

# Attention Alterations in Pediatric Anxiety: Evidence From Behavior and Neuroimaging

Michael T. Perino, Qiongru Yu, Michael J. Myers, Jennifer C. Harper, William T. Baumel, Steven E. Petersen, Deanna M. Barch, Joan L. Luby, and Chad M. Sylvester

## ABSTRACT

**BACKGROUND:** Pediatric anxiety disorders involve greater capture of attention by threatening stimuli. However, it is not known if disturbances extend to nonthreatening stimuli, as part of a pervasive disturbance in attention-related brain systems. We hypothesized that pediatric anxiety involves greater capture of attention by salient, nonemotional stimuli, coupled with greater activity in the portion of the inferior frontal gyrus (IFG) specific to the ventral attention network (VAN).

**METHODS:** A sample of children ( $n = 129$ , 75 girls, mean 10.6 years of age), approximately half of whom met criteria for a current anxiety disorder, completed a task measuring involuntary capture of attention by nonemotional (square boxes) and emotional (angry and neutral faces) stimuli. A subset ( $n = 61$ ) completed a task variant during functional magnetic resonance imaging. A priori analyses examined activity in functional brain areas within the right IFG, supplemented by a whole-brain, exploratory analysis.

**RESULTS:** Higher clinician-rated anxiety was associated with greater capture of attention by nonemotional, salient stimuli ( $F_{1,125} = 4.94$ ,  $p = .028$ ) and greater activity in the portion of the IFG specific to the VAN ( $F_{1,57} = 10.311$ ,  $p = .002$ ). Whole-brain analyses confirmed that the effect of anxiety during capture of attention was most pronounced in the VAN portion of the IFG, along with additional areas of the VAN and the default mode network.

**CONCLUSIONS:** The pathophysiology of pediatric anxiety appears to involve greater capture of attention to salient stimuli, as well as greater activity in attention-related brain networks. These results provide novel behavioral and brain-based targets for treatment of pediatric anxiety disorders.

<https://doi.org/10.1016/j.biopsych.2020.07.016>

Anxiety disorders, the most common form of pediatric psychopathology, predict many adverse consequences over time (1). Pediatric anxiety disorder pathophysiology involves greater capture of attention by threatening stimuli (2). However, it remains unclear if these attention disturbances extend to nonthreatening stimuli as part of a more pervasive pattern of increased attention to salient stimuli generally (3). Moreover, the neurobiology of attention-related disturbances in pediatric anxiety remains incompletely understood.

Capture of attention by threatening stimuli is thought to be central to the etiology of pediatric anxiety disorders (4). Experimentally inducing increased attention to threat increases anxiety symptoms in healthy volunteers (5), and cognitive retraining reducing the capture of attention to threat decreases anxiety in clinical pediatric samples (6). A fundamental unresolved issue is whether attention-related disturbances in pediatric anxiety are restricted to threat or extend to salient stimuli more broadly (7,8). Several investigators have proposed that anxiety disorders are associated with generalized increases in the involuntary capture of attention to all salient stimuli, not just to threatening stimuli (3,9). These theories associate anxiety with hypervigilance, a state of readiness characterized by a broadly increased focus of

attention to environmental stimuli (10,11). Of note, generalized increases in attention to salient stimuli may be specific to anxiety disorders, as depression has been associated with lesser capture of attention by salient stimuli (12,13), and a meta-analysis in attention-deficit/hyperactivity disorder (ADHD) reported no significant relation to involuntary attention capture (14).

Another fundamental unresolved issue is explicating the brain systems underlying attention alterations in anxiety disorders. While greater attention to threat has been linked to a distributed set of brain regions (15), the inferior frontal gyrus (IFG) has been one of the most well-replicated regions demonstrating higher activity in anxious children (16–20). Pediatric anxiety has been robustly associated with greater IFG activity during passive viewing of aversive images (16–18) as well as during the capture of attention by aversive images (18–20). In addition, variation in functional connectivity between the amygdala and IFG during the viewing of aversive images has been linked to elevated anxiety (21,22).

The significance of altered IFG activity in pediatric anxiety is incompletely understood. Closely juxtaposed regions are associated with different functional networks, including the default mode network (DMN), involved in internally focused

processing (23); the cingulo-opercular network (CON), involved in error detection and cognitive control (24); the frontoparietal network (FPN), involved in executive function (25); and the ventral attention network (VAN), involved in the involuntary capture of attention by salient stimuli (26). While all of these processes may be altered in anxiety disorders (27), we and others have previously hypothesized that the greater IFG activity in anxiety disorders derives from the functions supported by the VAN, given this network's role in the involuntary capture of attention (26); however, few studies provide rigorous tests of this hypothesis (28–30).

Defining the breadth and neurobiology of attention-related disturbances associated with anxiety disorders may alter research on treatment. Current research focuses largely on interactions between attention and threat (7). However, if pediatric anxiety involves greater capture of attention by salient stimuli more generally (9), interventions might need to train individuals to avoid distraction to all salient stimuli, rather than exclusively threatening stimuli. Defining the nature of the IFG activation altered in pediatric anxiety may provide additional targets for brain-based therapies such as transcranial magnetic stimulation. It is especially important to clarify the nature of attention-related disturbances in anxiety disorders in pediatric samples. With a median age of onset of anxiety disorders of 6 years (31), successful early treatment may prevent the poorer psychiatric and functional adult outcomes associated with pediatric anxiety disorders (32–34).

The current study tested 2 related hypotheses: 1) pediatric anxiety is associated with a generalized increase in the involuntary capture of attention to all salient stimuli; and 2) greater IFG activity associated with pediatric anxiety during the involuntary capture of attention derives from the portion of the IFG specific to the VAN. We designed 2 related experiments. In experiment 1, a Posner cueing paradigm measured involuntary capture of attention in 129 children (~8–12 years of age), about half of whom had an anxiety disorder. Involuntary capture of attention was measured to 4 different cue types (square box, angry face, neutral face, and simultaneous angry and neutral faces) using targets presented at 3 different timing delays relative to cue onset (200, 500, and 800 ms). Attention to the cues is operationalized as the improvement in reaction time when responding to targets that appear at the same versus opposite location as the cue. The 3 different cue-target delays are required in order to fully characterize the time course of the involuntary capture of attention, which includes the initial capture of attention (200 ms), followed by inhibition of return, in which attention is impaired at the cued location (500 ms and 800 ms) (35). We predicted that anxiety would be positively associated with a higher magnitude of initial attention capture (200-ms delay) to all 3 single cue types (square box, angry face, and neutral face). We tested for specificity by examining relations between attentional capture and comorbid symptoms of ADHD and depression. We further explored whether the magnitude of involuntary attention capture by these 3 cue types was related to selective attention for angry versus neutral faces in the condition in which both faces were presented simultaneously.

