

Active versus control Gaze-Contingent Music Reward Therapy (GCMRT) augmentation of cognitive behavioral therapy in the treatment of pediatric anxiety: protocol for a double-blind randomized controlled trial

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Abstract

Background Threat-related attention bias is an established correlate of anxiety disorders. Gaze-Contingent Music Reward Therapy (GCMRT), an eye-tracking based treatment, involves a music-based positive reinforcement training regimen of eye-gaze direction to reduce this bias. Recent studies have shown promise for GCMRT as an augmentative treatment to enhance the clinical impact of cognitive behavioral therapy (CBT). Yet, this augmentation approach has not been robustly tested among pediatric samples with anxiety disorders.

Methods This preregistered randomized controlled trial will compare the efficacy of randomly assigned active GCMRT vs. a control form of GCMRT among 120 patients (ages 8–17 years old) meeting DSM-5-TR criteria for an anxiety disorder, based on reduction in clinician-rated anxiety pre- to post-treatment between groups. Participants will receive active or control GCMRT alongside CBT. GCMRT involves a computer playing participant-selected music, which is linked to the patient's eye-tracking patterns on matrices of negative and non-negative valence faces. Music plays continuously in the control group, while the active group only hears music while looking at non-negative faces. Behavioral and neural indices of change in attention bias will serve as primary measures of intervention effectiveness. Threat-related attention bias will be indexed as prolonged eye-gaze dwell time on negative-valence faces relative to non-negative faces, with change in this metric across treatment capturing shifts in attention bias. Youth will also complete functional magnetic resonance imaging (fMRI) before and after treatment while resting and during a dot-probe task with threatening face cues. Brain-based implicit threat response will be assessed via a neural efficiency approach. Healthy youth will serve as a baseline comparison to patients on brain-based threat response. Linear mixed effects models will examine between-group trajectories of behavioral attention bias, neural threat-response indices, and anxiety symptoms over the course of treatment.

Discussion The present study will contribute to the literature by (1) determining whether GCMRT is an efficacious adjunct therapy to CBT for pediatric anxiety disorders, and (2) advancing our understanding of the neural mechanisms underlying GCMRT.

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Trial registration Clinicaltrials.gov: NCT06595953. Trial registration date: September 19th, 2024. Data acquisition began December 4th, 2024.

Keywords Attention bias modification · Eye-tracking · Cognitive behavioral therapy · Pediatric anxiety · Youth · Randomized controlled trial · fMRI

Background

Anxiety disorders are among the most common forms of pediatric psychopathology and can persist into adulthood [1], with increasing prevalence and marked impairment of youths' functioning [2–4]. One first-line treatment for pediatric anxiety, cognitive behavioral therapy (CBT) [4, 5], produces remission in approximately half of cases [6, 7], which has motivated recent studies to explore other treatment approaches that may improve outcome rates. Several studies [8–10] have provided promising evidence that gaze-contingent music reward therapy (GCMRT) may augment the clinical response to CBT among anxiety and mood disorders. However, this augmentation approach has not been robustly tested among pediatric samples with anxiety disorders. The current randomized controlled trial will test the general hypothesis that an active form of GCMRT as an add-on to CBT will produce a greater change in clinician-rated anxiety severity than a control form of GCMRT among pediatric patients with anxiety disorders.

GCMRT aims to reduce attentional bias to threat through a positive reinforcement training regimen of eye-gaze direction. Attentional bias toward threat represents a well-established correlate of anxiety disorders [4, 11]. Patients with anxiety disorders implicitly attend more to negative or threatening stimuli in their environment than to neutral or positive stimuli, which can increase their anxiety [11]. A threat-related attention bias occurs when negative-valence stimuli exert greater effects on attention allocation than neutral stimuli. Moreover, threat-related attention bias prospectively predicts the new onset of an anxiety disorder in unaffected youth or worsening anxiety symptoms over time in affected youth [4, 12], suggesting a pathway that initiates or sustains anxiety symptoms.

Randomized controlled trials have evaluated the efficacy of attention bias modification training (ABMT) for pediatric clinical anxiety disorders [13–15]. Meta-analytic findings have demonstrated a statistically robust, albeit clinically modest (Hedge's g range = 0.37–0.49), effect size of active versus control forms of ABMT [16, 17]. Several of these past trials have demonstrated statistically significant augmentation of CBT using a reaction time-based attention bias modification paradigm [18, 19]. However, researchers have suggested that the modest effect size of ABMT may reflect the targeting of reaction time-based performance, which shows weak reliability [20]. Measures of threat-related attention bias quantified through the assessment of gaze fixation show higher reliability estimates [9, 21, 22], which catalyzed the creation of GCMRT. Here, attention bias is operationalized as prolonged eye-gaze (i.e., increased dwell time) on negative-valence stimuli (e.g., faces) relative to non-negative ones. Indeed, both pediatric and adult patients with anxiety disorders demonstrate a greater percentage of eye-gaze-measured negative-valence bias compared to healthy age-matched peers [9, 10, 22, 23]. Accordingly, this eye-tracking-based GCMRT treatment involves an implicit training regimen targeting eye-gaze to modify attention bias away from threat while patients view matrices of faces containing both negative and non-negative emotional expressions.

