ORIGINAL ARTICLE

Abnormal Attention Modulation of Fear Circuit Function in Pediatric Generalized Anxiety Disorder

Erin B. McClure, PhD; Christopher S. Monk, PhD; Eric E. Nelson, PhD; Jessica M. Parrish, BA; Abby Adler, BA; R. James R. Blair, PhD; Stephen Fromm, PhD; Dennis S. Charney, MD; Ellen Leibenluft, MD; Monique Ernst, MD, PhD; Daniel S. Pine, MD

Context: Considerable work implicates abnormal neural activation and disrupted attention to facial-threat cues in adult anxiety disorders. However, in pediatric anxiety, no research has examined attention modulation of neural response to threat cues.

Objective: To determine whether attention modulates amygdala and cortical responses to facial-threat cues differentially in adolescents with generalized anxiety disorder and in healthy adolescents.

Design: Case-control study.

Setting: Government clinical research institute.

Participants: Fifteen adolescents with generalized anxiety disorder and 20 controls.

Main Outcome Measures: Blood oxygenation level–dependent signal as measured via functional magnetic resonance imaging. During imaging, participants completed a face-emotion rating task that systematically manipulated attention.

Results: While attending to their own subjective fear, patients, but not controls, showed greater activation to fearful faces than to happy faces in a distributed network including the amygdala, ventral prefrontal cortex, and anterior cingulate cortex ($P<.05$, small-volume corrected, for all). Right amygdala findings appeared particularly strong. Functional connectivity analyses demonstrated positive correlations among the amygdala, ventral prefrontal cortex, and anterior cingulate cortex.

Conclusions: This is the first evidence in juveniles that generalized anxiety disorder–associated patterns of pathologic fear circuit activation are particularly evident during certain attention states. Specifically, fear circuit hyperactivation occurred in an attention state involving focus on subjectively experienced fear. These findings underscore the importance of attention and its interaction with emotion in shaping the function of the adolescent human fear circuit.

Arch Gen Psychiatry. 2007;64:97-106

PEDIATRIC GENERALIZED ANXIETY disorder (GAD) confers major risk for adult psychopathologic abnormalities.[1] Numerous mechanisms may underlie this developmental association; one possibility is that early neural dysfunction associated with anxiety persists into adulthood. Functional magnetic resonance imaging (fMRI) research in anxious adults indicates dysfunction in a circuit involving periamygdala regions, the ventral prefrontal cortex (vPFC), and the anterior cingulate cortex (ACC).[2,3] Identifying comparable patterns in pediatric GAD would provide a critical step toward linking childhood anxiety and adult disorders.

Cognitive perturbations, particularly in attention to subjectively experienced threats, are central to the emergence of anxiety.[4-6] Functional MRI research[7-9] shows that variations in state anxiety modulate associations between attention and activation in a "fear circuit" encompassing the amygdala, vPFC, and ACC. Nevertheless, it remains unclear how this pattern of associations among attention, anxiety, and neural function evolves during development. The primary hypothesis emerging from neuroscience suggests that early developmental disruption of amygdala-PFC circuitry mediates the emergence of attention biases toward threats and subsequent anxiety disorders.[10] If so, then attention to threats should potentiate fear circuit activity differently in youths with and without GAD.

Almost no research, to our knowledge, examines associations among pediatric anxiety, attention to threat, and neural activity. The first published fMRI

Author Affiliations are listed at the end of this article.

study[11] of threat-cue processing in pediatric patients with anxiety found more amygdala activation to fearful faces vs neutral faces in patients than in controls during a block-design passive face-viewing task. Surprisingly, given adult data,[12] amygdala activation to fearful faces did not occur in healthy adolescents in the study by Thomas et al.[11] Regardless, that study did not constrain attention as recent adult studies[13,14] have done by examining activation in clearly defined attention states. The only other published fMRI study in pediatric anxiety disorders used an event-related attention-orienting paradigm. That study[15] found no between-group differences in amygdala activity to angry faces, but it did find enhanced right-sided vPFC activation in adolescents with GAD vs healthy adolescents. Taken together, these studies implicate the vPFC and the amygdala in pediatric anxiety.

Enhanced attention to internal threat is pathognomonic for anxiety disorders.[4,6] We developed a paradigm that explicitly manipulates attention focus toward and away from internal threat responses.[13] Using behavioral measures, we found evidence of perturbed attention in adolescents with anxiety disorders and in those with parental panic disorder.[5] Specifically, high-risk youths reported more fear and showed slowed response times to evocative faces. Moreover, in fMRI work among healthy individuals, we found this paradigm to engage a fear circuit encompassing the amygdala, vPFC, and ACC.[13] The present study uses this paradigm to test the hypothesis that attention modulation of the amygdala-based fear circuit differs between adolescent patients with GAD and controls. Specifically, we hypothesize that when attention is directed toward internal fear states, activation in this circuit to fearful faces vs happy faces is greater in patients with GAD than in healthy subjects. Moreover, we hypothesize that this pattern of amygdala hyperactivation is associated with parallel increases in PFC activation.