In experiment 2, a subset ( $n = 61$ ) of the participants performed a modified version of the same task while undergoing

functional magnetic resonance imaging (fMRI). To maximize power to detect brain activity/anxiety relations, we measured brain activity in each participant over 4 different types of trial blocks. Each block type contained only a single type of cue but contained a mixture of trials with different cue-target timing delays and trials in which the cue and target were at the same versus opposite locations. Thus, experiment 2 was maximally powered to detect the functional brain areas associated with altered attention capture in pediatric anxiety, rather than to dissociate neural activity associated with each individual trial component, which would not have been feasible. Based on prior work highlighting the role of the IFG in pediatric anxiety, fMRI analyses focused on activity in 8 a priori functional areas from several different functional networks (36), the VAN, DMN, CON, and FPN. We predicted that greater activity in the portion of the IFG specific to the VAN would be related to anxiety. We also examined whether the behavioral measures of involuntary attention capture in experiment 1 were related to the magnitude of activity in each IFG parcel in experiment 2. Finally, we performed an exploratory whole-brain fMRI analysis to contextualize whether our a priori analysis captured the strongest anxiety-brain relations during attentional capture.

## METHODS AND MATERIALS

### Participants

Participants ~8 to 12 years of age with and without anxiety disorders were recruited from metropolitan St. Louis. We oversampled for children with clinically significant anxiety by advertising at informational talks about child anxiety delivered by C.M.S. The institutional review board at Washington University School of Medicine approved all procedures. Informed consent was obtained from parents and assent was obtained from all child participants.

Of 178 parents who called for initial screening, 149 of the children were preliminarily enrolled. Exclusion criteria included current use of psychotropic medication, intellectual disability, autism, and learning disabilities. Of the 149 initial participants, 6 were later excluded due to evidence of a disqualifying diagnosis during face-to-face interview. Fourteen were excluded for poor task performance (see below). The final behavioral sample consisted of 129 children, 71 of whom agreed to participate in a subsequent neuroimaging visit. After excluding 10 children for excessive head motion or failure to tolerate scanning, the final neuroimaging sample consisted of 61 children (see Table 1).

### Clinical Measures

Parents and children were separately interviewed by master's-level clinicians (37,38). Clinician-rated measures included the Kiddie Schedule for Affective Disorders and Schizophrenia (39) to make consensus DSM-5 psychiatric diagnoses and the Pediatric Anxiety Rating Scale (PARS) (38) to obtain continuous measures of anxiety (see Reliability in Supplemental Methods). Participants completed questionnaires for depression (parent and child Children's Depression Inventory) (40), anxiety (parent and child Screen for Child Anxiety Related Disorders) (41), and ADHD (parent Conners Rating Scale, Third

**Table 1. Demographic and Diagnostic Characteristics, Which Were Clinician Rated Using the Kiddie Schedule for Affective Disorders and Schizophrenia**

	Behavioral Sample ( <i>n</i> = 129)	Scanning Sample ( <i>n</i> = 61)
Age, Years	10.56 ± 1.40 (7.69–13.46)	10.48 ± 1.32 (8.12–12.98)
Female	75 (58)	31 (51)
Ethnicity		
Caucasian	98 (76)	50 (82)
African American	10 (8)	3 (5)
Asian	2 (2)	1 (2)
Bi/multiracial	19 (15)	7 (11)
Area Deprivation Index	34.47 ± 21.38 (2–98)	31.41 ± 19.44 (2–91)
Current Diagnoses		
Anxiety disorder only	42 (32.6)	23 (38)
Depressive disorder only	3 (2.3)	0
ADHD only	6 (4.7)	0
Anxiety and depression	13 (10.1)	6 (10)
Anxiety and ADHD	4 (3.1)	2 (3)
Depression and ADHD	1 (0.8)	0
Anxiety, depression, and ADHD	2 (1.6)	0
No current diagnosis	58 (45)	30 (49)
Lifetime Diagnoses		
Anxiety disorder only	41 (31.8)	23 (38)
Depressive disorder only	3 (2.3)	0
ADHD only	5 (3.9)	0
Anxiety and depression	16 (12.4)	7 (12)
Anxiety and ADHD	4 (3.1)	2 (3)
Depression and ADHD	1 (0.8)	0
Anxiety, depression, and anxiety	3 (2.3)	0
No past diagnoses	56 (43.4)	29 (47)

Values are mean ± SD (range) or *n* (%).

ADHD, attention-deficit/hyperactivity disorder.

Edition) (42). Socioeconomic status was calculated with the Area Deprivation Index (43).

### Attention Task

Participants completed a computerized attention task (Figure 1). One of 4 cue types appeared to the left or right side of the screen for 150 ms: a square box, an angry face, a neutral face, or angry and neutral faces (one on each side of the screen). Following a cue-target onset delay of 200, 500, or 800 ms, a target arrow appeared randomly at the cued location (valid trials) or opposite location (invalid trials). Participants indicated whether the target arrow was oriented upward or downward via button press. In trials in which both an angry

face and neutral face were present, the angry face was defined as the cue. The two-face condition is analogous to the dot probe task widely used to measure selective attention for threat versus neutral stimuli (44). Subjects completed 480 total trials across 10 blocks, averaging 20 trials per trial type (see Supplemental Methods).

Median reaction time scores were calculated for each subject for each possible combination of trial-level variables (4 cue types × 3 cue-target delays × 2 cue/target validity possibilities) and entered as dependent variables into fully factorial repeated-measures general linear models, along with anxiety, sex, and age as predictors. PARS scores were used to minimize reporter bias, increase statistical power (45), and follow Research Domain Criteria (46). We operationalized involuntary capture of attention as the difference in reaction time for invalid minus valid trials in trials with single cues (square box, angry face, neutral face). We operationalized selective attention to threat or threat bias as the difference in reaction time for neutral minus angry cued trials from the two-face (dot probe) condition. All behavioral analyses were run in SPSS Version 25 (IBM Corp., Armonk, NY).

