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Research paper

# Responding to threat: Associations between neural reactivity to and behavioral avoidance of threat in pediatric anxiety

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ABSTRACT

*Background:* Despite broad recognition of the central role of avoidance in anxiety, a lack of specificity in its operationalization has hindered progress in understanding this clinically significant construct. The current study uses a multimodal approach to investigate how specific measures of avoidance relate to neural reactivity to threat in youth with anxiety disorders.

*Methods:* Children with anxiety disorders (ages 6–12 years; $n = 65$ for primary analyses) completed laboratory task- and clinician-based measures of avoidance, as well as a functional magnetic resonance imaging task probing neural reactivity to threat. Primary analyses examined the ventral anterior insula (vAI), amygdala, and ventromedial prefrontal cortex (vmPFC).

*Results:* Significant but distinct patterns of association with task- versus clinician-based measures of avoidance emerged. Clinician-rated avoidance was negatively associated with right and left vAI reactivity to threat, whereas laboratory-based avoidance was positively associated with right vAI reactivity to threat. Moreover, left vAI-right amygdala and bilateral vmPFC-right amygdala functional connectivity were negatively associated with clinician-rated avoidance but not laboratory-based avoidance.

*Limitations:* These results should be considered in the context of the restricted range of our treatment-seeking sample, which limits the ability to draw conclusions about these associations across children with a broader range of symptomatology. In addition, the limited racial and ethnic diversity of our sample may limit the generalizability of findings.

*Conclusion:* These findings mark an important step towards bridging neural findings and behavioral patterns using a multimodal approach. Advancing understanding of behavioral avoidance in pediatric anxiety may guide future treatment optimization by identifying individual-specific targets for treatment.

## 1. Introduction

Anxiety disorders are the most prevalent mental health disorders in youth and have the potential for a chronic course when not effectively addressed (Costello et al., 2005; Kessler et al., 2005; Merikangas et al., 2010). Most lifetime anxiety disorders emerge during childhood and adolescence, marking a period of particular risk (Beesdo et al., 2009; Gregory et al., 2007; Kessler et al., 2005). Considering the early age of onset and long-lasting consequences of anxiety, understanding the mechanisms that contribute to the maintenance of pediatric anxiety disorders could promote early detection and guide intervention development. Previous research has implicated elevated behavioral avoidance of threat as one such mechanism contributing to the maintenance of anxiety disorders (Whiteside et al., 2013). Maladaptive or excessive avoidance of potential threat is associated with poorer overall functioning in anxious youth, and avoidance is thought to contribute to the maintenance of pediatric anxiety disorders (Shimshoni et al., 2018; Silverman and Kurtines, 1997). In fact, reducing maladaptive avoidance through exposure is a key feature of current first-line psychosocial treatments for pediatric anxiety (Silverman et al., 2008).

Despite broad recognition of the central role of avoidance in anxiety disorders, a lack of specificity in the operationalization of avoidance has hindered progress in understanding this clinically significant construct. Avoidance of threat encompasses an array of heterogeneous behaviors

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and tendencies (Krypotos et al., 2015; LeDoux and Daw, 2018; Silverman et al., 2008). For example, avoidance behavior may involve intentional, conscious decisions to avoid anticipated threat (LeDoux and Daw, 2018), such as a child actively choosing not to attend a party to avoid the anticipated threat of a socially evaluative interaction. Alternatively, avoidance behavior may arise out of implicit determinations of threat or habitual patterns (LeDoux and Daw, 2018), such as a child who unknowingly avoids eye contact with unfamiliar peers.

In line with the complex constellation of behaviors encompassed by the broad construct of behavioral avoidance, previous studies have measured avoidance in a multitude of ways, including via performance on laboratory-based tasks and via reports of real-world behaviors, such as self-report, parent-report, and interview-based ratings (Etkin et al., 2021a; Etkin et al., 2021b; Krypotos et al., 2015; Silverman and Ollendick, 2005). Recent advances in motion-tracking technology and approaches that integrate information across multiple informants have improved the validity of measures of avoidance (Lebowitz and François, 2018). Despite these advances, these measures are typically considered in isolation (Lebowitz et al., 2018), leaving a critical gap in understanding of how distinct measures of avoidance relate to one another. For example, avoidance measures vary on the proximity and immediacy of the threat measured, as well as the need for explicit recognition of avoidance behavior. Some measures, such as the Yale Interactive Kinetic Environment Software (YIKES) task (Lebowitz and François, 2018), examine in-the-moment physical avoidance of continuously present stimuli. By measuring avoidance with physical movements, this task circumvents the need for explicit recall. In contrast, interview-based measures such as the Pediatric Anxiety Rating Scale (PARS; Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002) rely on explicit recall but integrate information from parents and children to capture a holistic measure of avoidance in children's daily lives. Unlike the YIKES task, this measure can assess anticipatory avoidance of prospective future threats. While both are considered avoidance measures, they are designed to assess different components of the broad construct of avoidance.

As suggested by LeDoux and Daw (2018), different operationalizations of avoidance are likely to have distinct underlying neural mechanisms. Decades of research showing a lack of consistent concordance among subjective, behavioral, and physiological measures of anxiety (e.g., Bradley and Lang, 2000; Lang, 1968) highlight the importance of considering responses to threat across multiple levels of analysis (LeDoux and Daw, 2018; Taschereau-Dumouchel et al., 2022). However, while parallel lines of research have demonstrated anxiety-related alterations in both neural reactivity to and avoidance of threat in anxious youth, scant research has examined how these processes might relate to one another.