Specifically, GCMRT employs positive reinforcement learning to target attentional bias toward threat. In the task, participant-selected music serves as a putative reinforcement to increase preferred behavior (i.e., allocating one's attention away from threat stimuli) – music plays only when participants' eye-gaze fixates towards non-negative faces on a matrix of negative and non-negative valence face cues. Thus, to hear their selected music continuously, participants in the active condition will be motivated (consciously or unconsciously) to allocate their attention away from negative face cues and increasingly direct their gaze toward non-negative cues. Conversely, during the control version of GCMRT, music plays continuously regardless of where the participant is looking to standardize receipt of music without valence-contingency. Several randomized controlled trials have

demonstrated promising reductions in attention bias to threat using GCMRT [8–10]. These studies have further suggested that GCMRT may better capture direct attentional components related to anxiety and may be more engaging than reaction time-based tasks.

Uncovering biomarkers related to treatment responsiveness may provide useful indices for personalized novel treatment approaches. Anxiety-related neural systems have been studied extensively using both task-based and resting-state fMRI data [24, 25]. Task-based paradigms have found perturbed responsiveness to threat, especially hyperactivity in the amygdala and insula [25]. Likewise, there are observable disruptions in resting-state intrinsic brain connectivity within regions related to emotion processing, including the default mode network and the executive control network, among individuals with anxiety disorders, even in the absence of threat [24]. However, few studies have identified reliable biomarkers related to both the presence of an anxiety disorder and to treatment responsiveness [26, 27]. Most research examines connectivity in resting-state separately from task-based functional magnetic resonance imaging (fMRI), overlooking potentially relevant correspondence between connectivity patterns [28]. Prior work has identified neural efficiency, defined as one's ability to accommodate distinct cognitive demands with minimal change in functional connectivity patterns, as a potential biomarker for anxiety [29]. Higher neural efficiency, as defined by Schultz and Cole [30], is quantified as less change in functional connectivity patterns between rest and task and relates to better cognitive functioning and task performance. This reflects reduced requirements for network reconfiguration during tasks. Among youth with anxiety, however, lower neural efficiency may relate to poorer treatment outcomes [29]. Thus, neural efficiency is a relevant biomarker to examine in relation to treatment response among youth with anxiety disorders receiving CBT + active or control GCMRT. To establish the association between anxiety and neural correlates of threat at baseline, healthy youth will complete the same resting-state and attention bias task-based fMRI scans to serve as a comparison sample.

Aims and hypotheses

The current trial has three aims: First, we aim to test the efficacy of GCMRT to augment CBT in a clinic setting among youth with anxiety disorders. We hypothesize that (Aim 1a) patients who receive the active form of GCMRT added to CBT will show a significantly greater reduction from pre to post-treatment in clinician-assessed anxiety severity, measured with the Pediatric Anxiety Rating Scale (PARS) [31], compared with patients who receive the control GCMRT added to CBT. We also hypothesize that (Aim 1b) patients who receive the active form of GCMRT added to CBT will manifest a greater significant reduction in secondary endpoints of anxiety. For secondary endpoints, response will be defined using the clinician-rated Clinician Global Impression Improvement (CGI-I) scale [32] and rated symptoms of anxiety on the Screen for Child Anxiety Related Disorders (SCARED) completed by parents and patients [33]. Second, we will assess changes in attention bias on the Matrix task (described below), which will be used to assess attention bias pre- to post-treatment, as a mediator of GCMRT treatment response (Aim 2). We hypothesize that treatment response to the active, relative to control, GCMRT will be mediated by changes in attention bias on the Matrix task as measured repeatedly during treatment. Third, measures of neural efficiency using resting-state and dot-probe attention bias task-based fMRI (described below), which will be used to assess neural correlates of attention bias pre- to post-treatment, will be evaluated in relation to diagnostic status and continuous anxiety measures, and overall treatment response in patients. Based on prior research [29], we hypothesize that neural efficiency at baseline will be lower among youth with anxiety disorders compared with healthy youth and will be negatively associated with anxiety symptoms, as rated by parents, patients, and rated by clinicians (Aim 3a). Further, we hypothesize that lower neural efficiency at baseline will be associated with poorer overall treatment response among patients (Aim 3b). We also expect GCMRT condition will moderate the relationship between neural efficiency and treatment response, such that patients in the active GCMRT condition will demonstrate a weaker relationship between neural efficiency and treatment outcomes compared to the control condition (Aim 3c).

Exploratory analyses, assuming sufficient quality post-treatment fMRI data among patients, will compare treatment-related changes in neural efficiency in patients undergoing treatment relative to healthy youth and among patients assessing active vs. control GCMRT-specific treatment effects. Finally, given the focus in past literature on GCMRT specifically for social anxiety disorder [8, 9], an exploratory analysis will examine eye-gaze dwell time on neutral-disgust matrices only among a subset of participants with social anxiety disorder. We hypothesize that treatment response to the active, relative to control, GCMRT will be mediated by changes in attention bias to neutral vs. disgust faces on the Matrix task as measured repeatedly during treatment only among the patients with social anxiety disorder.