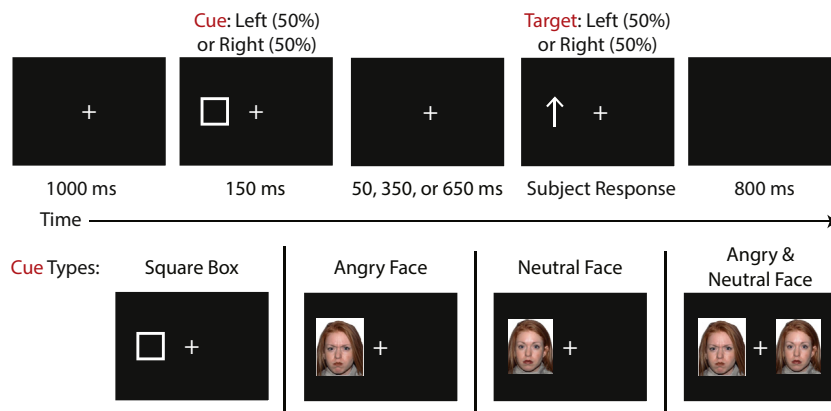
### Imaging Protocols and fMRI Task

Imaging was performed on a Siemens PRISMA 3T MRI scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. Structural images included a T1-weighted image (sagittal, 208 slices, 0.8-mm isotropic resolution, echo time = 2.22 ms, repetition time = 2400 ms, inversion time = 1000 ms, flip angle = 8°) and a T2-weighted image (sagittal, 208 slices, 0.8-mm isotropic resolution, echo time = 563 ms, repetition time = 3200 ms). Functional imaging was performed using a blood oxygen level-dependent (BOLD) multiband echo-planar sequence (repetition time = 720 ms, echo time = 33 ms, flip angle = 52°, 2.4-mm isotropic resolution, multiband factor = 7). Two spin-echo field maps were obtained (anteroposterior and posteroanterior) during each session with the same parameters.

It was not feasible to obtain enough fMRI data in each subject to estimate the BOLD response to each of the 24 different trial types. Therefore, the fMRI task was modified to a block design to maximize statistical power (47) by focusing on BOLD activity specific to cue type. Trials were blocked into groups of 5, in which each of the trials within a block contained a single cue type (e.g., square box); other trial-level variables were randomized. Blocks lasted approximately 18 seconds and included all trials regardless of accuracy (accuracy was uncorrelated to anxiety, *p* = .59). Blocks were separated by periods of fixation ranging from 9 to 33 BOLD frames. Four runs were obtained, each with 8 blocks (160 total trials). One run was discarded in 3 subjects (2 ended early and 1 had a computer error). FIRMM (Framework Integrated Real-time MRI Monitoring) (48) monitored motion (see Supplemental Methods).

### fMRI Preprocessing

fMRI preprocessing included correction of intensity differences attributable to interleaved acquisition, bias field correction, intensity normalization of each run to a whole-brain mode of



**Figure 1.** The task used to measure involuntary capture of attention. To begin each trial, 1 of 4 cue types appeared randomly at the left or right side of the screen for 150 ms. After a random delay of 50, 350, or 650 ms (resulting in a cue-target onset asynchrony of 200, 500, or 800 ms), a target appeared randomly on the left or side of the screen. The participants' task was to indicate whether the target was pointing upward or downward by pressing a button on a keyboard. Measures of attention are calculated as how much faster individuals were when the cue was on the same side of the screen as the target (valid trials) relative to trials when the cue was on the opposite side of the screen (invalid trials).

1000, linear realignment within and across runs (49), and linear registration of BOLD images to a Talairach Atlas (50), via the T2 and T1 images. Field map correction was performed using the FSL TOPUP toolbox (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TOPUP>). Atlas transformation, field distortion correction, and resampling to 3-mm isotropic atlas space were combined into a single interpolation (49,51). We censored frames with framewise displacement  $>0.9$  mm to reduce motion artifact (52). Functional task runs with fewer than 150 frames after censoring were excluded. FreeSurfer version 5.0.0 (<http://surfer.nmr.harvard.edu>) generated surfaces for each subject, and volumetric fMRI data were mapped to subject-specific surfaces using procedures adapted from the Human Connectome Project as implemented in Connectome Workbench 1.2.3 (<https://www.humanconnectome.org/>). fMRI data were aligned across subjects in surface space using spherical registration. Time courses for surface data were smoothed with geodesic 2-dimensional Gaussian kernels ( $\sigma = 2.55$  mm) (see Supplemental Methods).

### fMRI Task Processing

BOLD responses for each of the 4 cue types were modeled using a block design. Regressors were generated for each subject for each cue type by convolving a standard BOLD hemodynamic response function (53) with the task-block duration. For each subject, a general linear model modeled framewise BOLD activity at each vertex as a function of cue type, run baseline, and run linear trend. We extracted parameter estimates for each block type within 8 different functional areas representing 4 distinct functional networks in the IFG (36) (see Table S1). These functional areas encompass regions previously implicated in children with anxiety disorders (16–22). We ran a repeated-measures general linear model including cue type, anxiety (PARS), and the cue type  $\times$  anxiety interaction, with sex and age as covariates. Bonferroni corrections controlled for multiple comparisons. This same analysis was performed vertexwise across the brain to find clusters ( $p \leq .01$  and area  $\geq 100$  mm<sup>2</sup>) in an exploratory analysis using in-house software (<http://www.nil.wustl.edu/~fidl>).