The insula, amygdala, and ventromedial prefrontal cortex (vmPFC)—regions that show altered functioning and connectivity in anxiety disorders (e.g., Klumpp et al., 2012; McClure et al., 2007; Monk et al., 2008; Prater et al., 2013; Stein et al., 2007; Thomas et al., 2001)—play key roles in avoidance behavior (Aupperle and Martin, 2010; Martin, 2022). Specifically, converging evidence in adults with anxiety disorders and non-anxious children suggests that laboratory-based measures of behavioral avoidance are associated with elevated amygdala, vmPFC, and insula activation (Aupperle and Martin, 2010; Schlund et al., 2011; Schlund et al., 2010). Cross-species evidence highlights the role of the insula in active avoidance, which involves taking specific actions to avoid an aversive outcome (Cohodes et al., 2022; Limbachia et al., 2021; Luchsinger et al., 2021; Meine et al., 2021; Rogers-Carter et al., 2018). In particular, the ventral anterior insula (vAI) has generally been implicated in processing negative emotional stimuli and social threat via connections with the limbic system (Büchel et al., 1998; Chang et al., 2013; Phan et al., 2002; Sequeira et al., 2021; Uddin et al., 2017; Wang et al., 2018). The amygdala plays a central role in the expression of fear (LeDoux, 2007; Phelps et al., 2004; Phelps and LeDoux, 2005) and shows elevated activation in the presence of threat, including during avoidance tasks (Mobbs et al., 2009; Mobbs et al., 2007; Patrick et al., 2019). Finally, the vmPFC, which modulates fear expression (Etkin et al., 2015; Quirk and Beer, 2006; Suzuki and Tanaka, 2021), has been implicated in monitoring threat imminence and may be particularly involved in avoidance of distal threats (Mobbs et al., 2007; Patrick et al., 2019; Wendt et al., 2017). However, these patterns of association have not yet been tested in the context of pediatric anxiety disorders, and the associations between neural activation and other measures of avoidance, such as clinician ratings, remain unknown.

Interactions among these regions are also theorized to modulate avoidance behavior. Connections between the vmPFC and both the amygdala and the insula support adaptive emotion regulation and saliency detection (Banks et al., 2007; Delgado et al., 2008; Qin et al., 2014). On the other hand, functional connectivity between the amygdala and the anterior insula is linked to state anxiety (Baur et al., 2013). Thus, behavioral avoidance may be expected to be associated with weaker vmPFC-amygdala and vmPFC-insula functional connectivity and with stronger insula-amygdala functional connectivity.

Examining these associations holds important theoretical, methodological, and clinical implications. Theoretically, elucidating the associations among specific measures of threat responsivity can shed light on specific mechanisms through which neural processing of threat is translated into specific operationalizations of behavioral avoidance in pediatric anxiety disorders (Pine, 2007). This multimodal approach may be particularly important in this population, given the broad heterogeneity in children with anxiety disorders (Lebowitz et al., 2018). Methodologically, using multiple levels of analysis to investigate avoidance in pediatric anxiety disorders can explain previously observed discrepancies across distinct measures of avoidance (Kitt et al., 2022). Clinically, given the central role of reducing avoidance in treatment for children with anxiety disorders (Kendall et al., 2008; Silverman et al., 2008), advancing understanding of this behavioral hallmark can potentially guide future treatment optimization efforts by identifying individual-specific targets for treatment.

## 2. The present study

The current study uses a multimodal approach to investigate associations between neural reactivity to and avoidance of threat in children with anxiety disorders. We hypothesized that greater laboratory-based avoidance would be associated with stronger vAI, amygdala, and vmPFC activation, with stronger vAI-amygdala connectivity, and with weaker vmPFC-amygdala and vmPFC-vAI connectivity in response to threatening stimuli. Given evidence that laboratory-based behavioral measures and clinician-ratings of avoidance may capture distinct components of avoidance, we also examined associations with clinician-rated avoidance. We hypothesized that these two measures of avoidance would be correlated but that patterns of neural reactivity to threatening stimuli would differ in their associations with laboratory-based versus clinician-rated avoidance.

## 3. Method

### 3.1. Participants

Data used in the current study were collected as part of a randomized controlled trial (RCT) of psychosocial treatment for pediatric anxiety in New Haven, Connecticut. Seventy-six children with primary anxiety disorders completed measures of neural reactivity to and avoidance of threat prior to receiving treatment. All children were between the ages of 6 and 12 years old ($M = 8.83$, $SD = 1.89$; 28 female, 48 male; see Table 1 for descriptive statistics), and all participants met criteria for a primary anxiety disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013). Diagnoses were determined by trained evaluators using the Anxiety Disorders Interview Schedule-Child and Parent Versions

**Table 1**
Demographic information.

| | Participants |
|---|---|
| N | 76 |
| Female [N (%)] | 28 (36.84) |
| Male [N (%)] | 48 (63.16) |
| Age [years, M (SD)] | 8.83 (1.89) |
| Race [N (%)] | |
| Asian | 2 (2.63) |
| Black or African American | 3 (3.95) |
| White | 61 (80.26) |
| Multiracial | 8 (10.53) |
| Unknown | 2 (2.63) |
| Ethnicity [N (%)] | |
| Hispanic or Latino | 8 (10.53) |
| Not Hispanic or Latino | 67 (88.16) |
| Unknown | 1 (1.32) |