Methods

Study setting and trial design

This study is a randomized, double-blind, placebo-controlled clinical trial conducted at the National Institute of Mental Health (NIMH) in Bethesda, MD, USA. The study protocol was independently reviewed and approved by the NIMH Scientific Review Committee in the Fall of 2024, and was also peer-reviewed and approved by the NIMH Board of Scientific Counselors in the Fall of 2025. The trial is designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Supplement). Subjects will be seen by experienced clinicians during each phase of the study, who will monitor for potential risks. There are no known harms associated with GCMRT. Risks of treatment include emotional arousal that is commensurate with the level experienced by youth in their everyday lives. There is no patient or public involvement in the design, conduct, or reporting of the trial. The full study protocol, including prespecified hypotheses and analytic plan, has been preregistered (<https://osf.io/tywuk/>). Results of the completed trial will be publicly available on ClinicalTrials.gov.

The study employs a two-arm, parallel-group design. All participants receive manualized CBT for pediatric anxiety. Participants are randomized in a 1:1 ratio to receive either: (1) Active GCMRT, or (2) Control GCMRT, which is structurally identical to the active condition but without the contingency between gaze behavior and reward delivery. In the active condition, delivery of self-selected putatively rewarding music is contingent on gaze directed away from negatively-valenced stimuli (i.e., threat-related faces). In the control condition, music is delivered continuously regardless of gaze location.

GCMRT sessions are administered immediately before or after CBT sessions to evaluate whether attentional retraining augments CBT outcomes. Participants complete 12 weekly CBT sessions, with GCMRT administered during weeks 4–12 (nine sessions total). Each GCMRT session lasts approximately 15 min. A schematic of study procedures is provided in Fig. 1.

Sample size

The target sample size is $N = 120$ participants, randomized equally between conditions. This estimate assumes a Type I error rate of 0.05 and an effect size of $d = 0.4$ in a two-cell, parallel-group design without clustering of subjects in randomization. An effect size of 0.4 is consistent with results from meta-analyses examining the effects of ABMT on anxiety in youth [17]. This estimate is considered a lower bound because the estimated effect size derives from meta-analysis of studies using ABMT as opposed to GCMRT, which only has been used in three randomized clinical trials of anxiety disorders [8, 9, 34], with different control conditions across the three RCTs. Results from previous studies suggest that ABMT produces less robust effects on attention bias than GCMRT and less robust effects on clinical measures of anxiety. This may relate to the superior psychometric properties [21] of gaze-based measures used in GCMRT as compared to reaction time-based measures used in ABMT. Reductions in attention bias reflect engagement of the mechanism mediating therapeutic change for both ABMT and

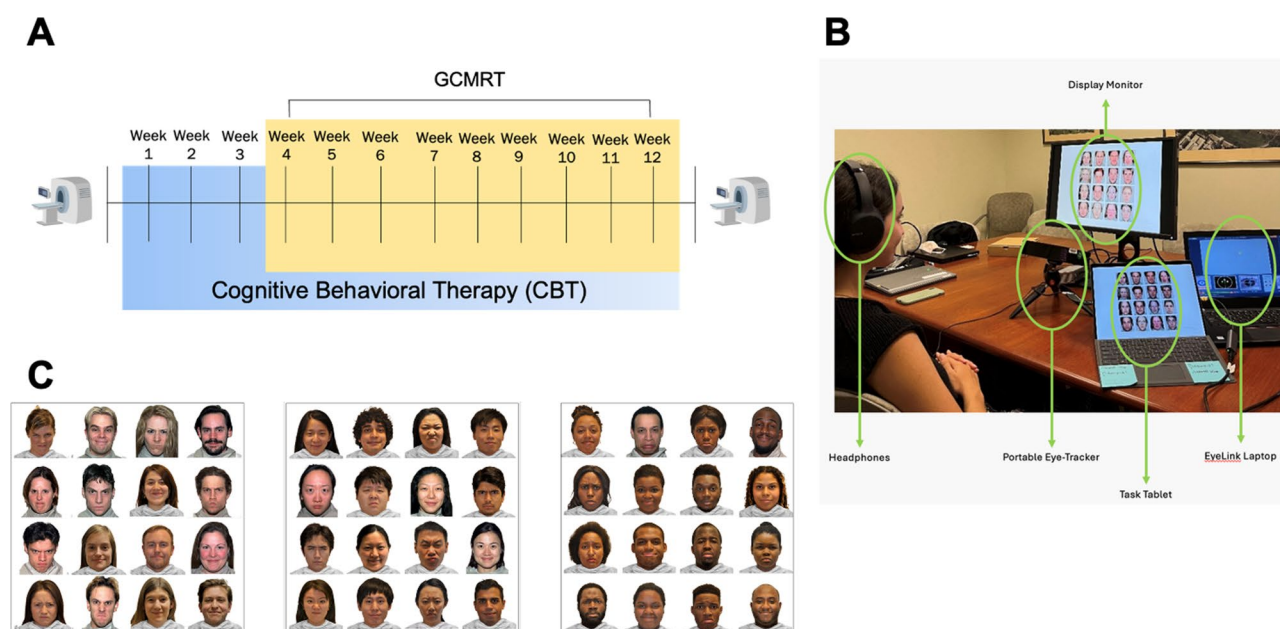


Fig. 1 Schematic of study procedures. Note: GCMRT = Gaze-Contingent Music Reward Therapy. **A.** General outline of GCMRT study timeline. **B.** Shows the GCMRT administration equipment set-up. **C.** Example 4 × 4 face matrices.

