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Amy K. Roy
New York University School of Medicine

Roma A. Vasa
Johns Hopkins University

Maggie Bruck
Johns Hopkins University

Karin Mogg
University of Southampton

Brendan P. Bradley
University of Southampton

See next page for additional authors

Authors
Amy K. Roy, Roma A. Vasa, Maggie Bruck, Karin Mogg, Brendan P. Bradley, Michael Sweeney, Lindsey Bergman, Erin B. McClure-Tone, and Daniel S. Pine

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Amy Krain Roy, Ph.D., Roma A. Vasa, M.D., Maggie Bruck, Ph.D., Karin Mogg, Ph.D., Brendan P. Bradley, Ph.D., Michael Sweeney, Ph.D., R. Lindsey Bergman, Ph.D., Erin B. McClure-Tone, Ph.D., Daniel S. Pine, M.D. and the CAMS Team

Dr. Roy is at the NYU Child Study Center at the New York University School of Medicine; Drs. Vasa and Bruck are at the Johns Hopkins School of Medicine; Drs. Mogg and Bradley are in the School of Psychology at the University of Southampton; Dr. Sweeney is at the New York State Psychiatric Institute; Dr. Bergman is in the Department of Psychiatry and Biobehavioral Science at the University of California Los Angeles; Dr. McClure-Tone is in the Department of Psychology at Georgia State University; and Dr. Pine is Chief, Section on Development and Affective Neuroscience at the National Institute of Mental Health.

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For reprint requests and/or correspondence, please contact Dr. Roy at the New York University Child Study Center, 215 Lexington Avenue, #1307; New York, NY, 10016 or by email at amy.roy@nyumc.org.

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ABSTRACT

Objective: To examine attention bias towards threat faces in a large sample of anxiety-disordered youths using a well-established visual probe task. **Method:** Study participants included 101 children and adolescents (ages 7- 18 years) with generalized anxiety disorder, social phobia and/or separation anxiety disorder enrolled in a multi-site anxiety treatment study. Non-anxious youths (*n* = 51; ages 9 – 18 years) were recruited separately. Participants were administered a computerized visual probe task that presents pairs of faces portraying threat (angry), positive (happy) and neutral expressions. They pressed a response-key to indicate the spatial location of a probe that replaced one of the faces on each trial. Attention bias scores were calculated from response times to probes for each emotional face type. **Results:** Compared to healthy youths, anxious participants demonstrated a greater attention bias towards threat faces. This threat bias in anxious patients did not significantly vary across the anxiety disorders. There was no group difference in attention bias towards happy faces. **Conclusions:** These results suggest that pediatric anxiety disorders are associated with an attention bias towards threat. Future research might examine the manner in which cognitive bias in anxious youth changes with treatment.

Keywords: anxiety disorders, children, adolescents, attention bias, threat

INTRODUCTION

Pediatric anxiety disorders affect approximately 10-15% of children and adolescents[1,2] and are associated with significant, enduring impairment[3,4] Although research on pediatric anxiety disorders is rapidly growing, knowledge of pathophysiology remains limited. Cognitive models suggest that biased processing of threats cause or maintain anxiety.[5-7] These models are supported by data demonstrating that anxious individuals preferentially allocate attention (i.e., show an attention bias) towards threatening, as compared to positive or neutral, stimuli. Further support is provided by neuroimaging findings of anxiety-related differences in the structure and function of brain regions implicated in the detection and processing of threatening stimuli.[8-12]

Two experimental attention-bias paradigms have been widely used to study the relationship between anxiety and attention bias: the emotional Stroop and visual probe tasks. The emotional Stroop[13] is based on principles of cognitive interference; attention bias is manifested by longer response times for color naming of threat vs. positive or neutral words. While extensively used, this task is criticized because performance may reflect processes beyond attention, such as interference in response selection or execution.[14,15] The visual probe task provides a more direct measure of attention by requiring responses to neutral probes that replace threat and non-threat stimuli.[14] In this task, two stimuli, one threatening and one neutral, are briefly presented side-by-side. The stimuli then disappear and one is replaced by a target probe. Participants must indicate on which side the probe appears using a button press. Attention bias towards threat is defined as faster reaction times to probes replacing threat stimuli compared with neutral stimuli.