METHODS

PARTICIPANTS

Fifteen medication-free adolescents with *DSM-IV* anxiety disorders participated, with 13 meeting the full criteria for current GAD on the Kiddie Schedule for Affective Disorders and Schizophrenia[16] and 2 with current GAD where it was unclear whether their anxiety was confined to other anxiety disorders. Comorbidity resembled patterns in other samples (**Table 1**).[17] Twenty healthy adolescents, matched to patients on age, sex, and IQ, served as controls. Assessment using the Kiddie Schedule for Affective Disorders and Schizophrenia[16] confirmed that all the controls were healthy. Other inclusion criteria for patients included clinically significant anxiety on the Pediatric Anxiety Rating Scale (PARS) (score $\geq$10),[18] significant impairment on the Child Global Assessment Schedule (score $<$60),[19] and persistent anxiety during 3 weeks of supportive therapy. Exclusion criteria were current Tourette syndrome, major depressive disorder (MDD), obsessive compulsive disorder, or conduct disorder; exposure to trauma; suicidal ideation; lifetime history of mania, psychosis, or pervasive developmental disorder; and IQ less than 70. The study was approved by the National Institute of Mental Health institutional review board, and all the participants and parents provided written informed consent and assent.

fMRI TASK

As described in detail elsewhere, the face-attention paradigm[13] acquired data in 4 epochs. During 3 epochs, participants adopted different attention states requiring them to make ratings of face stimuli on one of three 5-point scales (ratings ranged from 1 = not at all to 5 = very): "How afraid are you?" "How hostile is the face?" and "How wide is the nose?" During the fourth epoch, participants passively viewed stimuli. Epochs alternated during repeated viewing of 32 faces (8 stimuli from each of 4 emotion categories: fearful, happy, neutral, and angry) drawn from 3 widely used stimulus sets.[20-22] Each of these 32 faces was presented 4 times through Silent Vision glasses (Avotec Inc, Stuart, Fla), once in each of the 4 epochs/attention states. Order of face presentation and order of attention-state epochs were randomized. Rating and response time for each trial were recorded as behavioral data using a 5-key MRI-compatible glove device (MRI Devices Corp, Waukesha, Wis). The task used a rapid event-related mixed/hybrid design, with 32 interspersed "blank" trials, each 4000 milliseconds in duration.

Stimulus presentation occurred during one 160-trial run (14 minutes, 42 seconds), with 4 epochs/rating blocks comprising 10 randomly ordered 4000-millisecond events (8 face and 2 "null-event" trials). Instructions for epochs/rating blocks were presented for 3000 milliseconds before each epoch. An intertrial interval varying from 750 to 1250 milliseconds followed each event.

PROCEDURES

We used T2-weighted imaging (axial plane, 23 slices) on a 3-T scanner (GE Medical Systems, Milwaukee, Wis) (matrix, 64×64; repetition time, 2000 milliseconds; echo time, 40 milliseconds; field of view, 240 mm; voxels, $3.75\times3.75\times5.0$ mm). Images were acquired in 23 contiguous slices parallel to the anterior commissure–posterior commissure line. High-resolution T1-weighted anatomical images were acquired to aid with spatial normalization (number of 1-mm axial slices, 180; field of view, 256 mm; number of acquisitions, 1; repetition time, 11.4 milliseconds; echo time, 4.4 milliseconds; matrix, 256×256; inversion time, 300 milliseconds; and bandwidth, 130 Hz/pixel and 33 kHz/256 pixels).

fMRI PREPROCESSING

We discarded data from participants (4 patients and 3 controls) moving 1 or more voxels in any plane. We conducted analyses using the SPM99 software program (Wellcome Department of Neurology, London, England). We corrected functional data for slice timing and motion, co-registered them to the anatomical data, and spatially normalized and resliced them into isotropic 1-mm voxels. After completing these preprocessing steps, we evaluated the quality of the normalization procedure via visual inspection of fMRI images.

DATA ANALYSIS

We estimated event-related response amplitudes at the individual participant level for each event type in each attention set using the general linear model. The waveform for each event-related response was a rectangular pulse (4 seconds) convolved with the hemodynamic response function (HRF) specified by SPM99. We generated contrast images for each participant using pairwise comparisons of event-related responses across event types. We then divided each contrast image by the participant-specific voxel time series means, yielding values proportional to percentage of fMRI signal change.[23] Each contrast

Table 1. Demographic and Clinical Characteristics of Patients With Generalized Anxiety Disorder and Controls and Task Ratings by Group*

Measure	Patients (n = 15)	Controls (n = 20)
Age, y	11.67 (1.97)	12.19 (2.10)
IQ	112.5 (14.60)	115.6 (14.13)
Male sex, No. (%)	8 (53)	9 (45)
DSM-IV diagnoses (current), No. (%)		
Generalized anxiety disorder	13 (87)	0
Generalized anxiety disorder (probable)	2 (13)	0
Comorbid diagnoses (current), No. (%)		
Separation anxiety disorder	5 (33)	0
Social phobia	6 (40)	0
Specific phobia	3 (20)	0
ADHD	3 (20)	0
Other disorder	5 (33)	0
Pediatric Anxiety Rating Scale scores		
No. of anxiety symptoms	4.93 (0.26)	NA
Frequency of anxiety symptoms	3.53 (1.25)	NA
Severity of anxiety symptoms	3.27 (0.59)	NA
Clinical Global Impressions Scale score, severity at week 0	4.20 (0.78)	NA
Behavioral ratings		
How afraid—neutral	1.95 (0.76)	1.38 (0.62)
How afraid—fearful	2.29 (1.04)	2.06 (0.99)
How afraid—angry	3.03 (1.09)	2.44 (1.13)
How afraid—happy	1.54 (0.61)	1.15 (0.21)
Nose width—neutral	2.24 (0.44)	2.22 (0.55)
Nose width—fearful	2.30 (0.52)	2.18 (0.47)
Nose width—angry	2.77 (0.71)	2.67 (0.57)
Nose width—happy	2.52 (0.52)	2.59 (0.45)
Reaction times, ms		
How afraid—neutral	1863.06 (520.37)	1791.07 (361.56)
How afraid—fearful	2012.61 (600.42)	1830.28 (331.78)
How afraid—angry	2187.24 (555.85)	2006.90 (440.44)
How afraid—happy	1831.81 (490.61)	1602.93 (359.40)
Nose width—neutral	2095.34 (342.67)	1915.35 (309.19)
Nose width—fearful	2049.32 (281.63)	2042.79 (387.21)
Nose width—angry	2118.70 (368.87)	2111.97 (411.11)
Nose width—happy	1977.96 (351.32)	2078.40 (487.60)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; NA, not applicable.
*Data are given as mean (SD) except where indicated otherwise.

image was then smoothed using an isotropic Gaussian kernel (full width at half maximum, 11.4).