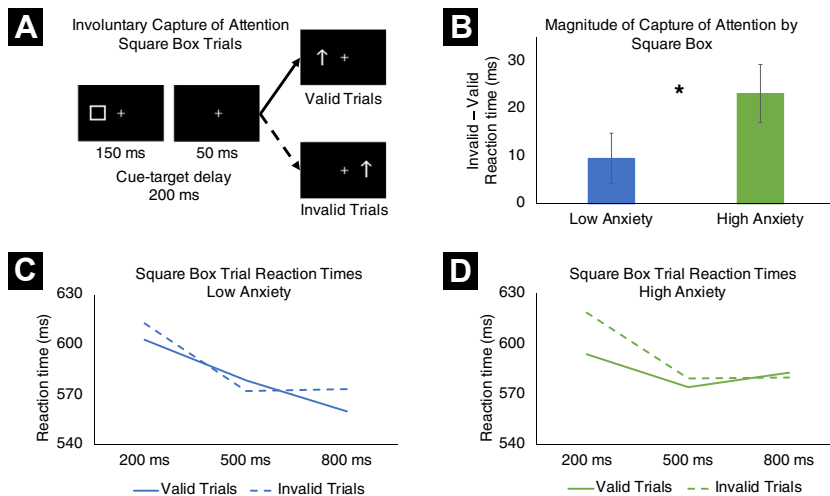
## RESULTS

### Sample Characteristics

Half of the sample (47% of the full sample, 51% of the scanning sample) met criteria for at least 1 current anxiety disorder (generalized anxiety, separation anxiety, social phobia). Anxiety as measured by clinicians with the PARS was not significantly related to sex ( $t_{127} = 1.346$ ,  $p = .181$ ) and had a small, nonsignificant relationship to age ( $r = -.163$ ,  $p = .065$ ). In the neuroimaging sample, anxiety was not significantly related to sex ( $t_{59} = 0.910$ ,  $p = .366$ ) or age ( $r = -.073$ ,  $p = .577$ ). There were no significant differences in anxiety ( $t_{127} = 0.366$ ,  $p = .715$ ), age ( $t_{127} = 0.148$ ,  $p = .883$ ), or sex ( $\chi^2_{1, N = 129} = 2.213$ ,  $p = .137$ ) between the children that did versus those who did not participate in scanning. Symptoms of depression and ADHD were low due to our recruitment strategy but were significantly correlated with symptoms of anxiety (Tables S2 and S3).

### Experiment 1: Involuntary Capture of Attention in Pediatric Anxiety

Higher anxiety was significantly related to greater involuntary capture of attention by the square box cues at the shortest cue-target delay (Figure 2, Tables S4–S7). We observed a significant interaction between anxiety, cue type, cue validity, and cue-target onset delay ( $F_{6,750} = 2.217$ ,  $p = .04$ ) (Table S5). Follow-up tests performed separately for each cue type revealed a significant 3-way interaction between anxiety, cue validity, and cue-target onset delay in the square box cue condition only ( $F_{2,250} = 3.025$ ,  $p = .05$ ) (Table S6). This interaction was explained by a significant interaction between anxiety and cue validity exclusively at the shortest cue-target delay ( $F_{1,125} = 4.938$ ,  $p = .028$ ) (see Figure 2 and Table S7). In these trials, higher anxiety was significantly related to faster reaction times for valid versus invalidly cued trials, consistent with greater involuntary attention capture in children with higher anxiety. Comorbid symptoms (depression, inattention, hyperactivity) did not significantly interact (all  $p > .05$ ) with task conditions (see Comorbidity in Supplemental Results). The significant



**Figure 2.** Anxiety is positively related to involuntary capture of attention by nonemotional salient stimuli. **(A)** The specific trial type that measures the initial capture of attention by salient, nonemotional cues. **(B)** The magnitude of the initial capture of attention by nonemotional cues in children with high versus low anxiety. This magnitude is calculated as how much faster reaction time was for validly cued trials with the 200-ms cue-target onset delay relative to invalidly cued trials. **(C, D)** Reaction times for participants with low/high anxiety (median split of Pediatric Anxiety Rating Scale) for discriminating targets appearing at the same (valid trials) or opposite side (invalid trials) of the screen relative to the square-box cue in trials with the shortest cue-target delay. All statistical analyses used anxiety scores (Pediatric Anxiety Rating Scale) as a continuous variable.

relation between anxiety and attention did not differ between the children who subsequently participated in imaging versus those who did not (Fisher's  $r$ -to- $z$  transformation = .1,  $p = .92$ ).

There was no relationship between anxiety and involuntary capture of attention to either the angry or neutral face cue (Table S6). In a typical Posner cueing paradigm, reaction times to targets at cued (valid) locations are faster relative to targets at uncued (invalid) locations at short cue-target delays such as 200 ms. While this typical pattern held in the current study for square box cues, participants were faster at responding to targets at the invalid versus the valid location at the shortest cue-target delay for the face cues (see Figure S1). This pattern suggests that face cues may have obscured the percept of the target, i.e., forward masking (54,55). There were no significant interactions that included anxiety in the two-face (dot probe) condition (see Table S6). The magnitude of involuntary attention capture at the shortest cue-target onset delay to the square box cue was not significantly related to selective attention to threat in the two-face trials at 200 ms ( $r_{127} = .143$ ,  $p = .106$ ), 500 ms ( $r_{127} = .034$ ,  $p = .698$ ), or 800 ms ( $r_{127} = .022$ ,  $p = .807$ ).

### Experiment 2: Attention-Related Brain Activity Associated With Pediatric Anxiety

Figure 3 depicts a whole-brain analysis of activity evoked during the attention-orienting task. As expected, activity was elicited in control and attention-related brain networks, including in the VAN (26), dorsal attention network (56), salience network (57), DMN (23), FPN (25), and CON (24). Activity also increased in the hand area of the left motor cortex, but not in other portions of motor cortex, consistent with participants making right-handed button presses.

After applying Bonferroni corrections, higher anxiety was significantly related to greater activity during the task, across all cue types, exclusively in a VAN functional area of the IFG (main effect of anxiety [ $F_{1,57} = 10.314$ ,  $p = .002$ ,  $\eta_p^2 = .153$ ])

