification of Procedures and Data Collection Tools:

This study involves only psychiatric interviews, well validated, commonly used rating scales, computer-based cognitive tasks that do not involve deception or distressing the participant, and a noninvasive procedure (magnetic resonance imaging scans without sedation or contrast). Thus, this study does not involve any risks greater than routine risks of a routine physical or psychological examination. This study was developed in consultation with NIMH Program to adhere to the NIMH roadmap for investigating novel therapeutics (NIMH Strategic Plan 3.1). It may benefit participants by providing a more comprehensive psychiatric assessment to them than usual care. It may benefit society in that the study has a high likelihood of providing novel information critical to the development of a nonpharmacologic treatment for a serious psychiatric condition. Overall, the risk/benefit ratio favors societal and individual benefits.

Study assessment procedures include behavioral testing and MRI scanning. These will take place over the course of two weeks with two on-site visits. Common risks include loss of school time and increased psychological stress as a result of participation. We have found that the proposed study period has been well-tolerated by child psychiatric outpatients. During the assessment days, participants will be given as many breaks as needed between to reduce fatigue and ensure adequate effort/concentration. To minimize loss of school time (or parental work commitments), some evening and weekend assessment times will be offered. Participants will also be able to complete assessments at times most convenient for them including days off from school, holiday breaks and summer vacation. In addition, this protocol incorporates online assessment where possible to reduce loss of personal/occupational/school time.

With regards to clinical assessments, there are minimal risks associated with completion of cognitive tests (WASI-II) or rating scales. Children may experience some frustration if they lose points during cognitive testing. They also may also become bored with some of the procedures. Furthermore, some questions during the clinical interview or completion of parent/self-report rating scales may be deemed "personal" in nature; therefore, adolescents and their parents will be informed that they do not have to answer any questions they do not feel comfortable answering. Adolescents may divulge information suggesting that they are in danger, requiring urgent psychiatric care or reporting to authorities.

Drs. Penner or Stoddard will supervise all clinical portions and respond to urgent psychiatric issues per standard of care. Caregiver concerns on follow up phone call will be evaluated by Drs. Stoddard or Penner immediately. Any online forms will be reviewed by Drs. Stoddard or Penner within three business days of receipt. Should any information arise suggesting the adolescent is in danger to self, others, or psychiatrically disabled, Drs. Stoddard or Penner will immediately be contacted to establish safety and coordinate appropriate care. Drs. Stoddard or Penner will be contacted for any suspected child abuse and neglect; they will coordinate reporting and safety maintenance as mandated by law. Dr. Stoddard, the PI, will always be contacted via pager in the event of any suspected safety concern, urgent, or emergent clinical issue.
Procedures and timing for reportable events will be as defined by current applicable COMIRB policies (specifically, Safety Report Policy, Continuing Review Policy, and Unanticipated Problem Reporting Policy located here: https://www.ucdenver.edu/research/comirb/policies) and NIMH Reportable Events Policy. Reportable events discovered by study personnel will be to Dr. Stoddard immediately upon discovery via pager. Any such event will be reported to COMIRB according to COMIRB Safety Report Policy. Reporting by the PI, COMIRB, and ISM to the NIMH PO will comply with the NIMH Reportable Events Policy.

Regarding completion of behavioral tasks, it is likely that adolescents will become mildly frustrated or annoyed when completing certain behavioral tasks. During these tasks, adolescent mood will be monitored to ensure that

the adolescent does not become overly frustrated. Prior use of these tasks has shown that children with clinically significant irritability are generally able to complete these tasks without difficulty or significant negative affect.

With regards to fMRI, some children may become nervous or uncomfortable during MRI scanning. High noise environment is a risk of fMRI and all adolescents are required to wear ear protection. All adolescents are warned of unusual sensations during fMRI which are possible due to nerve stimulation. Standard MRI metal screens and MRI-safe gowns will be employed to ensure no ferromagnetic or electronic material will be brought in by the participant into the scanner. A number of procedures have been established to reduce the discomfort of adolescents during neuroimaging protocols (see Protection Against Risks below). As with all Brain Imaging Center protocols, every effort will be made by Brain Imaging Center personnel to engage adolescents by creating a pleasant and positive atmosphere. In the event that a child cannot complete the assessment in the allotted time, an additional day of testing may be scheduled if agreed to by the child and parent/guardian.