We also analyzed functional connectivity.[24] For each participant, functional connectivity was examined between each amygdala region of interest (ROI) and the entire brain. The mean echoplanar imaging time series over the ROI was extracted, mean corrected, and then normalized (root-mean-square). The resulting time series was entered into a general linear model as the sole regressor of interest. The data for the model comprised the smoothed, spatially normalized whole-brain echoplanar imaging data. High- and low-pass filtering were used (using a 128-second cutoff time and the SPM99-provided canonical HRF, respectively). Regression coefficients, corresponding to the voxelwise regressor of interest, were entered into a second-level analysis.

For all group-level analyses, we used a random-effects model focused on ROIs.[25] Because we entered the study with an a priori hypothesis, we defined ROIs a priori and used the Gaussian random field threshold ($\alpha = .05$). To adjust for multiple comparisons, we applied the small-volume correction in each region. We defined ROIs to include the bilateral amygdala, vPFC, and ACC using standard anatomical criteria[26] on a single Montreal Neurological Institute (MNI) template. These ROIs were applied to all the normalized brains at the group level. Coordinates were converted from MNI to Talairach space for this article.

STATISTICAL TESTS

Analyses of between-group differences in behavioral data relied on repeated-measures analyses of variance (ANOVAs). For functional connectivity analyses of fMRI data, we used *t* tests generated from a group-level random-effects model. These tests examined amygdala connectivity in the entire data set of 35 adolescents and between-group differences in connectivity. For analyses of group differences in task-related fMRI activation, we selected 1 key contrast on an a priori basis. This contrast was restricted to the "how afraid" attention state, and it compared activation during fear-face, relative to happy-face, viewing (ie, the "afraid-fear vs afraid-happy" contrast). Selection of this contrast was based on 2 factors. First, all previous pediatric and adult anxiety fMRI studies have restricted analyses to a single attention set. Our explicit focus on the "how afraid" set was based on previous behavioral research with this task.[5] Second, we focused specifically on the contrast of fearful vs happy faces because previous work most consistently demonstrates amygdala activation and anxiety-related between-group differences in amygdala activation specifically for fear faces. Moreover, research in youths suggests that neutral expressions constitute a suboptimal baseline.[11] Happy faces, which constitute a less ambiguous

Table 2. Voxels With Significant Emotion Type (Fear vs Happy) × Group Interactions in the "How Afraid Are You?" Attention State and the Significant Post Hoc Attention State × Emotion Type × Group Interactions*

Primary Analysis: "How Afraid" Attention State (Emotion Type × Group)								Post hoc Analysis		
Brodmann Area	Region	Volume, mm	x	y	z	t_{32}	*P* Value	*df*	F	*P* Value
28	Right amygdala	2576	18	−3	−13	3.72	.005	2.43, 80.38	3.54	.03
			30	−6	−8	3.37	.01	3.80, 125.44	2.75	.03
	Left amygdala	2344	−12	−6	−8	3.95	.003	4.47, 147.40	0.57	.70
			−8	−5	−12	3.74	.004	3.31, 109.11	1.73	.08
			−16	−8	−6	3.65	.005	1.71, 54.70	1.14	.32
47	Right vPFC	11 800	38	31	−3	3.53	.02	4.13, 136.19	1.93	.10
			36	35	−7	3.13	.047	4.02, 132.79	3.30	.01
24	ACC	32 504	8	5	31	4.41	.004	4.07, 134.18	1.85	.12
10			4	49	12	3.29	.049	4.62, 152.30	.77	.56
32			4	6	40	3.53	.03	3.05, 100.57	3.05	.03
			2	6	44	3.48	.04	4.28, 141.28	1.76	.14

Abbreviations: ACC, anterior cingulate cortex; vPFC, ventral prefrontal cortex.
*All voxelwise *t* values are significant at $\alpha = .05$ corrected for multiple comparisons in each region. Results of post hoc 3-way analyses of variance are Greenhouse-Geisser corrected. Each line in the table represents data for 1 voxel within the specified neural region.

alternative to neutral faces, have been used successfully as comparison stimuli in previous studies of clinical patients.[27,28]

Tests proceeded in 2 stages. First, we examined group-level differences for the "afraid-fear vs afraid-happy" contrast. Primary random-effects analyses with small-volume correction ($\alpha = .05$) focused on the bilateral amygdala; additional analyses examined activation in the vPFC and ACC. Second, for peak activations that surpassed this initial threshold, we conducted a subsequent analysis using data from all attention sets in the face task to determine whether findings were specific to the "how afraid" rating condition. This analysis subjected participant-level contrast values in locations identified as peaks in the initial analysis (each presented in MNI coordinates) to a series of 3-factor ANOVAs to test for group × attention state × face type interactions. These ANOVAs had one 2-level between-subject factor (group [GAD vs healthy]) and two 4-level within-subject factors (attention state [afraid, hostility, nose width, and passive] and face emotion type [fearful, happy, angry, and neutral]).