Table 1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
8-17 years old (participants who assent at age 17 but turn 18 during the course of the study will be eligible to re-consent as adults to complete all procedures)	Any serious medical condition (or condition that interferes with fMRI scanning for HV)
IQ-scores >70 as assessed by the WASI	Pregnancy
Fluent in English	Current use of any psychoactive substances
Patient group will have a current clinician-confirmed primary diagnosis of separation anxiety disorder, generalized anxiety disorder, or social anxiety disorder	Current diagnosis of Tourette's disorder, OCD, PTSD, conduct disorder, major depressive disorder, or ADHD of sufficient severity to require pharmacotherapy
Willingness to complete 12 weekly CBT sessions	Current suicidal ideation
	Past or current history of mania, psychosis, or severe pervasive developmental disorder

GCMRT. This justifies viewing the effect size estimate and corresponding sample size as lower-bound estimates. Data for the first primary aim will be analyzed using a linear mixed-effects model, allowing for fixed treatment effect over time and random subject effects on the primary outcomes of clinician-rated anxiety levels.

Participant recruitment and eligibility

Participants are recruited from an ongoing NIH study protocol involving youth seeking treatment for anxiety disorders. Recruitment for this study began in December 2024 and remains ongoing. The study is advertised using mailed flyers and clinical referrals. Eligibility is initially assessed via telephone screening, followed by an in-person baseline evaluation including structured diagnostic interviews and cognitive assessment. Families who indicate interest in participation receive further information about the trial via a phone-screening call and are asked to provide general information about the potential study participant (e.g., presenting anxiety symptoms, age, etc.). If the individual meets eligibility criteria (listed in Table 1) based on this initial phone assessment, the families are invited onsite for a more thorough screening visit. Patients requiring concomitant care with medication will not

be enrolled in the protocol but can still receive care in a more flexible manner in another protocol with the same principal investigator. Healthy volunteers (HV) are assessed in the same way as potential patient participants and abide by all the same exclusion criteria. HV must not fulfill criteria for a current or lifetime DSM-5-TR psychiatric disorder, which is confirmed by a trained clinician administering the K-SADS [35] to the child and the parent. An additional exclusion criterion for HV is MRI contraindication (e.g., permanent retainer, metal in the body). All participants must have an IQ > 70, as assessed by the Wechsler Abbreviated Scale of Intelligence, second edition [36]. Participants incur no cost for participation. Travel expenses may be reimbursed in accordance with NIH policy.

Randomization and blinding

After baseline screening and three CBT sessions involving psychoeducation and treatment planning, patients are randomized to either the active or control condition of GCMRT. Random assignment is conducted using a one-to-one ratio via the Clinical Trial Randomization Tool [37] with a maximally tolerated imbalance (MTI) procedure, which specifies how unbalanced the group sizes can ever become during the randomization sequence (MTI = 3 for the current trial). The study is double-blind; participants, clinicians, outcome assessors, and families are all unaware of treatment assignment. All randomization procedures (i.e., sequence and assignment) are conducted by an independent study personnel member to maintain blinding of the principal investigator and treating clinicians. In the case of interim analysis, the blind will only be lifted by the individual conducting the analysis, who will have no contact with patients. Additional blinding measures are in place to prevent inadvertent blind breaking. For example, participants wear noise-cancelling headphones during the task to prevent the experimenters from overhearing the pattern of music. Additionally, neither the principal investigator nor clinicians are ever in the same room as the participant when the GCMRT task is being administered. Participants are explicitly instructed not to discuss their GCMRT experience with the researchers or their clinicians. Lastly, access to the randomization sequence is password-protected and only available to an independent study personnel member who reveals each successive patient's condition allocation (using a blinded color-condition name) after they have consented into the protocol. Personnel who interact directly with the study subjects will not be aware of the assigned treatment condition (i.e., "double-blind"). Parents will not be in the room when GCMRT is conducted.

Measures

Primary outcome measures

The primary outcome measure is the clinician-rated PARS, a continuous measure of anxiety symptoms and related functional impairment in youth [31]. The measure comprises a 50-item checklist assessing seven dimensions of global anxiety severity/impairment: (1) number of symptoms, (2) frequency of symptoms, (3) severity of distress associated with anxiety symptoms, (4) severity of physical symptoms, (5) avoidance, (6) interference at home, and (7) interference outside of home. Each item is rated on a 0–5 scale by a clinician based on parent- and child-report. The total score is calculated based on a sum of subscales 2, 3, 5, 6, and 7. Total scores range from 0 to 25, with higher scores reflecting greater levels of anxiety. Scores above 11.5 indicate the presence of an anxiety disorder. The PARS shows moderate test-retest reliability (0.55) and excellent internal consistency (intraclass correlation coefficient [ICC] = 0.97) [31]. PARS is assessed at baseline, mid-treatment, and post-treatment.