(ADIS-C/P; Silverman et al., 2001) and were confirmed by a child and adolescent psychologist. In addition, all child participants had not yet begun pubertal development, as indicated by a score of <2 on the Petersen Pubertal Development Scale (Petersen et al., 1988). Child participants were also required to have an IQ above 80, as assessed using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Exclusionary criteria for child participants included: a) pervasive developmental disorders, neurological disorders, or psychotic disorders; b) high risk for harming self or others; c) current psychosocial or psychopharmacological treatment; d) a lifetime history of neurological illness or head injury resulting in loss of consciousness longer than five minutes; e) visual or physical disability that would interfere with seeing stimuli presented on a screen or rapidly and repeatedly clicking a mouse button; and f) contraindication for MRI scanning (e.g., braces, claustrophobia, or metal implants). Additionally, given the central role of parents in the larger RCT, children were excluded from participation if their parents met the following exclusionary criteria: a) pervasive developmental disorders, mental retardation, selective mutism, bipolar disorder, psychotic disorders, or drug/alcohol abuse or dependence; b) lived with the child for <1 year prior to the start of the study; or c) had attempted suicide within the past 6 months.

### 3.2. Procedure

All procedures were reviewed and approved by the Yale University Institutional Review Board. Child participants and their parents first provided their informed assent/consent. To confirm eligibility, all child participants and their parents completed the ADIS-C/P (Silverman et al., 2001). All diagnoses were determined by trained evaluators and confirmed by a child and adolescent psychologist. Trained evaluators also administered a clinician rating of the child's real-world avoidance over the past week, and child participants completed a laboratory-based measure of behavioral avoidance of threatening stimuli (see Measures). Evaluators completed significant training, including formal training, viewing videos of 'gold standard' administration, practice administration, and shadowing advanced evaluators prior to administering the interview measures (including the ADIS and the Pediatric Anxiety Rating Scale; see Measures). For the ADIS, the instrument developer (co-author WKS) oversaw all training and usage. Shortly following this clinical assessment, during a separate scanning visit, child participants completed a functional magnetic resonance imaging (fMRI) task probing children's neural reactivity to threatening versus neutral face stimuli. The average number of days between the initial clinical assessment and the fMRI scanning visit was 15.28 days (range: 1–38 days). Child participants received monetary compensation ($50) for participating in the MRI scanning session, as well as an additional $50 if they completed all components of the scanning session.

### 3.3. Measures

#### 3.3.1. Anxiety symptom severity

Child participants completed the Screen for Child Anxiety Related Emotional Disorders – Child Version (SCARED-C; Birmaher et al., 1997) as a self-reported measure of anxiety symptom severity. The SCARED-C has good test-retest reliability, internal consistency, and discriminant validity (Birmaher et al., 1999; Birmaher et al., 1997; Etkin et al., 2021b; Hale et al., 2011). The SCARED-C assesses 41 anxiety symptoms on a 3-point Likert-type scale ranging from 0 ("Not True or Hardly Ever True") to 2 ("Very True or Often True"). Scores are summed across items to isolate a measure of total anxiety symptom severity, with possible total scores ranging between 0 and 82. In the current sample, scores ranged from 6 to 58, and Cronbach's alpha was 0.87.

#### 3.3.2. Avoidance measures

**Clinician-Rated Avoidance.** Trained evaluators administered the Pediatric Anxiety Rating Scale (PARS; Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002) to obtain a clinician-rated measure of children's avoidance of threat. The PARS has satisfactory convergent and divergent validity, good internal consistency, and adequate test-retest reliability (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002). An interview-based measure, the PARS consists of 50 items assessing children's anxiety symptoms over the past week prior to the clinical interview. Following separate interviews conducted with both the parent and child, trained evaluators consolidate the information gleaned from both informants. For the present study, we isolated the avoidance section of the PARS, which consisted of the trained evaluator's overall rating of the child's recent avoidance on a 6-point Likert-type scale ranging from 0 ("None") to 5 ("Extreme"). A score of 3 ("Moderate") or above on this Likert-type scale indicates clinically significant levels of avoidance. In the current sample, clinician-rated avoidance ranged from 0 to 4.

**Laboratory Task-Based Avoidance.** Child participants completed a Yale Interactive Kinetic Environment Software (YIKES) task (Lebowitz and François, 2018) as a laboratory-based measure of avoidance of threat. In the YIKES task, participants physically move from side to side to catch randomly presented falling targets in a life-sized virtual environment, with their images dynamically embedded in this virtual environment using motion-tracking technology (Microsoft, Washington, USA). The targets are uniformly distributed across the width of the screen, and participants are instructed to try to catch as many of these falling targets as possible. Unrelated to this goal, pairs of task-irrelevant face stimuli (one angry, one neutral) are continuously presented on either side of the virtual environment (Fig. 1). The threatening stimulus (i.e., the angry face) alternates sides of the screen, with a total of six distinct stimulus pairs presented for a minute each. A growing body of research indicates that the angry face stimuli evoke avoidance behavior, as measured using the YIKES task, in children with anxiety disorders (Abend et al., 2021; Lebowitz and François, 2018).