RESULTS

BEHAVIOR

Behavioral data indicated no between-group differences in ratings ($F_{1,33} = 1.61$; $P = .21$) or reaction times ($F_{1,33} = 0.26$; $P = .62$) (Table 1). In addition, no significant 3-way interactions (group × attention state × face type) emerged for ratings ($F_{3.84,126.73} = 1.28$; $P = .28$) or reaction times ($F_{4.66,153.89} = 2.09$; $P = .07$). Two-way interactions between group and attention state and face type were nonsignificant ($F_{1,33} = 0.31$-2.89; $P = .77$-$.07$). For illustrative purposes, in Table 1 we provide data from the fear rating and the nose rating conditions.

Between-group differences were expected in the former condition, where a nonsignificant trend was evident, but not in the latter condition. Patients and controls exhibited comparable patterns of behavioral response across conditions, with highest fear ratings for angry faces (Greenhouse-Geisser–corrected $F_{1.95,64.42} = 43.95$; $P < .001$; $P < .001$ for all pairwise comparisons between face types) and highest nose-width ratings for happy faces (Greenhouse-Geisser–corrected $F_{2.49,82.26} = 15.05$; $P < .001$; $P < .001$ for all pairwise comparisons between face types). Given the absence of between-group behavioral differences, interpretation of between-group differences in neural activation cannot be attributed to between-group differences in performance.

TASK-RELATED AMYGDALA ACTIVATION

We tested the hypothesis that the "afraid-fear vs afraid-happy" contrast would elicit more activity in patient vs control amygdalae. This hypothesis was supported by significant group × emotion type interactions, indicating that patients with GAD showed significantly greater relative bilateral amygdala activation to fearful vs happy faces in this attention state than healthy adolescents (**Table 2** and **Figure 1**).

Follow-up ANOVAs on the blood oxygenation level–dependent responses in the 2 identified peak suprathreshold voxels in the right amygdala revealed significant 3-way interactions (group × attention state × face type) ($P \leq .05$ for all) (Table 2 and Figure 1). No significant interactions were evident in peak voxels in the left amygdala. For the right amygdala, post hoc analyses decomposed the significant 3-way interactions.

Figure 1A presents the topography of the peak activations in the right amygdala where the 3-way interactions emerged. Post hoc analyses generated comparable profiles for the 2 peak voxel activations; for illustrative purposes, Figure 1B and C display bar graphs for the post hoc analyses in 1 of these activations, examining right amygdala activation in each condition relative to the null-event baseline. One post hoc analysis revealed a significant group × emotion type interaction in the "how afraid" attention set ($F_{2.36,77.70} = 4.05$; $P = .02$). As shown in Figure 1B, group differences in right amygdala activation emerged during fearful-face viewing. A similar trend occurred during angry-face viewing but not during happy- or neutral-face viewing.

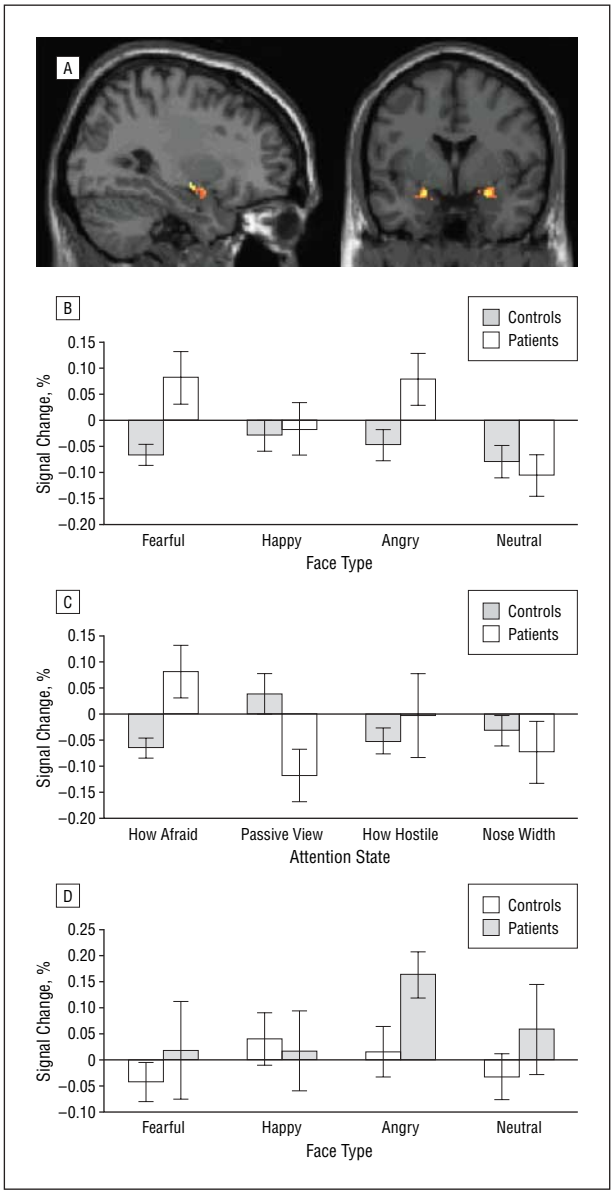

Figure 1. The "afraid-fear vs afraid-happy" contrast yielded evidence of group differences in activation in the right, but not the left, amygdala. A, Significantly greater activation is seen in patients than in controls ($P<.05$, small-volume corrected) during the "How afraid are you?" attention state for fearful faces vs happy faces in the right amygdala (Montreal Neurological Institute coordinates: 30, −6, −8). Highlighted areas indicate regions where the differences in activation between groups were significant. B and C, Bar graphs of activation in this voxel relative to the task null-event baseline for the post hoc analyses in the same activation. B, Group × face emotion type interaction in the "how afraid" attention set, in which patients showed greater relative activation than controls to fearful faces. C, Group × attention set activation for fearful faces. Enhanced right amygdala activation in generalized anxiety disorder was limited to the "how afraid" attention set. D, This pattern contrasts markedly with the activation observed in the left amygdala, where although 3-way interactions were nonsignificant (Table 2), greater activation was evident to angry, but not fearful, faces in the "how afraid" attention set. Error bars represent SE values.