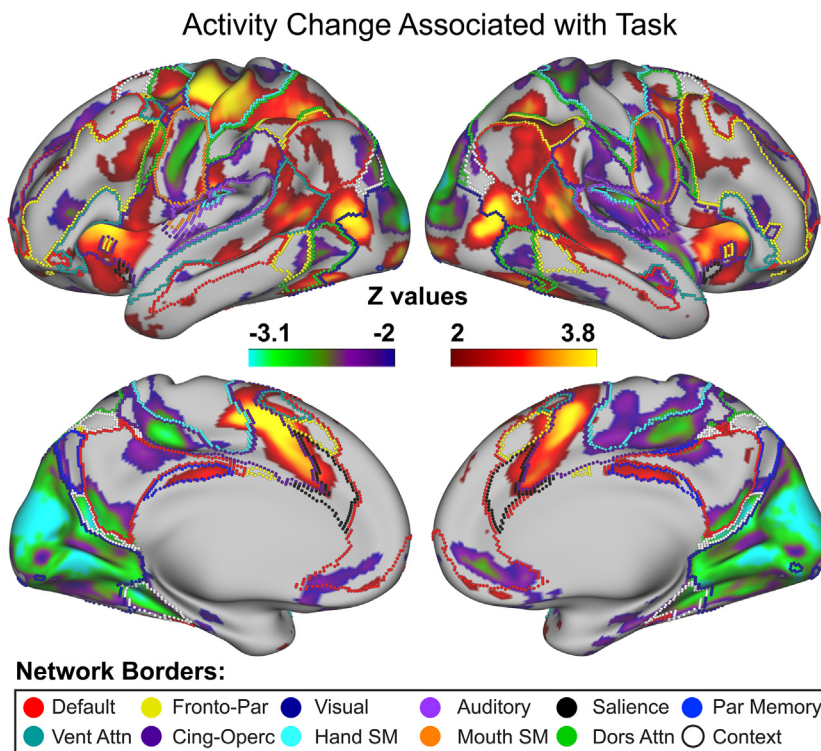
(see Figure 4A, B). The relation of anxiety to activity in this VAN area was significantly greater than the relation of anxiety to activity in functional areas in the DMN ( $t_{58} = 2.51$ ,  $p = .015$ ), CON ( $t_{58} = 2.06$ ,  $p = .04$ ), and another nearby region in the VAN ( $t_{58} = 2.91$ ,  $p = .005$ ) (see Table S8). We did not observe any statistically significant cue  $\times$  anxiety interactions in any of the a priori defined functional areas. After applying Bonferroni corrections, activity in the VAN IFG parcel was not significantly related to symptoms of depression, inattention, or hyperactivity (see Table S9). Additionally, the relation of anxiety was significantly greater than the relation of inattention to activity in this functional area ( $t_{58} = 2.23$ ,  $p = .03$ ).

There was a significant correlation between the involuntary capture of attention by square box cues at the shortest cue-target delay (200 ms) in experiment 1 and activity in the VAN portion of the IFG in experiment 2 in blocks with square box cues ( $r_{59} = .421$ ,  $p = .001$ ). This significant relation suggests that variation in activity in the VAN-IFG parcel is related to variation in the involuntary capture of attention as measured outside the scanner (see Table S10).

Results of an exploratory whole-brain analysis are reported here to contextualize the hypothesis-driven analysis and described in detail in the Supplement. Across the brain, we observed 3 clusters ( $p \leq .01$  and area  $\geq 100$  mm<sup>2</sup>) where brain activity during the attention task was significantly related to anxiety: a cluster in the right IFG that overlapped with the VAN functional area from the hypothesis-driven analysis, a cluster in the left superior temporal gyrus assigned to the VAN, and a cluster in the right frontal pole assigned to the DMN (see Figure 4C and Table S11). In all instances, higher anxiety was associated with higher regional brain activity.

### DISCUSSION

The current study suggests that clinician-rated anxiety severity in children is associated with greater involuntary capture of attention by salient, nonemotional stimuli. Both anxiety and



**Figure 3.** Significant activity change ( $p < .05$ ) associated with the task. The task elicits widespread brain activity, including in brain networks implicated in executive function and control of attention. The images above illustrate the main effect of task in the imaging analysis, similar to average evoked activity regardless of level of anxiety. Warm colors indicate activity increases, while cool colors indicate activity decreases relative to a fixation baseline. Borders indicate the boundaries of functional brain networks as determined by a study of adults (70). Activity modulations are noted across much of the brain, including in the ventral attention (Vent Attn), dorsal attention (Dors Attn), salience, frontoparietal (Fronto-Par), and cingulo-opercular (Cing-Operc) networks. Note that activity in the motor network was restricted to the hand representation in the left hemisphere, consistent with subjects making right-handed button presses. Par, parietal; SM, somatosensory-motor.

involuntary capture of attention were positively associated with greater activity in a VAN-specific portion of the IFG. While prior work established that anxiety is linked to selectively attending to threatening stimuli (58), our results suggest that anxiety is more broadly related to greater capture of attention by salient nonemotional stimuli, which may have important implications for the pathophysiology and treatment of pediatric anxiety.

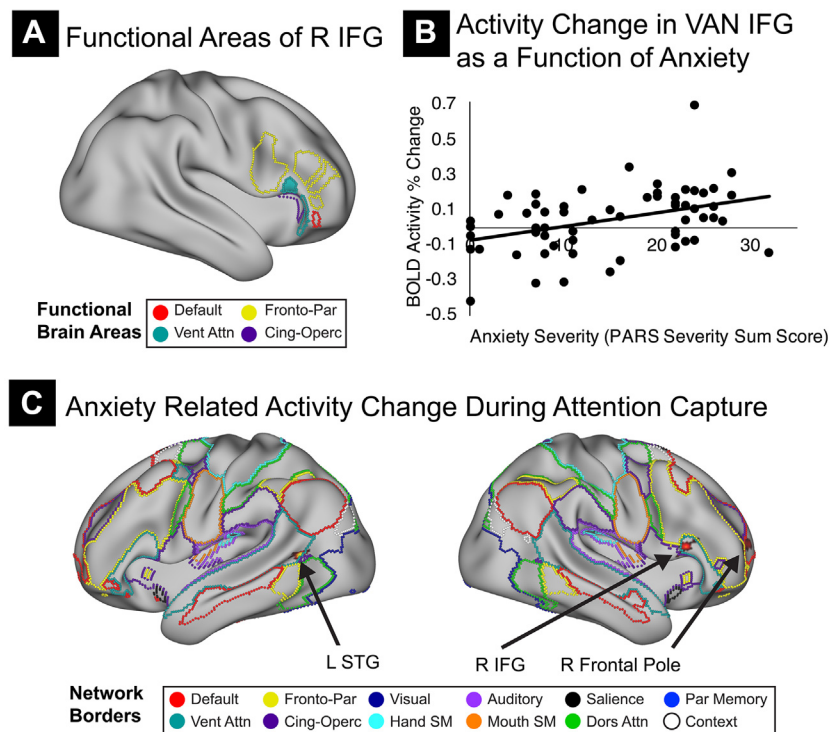
Behavioral results from experiment 1 provide direct support for the hypothesis that pediatric anxiety relates to greater involuntary capture of attention by salient, nonemotional stimuli. Previous work had indirectly supported this hypothesis, including developmental studies showing that infants with generalized increased reactivity to salient stimuli are at heightened risk for developing anxiety disorders (29,59–61), and work showing greater involuntary capture of attention by threat relates to greater capture of attention by nonemotional stimuli in anxious youths (3). These results have relevance for how mental health professionals understand symptom presentation. Anxiety appears to include difficulty maintaining attention in the presence of competing stimuli, regardless of threat valence (10,11). Training children to attend to neutral as opposed to threatening stimuli improves anxiety disorder symptoms (6), though effect sizes are modest. Our results suggest that a complementary approach may be to intervene on more fundamental aspects of attention by training patients to maintain focus on specific goals while ignoring other salient stimuli, irrespective of the emotional valence of distractors (27).