Kinect-motion tracking technology provided continuous measurements of child participants' movement in relation to the two task-irrelevant face stimuli. Using these continuous measurements, we isolated an index of avoidance of the threatening stimuli for each participant by comparing the average distances at which participants turned away from the two stimulus types. Specifically, we identified times at which the participant changed directions, and we calculated the average distance (relative to the size of the virtual environment, with the angry face set as zero and the neutral face set as one) at which participants turned away from each stimulus type (fearful or neutral face) when moving towards that side of the virtual environment. In line with prior work using the YIKES task, we subtracted the distance at which participants turned away from the angry face from one so that both "turning points" reflected the average distance at which participants turned away relative to the relevant stimulus. We then subtracted the average turning point away from the angry face from the average turning point away

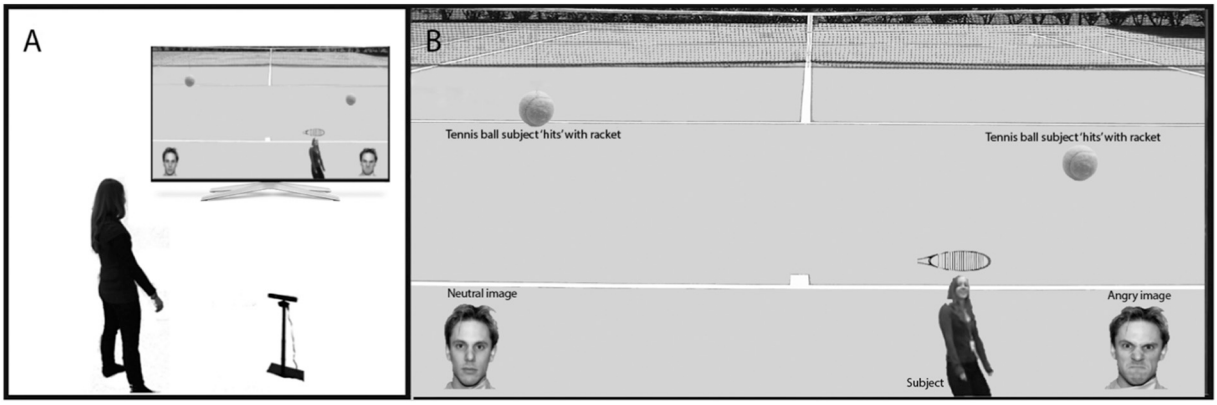


**Fig. 1.** The Yale Interactive Kinetic Environment Software (YIKES) Task.
During the YIKES task, participants' images are dynamically embedded in a virtual environment on a large television screen using motion sensing software. Participants physically move from side to side in front of the television screen to catch virtual falling targets for points. Throughout the task, pairs of task-irrelevant face stimuli (one angry, one neutral) are presented on either side of the virtual environment. Adapted with permission from "Using Motion Tracking to Measure Avoidance in Children and Adults: Psychometric Properties, Associations with Clinical Characteristics, and Treatment-Related Change" by E. R. Lebowitz & B. François, 2018, *Behavior Therapy, 49*(6), p. 853–865.

from the neutral face (Lebowitz and François, 2018; Lebowitz et al., 2015):

Avoidance index = average turning point away from neutral face – average turning point away from angry face.

This index of YIKES-based avoidance has been found to have good test-retest reliability and good convergent and divergent validity (Lebowitz and François, 2018). In the current sample, laboratory-based avoidance indices for the faces run of the task ranged from −0.04 to 0.03, similar to that seen in separate samples of similarly aged youth (e.g., Kitt et al., 2022).

#### 3.3.3. Neural reactivity to fearful versus neutral faces

Child participants completed an event-related fMRI paradigm probing neural reactivity to fearful versus neutral social stimuli. During this task, participants viewed face stimuli, selected from the NimStim set of facial expressions (Tottenham et al., 2009), exhibiting either fearful or neutral expressions. Participants completed two runs of 48 trials each (24 trials of face stimuli with fearful expressions, 24 trials of stimuli with neutral expressions), with each face stimulus presented for 500 ms. Stimulus presentation was randomized but fixed across participants. To ensure engagement with the task, participants were instructed to press a button every time they saw any neutral face stimulus presented during the task. The child's parent was physically present in the scanner room during one run of the task (with the order of runs counterbalanced across consecutive participants). As the current study aimed to examine associations with general patterns of neural reactivity to threat, neural responses were averaged across the two runs. As in prior studies (Hariri et al., 2002), all analyses in this study examined differences in neural responses to faces exhibiting fearful versus neutral expressions as the measure of neural reactivity to threat. Acquisition and preprocessing of neural data followed the same parameters as in previous work from this RCT (Kitt et al., 2023; see Supplemental Material).

#### 3.3.4. Statistical analyses

We used Pearson's correlation to compare the two metrics of avoidance (performance on the in-laboratory behavioral task and clinician rating of real-world recent avoidance) and to examine the associations between each metric and anxiety symptom severity. To investigate the association between neural reactivity to and avoidance of threatening versus neutral face stimuli, we conducted a series of linear models with avoidance (laboratory-based and clinician-rated) as the dependent variable and neural reactivity to fearful versus neutral faces as the independent variable. Youth age, sex, scan order, and mean framewise displacement were included as covariates in all models. A separate set of models was run for each avoidance measure (laboratory-based or clinician-rated avoidance), and separate models were run for each brain region selected a priori (vAI, amygdala, and vmPFC) for activation analyses and for each pair of brain regions (vAI-amygdala, vmPFC-amygdala, and vmPFC-vAI) for connectivity analyses. For associations between avoidance and dorsal anterior insula activation to fearful versus neutral faces and for associations between neural activation to threat and anxiety symptom severity, please see the Supplemental Material.