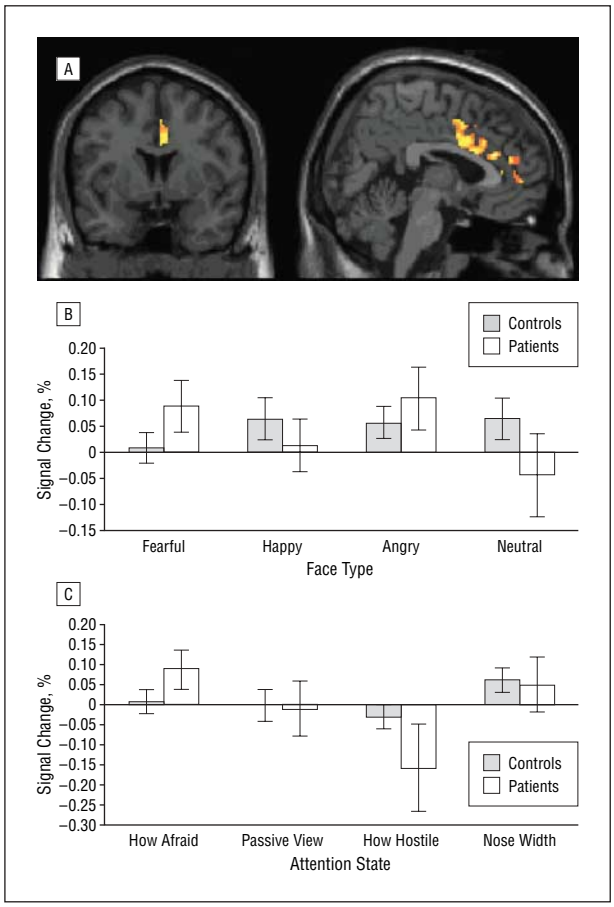

Figure 2. Significant group differences were evident in anterior cingulate cortex (ACC) activation. A, Patients with generalized anxiety disorder (GAD) had significantly more activation than controls ($P<.05$, small-volume corrected) during the "How afraid are you?" attention state for fearful vs happy faces in the ACC (Montreal Neurological Institute coordinates: 4, 6, 40). Highlighted areas indicate regions where the differences in activation between groups were significant. B, Bar graph of activation relative to the task null-event baseline for post hoc analyses in this voxel shows that patients showed greater relative activation than controls to fearful faces in the group × emotion type interaction in the "how afraid" attention set. C, Enhanced ACC activation to fearful faces in patients with GAD emerged only in the "how afraid" attention set. Error bars represent SE values.

Another post hoc analysis showed this group × emotion type interaction to be restricted to the "how afraid" attention state ($F_{2.16,71.30}=4.87$; $P=.009$). Figure 1C presents data for a post hoc analysis examining fearful-face viewing across the 4 attention states. As shown, enhanced right amygdala activation in GAD was evident only in the "how afraid" state. Finally, we found no significant correlations between activation in right amygdala voxels for the "afraid-fear vs afraid-happy" contrast and severity of anxiety, as rated on the PARS ($P>.05$ for all).

TASK-RELATED PFC ACTIVATION

In secondary analyses, we tested the hypothesis that the "afraid-fear vs afraid-happy" contrast also would elicit more activity in patient than control vPFC and ACC regions. Results indicated that patients with GAD showed significantly greater activation in voxels in the right vPFC and ACC to fearful vs happy faces than did healthy adolescents (Table 2). Subsequent 3-way repeated-measures ANOVAs for each significant voxel evaluated the degree to which between-group differences occurred specifically during the "afraid-fear vs afraid-happy" contrast.

These ANOVAs revealed a significant 3-way interaction in the ACC (Table 2 and **Figure 2**A and B). As

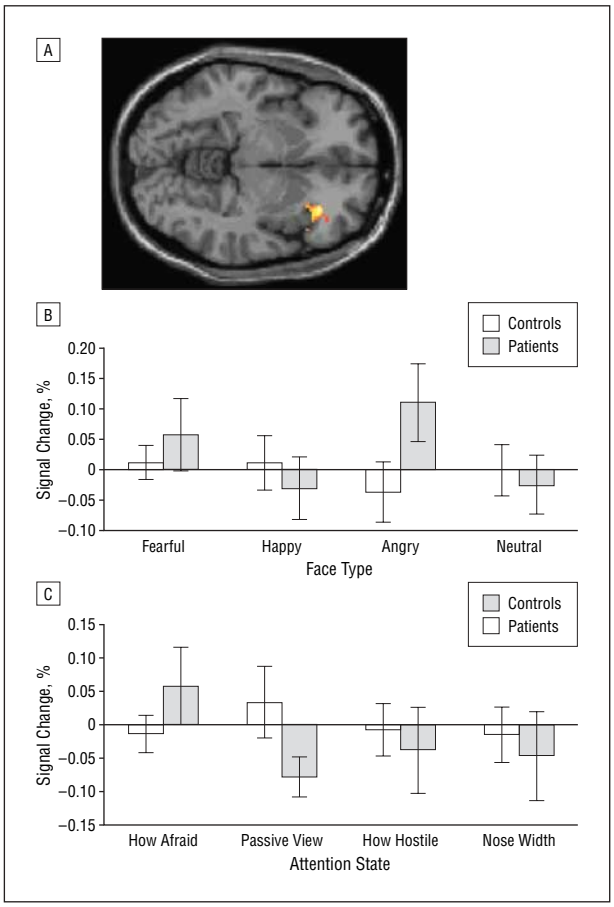

Figure 3. Ventral prefrontal cortex activation differed according to attention state and emotion type between patient and control groups. A, Significantly greater activation emerged in patients with generalized anxiety disorder (GAD) than in controls ($P<.05$, small-volume corrected) during the "How afraid are you?" attention state for fearful vs happy faces in the right ventral prefrontal cortex (vPFC) (Montreal Neurological Institute coordinates: 36, 35, −7). B, Bar graph shows that enhanced activation in GAD was limited to fearful and angry faces in the "how afraid" attention set. C, Enhanced vPFC activation to fearful faces differed strikingly between the "how afraid" and passive-viewing attention states. Error bars represent SE values.