Counter to our original hypothesis, there was no relation between pediatric anxiety and behavioral measures of attention to angry and neutral faces. All participants, irrespective of

anxiety, were faster in responding to targets at locations that had previously been empty as opposed to locations that had been occupied by faces at the shortest cue-target delay. We suggest that the observed null effect observed in the behavioral task may be due to forward masking (54,55) in which faces obscured the percept of the subsequently appearing target. Similar forward masking effects may complicate the interpretation of prior work examining attention to angry versus neutral faces in anxiety disorders.

In line with our original hypothesis, experiment 2 demonstrated that participants with higher anxiety had greater activity specifically in the VAN portion of the IFG during the task eliciting involuntary attention capture. Furthermore, activity in the VAN-IFG during experiment 2 was strongly related to the magnitude of involuntary attention capture in experiment 1. Because activity was greater in the VAN-IFG for children with higher anxiety regardless of cue type, we suggest that the neural data support the hypothesis that individuals with higher anxiety had increased attention to all cue types, including the faces. Exploratory whole-brain analyses identified greater activity in VAN regions in both the right IFG and the left superior temporal gyrus (56), as well as in a right frontal pole in the DMN, confirming that our hypothesis-driven analysis captured the strongest relationships between anxiety and attention-related brain activity.

Our results may provide a specific target for neurostimulation techniques, such as transcranial magnetic stimulation (62) in the portion of the IFG specific to the VAN. Stimulating this exact location to reduce VAN activation may be more effective than targeting closely juxtaposed functional



**Figure 4.** A priori and exploratory analyses examining activity change associated with anxiety. **(A)** The 8 a priori defined functional areas within the inferior frontal gyrus (IFG) in which we explored the relation between anxiety and brain activity during the attention task. The outlines depict all regions, while the solidly colored area is the portion of the IFG within the ventral attention network (VAN), which was the only region in which activity was significantly related to anxiety after Bonferroni correction. **(B)** Brain activity elicited in this IFG region within the VAN during the involuntary capture of attention is correlated with anxiety severity (Pediatric Anxiety Rating Scale [PARS]), while controlling for age and sex. Results were unchanged when excluding the single outlier data point. **(C)** Results from our exploratory whole-brain analyses, examining the effect of anxiety during the attention task, while controlling for age and sex. Borders indicate the boundaries of functional brain networks as determined by a study of adults (70). Using a threshold of  $p \leq .01$  and surface area  $\geq 100 \text{ mm}^2$ , we observed 3 clusters, **(A)** in the left superior temporal gyrus (L STG), **(B)** near the a priori selected right IFG (R IFG), and **(C)** in the R frontal pole (default mode network). In each case, higher anxiety was associated with higher regional brain activity. BOLD, blood oxygen level-dependent. Attn, attention; Cing-Operc, cingulo-opercular; Dors, dorsal; Fronto-Par, frontoparietal; Par, parietal; SM, somatosensory-motor; Vent, ventral.

areas from the DMN (23), CON (24), or FPN (25). While prior studies have detected altered activity in the IFG in pediatric anxiety (16–22), the current study clarifies for the first time that this altered activity is specific to the VAN. This current study is consistent with prior work demonstrating alterations in functional connectivity of the VAN in children with high anxiety (63).

The current study should be considered in light of its limitations. Forward masking appears to have confounded our measure of involuntary capture of attention by angry and neutral faces in experiment 1. Similar effects may have confounded past studies relating anxiety and attention to faces, and future studies could alleviate this problem by using cues that do not spatially overlap with targets (e.g., positioning the targets slightly below the cues). Also, our analytic strategy was to use separate experiments to parse the nuanced effects of anxiety on behavioral measures of attention (experiment 1) and to determine the associated neurobiological underpinnings (experiment 2). Experiment 2 maximized power to detect brain/anxiety relations at the expense of not modeling each individual trial-level variable present in experiment 1. Future studies could incorporate event-related designs using single cue types (e.g., only square box cues) to dissociate how anxiety relates to valid versus invalid trials, different cue-target delays, and cue from target-related brain activity. We predict that anxiety would be positively associated with activity for all salient cues and for invalid targets at short cue-target delays (e.g., 200 ms). Finally, future work is required to contextualize the reported abnormalities within the larger framework of cognitive and neurobiological processes affected by anxiety, including alterations in error monitoring (64) and the CON (65),

in executive function (66) and the FPN (67), in fear extinction (68) and the DMN (69), and in related cognitive factors such as intelligence.

This study demonstrates that pediatric anxiety disorders are associated with greater involuntary capture of attention by salient stimuli, coupled with greater activity in the VAN. These results inform our conceptualization of the pathophysiology of pediatric anxiety and provide targets for new treatment development.

#### ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institutes of Mental Health (National Institutes of Health Grant Nos. K23MH109983 [to CMS] and R01MH122389 [to CMS]; National Institutes of Mental Health Grant Nos. 2T32MH100019-06 [for MTP, to JLL and DMB] and R01MH090786 [to DMB]), the James S. McDonnell Foundation (Grant No. 220020534 [to SEP]), and generous funds from the Taylor Institute and Parker Fund (to CMS).

We thank Gordon Shulman for feedback on an earlier version of this manuscript. We also thank the dedicated staff (Kathy Pope, Beth Brunsworth, and Riley Groves) who made this project possible. Finally, we also extend thanks to the schools, administrators, and counselors who helped with recruitment of participants for this project.

The authors report no biomedical financial interests or potential conflicts of interest.

#### ARTICLE INFORMATION

From the Department of Psychiatry (MTP, MJM, JCH, DMB, JLL, CMS), Department of Neurology (SEP), Department of Neuroscience (SEP), Mallinckrodt Institute of Radiology (SEP), and Department of Psychological and Brain Sciences (DMB), Washington University School of Medicine in St. Louis, St. Louis, Missouri; Department of Psychology (QY), San Diego State

University, and Department of Psychiatry (QY), University of California San Diego School of Medicine, San Diego, California; and the Department of Psychiatry and Behavioral Neuroscience (WTB), University of Cincinnati School of Medicine, Cincinnati, Ohio.