Consistent with Brain Imaging Center protocol, a urine pregnancy test will be given to adolescent females to prevent incidental research MRI scan of pregnant subjects. Pregnancy is an exclusion criterion for the study and this will be discussed during the informed consent process. Families will be notified that positive pregnancy screening results will be disclosed to the adolescent only to conform with the Colorado minor consent and confidentiality law. Pregnant adolescents will be excluded from all arms of the study, due to the high likelihood that a positive test will result in acute distress that may confound the study due to a systematic assignment of distressed, pregnant adolescents to the non-MRI arm. Consultation of a positive result will be with a licensed clinician on call for the scan to provide consultation on the interpretation of a positive urine pregnancy screen, rights, and referrals. Pregnant females may re-enroll when they are no longer pregnant.

There are a number of potential risks associated with use of MRI scanning procedures which we will also seek to minimize. First, the magnet within the scanner can cause electric devices including pacemakers, beepers, and watches to malfunction, and some magnetic items can be pulled into the magnet. Therefore, in line with Brain Imaging Research Center requirements, all MRI participants will complete a questionnaire regarding the presence of metal/ electronic devices. Prior to scanning, this questionnaire will be reviewed in detail with the adolescent and their parents to ensure that the adolescent does not have any metal on or in his/her body, and we will ask him/her to take off any metal objects he/she may be wearing (such as a watch or jewelry). Adolescents with implanted electrical devices or ferromagnetic foreign bodies in critical soft tissues will be excluded from the MRI portion of this study. Another risk is the high noise-level of an operating MRI machine. Thus, all MRI participants will be required to wear ear protection.

Another risk associated with MRI scanning is anxiety or discomfort related to being inside the magnet bore. For those individuals who have concerns about the MRI examination, are anxious about the procedure, or simply have difficulty lying still, behavior modification is offered. The MRI-simulator (“mock scanner”) at the Brain Imaging Research Center (BIC) allows for acclimation to MR protocols, improves comfort, and decreases potential anxiety. All children will complete a mock scan prior to actual MRI scanning. Further, to reduce anxiety, a professionally edited videotape of a child having an MRI is available for viewing, and the adolescents and their families may also see the MRI scanner in advance. Parents may also watch their child in the scanning room during MRI procedures via video monitoring if desired. Due to the COVID-19 pandemic, the BIC may restrict access to the mock scanner. A real-scanner acclimation procedure will be used in the event that the mock scanner is not available. The information in the mock scanner protocol will be reviewed with the participants, which includes images of the mock scanner. Additionally, the actual MRI scanner will be shown to subjects prior to scanning for comparison. Real-scanner acclimation to the noise will occur over 8 minutes during the short calibration sequences and longer structural scans prior to the task. Total time for acclimation in the real scanner is the same as for the mock scanner. Scanning sessions will be terminated immediately upon the request of the adolescent, or if the adolescent becomes upset by the noise, claustrophobia, anxiety or poor performance during testing.

No sedation is used. The on-call clinician will also consult with any adolescent participant who becomes distressed through the course of MRI acquisition, or any other portion of the study. For imaging, participants will be notified during the informed consent process that their neuroimages will not be clinically read by a radiologist or other qualified physician. Regardless, Dr. Stoddard or Dr. Penner will immediately be notified of suspicion of any neuroimaging anomaly detected by study personnel. A licensed clinician will review suspected anomaly. If the clinician shares suspicion or cannot explain the anomaly as non-significant, e.g. a common imaging artifact, the

clinician on call will report it to the adolescent's parents or guardian and provide them a copy of their image for their practitioner to review.