All analyses used an alpha of 0.05 and were conducted in R (R Core Team, 2021). Across measures, values more extreme than 3 standard deviations from the mean were excluded from analyses as outliers. Due to the preliminary nature of this work, we did not correct for multiple comparisons. For whole-brain voxel-wise analyses, please see the Supplemental Material. Eleven participants were excluded from analyses involving fMRI data because >15 % of their data would need to be regressed out due to motion outliers as determined by framewise displacement ($n$ = 3), because their in-scanner mean absolute translational motion in any of the 6 rigid directions was above 5 mm in either run of the fMRI task ($n$ = 6), or because visual inspection of the data revealed extreme motion slice artifacts ($n$ = 2; resulting $n$ for analyses using neuroimaging data = 65). Participants who were excluded from fMRI analyses did not differ from included participants on age, sex, or anxiety ($ps \geq .430$). See the Supplemental Material for sensitivity analyses with distinct motion criteria (Table S2). In addition, data were excluded from relevant analyses for values >3 standard deviations from the mean in neural activation or connectivity to fearful versus neutral faces: left vAI activation ($n$ = 1), left and right amygdala activation ($n$ = 1), left vmPFC activation ($n$ = 1), right vmPFC activation ($n$ = 2), right vAI-right amygdala connectivity ($n$ = 1), right vAI-left amygdala connectivity ($n$ = 1), left vAI- left and right amygdala connectivity ($n$ = 2), bilateral vmPFC-amygdala connectivity ($n$ = 1), bilateral vmPFC-right vAI connectivity ($n$ = 3), and bilateral vmPFC-left vAI connectivity ($n$ = 1).

## 4. Results

### 4.1. Comparing metrics of avoidance of threat

Child-reported anxiety symptom severity was significantly positively correlated with clinician-rated avoidance, $r(72) = 0.33$, $p = .004$, such that children who reported higher levels of anxiety had greater clinician-rated avoidance. By contrast, child-reported anxiety symptom severity was not significantly associated with laboratory-based avoidance, $r(73) = -0.18$, $p = .122$. Clinician-rated avoidance was not significantly

correlated with laboratory-based avoidance, $r(73) = -0.19$, $p = .103$ (Fig. S1 in Supplemental Material).

### 4.2. Relating neural activation to fearful versus neutral faces and avoidance of threat

#### 4.2.1. Insula activation to fearful versus neutral faces

Laboratory-based avoidance was significantly, positively associated with right vAI activation to fearful versus neutral faces ($b = 0.02$, $SE = 0.01$, $\beta = 0.28$, $t(59) = 2.24$, $p = .029$; Fig. 2a.). Laboratory-based avoidance was not significantly associated with left vAI activation to fearful versus neutral faces ($b = 0.01$, $SE = 0.01$, $\beta = 0.20$, $t(59) = 1.62$, $p = .110$). Conversely, clinician-rated avoidance was significantly, negatively associated with right ($b = -1.20$, $SE = 0.58$, $\beta = -0.27$, $t(58) = -2.10$, $p = .041$) and left ($b = -1.35$, $SE = 0.52$, $\beta = -0.32$, $t(58) = -2.61$, $p = .012$) vAI activation to fearful versus neutral faces (Fig. 2b.).

#### 4.2.2. Amygdala activation

Laboratory-based avoidance was not significantly associated with right amygdala activation to fearful versus neutral faces ($b = -0.01$, $SE = 0.02$, $\beta = -0.09$, $t(57) = -0.71$, $p = .484$); however, there was a close trending, positive association between clinician-rated avoidance and right amygdala activation to fearful versus neutral faces ($b = 2.22$, $SE = 1.12$, $\beta = 0.25$, $t(56) = 1.97$, $p = .053$). Left amygdala activation to fearful versus neutral faces was not significantly associated with either avoidance measure (laboratory-based: $b = 0.02$, $SE = 0.01$, $\beta = 0.17$, $t(58) = 1.30$, $p = .199$; clinician-rated: $b = -0.31$, $SE = 0.89$, $\beta = -0.05$, $t(57) = -0.36$, $p = .724$).

#### 4.2.3. Ventromedial prefrontal cortex activation

Neither laboratory-based nor clinician-rated avoidance was significantly associated with right or left vmPFC activation to fearful versus neutral faces ($ps \geq .571$).

### 4.3. Relating functional connectivity and avoidance of threat

#### 4.3.1. Ventral anterior insula – amygdala functional connectivity

Functional connectivity to fearful versus neutral faces between the vAI and amygdala was not significantly associated with laboratory-based avoidance ($ps \geq .410$). However, left vAI-right amygdala functional connectivity to fearful versus neutral faces was significantly, negatively associated with clinician-rated avoidance ($b = -0.60$, $SE = 0.26$, $\beta = -0.30$, $t(56) = -2.30$, $p = .025$; Fig. 3). Left vAI-left amygdala and right vAI-amygdala (left and right) connectivity to fearful versus neutral faces were not significantly associated with clinician-rated avoidance ($ps \geq .282$).