Numerous adult studies report an attention bias towards threat in clinical and non-clinical samples.[16-18] Research using the Stroop and visual probe tasks has demonstrated greater attention towards threat stimuli across various disorders, namely generalized anxiety disorder (GAD),[16,19] social phobia (SP),[20] post-traumatic stress disorder (PTSD),[21] obsessive-compulsive disorder (OCD),[22] and panic disorder.[23,24] Orienting towards threat typically occurs with brief stimulus presentations, suggesting that this bias manifests early in information processing.[20,25]

Studies of threat bias in pediatric anxiety disorders have been limited and most have used small, heterogeneous samples. Earlier studies using a visual probe task with word stimuli or an emotional Stroop task report findings similar to adult studies, i.e., an enhanced attention bias towards threat in anxious participants.[26-29] This result was replicated recently in a study of clinically anxious and non-anxious children using a visual probe task with threat-related, neutral, and pleasant pictures.[30] A previous study using this task found the same attention bias towards threat in a clinically anxious pediatric sample; however a similar bias was also observed in healthy non-anxious children and adults.[31] Another recent study found no bias towards threat faces in children with GAD or healthy controls (Waters et al., in press). However, when the GAD group was divided by parent-reported anxiety severity, the more severe group showed a bias towards both happy and threat faces. Monk et al.,[11] in contrast, found a bias *away* from threat faces in pediatric GAD, possibly due to the testing environment, which was an MR scanner rather than a laboratory setting.

In summary, data in adults document consistent associations between anxiety and vigilance for threat on a visual probe task. Similar associations have been demonstrated in children and adolescents, although there has been greater inconsistency, possibly due to small samples, restricted age ranges, and/or different testing contexts. This suggests the need for studies in larger pediatric anxiety samples across a broader age range tested with consistent visual probe methods similar to those used in adults.

The current study uses the same emotional face visual probe paradigm employed in previous pediatric[11,32] and adult studies,[16,20,25] to examine attention bias in 101 children and adolescents with three specific childhood anxiety disorders: separation anxiety disorder (SAD), generalized anxiety disorder (GAD), and social phobia (SP). Participants were recruited through a multi-site anxiety treatment study and were administered the visual probe task prior to treatment and at several time points during the treatment course. This study reports on the results of the pre-treatment assessment. Data from this large cohort allow us to test specific hypotheses and investigate exploratory questions not previously examined. First, based on the adult literature[16-20] and most studies of youth,[26-30] we predict that children and adolescents with anxiety disorders, but not healthy youths, will show a selective attention bias towards threat faces. Similarly, we predict that this attention bias will correlate with anxiety severity, suggesting a greater bias in patients who are more anxious. Exploratory analyses examine whether bias is specific to particular disorders and face types (e.g. threat vs. happy).

METHOD

Participants

The visual probe task was completed by 125 children and adolescents with anxiety disorders participating in a multi-site treatment study, the Child/Adolescent Anxiety Multimodal Study (CAMS) (Study sites include: Johns Hopkins Medical Institutions, New York State Psychiatric Institute, Western Psychiatric Institute and Clinic, Temple University, Duke University Medical Center, University of California at Los Angeles). This randomized controlled trial examined the efficacy of cognitive-behavioral and pharmacological interventions for SAD, GAD, and SP. Participants were included in the overall CAMS study if they received a principal diagnosis of at least one of these disorders based on the Anxiety Disorder Interview Schedule for Children (ADIS-IV-C).[33] CAMS exclusion criteria included a current diagnosis of Major Depressive Disorder (MDD) or Post-Traumatic Stress Disorder (PTSD), and current use of psychotropic medication (stable treatment with a psychostimulant was permitted).

Of the 125 CAMS participants who completed the visual probe task, 24 were excluded from further analyses. Six were excluded because more than 50% of their reaction time (RT) data were missing (e.g. due to errors or outliers), which suggests they did not engage appropriately in the task. Additionally, 18 participants with comorbid Attention-Deficit/ Hyperactivity Disorder (ADHD) were excluded because of the possible influence of these symptoms or associated medications on task performance.[34] This resulted in a final count of 101 clinically anxious participants (49% female; mean age = 11.5 years, *SD* = 2.8, range 7.1 – 17.5 years).

Healthy non-anxious participants were recruited using advertisements and through ongoing studies at the National Institutes of Mental Health and the NYU Child Study Center. Briefly, all participants were free of current psychopathology, any medication, or medical illness. Consistent with the clinical sample, all healthy participants met the selection criterion of no more than 50% of missing RT data on the visual probe task. This resulted in a healthy control sample of fifty-one children (45% female; mean age = 13.6 years; *SD*= 2.7; range 9 – 17.6 years).