Monitoring and responding to adverse events is primarily the responsibility of Dr. Stoddard, the PI, a board-certified child psychiatrist with COMIRB oversight. An Independent Safety Monitor (ISM) will be responsible for an annual review of adverse events and will be notified unanticipated problems or adverse events. James McGough, MD, has agreed to the ISM role. He is a board-certified child psychiatrist and an expert in cognitive trials involving youth with affective and disruptive behavioral disorders. Dr. McGough meets financial and professional independence criteria from all members of the study team as described by the NIMH Policy Governing the Monitoring of Clinical Trials.

The ISM, Dr. McGough, will be immediately notified of any serious adverse event. In addition, once yearly, he will receive data on accrual, all reportable events, and post-IBT mood scale scores for all treatment arms for a cumulative assessment of study safety. Dr. McGough will be granted access for any inquiry about data quality and management. Based on this information he will send a letter to the NIMH PO recommending the suspension, termination, or continuation of the study.

All study assessment information will be considered confidential. Data will be stored in locked-file cabinets at CU behind a locked door. Participant data will be stored using subject identification numbers only to reduce breaches in confidentiality. Identification numbers will code data entered for computer analysis, and the data coordinator will keep all names and code numbers. Findings will be made available to legitimate agents of the adolescents (parents, schools, treating psychologists, physicians), and only with the express, written consent of the parents/guardians. All publications and presentations will report on deidentified data.

Criteria for Stopping

If more than 75% of enrollees allotted to any treatment arm do not complete the protocol, the PI will review the feasibility of that arm with the ISM. The study will be stopped if there is any Serious Adverse Event related to the research. The PI, ISM, COMIRB, and NIMH will determine if changes are needed for the research to continue or if it will be closed.

E. Potential Scientific Problems:

This study is designed to assess the targets of IBT for the treatment of clinically significant irritability in patients, i.e. we are testing the association between the targets and severity of irritability within clinically irritable patients. This study does not include a group of non-irritable patients. The mechanism of IBT's effect on irritability is unknown. While the training is designed to target hostile interpretation bias via reinforcement learning, the training may work through alternative means. For example, youths with severe, chronic irritability have deficits in labeling face-emotions.[66,67] The training may work through increasing emotion recognition; such training has been proposed to treat irritability.[10] In this case, this study will generate measures of reliability and neural response for future investigations. Indeed, procedures for exploratory Aim 3 will gather preliminary evidence of efficacy.

F. Data Analysis Plan:

Development of Computational Models. The application of computational models of learning to behavior and neural response is integral to both the training and scientific aims of this proposal. We will apply well-established models of human reinforcement learning (variants of Rescorla-Wagner and Pierce-Hall that incorporate stimulus generalization[68,69]) and assess their fit to IBT data. Goodness of fit will be assessed with expectation-maximization and maximum-likelihood algorithms. Models will also be tested in secondary analyses of IBT data of youths with DMDD from Dr. Leibenluft's lab. The parameters for the model will be (a) parameters determining initial value, i.e. probability of angry, for each stimulus, (b) learning rate, (c) a parameter determining degree of generalization among stimuli, (d) reliability of judgments (inverse choice temperature). Simulation of the model under parameters estimated from the data will yield predictions for the trialwise likelihood that each face is considered angry and of the trialwise prediction error. (Note: these last two variables could be used as predictors in the fMRI analysis.) For transparency, analytic code (not any data) for all models will be posted to online software development repositories.

Hypothesis Testing. To maintain rigor, all analyses will involve omnibus models with appropriate diagnostics for model fit and influential data. Minimization procedures should ensure balance on the environmental and biological factors (sex, age, SES, and IQ) that may influence hypothesized associations. Additional potential factors are anxiety, depression, pubertal development, and in- or out-of-scanner training. The effects of all of these factors on independent variables will be assessed. If an imbalance across training groups occurs in any of these factors or a significant association is detected between these factors and an independent variable, it will be entered into the omnibus model as a covariate.

Hypothesis 1.1: Baseline hostile interpretation bias is associated with baseline irritability. Linear regression with pre-training balance point (interpretation bias) as a dependent variable and pre-training ARI (irritability) as an independent variable.