Secondary outcome measures

The Clinical Global Impression of Improvement Scale (CGI-I) is a clinician-rated measure of global symptom improvement [32]. CGI-I scores range from 1 to 7, with lower scores reflecting greater levels of improvement.

Participants with CGI-I ratings of ≤ 3 at CBT week 12 are categorized as a treatment “responder” and participants with scores > 3 are counted as a “non-responder.”

The SCARED is a 41-item self- and parent-report measure of pediatric anxiety symptoms [33]. The mean of total parent and child ratings will be used as this secondary outcome measure. Items are rated from 0 (*Not True or Hardly Ever True*) to 2 (*Very True or Often True*). Responses to each item are summed to generate a total score, ranging from 0 to 82. Higher scores indicate greater levels of anxiety, with scores above 25 suggesting the presence of an anxiety disorder. The SCARED has good to excellent test-retest reliability (0.70–0.90) [38] and good internal consistency ($\alpha = 0.91$) [39].

The Self-Efficacy Questionnaire for Children (SEQ-C), is a 24-item self-report measure of self-efficacy in youth [40]. Self-efficacy is defined as one’s perceived ability to achieve goals and exert control over one’s emotions, actions, and environment, and has been shown to play a role in anxiety severity and treatment outcomes in youth and adults [41, 42]. Items are rated on a 1 to 5 Likert scale. Total scores range from 24 to 130, with higher scores indicating greater self-efficacy. The SEQ-C has been shown to demonstrate good internal consistency ($\alpha = 0.88 - 0.89$) [40, 43].

The Youth Exposure Efficacy Scale for Anxiety (YES-A), is a 10-item self-report measure of self-efficacy administered by the clinician to the patient at every other CBT session, starting at CBT week 4. The YES-A is adapted from the Self-Efficacy During Exposure-Child (SEE-C) measure, a 9-item measure which assesses youth’s perceived state self-efficacy during therapy exposures using a 5-point Likert scale [44]. The YES-A is specifically designed to assess youth’s feelings of empowerment and confidence in managing their own anxiety symptoms as it relates to in-session CBT exposures.

After the last session of GCMRT, participants complete a debriefing form. They are asked to indicate how they felt during the music task on a visual analog scale anchored to a range of opposing emotions (e.g., Comfortable – Uncomfortable, Anxious – Relaxed, etc.). They are also asked to write-in a response to an open-ended question gauging their awareness of the task condition assignment (“What do you think the purpose of the music was during the task?”) at the beginning of treatment, mid-treatment, and end of treatment. Participants complete these answers electronically or on a paper sheet that is placed in a sealed envelope and reviewed by a study personnel member who does not have contact with participants.

Measures of comorbid symptom clusters

Elevated levels of anxiety frequently co-occur with increased symptoms of depression [45] and irritability [46]. Baseline levels of these comorbid symptom clusters will be explored as moderators of training effects. Further, whether training effects of GCMRT generalizes to changes in depression and irritability symptoms mid- and post-treatment will be explored.

The Mood and Feelings Questionnaire (MFQ) short-form is a 13-item self-report measure of depressive symptoms in children [47]. Items are rated both by patients and by their parents on a scale from 0 to 2; with the overall score ranging from 0 to 26. Higher scores reflect higher levels of depression, with scores greater than 8 indicating the potential presence of clinically significant depression. The MFQ has excellent internal consistency ($\alpha = 0.91 - 0.93$) [48].

The Affective Reactivity Index (ARI) is a 7-item dual-informant (parent and child) measure of irritability in children [49]. Items are rated on a scale from 0 to 2; with the overall score ranging from 0 to 12. Higher scores reflect higher levels of irritability. The ARI has good to excellent internal consistency ($\alpha = 0.88-0.92$) and test-retest reliability (0.88–0.90) [50].

Treatment and tasks

Attention allocation eye-tracking tasks

This protocol involves two related attention allocation eye-tracking tasks (see Fig. 1): (1) the GCMRT eye-tracking task for attention retraining at CBT sessions 4–12, and (2) the Matrix eye-tracking task for attention allocation assessment pre-, mid-, and post-treatment. In both eye-tracking tasks, participants view matrices of faces with varying emotional-related stimuli (i.e., a four-by-four matrix with 16 faces). Each of these matrices contains both non-negative and negative faces displaying pairs of emotions (i.e., eight disgust and eight neutral faces; eight sad and eight happy faces; eight angry and eight happy faces). Given prior literature in anxiety disorders finds biases across a range of emotions [51–55], these various negative-nonnegative condition-pair contrasts were originally designed to elicit strong emotional responses and model specificity in biased attentional deployment and different symptoms [51, 56–58].