Clinical Assessment

Anxious and healthy participants were assessed using slightly different semi-structured diagnostic interviews and abbreviated intelligence measures. All measures are validated for use with children and adolescents.

<u>CAMS Participants</u>: While the baseline evaluation of the CAMS study included multiple measures of anxiety, only select measures utilized in the current study are described here. To evaluate past and current psychiatric diagnoses, trained independent evaluators

interviewed parents and children separately using the ADIS-IV-C[33]. The ADIS-IV-C evaluates the presence of anxiety disorders, as well as the full range of psychiatric disorders assessed by other semi-structured interviews. Following this, the independent evaluator completed the Pediatric Anxiety Rating Scale for Children (PARS),[35] resulting in child, parent, and evaluator ratings of specific anxiety symptoms and overall distress. Parents and children also completed the Screen for Anxiety and Related Disorders (SCARED)[36] and the children completed the Multidimensional Anxiety Scale for Children (MASC)[37]. The vocabulary and block design subtests of the WISC-III [38] were administered as an estimate of intellectual ability.

Healthy Control Participants: Participants from NIMH were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children- Present and Lifetime Version (K-SADS-PL)[39] and participants from NYU were evaluated using the ADIS-IV-C.[33] Different diagnostic instruments were used because each site had existing well-established procedures for specific interviews. The availability of well-trained, reliable clinicians ($\kappa > 0.70$) was felt to outweigh any disadvantages associated with the minimal differences between the interviews.

Only participants free of current or past psychiatric diagnosis were included in the study. Participants completed either the four subtest version (NIMH) or two subtest version (NYU) of the Wechsler Abbreviated Scale of Intelligence (WASI).[40] A subset of healthy controls also completed the SCARED-Parent and Child versions (70.6% of parents and 74.5% of children).

Visual Probe Task

This task has been used extensively in prior studies investigating the relationship between anxiety and attention bias.[11,16,25,32] Face stimuli include photographs of positive (happy), threat (angry), and neutral expressions portrayed by 64 different actors (50% male).

A single trial consists of a pair of photographs of the same actor presented side by side on a computer screen; one photograph displays a neutral expression and the other expresses either an angry or happy expression. A total of 32 angry-neutral trials and 32 happy-neutral trials were presented. Half of the trials displayed the emotional expression on the right, and the other half displayed the emotional expression on the left. Additionally, sixteen trials of neutral-neutral face pairs were presented. The task was presented using EPrime software (Psychology Software Tools, Pittsburgh). Participants sat approximately 50 cm from the computer. The task began with 32 practice trials followed by 80 trials presented in random order, during which reaction time (RT) data were collected.

Each trial began with a 500-msec centrally presented fixation cross, which was followed by a face-pair presented for 500 msec. Immediately after the display of the face-pair, a single-asterisk "probe" was displayed for 1100 msec on the left or right side of the screen in the location of one of the faces. Participants were instructed to indicate, as quickly and accurately as possible, whether the probe appeared on the right or the left using the keyboard. The inter-trial interval varied randomly between 750 and 1250 msec.

Data Analysis

As in previous studies,[20,32] data from trials with errors were excluded, as were RTs that were less than 200 msec or more than two standard deviations above each subject's mean RT. Nine participants (6 anxious patients, 3 healthy controls) were excluded because more than 50% of their RT data were missing due to errors or outliers. For the remaining participants (N = 152 across groups), the mean amount of RT data that were missing was 10.2% (SD = 8.0), and there was no significant difference between the groups on this variable ($t[150] = 1.11$, $p = .27$). Chi square tests and independent sample t-tests were used to examine group differences in age, gender, race, socioeconomic status (SES) as measured by the

Hollingshead Four Factor Index,[41] estimated full scale IQ, and RTs on neutral face trials, an unbiased estimate of overall response speed.

To test primary study hypotheses, attention bias scores were derived from a standard formula used in prior research.[11,25,32] For each subject, attention bias scores for angry faces were calculated by subtracting the mean RT on trials where the angry face and probe appeared on the same side of the display from the mean RT on trials where the angry face and probe appeared on opposite sides of the display. Positive values reflect a bias toward the angry relative to the neutral face, whereas negative values reflect a bias away from threat. Bias was calculated in a similar fashion for happy faces. T-tests were used to examine group differences in bias scores and absolute differences from zero. Due to group differences in age, race, IQ and mean RT, analyses of covariance were also conducted. For these subsequent analyses, only participants with complete data were included (99 anxious and 46 healthy youths). Given that each statistical analysis was conducted to answer a specific independent research question and involved a unique set of dependent variables (i.e., threat bias, happy bias), correction for multiple comparisons was not deemed necessary.