#### 4.3.2. Ventromedial prefrontal cortex – amygdala functional connectivity

Laboratory-based avoidance was not significantly associated with bilateral vmPFC connectivity with either the right or left amygdala ($ps \geq .787$). Conversely, bilateral vmPFC-right amygdala functional connectivity to fearful versus neutral faces was significantly, negatively associated with clinician-rated avoidance ($b = -0.42$, $SE = 0.18$, $\beta = -0.30$, $t(56) = -2.36$, $p = .022$; Fig. 4). Clinician-rated avoidance was not significantly associated with bilateral vmPFC-left amygdala connectivity to fearful versus neutral faces ($p = .268$).

#### 4.3.3. Ventromedial prefrontal cortex – insula functional connectivity

Neither avoidance measure was significantly associated with vmPFC-vAI functional connectivity to fearful versus neutral faces ($ps \geq .200$).

## 5. Discussion

The current study takes a multimodal approach to begin to elucidate associations between neural reactivity to and avoidance of threat in pediatric anxiety disorders. Findings revealed significant associations between neural reactivity to fearful versus neutral face stimuli and behavioral avoidance; however, the patterns that emerged were distinct for laboratory-based versus clinician-rated measures of avoidance. Laboratory-based avoidance was *positively* associated with right insula reactivity to fearful versus neutral faces, whereas clinician-rated avoidance was *negatively* associated with left and right insula reactivity to fearful versus neutral faces. Distinct patterns also emerged for functional connectivity among key regions involved in avoidance. Specifically, clinician-rated avoidance was significantly, negatively associated with left vAI-right amygdala and bilateral vmPFC-right amygdala functional connectivity to fearful versus neutral faces; by contrast, laboratory-based avoidance was not significantly associated with functional connectivity between these regions. These distinct patterns of association between avoidance and neural reactivity to fearful versus neutral faces may help to untangle the nature of threat responsivity and specific components of avoidance in youth anxiety. Taken together, these results shed light on the neural underpinnings of key dimensions of avoidance.

Key differences in the type of threat involved in each of the two avoidance measures may help to explain this unique pattern of results. The laboratory task involves a continuously present, immediately proximal threat. By contrast, the clinician-rated measure, which draws heavily upon child and parent conscious awareness and explicit recall of a child's avoidance of future potential threats, is more likely to capture avoidance behaviors that involve anticipatory behaviors to avoid a possible future threat. The proximity of the threat may impact the differential pattern of results seen across measures of avoidance. In non-

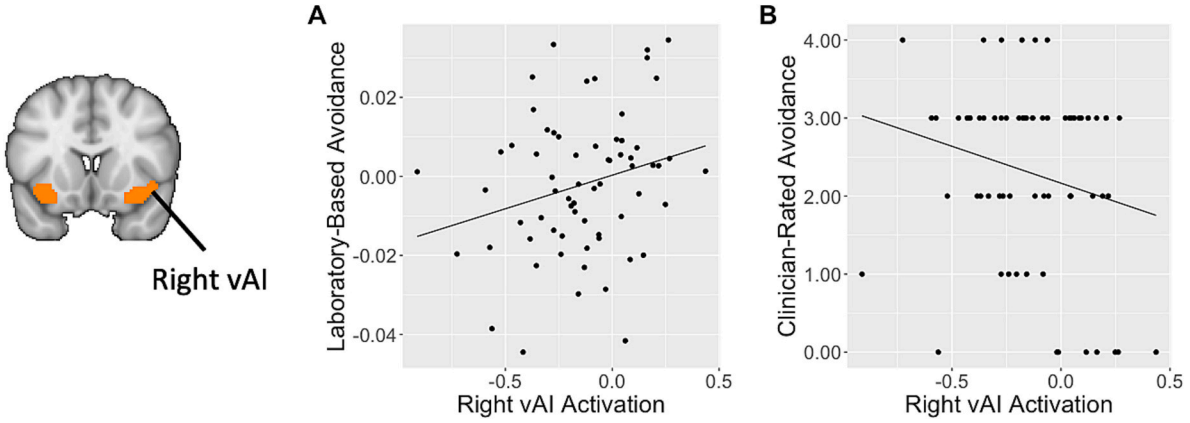


**Fig. 2.** Associations between right ventral anterior insula (vAI) reactivity to fearful versus neutral faces and both laboratory-based and clinician-rated avoidance. (A) Right vAI reactivity to fearful versus neutral faces was significantly, positively associated with laboratory-based avoidance. (B) By contrast, right vAI reactivity to fearful versus neutral faces was significantly, negatively associated with clinician-rated avoidance.