shown, ACC-related, between-group differences in activation showed parallels with those observed in the right amygdala in that they were strongest in the "how afraid" attention state ($F_{3,99}=2.57$; $P=.06$) (Figure 2C). Similarly, a significant 3-way interaction was apparent in the right vPFC (Table 2). As it did for the amygdala and the ACC, the magnitude of the between-group difference in vPFC activation to fearful faces differed markedly between the "how afraid" and "passive-viewing" attention states (compare Figure 1C and **Figure 3**C). Parallels also emerged between the amygdala and the vPFC in responses to angry faces (compare Figure 1B and Figure 3B).

FUNCTIONAL CONNECTIVITY ANALYSES

These analyses focus on the right amygdala, given stronger evidence of task-specific group differences for this structure, relative to the left amygdala. Results examining patterns of functional connectivity in the entire sample of 35 participants revealed a strongly positive correlation between activity in the right amygdala and the right vPFC, with no significant negative correlations in ROIs (**Table 3**). These findings suggest that performance of the task paradigm is associated with strong functional connectivity in a distributed amygdala-vPFC network. Group differences in connectivity between the right amygdala and the vPFC, however, were not evident.

Given that this is the first study to examine amygdala connectivity in adolescents, we also present results for between-group comparisons at locations beyond the ROIs. Table 3 provides results using a $P<.001$ uncorrected threshold with an extent threshold of 10 voxels. This analysis revealed multiple areas of positive and negative correlation. A between-group difference emerged in functional connectivity between the insula and the right amygdala (38, 11, −14; $t=4.81$; $P<.001$, uncorrected), with greater connectivity evident for patients than for healthy subjects (**Figure 4**). Degree of connectivity seemed to relate to severity of anxiety; in the patient group, magnitude of connectivity correlated significantly and negatively with total PARS score (Spearman $r=-0.51$; $P=.05$). Moreover, between-group differences also emerged in the posterior cortical regions ($P<.001$, uncorrected, for all), mostly in the cingulate gyrus but also in the precuneus and lingual gyrus. These differences reflected stronger negative correlations with right amygdala activity in patients than in controls. No further between-group differences were evident using either the small-volume corrected–focused ROI analyses with $\alpha=.05$ or the exploratory approach.

COMMENT

Two main fMRI findings emerged from this study. First, group differences in right amygdala activation varied with participants' attentional focus. Patients with GAD exhibited greater activation than healthy subjects during fearful- vs happy-face viewing when attending to subjective fear. Second, between-group differences in amygdala response emerged against a backdrop of strong coactivation in a distributed fear circuit for the sample as a whole. Functional connectivity analyses demonstrate strong relationships between changes in amygdala activity and activity throughout a ventrally and medially distributed circuit. Moreover, analyses of task-related changes in the PFC demonstrated between-group differences in the ACC and vPFC that paralleled those found in the right amygdala. Between-group differences occurred only when participants' attention focused on subjective fear.

In addition to these fMRI results, we found that rating behavior varied as a function of attention-task demands and stimulus features, as in previous studies.[5,13] Rating and reaction-time patterns were identical to those observed previously. No difference was evident, however, between patients with GAD and healthy adolescents despite between-group differences in neural activation. Nevertheless, although statistically nonsignificant, the patterns in the present study resembled those observed previously,[5] with higher ratings and slower reaction times during the fear-attention condition in patients with GAD than in healthy adolescents.

Controversy surrounds the interpretation of between-group differences in fMRI activation as they relate to between-group differences in task performance. Some re-

Table 3. Right Amygdala Connectivity: Voxels With Significant Associations With the Right Amygdala*

Contrast	x	y	z	*t*	*P* Value	Region	Brodmann Area	k
Connectivity in all participants, independent of group status	40	21	–9	4.25	.03 (SVC)	Right vPFC	47	40
Greater positive connectivity in patients vs controls	38	11	–14	4.81	<.001 (Uncorrected)	Right insula	13	17
Greater negative connectivity in patients vs controls	10	–55	19	4.81	<.001 (Uncorrected)	PCC	23	140
	12	–51	27	4.37		PCC	31	140
	–2	–53	28	3.66		PCC	31	140
	–15	–35	35	4.77		PCC	31	38
	–6	–54	14	4.09		PCC	23	34
	–8	–47	37	3.69		Left precuneus	31	12
	32	–56	0	4.38		Right lingual gyrus	19	20

Abbreviations: PCC, posterior cingulate cortex; SVC, small-volume corrected; vPFC, ventral prefrontal cortex.
*Each line in the table represents data for 1 voxel within the specified neural region.

searchers view group differences in task performance as experimental confounds.[29] From this perspective, the absence of group differences in task performance facilitates meaningful interpretations of observed group differences in neural responses. In particular, differences in activation cannot be dismissed as artifacts of differential compliance with or capacity to perform the behavioral task. Thus, matched task performance represents a potential strength. Other researchers, however, view differences in task performance as necessary for interpreting differences in activation.[30] Both positions make cogent arguments that bear careful consideration.