Hypothesis 1.2: Active but not sham, IBT will reduce hostile interpretation bias. Mixed-effects linear regression with balance point (interpretation bias) as a dependent variable and training condition (active vs. sham), and time of interpretation bias assessment (pre- or post-training) as independent variables of interest and person as a grouping variable and random effect. Similar models will test for group differences in active or sham IBT on other measures of hostile interpretation bias after training.

Hypothesis 2.1: The rate of learning new associations to ambiguous faces training will be associated with baseline irritability. For those in the active condition, linear regression will test the association between pre-training ARI (irritability) and learning rate to reversal feedback of baseline angry judgments to the two ambiguous morphs.

Hypotheses 2.2 and 2.3: Active, but not sham, IBT will evoke greater neural response in threat-learning systems. For each person, learning will be modeled with regressors coding the "value" or trialwise likelihood that a participant considers the morph to be angry. The amplitude of BOLD %signal change (activity) or amygdala covariance (generalized psychophysiological interaction; connectivity) related to these regressors represents neural response to value. Critically, these regressors represent learning itself where value is changing towards benign judgments in the active training condition to two ambiguous morphs. These will be carried forward to the second level mixed-effects linear models of the effects of morph by pre-training ARI by training condition. A voxel-wise threshold of $p<.001$, whole-brain, cluster corrected to $p<.05$ via permutation testing or Monte Carlo simulation as appropriate,[68] will be used to identify significant associations. A three-way interaction of change in value by morph by training condition will indicate neural areas where learning is influenced by irritability in active but not sham training of reversals of ambiguous morphs. In addition, our *a priori* identification of the likely role of the amygdala, OFC, and ACC justifies follow-up region-of-interest analyses of mean activity or connectivity extracted from these areas with the same omnibus mixed-effects model.

Exploratory Hypothesis 3.1: Change in irritability after training is associated with change in hostile interpretation bias. We will investigate this relationship with mixed-effects linear models with ARI (irritability), balance-point (interpretation bias), and time of assessment (pre- or post-training) as within-person variables.

Exploratory Hypothesis 3.2: Change in irritability after training is associated with magnitude of neural threat-learning system response. We will investigate this relationship with mixed-effects linear models with ARI (irritability), mean value-associated connectivity or activity in the amygdala, OFC, and ACC, and time of assessment (pre- or post-training) as within-person variables.

As requested by NIMH scientific review, I will conduct two additional, secondary analyses: 1) a mediation analysis of active IBT on change in irritability and 2) a multivariate analysis of the shared and unique effects of irritability, anxiety, and depression on hostile interpretation bias.

Power analysis. For Aim 1, a sample size of 100 achieves 80% power to detect an effect size of the expected association of at least $r=.25$ between baseline hostile interpretation bias and baseline irritability using Pearson correlation at a one-tailed alpha of .05. Thus, the proposed study will have sufficient power to detect small to medium sized interaction effects. The study is overpowered for detecting expected effects of IBT on hostile interpretation bias which should be large.[12,13] For Aim 2, a sample size of 100 likewise achieves more than 80% power to detect the expected large association between baseline irritability and learning. For imaging, using a medium effect size of a term in a general linear model ($R^2=.15$), the required sample for 80% power is 50 individuals (p=.05). Our previous study that examined IBT-related changes to face-emotions was medium to large in the orbitofrontal cortex.[13] Thus, the proposed study will have sufficient power to detect small to medium sized interaction effects. Aim 3 is exploratory; this study may estimate effect sizes for future research.

G. Summarize Knowledge to be Gained:

The NIMH requires evidence of neural or cognitive mechanism prior to continuing the development of novel treatments. This study is designed to establish the two most likely targets of IBT's effect on irritability. These neurocognitive targets are hostile interpretation bias and learning circuitry response. The successful completion of this proposed research will establish the neurocognitive basis for a go/no-go randomized controlled trial of the efficacy of IBT for clinical irritability. Next, as evidenced in the analytic plan, this project is designed to provide hypothesis-generating information about hostile interpretation bias and threat learning in irritable youth, who may be vulnerable to aberrant threat processing. This contribution would be significant because it will further develop an evidence based, nonpharmacologic, and inexpensive treatment for irritability that targets specific neurocognitive mechanisms

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