Address correspondence to Michael T. Perino, Ph.D., at [mperino@wustl.edu](mailto:mperino@wustl.edu), or Chad M. Sylvester, M.D., Ph.D., at [chad.sylvester@wustl.edu](mailto:chad.sylvester@wustl.edu).

Received Jan 31, 2020; revised Jun 30, 2020; accepted Jul 8, 2020.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.biopsych.2020.07.016>.

## REFERENCES

- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62:593–602.
- Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IJzendoorn MH (2007): Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychol Bull* 133:1–24.
- Sylvester CM, Hudziak JJ, Gaffrey MS, Barch DM, Luby JL (2016): Stimulus-driven attention, threat bias, and sad bias in youth with a history of an anxiety disorder or depression. *J Abnorm Child Psychol* 44:219–231.
- Shechner T, Jarcho JM, Britton JC, Leibenluft E, Pine DS, Nelson EE (2013): Attention bias of anxious youth during extended exposure of emotional face pairs: An eye-tracking study. *Depress Anxiety* 30:14–21.
- Bradley BP, Mogg K, Lee SC (1997): Attentional biases for negative information in induced and naturally occurring dysphoria. *Behav Res Ther* 35:911–927.
- Shechner T, Rimón-Chakir A, Britton JC, Lotan D, Apter A, Bliese PD, et al. (2014): Attention bias modification treatment augmenting effects on cognitive behavioral therapy in children with anxiety: Randomized controlled trial. *J Am Acad Child Adolesc Psychiatry* 53:61–71.
- Cisler JM, Koster EHW (2010): Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychol Rev* 30:203–216.
- Teachman BA, Joormann J, Steinman SA, Gotlib IH (2012): Automaticity in anxiety disorders and major depressive disorder. *Clin Psychol Rev* 32:575–603.
- Eysenck MW, Derakshan N, Santos R, Calvo MG (2007): Anxiety and cognitive performance: Attentional control theory. *Emotion* 7:336–353.
- Richards HJ, Benson V, Donnelly N, Hadwin JA (2014): Exploring the function of selective attention and hypervigilance for threat in anxiety. *Clin Psychol Rev* 34:1–13.
- Seefeldt WL, Krämer M, Tuschen-Caffier B, Heinrichs N (2014): Hypervigilance and avoidance in visual attention in children with social phobia. *J Behav Ther Exp Psychiatry* 45:105–112.
- Brand N, Jolles J (1987): Information processing in depression and anxiety. *Psychol Med* 17:145–153.
- Hammar A (2003): Automatic and effortful information processing in unipolar major depression. *Scand J Psychol* 44:409–413.
- Huang-Pollock CL, Nigg JT (2003): Searching for the attention deficit in attention deficit hyperactivity disorder: The case of visuospatial orienting. *Clin Psychol Rev* 23:801–830.
- Strawn JR, Dominick KC, Patino LR, Doyle CD, Picard LS, Phan KL (2014): Neurobiology of pediatric anxiety disorders. *Curr Behav Neurosci Rep* 1:154–160.
- McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJR, et al. (2007): Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Arch Gen Psychiatry* 64: 97–106.
- Strawn JR, Bitter SM, Weber WA, Chu W-J, Whitsel RM, Adler C, et al. (2012): Neurocircuitry of generalized anxiety disorder in adolescents: A pilot functional neuroimaging and functional connectivity study. *Depress Anxiety* 29:939–947.
- Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, et al. (2006): Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *Am J Psychiatry* 163:1091–1097.
- Hare TA, Tottenham N, Galvan A, Voss HU, Glover GH, Casey BJ (2008): Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biol Psychiatry* 63:927–934.
- Telzer EH, Mogg K, Bradley BP, Mai X, Ernst M, Pine DS, et al. (2008): Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biol Psychol* 79:216–222.
- Guyler AE, Lau JYF, McClure-Tone EB, Parrish J, Shiffrin ND, Reynolds RC, et al. (2008): Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch Gen Psychiatry* 65:1303–1312.
- Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. (2008): Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Arch Gen Psychiatry* 65:568–576.
- Raichle ME (2015): The brain's default mode network. *Annu Rev Neurosci* 38:433–447.
- Dosenbach NUF, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, et al. (2006): A core system for the implementation of task sets. *Neuron* 50:799–812.
- Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, et al. (2007): Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci U S A* 104:11073–11078.
- Corbetta M, Patel G, Shulman GL (2008): The reorienting system of the human brain: From environment to theory of mind. *Neuron* 58:306–324.
- Sylvester CM, Corbetta M, Raichle ME, Rodebaugh TL, Schlaggar BL, Sheline YI, et al. (2012): Functional network dysfunction in anxiety and anxiety disorders. *Trends Neurosci* 35:527–535.
- Sylvester CM, Barch DM, Harms MP, Belden AC, Oakberg TJ, Gold AL, et al. (2016): Early childhood behavioral inhibition predicts cortical thickness in adulthood. *J Am Acad Child Adolesc Psychiatry* 55:122–129.e1.
- Rogers CE, Sylvester CM, Mintz C, Kenley JK, Shimony JS, Barch DM, et al. (2017): Neonatal amygdala functional connectivity at rest in healthy and preterm infants and early internalizing symptoms. *J Am Acad Child Adolesc Psychiatry* 56:157–166.
- Sylvester CM, Pine DS (2018): The biological bridge between behavioral inhibition and psychopathology. In: Perez-Edgar K, Fox NA, editors. *Behavioral Inhibition: Integrating Theory, Research, and Clinical Perspectives*, 1st ed. (309–355). Cham, Switzerland: Springer, 309–355.
- Merikangas KR, He J-P, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. (2010): Lifetime prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry* 49:980–989.
- Franz L, Angold A, Copeland W, Costello EJ, Towe-Goodman N, Egger H (2013): Preschool anxiety disorders in pediatric primary care: Prevalence and comorbidity. *J Am Acad Child Adolesc Psychiatry* 52:1294–1303.e1.
- Ginsburg GS, Becker EM, Keeton CP, Sakolsky D, Piacentini J, Albano AM, et al. (2014): Naturalistic Follow-up of youths treated for pediatric anxiety disorders. *JAMA Psychiatry* 71:310–318.
- Benjamin CL, Harrison JP, Settapani CA, Brodman DM, Kendall PC (2013): Anxiety and related outcomes in young adults 7 to 19 years after receiving treatment for child anxiety. *J Consult Clin Psychol* 81:865–876.
- Klein R (2000): Inhibition of return. *Trends Cogn Sci* 4:138–147.
- Gordon EM, Laumann TO, Adeyemo B, Huckins JF, Kelley WM, Petersen SE (2016): Generation and evaluation of a cortical area parcellation from resting-state correlations. *Cereb Cortex* 26:288–303.
- Isaacs E (2001): Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med* 345:466–467.
- [No authors listed] (2002): The Pediatric Anxiety Rating Scale (PARS): Development and psychometric properties. *J Am Acad Child Adolesc Psychiatry* 41:1061–1069.



39. Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA, *et al.* (1985): The assessment of affective disorders in children and adolescents by semistructured interview: Test-retest reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode Version. *Arch Gen Psychiatry* 42:696–702.
40. Kovacs M (1992): *Children's Depression Inventory*. North Tonawanda, NY: Multi-Health Systems.
41. Behrens B, Swettlitz C, Pine DS, Pagliaccio D (2019): The Screen for Child Anxiety Related Emotional Disorders (SCARED): Informant discrepancy, measurement invariance, and test-retest reliability. *Child Psychiatry Hum Dev* 50:473–482.
42. Conners CK (2006): *Attention Deficit Hyperactivity Disorder: The Latest Assessment and Treatment Strategies*, 3rd ed. Kansas City, MO: Compact Clinicals.
43. Kind AJH, Buckingham WR (2018): Making neighborhood-disadvantage metrics accessible - The neighborhood atlas. *N Engl J Med* 378:2456–2458.
44. Bar-Haim Y (2010): Research review: Attention bias modification (ABM): A novel treatment for anxiety disorders. *J Child Psychol Psychiatry* 51:859–870.
45. Royston P, Altman DG, Sauerbrei W (2006): Dichotomizing continuous predictors in multiple regression: A bad idea. *Stat Med* 25:127–141.
46. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, *et al.* (2010): Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry* 167:748–751.
47. Bandettini PA, Cox RW (2000): Event-related fMRI contrast when using constant interstimulus interval: Theory and experiment. *Magn Reson Med* 43:540–548.
48. Dosenbach NUF, Koller JM, Earl EA, Miranda-Dominguez O, Klein RL, Van AN, *et al.* (2017): Real-time motion analytics during brain MRI improve data quality and reduce costs. *Neuroimage* 161:80–93.
49. Ojemann JG, Akbudak E, Snyder AZ, McKinsty RC, Raichle ME, Conturo TE (1997): Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. *Neuroimage* 6:156–167.
50. Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme.
51. Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, *et al.* (2004): A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *Neuroimage* 23:724–738.
52. Siegel JS, Power JD, Dubis JW, Vogel AC, Church JA, Schlaggar BL, *et al.* (2014): Statistical improvements in functional magnetic resonance imaging analyses produced by censoring high-motion data points. *Hum Brain Mapp* 35:1981–1996.
53. Boynton GM, Engel SA, Glover GH, Heeger DJ (1996): Linear systems analysis of functional magnetic resonance imaging in human V1. *J Neurosci* 16:4207–4221.
54. Posner MI, Cohen Y (1984): Components of visual orienting. In: Bouma H, Bouwhis DH, editors. *Attention and Performance X: Control of Language Processes (Attention and Performance Series)*. Hillsdale, NJ: Erlbaum, 531–556.
55. Feczko E, Shulman GL, Petersen SE, Pruetz JR Jr (2014): Interactions between concentric form-from-structure and face perception revealed by visual masking but not adaptation. *J Vis* 14:15.
56. Vossel S, Geng JJ, Fink GR (2014): Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. *Neuroscientist* 20:150–159.
57. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27:2349–2356.
58. Roy AK, Vasa RA, Bruck M, Mogg K, Bradley BP, Sweeney M, *et al.* (2008): Attention bias toward threat in pediatric anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 47:1189–1196.
59. Sylvester CM, Smyser CD, Smyser T, Kenley J, Ackerman JJ, Shimony JS, *et al.* (2018): Cortical functional connectivity evident after birth and behavioral inhibition at age 2. *Am J Psychiatry* 175:180–187.
60. Fox NA, Henderson HA, Marshall PJ, Nichols KE, Ghera MM (2005): Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annu Rev Psychol* 56:235–262.
61. Kagan J (2002): Childhood predictors of states of anxiety. *Dialogues Clin Neurosci* 4:287–293.
62. Clarke PJF, Browning M, Hammond G, Notebaert L, MacLeod C (2014): The causal role of the dorsolateral prefrontal cortex in the modification of attentional bias: Evidence from transcranial direct current stimulation. *Biol Psychiatry* 76:946–952.
63. Sylvester CM, Barch DM, Corbetta M, Power JD, Schlaggar BL, Luby JL (2013): Resting state functional connectivity of the ventral attention network in children with a history of depression or anxiety. *J Am Acad Child Adolesc Psychiatry* 52:1326–1336. e1325.
64. Fitzgerald KD, Taylor SF (2015): Error-processing abnormalities in pediatric anxiety and obsessive compulsive disorders. *CNS Spectr* 20:346–354.
65. Markett S, Montag C, Melchers M, Weber B, Reuter M (2016): Anxious personality and functional efficiency of the insular-opercular network: A graph-analytic approach to resting-state fMRI. *Cogn Affect Behav Neurosci* 16:1039–1049.
66. Liu Y, Gehring WJ, Weissman DH, Taylor SF, Fitzgerald KD (2012): Trial-by-trial adjustments of cognitive control following errors and response conflict are altered in pediatric obsessive compulsive disorder. *Front Psychiatry* 3:41.
67. Modi S, Kumar M, Kumar P, Khushu S (2015): Aberrant functional connectivity of resting state networks associated with trait anxiety. *Psychiatry Res* 234:25–34.
68. Graham BM, Milad MR (2011): The study of fear extinction: Implications for anxiety disorders. *Am J Psychiatry* 168:1255–1265.
69. Zhao X-H, Wang P-J, Li C-B, Hu Z-H, Xi Q, Wu W-Y, *et al.* (2007): Altered default mode network activity in patient with anxiety disorders: An fMRI study. *Eur J Radiol* 63:373–378.
70. Power Jonathan D, Cohen Alexander L, Nelson Steven M, Wig Gagan S, Barnes Kelly A, Church Jessica A, *et al.* (2011): Functional network organization of the human brain. *Neuron* 72:665–678.