Associations between attention bias and clinical anxiety variables were examined using Pearson correlations and linear regression. To examine associations with specific anxiety disorders, three dichotomous variables were created indicating presence or absence of each of the three primary anxiety disorders. Attention bias was then regressed on these three variables. While it would have been preferable to compare participants with single diagnoses, this was not feasible due to comorbidity (see Table).

RESULTS

Group Characteristics

Within the anxious group, 78 (77%) met criteria for SP, 82 (81%) for GAD, and 59 (58%) for SAD with a high level of comorbidity (see Table).

The anxious and healthy groups did not differ in gender ratio (X^2 [continuity correction] = .16, *df* = 1, *N* = 152, *p* = .69) or SES (*t*[138] = 0.87, *p* = .39) (see Table). The anxious group (*M* = 11.5 years, *SD* = 2.8) was significantly younger than the healthy group (*M* = 13.6 years, *SD* = 2.7) (*t*[150] = 4.25, *p* < .001) and had a greater ratio of white to non-white participants (X^2 [continuity correction] = 11.17, *df* = 1, *N* = 147, *p* = .001). Mean estimated full scale IQ scores were significantly lower in the anxious (*M* = 102.8; *SD* = 16.9; data missing on 3 participants) than healthy (*M* = 110.7; *SD* = 14.8; data missing on 1 subject) (*t*[146] = 2.82, *p* = .006) group. Also, the anxious group showed slower psychomotor performance than the healthy group, as reflected by the mean RT on neutral trials (Anxious: *M* = 572 ms; *SD* = 130; Healthy: *M* = 488 ms; *SD* = 94; *t*[150] = 4.55, *p* < .001).

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As the groups differed on several descriptive variables, we examined the association between these measures and both happy and threat bias. No significant relationships emerged between threat bias and age (Anxious: *r* = -.004, *p* = .97; Healthy: *r* = .11, *p* = .45; Overall: *r* = -.05, *p* = .47), estimated IQ scores (Anxious: *r* = -.06, *p* = .54; Healthy: *r* = .08, *p* = .57; Overall: *r* = -.05, *p* = .53), race (Anxious: r_{pb} = .02, *p* = .87; Healthy: r_{pb} = .24, *p* = .11; Overall: r_{pb} = .14, *p* = .10), or mean RT on neutral trials (Anxious: *r* = .15, *p* = .15; Healthy: *r* = -23, *p* = .11; Overall: *r* = .13, *p* = .11). Similarly, no significant relationships emerged between happy bias and age (Anxious: *r* = -.14, *p* = .17; Healthy: *r* = -.08, *p* = .60; Overall: *r* = -.11, *p* = .17), estimated IQ scores (Anxious: *r* = -.004, *p* = .97; Healthy: *r* = -.07, *p* = .63; Overall: *r* = -.02, *p* = .82), race (Anxious: r_{pb} = -.01, *p* = .90; Healthy: r_{pb} = -.21, *p* = .15;

Overall: r_{pb} = -.09, *p* = .30) and mean RT on neutral trials (Anxious: *r* = -.07, *p* = .51; Healthy: *r* = -.18, *p* = .22; Overall: *r* = -.09, *p* = .27).

Bias Scores for Threat Faces

Group Differences. Group comparison showed significantly greater threat bias scores in anxious (*M* = 10.7 ms, *SD* = 38.6), relative to healthy youths (*M* = -7.96 ms, *SD* = 31.4) (*t*[150] = 2.98, *p* = .003; Cohen's *d* = 0.53, see Figure). The mean threat bias score in anxious patients differed from zero (*t*[97] = 2.52, *p* = .01), indicating bias towards threat, while the mean in healthy youths did not differ from zero (*t*[50] = 1.53, *p* = .13). This group difference persisted in the ANCOVA controlling for age, race, IQ, and mean RT during neutral trials (Anxious: *M* = 10.0 ms, *SD* = 37.8; Healthy: *M* = -4.8 ms, *SD* = 29.8; *F*[1, 145] = 3.96, *p* = .049, partial eta^2 = .03).