The face matrices are comprised of half female and half male faces. The four inner faces of the matrices always contain two negative and two non-negative face cues. These paradigms use faces drawn from datasets used for other face processing tasks deployed for research with children [59, 60]. The Matrix task and GCMRT task consist of two different sets of face matrices (Set A and Set B). Participants are instructed to look freely at the face matrices (900 × 900 pixels), which are presented in a randomized order.

Eye-gaze is captured using an EyeLink Portable Duo eye-tracking apparatus (SR-research, Ottawa, Ontario, Canada) that operates in remote mode using a forehead sticker. Real-time binocular eye-tracking data are continuously recorded throughout the task using a 25 mm lens at 1000 Hz, with a 1920 × 1080 pixel display resolution. Data are processed using EyeLink DataViewer software (SR-research, Ottawa, Ontario, Canada). Stable eye-gaze fixations of at least 100 ms are registered based on their location for two areas of interest: negative-valence faces (i.e., angry, disgust, sad), and non-negative valence faces (i.e., happy, neutral). The sum of sustained gaze fixations across matrices and conditions is acquired to quantify “dwell time.” Attention bias is indexed by the duration during which subjects view negative as opposed to neutral or positive face emotion displays. All participants are seated approximately 520 mm away from the eye-tracker and completed the task in the same experimental room with identical screen dimensions (475 × 270 mm) and lighting. Data are excluded if fewer than 20 (out of 30 matrices) contain at least one valid fixation (≥ 100 ms) within a block.

Gaze-contingent music reward therapy (GCMRT)

GCMRT, described above, is an eye-tracking based attention training paradigm in which gaze behavior is paired with auditory reward (self-selected music). Participants are randomly assigned to receive either active or control GCMRT, which is administered by a blinded research assistant on a study desktop prior to or following each CBT session. During task administration, the research assistant remains in the test room but stays blinded given they cannot hear the music playing due to the participant wearing noise-cancelling headphones. In the active condition, music playback is suspended whenever gaze is directed toward negatively-valenced stimuli, reinforcing attentional disengagement. In the control condition, music is played continuously, independent of gaze behavior. At each session, participants select 3–5 songs from an extensive music library that is regularly updated with popular contemporary music from various genres. During each GCMRT session, 30 matrices of faces are presented for 24 s each. Participants complete nine GCMRT sessions (~12–15 min each) during weeks 4–12 of CBT.

Matrix eye-tracking task

The Matrix eye-tracking task is completed at baseline, mid-treatment, and post-treatment to assess attention allocation. This task is identical to the GCMRT task with the exception that it does not contain any music. In the Matrix task, 90 matrices are displayed in three blocks, each of which contained 30 trials of the same three

condition-pairs as the GCMRT task. Before each trial, a fixation cross is presented until the eye-tracker records a continuous fixation (1000 ms) to ensure that participants' gaze begins at the center of the succeeding matrix. Matrices are presented for 6000 ms, followed by an inter-trial interval of 2000 ms. Each block lasts for 8–10 min for a total of approximately 45 min for the entire Matrix task including calibration and breaks.

Cognitive behavioral therapy (CBT)

All patients receive 12 weekly individual sessions of manualized CBT [61] administered by a licensed psychologist who specializes in the treatment of anxiety in youth. Therapists are trained on the CBT protocol by experts at the Yale Child Study Center [62]. There will be bi-weekly discussions between the treating clinicians and principal investigator to monitor protocol adherence and treatment progress. Each CBT session lasts 40–60 min, with additional home practice to build on the exposures completed during sessions. Treatment begins with an introduction to CBT, psychoeducation on anxiety, and self-monitoring of symptoms for several weeks to identify patterns. After the first three weeks of treatment, youth are instructed to complete their first out-of-session exposure. Beginning at session four, youth practice in-session exposures and cognitive restructuring with the therapist. Parents are involved in three sessions over the course of treatment to facilitate assessment of the child's psychopathology and improvement over treatment. Additionally, home practice information is communicated to the parents.

Functional magnetic resonance imaging (fMRI)

Dot-probe attention bias task and resting-state fMRI

Youth with anxiety disorders and a healthy comparison sample of youth will complete an event-related dot-probe fMRI task [63] alongside a resting-state scan at two time points. Scans will be completed at baseline and after CBT treatment for patients, and for HV the task will be completed at two time points approximately 12 weeks apart. During the resting-state fMRI, youth passively view a fixation cross for 10 min and are encouraged to remain awake. Two resting-state runs are completed at each scan for a total of 20 min.

Immediately following the resting-state fMRI, youth also complete a threat-based emotional dot-probe task. The dot-probe task consists of four conditions presented in a randomized order: (1) congruent trials, in which a threat and neutral face-pair appear and the probe arrow appears in the location of the threatening face, (2) incongruent trials, in which a threat and neutral face-pair appear and the probe arrow appears in the location of the neutral face, (3) neutral trials, in which a neutral-neutral face-pair appears, serving as a non-threat control condition and (4) baseline trials, in which no faces are shown, serving as a no-face control condition. The dot-probe task uses Picture Set B from the TAU-NIMH Attention Bias Measurement Toolbox.