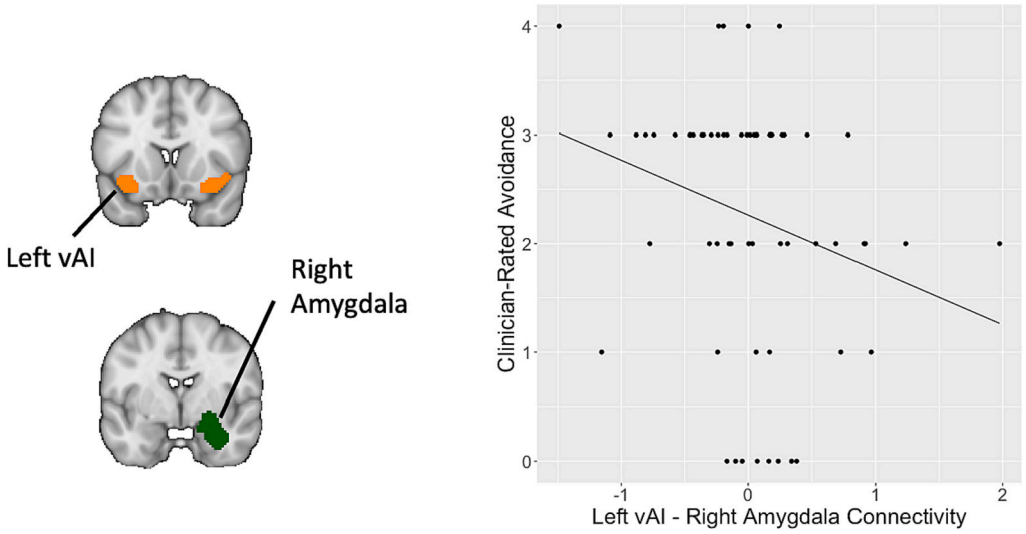


**Fig. 3.** Association between left vAI-right amygdala functional connectivity to fearful versus neutral faces and clinician-rated avoidance.
Left vAI-right amygdala functional connectivity to fearful versus neutral faces was significantly, negatively associated with clinician-rated avoidance.

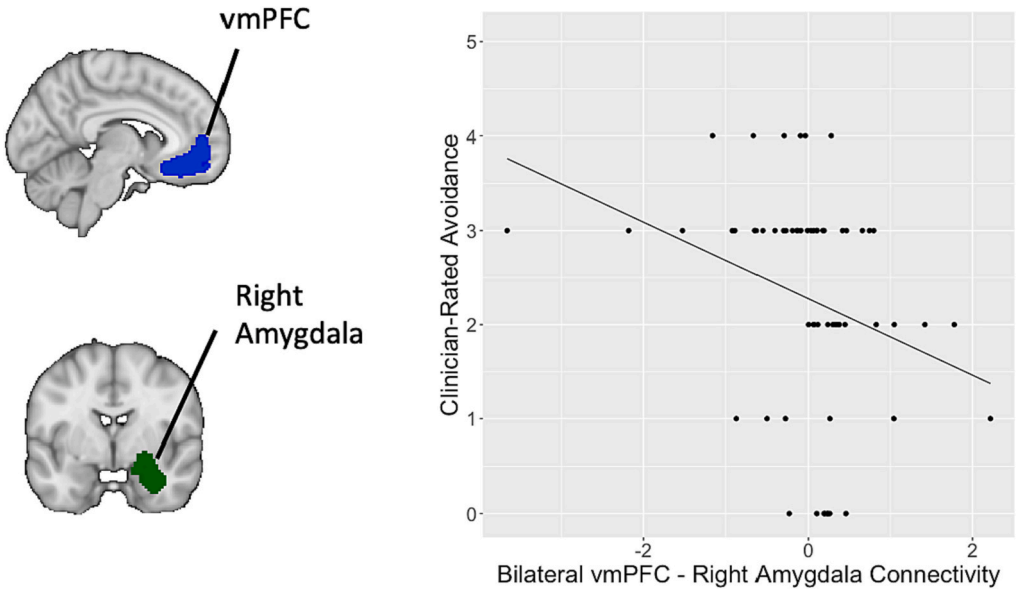


**Fig. 4.** Association between bilateral vmPFC-right amygdala functional connectivity to fearful versus neutral faces and clinician-rated avoidance.
Bilateral vmPFC-right amygdala functional connectivity to fearful versus neutral faces was significantly, negatively associated with clinician-rated avoidance.

anxious samples, insula activation has been found to increase as the proximity of a threat increases (Wendt et al., 2017). Thus, the distinct associations with insula activation may reflect differences between avoidance of an immediately proximal threat during the laboratory task compared to the more anticipatory form of future threat captured by the clinician rating.

The operationalization of avoidance using explicit recall may also help to explain our connectivity findings. Potentially consistent with our finding of a negative association between amygdala-vmPFC connectivity to threat and clinician-rated avoidance, previous research has found that parent- and child-reported avoidance of trauma-related triggers is negatively associated with amygdala-medial PFC connectivity in the context of pediatric post-traumatic stress disorder (Wolf and Herringa, 2016). Moreover, in line with the observed negative association between insula-amygdala connectivity and clinician-rated avoidance, young adults reporting greater social inhibition (i.e., avoidance of social situations and withdrawal from unfamiliar people) have been found to show reduced insula-amygdala connectivity (Blackford et al., 2014). Thus, our findings align with previous research finding an association between explicit reports of avoidance behavior (here indexed by our clinician rating) and functional connectivity between key brain regions involved in avoidance.

While these distinct associations between neural reactivity to threat and laboratory-based versus clinician-rated avoidance may help to elucidate the distinct components of avoidance captured by these two metrics, an alternative explanation of these discrepant findings relates to the lack of coherence across modalities. Of note, the laboratory- and clinician-based measures of avoidance were not significantly correlated with one another in the current sample, a finding that replicates recent research in a separate sample (Kitt et al., 2022). Importantly, self-reported measures of clinically significant constructs often show little coherence with laboratory-based measures aiming to capture the same construct (e.g., Cyders and Coskunpinar, 2011; Krypotos et al., 2018). This lack of coherence across measures could indicate that these two

types of measures are capturing distinct components of the same construct, or it could indicate that the two measures are capturing two entirely distinct constructs (Cyders and Coskunpinar, 2011). Future research should continue to explore the degree to which these measures quantify the same underlying construct to ensure the validity of our phenotypes of avoidance.