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Clinical Measures. There were no associations between threat bias and anxiety severity in the anxious group alone (MASC: *r* = -.01; PARS-Clinician: *r* = -.10; PARS-Child: *r* = .05; PARS-Parent: *r* = -.12, all *NS*) or across groups (SCARED-Parent: *r* =.14; SCARED-Child: *r* = .02).

Individual Anxiety Disorders. No evidence of a relationship between threat bias and specific anxiety diagnoses emerged. A regression of threat bias on individual anxiety diagnoses showed no significant results (R^2 = .01; $F < 1$), suggesting that threat bias relates to the presence of any anxiety disorder, as opposed to one or another specific diagnosis. Additionally, the correlation between threat bias and number of anxiety diagnoses was not significant (*r* = -.02, *p* = .87).

Bias Scores for Happy Faces

Group Differences. Anxious and healthy groups did not differ in their happy bias scores (*t*[150] = 0.19, *p* =.99). Mean bias scores were 2.1 ms (*SD* = 34.9) for patients, and 2.2

ms (*SD* = 33.1) for healthy youths, with no difference in bias from zero for either the anxious ($t[100] = .60$, $p = .55$) or healthy group ($t[50] = 0.48$, $p = .63$). No group differences emerged after controlling for age, race, IQ, and mean RT on neutral trials ($F[1,145] = .31$, $p = .58$).

Clinical Measures: Happy bias scores did not correlate with self-reported anxiety in the anxious group (MASC: $r = -.08$; PARS- Clinician: $r = .13$; PARS-Child: $r = .05$; PARS-Parent: $r = .12$, all *NS*) or across groups (SCARED-Parent: $r = -.04$; SCARED-Child: $r = -.004$).

Individual Anxiety Disorders: Within the anxious group, a regression analysis of happy bias scores as the dependent variable, and anxiety diagnosis as dichotomous predictor variables, showed no significant results ($R^2 = .01$; $F < 1$). Correlational analysis of happy bias scores and number of anxiety diagnoses was not significant suggesting no relationship between happy bias severity and anxiety comorbidity ($r = -.04$, $p = .67$).

DISCUSSION

Children and adolescents with SP, GAD, or SAD, but not healthy youths, demonstrated an attention bias towards angry faces on a visual probe task. These results are consistent with several prior studies in anxious youth.[26-30] The present results are also consistent with work in anxious adults, which reveals consistent evidence of attention biases towards threat words and angry faces.[16,19,20] These findings support theories suggesting that anxious individuals manifest a selective processing bias towards threat[5,6] due to a perturbation in neural mechanisms controlling vigilance.[42]

Of note, the current data differ from some other recent studies of anxious youth.[11,31,32] For example, in the present study, healthy youths showed no attention bias towards angry faces, whereas this bias has been observed for other types of threat stimuli in healthy children (e.g., pictures of dogs, snakes, guns).[31] Angry faces differ from threat pictures in several ways including emotional valence, subjective threat value, novelty, and complexity, all of which may impact attention processes.[6] Moreover, two other studies, using the same visual probe paradigm employed in the current study, report an attention bias *away* from angry faces in children and adolescents with either PTSD or GAD.[11,32] Differences between the current results and these prior studies may reflect the differing circumstances across the three studies. For example, in Pine et al. [32], the children experienced severe maltreatment and subsequent PTSD. One might expect that severely maltreated children might develop strong automatic tendencies to avoid angry faces, contributing to an attention bias away from threat. As such, the current data provide some support for distinctions between PTSD and other anxiety disorders based on information-processing profiles that may reflect differences in pathophysiology.[43,44] Similarly, a recent functional magnetic resonance imaging study demonstrated an attention bias away from threat in adolescents with GAD.[11] The anxiogenic environment of the MR scanner may have influenced the direction of the bias, leading to different results from those studies conducted in a laboratory or clinic. Research with anxious adults suggests that, under certain conditions, high levels of state anxiety may elicit cognitive suppression or avoidance responses that oppose attention biases towards threat.[13,45] Therefore, the current results do not contradict these data, but rather highlight the sensitivity and variability in attention biases in pediatric samples under varying contexts. Additional research is needed specifically evaluating the effect of emotional and environmental factors on attention biases.

The findings from this study highlight the interactions between cognitive and emotional brain systems in the pathophysiology of anxiety disorders. An attention bias towards threat suggests that brain circuits mediating threat detection in anxious children may be hypersensitive.[42] Consistent with this, neuroimaging studies of anxious children have demonstrated structural and functional abnormalities in regions implicated in emotion processing, including the amygdala and prefrontal cortex.[9-12] It is still unknown whether these anxiety-related differences in brain anatomy and function precede or follow the development of anxiety disorders in youth. Further studies of attentional processes and associated neural activity using longitudinal and high-risk developmental designs are needed to answer these important etiological questions.