During the dot-probe task, participants are presented with a fixation cross for 500 ms followed by standardized face-pairs shown vertically on a screen (1440 × 900 pixel) for 500 ms. Face-pairs either contain two female faces or two male faces. A left or right-facing arrow probe (< or >) appears in the location vacated by one of the two faces for 1000 ms. Both the direction and location of the probe (left or right, top or bottom) are counterbalanced. Participants are instructed to respond as quickly and as accurately as possible with a left or right button press indicating the direction of the probe. The task consists of two runs, each of which contains 213 trials. The inter-trial interval varies in length ($M=500$ ms; $SD=156$ ms) with 53 additional null trials, in which a blank screen is shown for the entire duration of the trial, increasing jitter times. There are 40 baseline trials, 40 threat-congruent trials, 40 threat-incongruent trials, and 40 neutral-neutral trials (described above).

Data acquisition

Functional neuroimaging data are acquired using a 3.0 Tesla GE scanner (Waukesha, WI) with a 32-channel head coil. For the dot-probe task, a T2*-weighting gradient echo pulse sequence is acquired across 450 volumes at the following specifications: repetition time [TR]=1250 ms, echo time [TE]=27 ms, flip angle=65°, FOV=24 cm², matrix=96×96, voxel size=2.5 mm isotropic, multiband acceleration factor=2, number of slices=42. A field map is acquired for distortion correction with alternating phase encoding gradients at the following specifications: TR=1250 ms, TE=27 ms, flip angle=50°, FOV=24 cm², matrix=96×96, voxel size=2.5 mm isotropic.

For resting-state, a multi-echo planar imaging sequence is acquired with the following specifications: TR=2000 ms, TE_{1,2,3}=14.8, 28.4, 42.0 ms, flip angle=77°, matrix size=64×64, 34 axial interleaved slices, voxel size=3.8 mm, volumes=300 per echo (900 total per run).

A T1-weighted, magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) sequence is acquired for co-registration (TE=min full, TI=900 ms, flip angle=7°, slice thickness=1 mm, FOV=256mm³, matrix=256×256×176, bandwidth=25.00 Hz per 256 voxels, voxel size=1 mm isotropic).

Statistical analyses

Clinical outcomes

All analyses will follow an intent-to-treat approach, including all randomized participants with available data. Primary clinical analyses will evaluate the effect of GCMRT treatment condition on PARS scores over time using linear mixed-effects models. Models will include fixed effects for treatment group, time, and the Group × Time interaction; and random effects for subject-level intercepts. Sex will be included as a covariate. Age and baseline anxiety severity will be included as additional covariates if groups differ significantly at baseline. Secondary analyses will evaluate continuous outcomes (e.g., SCARED) using mixed-effects models, and categorical outcomes (i.e., CGI-I ratings of ≤3 at CBT week 12=treatment “responder,” and ratings >3 = “non-responder”) using chi-square tests. A moderation analysis will evaluate the baseline attention bias (percentage of negative dwell time) by GCMRT treatment group interaction. A mediation analysis will evaluate whether change in attention bias is a mediator of treatment effects (i.e., PARS). The significance threshold for all primary and secondary clinical analyses will be two-tailed set at $\alpha=0.05$. Some degree of missingness is expected. As such, primary analyses will use full information maximum likelihood. Multiple imputation or listwise deletion approaches may be considered depending on the extent of missing data and whether data is missing completely at random.

Imaging data

Primary analyses of neuroimaging data will evaluate neural efficiency combining resting and task-based imaging. Our workflow will build on methods established by Linke, et al. [29]. Functional MRI data will be preprocessed using a standardized pipeline such as fMRIPrep. We will apply a whole-brain parcellation scheme to extract time series data from cortical and subcortical regions ensuring comprehensive brain coverage. Noise signals will be regressed from both resting-state and task-based time series; for the dot-probe task, the onset of face-pair stimuli will also be regressed out. Functional connectivity will be quantified using partial correlations, which estimate direct connectivity between pairs of regions and have been shown in prior work to provide reliable estimates of functional connectivity [29]. Following preprocessing, each participant will have two connectivity matrices: one representing resting-state connectivity and the other representing task-based connectivity. To quantify neural efficiency, we will vectorize (i.e., unwrap) the upper triangular elements of both matrices and compute a similarity score. We will use an independent samples t-test to compare neural efficiency between patient and healthy volunteer groups at baseline; correlations will be applied to relate neural efficiency to self-reported anxiety (e.g.,

SCARED) among HVs and patients. A linear mixed-effects model will be used to assess whether neural efficiency at baseline is associated with change in PARS ratings over the course of treatment. The interaction with GCMRT condition will be added in a second step to assess whether neural efficiency relates to GCMRT-specific treatment effects. Additional exploratory analyses, assuming sufficient quality post-treatment scanning data collection, will use a mixed-effects model to examine changes in neural efficiency pre- to post-treatment in patients relative to healthy youth. A second exploratory mixed model would probe the interaction by GCMRT condition in patients only. Age, sex and IQ will be considered as covariates in all analyses.