Differences in informant across measures could also contribute to the distinct patterns of associations between neural and behavioral responding observed in the current study. Whereas the laboratory-based measure relies solely on the child's behavior, the clinician rating of real-world avoidance integrates both the child's and parent's reports into a single measure of avoidance. Previous research emphasizes the importance of considering both child and parent reports for reliable, valid assessments of children's behavior (Haynes and O'Brien, 2000; Whiteside et al., 2013). The current study's multimodal approach provides a nuanced investigation into neural correlates of two commonly used measures of behavioral avoidance across multiple informants. Future research incorporating additional measures of avoidance would further strengthen our understanding of children's neural and behavioral responses to threat. For example, daily diaries or ecological momentary assessment could provide additional perspectives about children's real-world avoidance behaviors outside the laboratory (Price et al., 2016). Incorporating additional measures capitalizing on innovative advances in event sampling methodologies could help to further explicate the nuances in types of avoidance exhibited by children with anxiety disorders in their daily lives.

Of note, while we discuss these results in terms of threat responsivity, it is important to consider how salience detection may impact these results. Our fMRI task uses face stimuli, which are linked with both threat responding and salience detection (Markett et al., 2020; Santos et al., 2011). It is likely that the associations detected in this study were influenced both by threat and salience, and it is difficult to distinguish between effects of threat versus salience in the present task design. One possible approach to begin to examine this question utilizes the specific contrasts between stimuli in the fMRI task. In the current study, we have attempted to isolate the effects of threat by examining the contrast between neural reactivity to fearful versus neutral faces. Examining the contrast between all face stimuli and baseline could reflect the effects of salience more broadly. In the current study, the pattern of results in our primary analyses is specific to the fearful versus neutral faces contrast (see Table S1 in the Supplemental Material). Thus, while both threat and saliency are likely to contribute to the brain-behavior relations observed in this study, some initial evidence suggests that these associations may be driven more by threat, in line with our hypotheses. We acknowledge that future work will be important to distinguish between the effects of threat versus salience in understanding neural mechanisms associated with different forms of avoidance in pediatric anxiety.

It is important to consider these results in the context of several limitations. First, the restricted range of our sample limits the ability to draw conclusions about these associations across children with a broader range of symptomatology. Our sample of treatment-seeking children with diagnosed anxiety disorders allowed us to examine specific questions regarding the association between neural reactivity to and avoidance of threat within this clinically anxious sample. However, in future studies, it will be important to examine these associations across children with a broader range of symptomatology, including children with sub-threshold anxiety and children without anxiety symptoms, to enhance the generalizability of these results. Second, it is important to interpret these results in the context of the limited diversity of our sample, which may limit the generalizability of findings. The majority of child participants in our sample identified as White and not Hispanic or Latino, such that our sample does not reflect the local demographic distribution in our recruitment area. Moreover, although we aimed to collect a sample that was balanced across male and female child participants, our final sample had a higher proportion of male child participants. Particularly given patterns of limited inclusion of historically underrepresented populations in clinical research (Pina et al., 2019), it is crucial that future studies examine these results in more diverse samples to test the generalizability of our current findings. Third, the motion criterion that we employed in the current study was relatively lenient (5 mm mean absolute translational motion). In setting the motion criterion for the current study, we considered the trade-offs between threshold stringency and the amount of data exclusion. Given previous work showing that anxious children show elevated head motion during fMRI scans (e.g., Price et al., 2014) and the modest nature of our sample size, we chose to maintain the 5 mm mean absolute translational motion criterion that we (Kitt et al., 2023) and others (e.g., Butterfield et al., 2019; Price et al., 2014) have employed in prior work. We note that future research with larger samples will be important for testing the extent to which these findings are robust across more stringent motion thresholds.

In conclusion, the results of this study indicate specific patterns of association between neural reactivity to and avoidance of threat in children with anxiety disorders across both the laboratory and children's daily lives. This study's multimodal approach presents an important early step towards bridging the gap between neural findings and clinical observations and highlights the importance of considering multiple units of analysis when examining complex constructs such as avoidance. Considering the central role of avoidance as a target of first-line psychosocial treatments for pediatric anxiety disorders, further understanding individual differences in distinct types of avoidance behaviors could mark an important step towards greater personalization of treatment. Continuing to explore these associations will provide essential insight into the processes by which neural processing of threat translates into maladaptive behavioral outcomes and thus may ultimately inform optimized treatments for pediatric anxiety disorders.

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## CRediT authorship contribution statement

**Elizabeth R. Kitt:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Sadie J. Zacharek:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Paola Odriozola:** Writing – review & editing, Formal analysis, Data curation. **Cristina Nardini:** Writing – review & editing, Investigation, Data curation. **Grace Hommel:** Writing – review & editing, Investigation. **Alyssa Martino:** Writing – review & editing, Investigation. **Tess Anderson:** Writing – review & editing, Investigation. **Hannah Spencer:** Writing – review & editing, Investigation. **Alexis Broussard:** Writing – review & editing, Data curation. **Janice Dean:** Writing – original draft. **Carla E. Marin:** Supervision. **Wendy K.**

**Silverman:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Eli R. Lebowitz:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Dylan G. Gee:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.01.204.

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