Continuous measures of anxiety did not correlate with attention bias, which contrasts the findings of Waters et al. (in press), who found positive relationships between parental report of child anxiety severity and attention bias for happy and angry faces in children with GAD. While these studies used the same attention task, the sample in Waters et al. was younger (ages 7 – 12 years) than the present one, and the studies used different measures of anxiety symptoms, limiting direct comparison of results. In the present study, attention bias measures did not differ among the three anxiety disorders. However, high comorbidity complicated efforts to isolate associations with one or another anxiety disorder. Studies of children with single anxiety disorder diagnoses might reveal specific associations, though the generalizability of such studies would be limited given the high rates at which anxiety disorders co-occur in clinical samples.[46]

The current findings should be evaluated in light of study limitations. First, while the multi-site design of the CAMS study allowed us to recruit a very large sample of anxiety-disordered youth, it may also have increased the variability of the data because environmental conditions could not be precisely controlled across the seven study sites. However, no site differences (all F-values <1) were found for the primary dependent measures of threat or happy bias in either the anxious or healthy youths. Second, the anxious and healthy groups were not matched on age, race, IQ, or mean RT during neutral trials. After controlling for these variables, the group difference in threat bias remained, albeit at a lower statistical threshold. This likely reflects reduced statistical power caused by the inclusion of multiple covariates that were not associated with the dependent variable. Replication with more closely matched samples is needed to test the reliability of the group differences we observed. Third, the magnitude of between-group differences was not large, in terms of absolute milliseconds or effect size. Nevertheless, the magnitude found here replicates that in prior studies, suggesting that differences are reliably detectable with appropriately-powered studies.

Overall, the present study provides support for the relationship between pediatric anxiety and attention bias towards threat. Further research is needed to evaluate the robustness of this association and the specific circumstances that influence it. Additionally, unanswered questions remain regarding the role of this bias in the etiology or maintenance of these disorders, as well as how it may relate to treatment response. Analysis of the visual probe data collected during the treatment and outcome phases of the CAMS study will provide an opportunity to examine the latter question. However, longitudinal studies are needed to examine the specificity of these attentional processes and their role in the development of pediatric anxiety disorders and subsequent mood and anxiety disorders in adulthood.

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Table: Characteristics of Anxious and Healthy Control Participants

Characteristic	**Anxious (n = 101) Mean (SD)**	**Healthy (n = 51) Mean (SD)**	**Statistic**	**p**
Gender	52% male	55% male	$X^2 = .16$	ns
Age	11.53 (2.83)	13.56 (2.66)	t (150) = -4.25 d = 0.73	< .001
Hollingshead SES	3.73 (1.11)	3.49 (1.61) (n = 41)	t (140) = 1.04 d = 0.19	ns
Race	82% White	54.3% White (n = 46)	$X^2 = 12.56$	< .001
Full Scale IQ	102.8 (16.90) (n = 98)	110.74 (14.58) (n = 50)	t (146) = -2.818 d = 0.49	.006
SCARED				
Child Report	23.1 (14.0) (n = 84)	13.9 (9.7) (n = 38)	t (120) = 4.23 d = 0.72	< .001
Parent Report	30.9 (15.4) (n = 85)	6.3 (4.6) (n = 36)	t (119) = 13.37 d = 1.86	< .001
Mean RT on neutral trials	571.97 (129.94)	488.02 (93.98)	t (150) = 4.550 d = 0.70	< .001
Anxiety Comorbidity	Number (%)			
Single Diagnosis				
- SP	7 (6.9%)	---		
- GAD	8 (7.9%)			
- SAD	5 (5.0%)			

<u>Two Diagnoses</u> - SP + GAD - GAD + SAD - SP + SAD	 27 (26.7%) 10 (9.9%) 7 (6.9%)	 ---		
<u>Three Diagnoses</u> - SP + GAD + SAD	 37 (36.6%)	 ---		

SCARED = Screen for Anxiety and Related Disorders; SP= Social Phobia, GAD= Generalized Anxiety Disorder, SAD= Separation Anxiety Disorder.

Figure Caption:

Mean attention bias scores (in msec, with standard error bars) for threat faces in anxious patients and normal controls.

Disclosure

The authors have no financial relationships to disclose.

Figure
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