A previous behavioral study[5] in adolescents, using the task used in the present imaging study, found associations between anxiety diagnosis and task performance. However, this study differed from the present study in several ways, including population sampled, sample size, and setting. Thus, the failure in the present, smaller fMRI study to detect statistically significant behavioral differences is not entirely surprising. Indeed, it is consistent with the possibility that fMRI activation more sensitively indexes anxiety-related disruptions in amygdala function than does behavioral perturbation.[31,32]

As noted previously herein, an earlier fMRI study[11] also found greater amygdala activation during fearful-face viewing in youths with anxiety disorders relative to healthy comparisons. The authors suggested that fearful faces evoke amygdala responses because they are novel and imply that a threat is emanating from an ambiguous source; this interpretation is consistent with some findings in adults.[33,34] However, because this previous study relied on a block design and collected no behavioral data during imaging, it left open questions about factors that may contribute to amygdala hyperactivity. By constraining attention, the present study adds an element that may help more clearly elucidate cognitive mechanisms contributing to amygdala hyperactivity. Specifically, right amygdala hyperactivity to fearful faces in pediatric GAD occurred when attention was directed to personally relevant, emotionally salient aspects of a stimulus but not in other attention states.

As illustrated in the bar graphs in Figure 1, we also found evidence of negative blood oxygenation level–dependent signal responses in the amygdala when participants viewed certain face types in varying attention states. Controversy persists concerning interpretations of such negative blood oxygenation level–dependent values; although some recent evidence suggests that they indicate reductions in neural activity,[35] this perspective is not universally accepted. Similar negative blood oxygenation level–dependent values have been obtained in studies of face processing examining amygdala activation in adults, particularly when participants focused their attention selectively,[36] and in healthy youths during passive fearful-face viewing.[11] In light of these findings, it is possible that the deactivation evident in Figure 1B-D partially reflects the effect of attention state on amygdala functioning. Other interpretations, however, are plausible; consequently, this issue warrants further study.

In contrast to the paucity of fMRI studies in adolescents, considerable research examines the amygdala response to evocative faces in adult psychopathologic abnormalities. This work provides relatively consistent evidence of enhanced amygdala reactivity to fearful and other negatively valenced facial expressions in a range of mood and anxiety disorders. Increased amygdala response is found consistently in adults with MDD, posttraumatic stress disorder, and social anxiety disorder.[2,37,38] Enhanced response to fearful faces does not occur in obsessive compulsive disorder, consistent with nosologic distinctions between obsessive compulsive disorder and other anxiety disorders.[39]

Substantive questions remain, however, concerning the specificity of relationships among amygdala activity, face processing, and diagnosis. Findings in adults show between-group differences in amygdala activity for fearful and angry faces; some evidence of hyperactivation to angry faces also emerged in the present study. Furthermore, as of this writing, no study in adults has directly compared neural activation during evocative-face viewing among healthy subjects and groups of patients with varied mood or anxiety disorders, and neither has any study of anxious adults carefully controlled attention. Such research is needed to elucidate whether specific disorders show distinctive patterns of neural responsivity to emotionally salient cues.

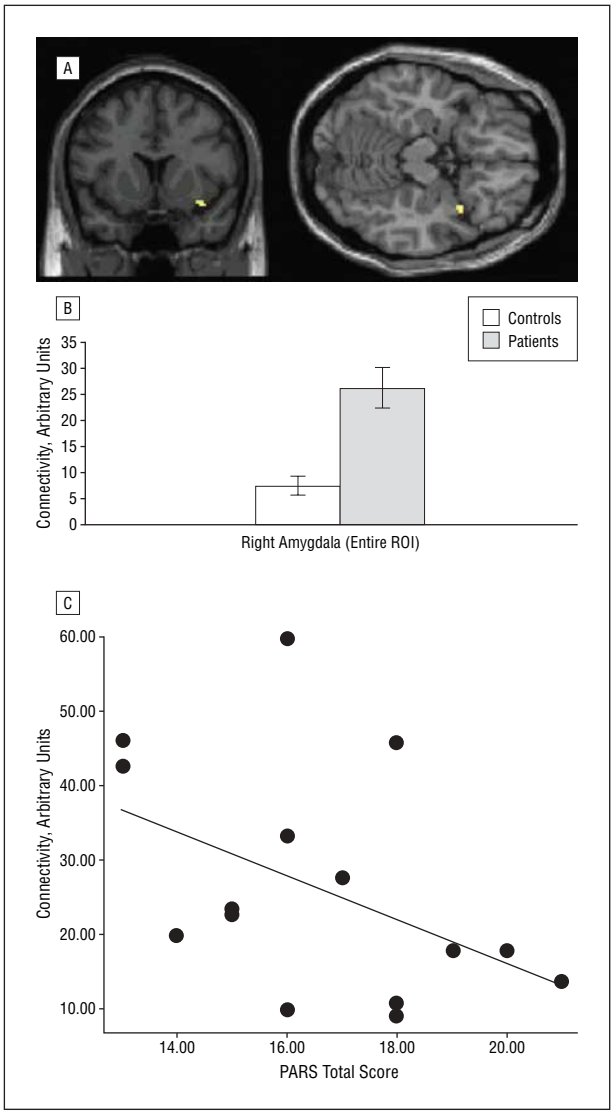

Figure 4. Connectivity between the amygdala and varied neural structures was evident. A and B, Patients showed significantly greater connectivity than controls between activation in the insula (Montreal Neurological Institute coordinates: 38, 11, −14) and the right amygdala region of interest (ROI) ($P<.001$). Highlighted areas in A indicate regions where the differences in activation between groups were significant. Error bars represent SD. C, Total score on the Pediatric Anxiety Rating Scale (PARS) correlated significantly and negatively (Spearman $r=-0.51$; $P=.05$) with magnitude of connectivity between the right amygdala ROI and the insula (MNI coordinates: 38, 11, −14).