Discussion

Attentional bias toward threat is a key mechanism underlying anxiety disorders that is not explicitly targeted by CBT [11]. GCMRT may influence attentional bias through “bottom-up” mechanisms by directly retraining salience contingencies using principles of reinforcement learning. Despite promising early evidence, GCMRT has not yet been systematically examined as a complementary augmentation to CBT among a large sample of children and adolescents with anxiety disorders. Thus, further research is needed.

This study will be the largest randomized controlled trial among children and adolescents with anxiety disorders using fMRI to assess neural changes in attention bias over the course of CBT augmented with GCMRT. Randomization assignment is double-blinded, such that clinicians, the principal investigator, research coordinators, patients, and their families are not aware of their GCMRT treatment condition. A number of procedures are in place to mitigate risk for potential blind-breaking, such as the use of noise-cancelling headphones during the task administration, ensuring the treating clinician is never in the same room as the participant during GCMRT administration, and a standardized script reminder to participants to ensure they do not discuss the details of the GCMRT training with the research assistants or their treating clinicians. A debriefing form will also be administered to all patients at the end of treatment asking for their thoughts on the training. Finally, the use of clinician-rated assessment, rather than self-report, as the primary outcome measure will reduce any potential for self-report desirability bias.

Despite strengths of the preregistered design, there are several limitations worth noting. First, all patients with anxiety disorders will be medication-free and will receive CBT with either active or control GCMRT. Thus, findings will not be generalizable to other efficacious treatments, such as medication. However, the goal of the current study is to determine whether GCMRT enhances outcomes above and beyond the current strongest evidence-based psychological treatment for anxiety, CBT. Second, a two-arm design was selected to maximize sample size in each group and increase power to detect significant effects. There may be expectancy effects associated with the receipt of any additional augmentative treatment. However, a three-arm design, in which one group only receives CBT without an active or control GCMRT, was not pursued due to power concerns. Third, patients with various anxiety disorders will be included (i.e., social anxiety disorder, generalized anxiety disorder, separation anxiety). As such, training stimuli cannot be tailored to specific subtypes of anxiety disorders, again due to power concerns. However, CBT exposures are tailored according to the relevant subtype of anxiety disorder. Moreover, an exploratory analysis of specific changes in attention allocation to neutral-disgust face pairs among a social anxiety disorder subgroup is included to partially address this concern. Fourth, patients with depression or OCD are excluded, thus findings will not be generalizable to these related conditions.

In summary, this is the largest randomized controlled trial to date among children and adolescents with anxiety disorders that will test the efficacy of a novel, computer-based attention bias training, GCMRT, which aims to reduce heightened attention bias towards threat. GCMRT will be delivered alongside manualized CBT for pediatric anxiety disorders, which targets distinct top-down mechanisms to complement the bottom-up attention retraining approach. The GCMRT training has embedded characteristics to enhance motivation and engagement, in that participants select their own preferred music tracks at each session to play throughout the training. Lastly, task-based and resting-state fMRI will be analyzed before and after treatment to delineate mechanisms that

may guide future treatment selection. This study has the potential to contribute to the development of personalized treatments for pediatric anxiety disorders and delineate the mechanisms underlying a predictive association between baseline attentional bias both behaviorally and on a neural level.

Abbreviations

ABMT	Attention Bias Modification Training
ARI	Affective Reactivity Index
CBT	Cognitive behavioral therapy
CGI	Clinical Global Impressions-Improvement Scale
CONSORT	Consolidated Standards of Reporting Trials
fMRI	functional magnetic resonance imaging
FOV	field of view
GCMRT	gaze-contingent music reward therapy
HV	healthy volunteers
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
MFQ	Mood and Feelings Questionnaire
MTI	maximally tolerated imbalance
PARS	Pediatric Anxiety Rating Scale
PI	principal investigator
SCARED	Screen for Child Anxiety Related Disorders
SEQ-C	Self-Efficacy Questionnaire
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TE	Echo time
TR	Repetition time

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Author contributions DSP is the principal investigator for the project. DSP, MEB, SPH, KML, EB, WKS, YBH and AL conceptualized the initial trial design. MEB, MK, KML, EB, LAM, EC, and AR implement the trial and manage data acquisition. The manuscript was written by MEB, with significant contributions and revisions from DSP, SPH, MK, KML, EB, WKS, YBH, AL, LAM, EC, and AR. All authors have approved the submitted version and have agreed to be personally accountable for their contributions.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate All procedures were approved by the NIMH Institutional Review Board in accordance with the principles of the Belmont Report and the ethical standards set forth in the Declaration of Helsinki. Written informed consent is obtained from parents or legal guardians by trained clinicians, and assent is obtained from all participants prior to enrollment, including consent/assent to publicly share data. Participation is completely voluntary and participants may request to withdraw their participation at any time. Any protocol amendments will require approval by the NIH Institutional Review Board. The principal investigator will ensure all mechanisms used to share data will include proper

plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant).

Consent for publication Not applicable.

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Competing interests The authors declare no competing interests.

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