Although adults with acute disorders consistently show amygdala hyperactivity, it remains uncertain how elevated activity relates to pathogenesis. For example, amygdala hyperactivity may represent a correlate of anxious states, a complication of chronic psychopathologic abnormalities, or a risk factor. Treatment has been shown to modulate amygdala hyperactivity, consistent with the possibility of state effects.[27,37,40] Other studies, however, support trait-marker hypotheses. For example, a polymorphic variant of the serotonin transporter associated with risk for MDD predicts enhanced amygdala activation to evocative faces in asymptomatic, high-risk individuals.[41] For the present sample, the lack of a correlation between the PARS rating and amygdala activation could suggest trait effects. Finally, previous data in another study using this task demonstrate an association between parental panic disorder and behavioral response to evocative faces in the "how afraid" attention state.[5] These data also suggest that trait effects affect response to evocative-face viewing in some attention states.

Studies in adults implicate the ventral and medial PFC regions, and the amygdala, in various forms of psychopathologic abnormalities. Evidence is perhaps strongest in adult MDD, where lesion studies, brain imaging data, and postmortem investigations document abnormalities in relatively broad expanses of the PFC, particularly the ventral and medial components.[42] Moreover, functional connectivity analyses suggest that amygdala abnormalities in MDD reflect dysfunction in a neural circuit encompassing these PFC regions.[43,44] Less evidence implicates the PFC in anxiety disorders. However, consistent with signs of enhanced vPFC/ACC activation in anxious participants in the present study, we detected, in another study,[15] enhanced right vPFC activation in adolescent GAD. Thus, these 2 studies document consistent evidence of enhanced vPFC activity in pediatric GAD.

The present results for the PFC reveal consistencies and inconsistencies with data in adults. As in studies of adults, these analyses detected a vPFC region where strong positive amygdala connectivity emerged.[24,43,44] However, we did not detect negative connectivity between more dorsal PFC-based regions and the amygdala, although we did detect relatively strong negative connectivity in patients with GAD with many posterior cortical regions. The different topography found in the present study, relative to studies in adults, may relate to differences in task methods or to functional developmental changes in amygdala-PFC circuitry.

As noted previously herein, we also found some evidence of task-related between-group differences in cortical neural response and connectivity. Specifically, as in the right amygdala, between-group differences restricted to the "how afraid" condition emerged in the ACC and the vPFC. Given the known role of both PFC subregions in modulating attention in varying contexts,[45] 1 interpretation of these results is that attention-related between-group differences in amygdala response to fear faces might be "gated" by differential PFC modulation of the amygdala. Alternatively, the co-activation of amygdalar and prefrontal cortical regions could indicate a disruption of reciprocal projections between the 2 regions rather than a modulatory impairment.

Moreover, connectivity analyses suggested the presence of greater coupling in patients with GAD between the amygdala and the insula. These findings, too, implicate perturbations in PFC-amygdala circuitry in pediatric GAD. We did not include the insula as an ROI for a priori analyses because of the paucity of research on this structure in pediatric patients with anxiety. However, some evidence in adults indicates that the insula may participate in evaluating rewarding or punitive properties of stimuli and feeling emotions.[46,47] Furthermore, a recent study[40] in healthy adults showed that anxiolytic medication decreased activation to negative faces in the bilateral amygdala and the insula. Consequently, findings of connectivity between these 2 regions are of interest.

For other PFC regions, data documenting strong amygdala-PFC connectivity suggest that the observed between-group differences in amygdala response emerge in a task inducing strong functional coupling between the amygdala and ventral expanses of the PFC known to exhibit rich anatomical interconnections.

The finding of a negative correlation between PARS scores and connectivity in the insula/amygdala is broadly consistent with findings from Pezawas and colleagues,[24] who found reductions in positive connectivity between the ventral medial PFC and the amygdala in adults with an *S* allele of the *5HTTLPR* gene. Moreover, Pezawas and colleagues also found an inverse correlation between the magnitude of positive connectivity and the amount of temperamental anxiety, consistent with the inverse correlation we found with PARS scores. Both sets of findings suggest that individual differences in anxiety reflect perturbations in expected positive coupling between the vPFC and the amygdala.

The present findings are tempered by several limitations. First, the results are based on relatively small samples. However, small sample size typically contributes to type II rather than type I error, thus potentially obscuring true-positive effects. Given that we obtained positive findings, type II error is less of a concern. Second, aspects of the sample limit generalizability. Although we excluded patients with a history of MDD or trauma, most patients with GAD exhibited comorbidity, as is typical.[48] Indeed, a recent multisite study[49] found that only 5 patients of 128 with anxiety disorders presented with a "pure" form of GAD. For the present study, we chose to focus on GAD, rather than other anxiety disorders, because longitudinal data indicate particularly strong associations between GAD and several adult conditions.[1] Future research might replicate this study, comparing results across groups with social phobia or separation anxiety disorder and GAD. Similar to the recent multisite treatment study, we enrolled only patients with persistent GAD across a 3-week period of supportive psychotherapy. This procedure has the advantage of limiting participants to adolescents exhibiting relatively severe and persistent anxiety comparable with those in the community who require treatment. However, these individuals may not be representative of milder or more transient GAD cases in the community. Third, the cognitive task is limited on several fronts. In particular, 1 component of this task requires participants to attend to their own feelings of fear. This manipulation is designed to engage psychological processes central to clinical disorders. Although subjective report is important for clinically focused and neuroscientific research,[50] methods that rely on introspection are subject to biases related to expectancy or participant demands. Currently, no "gold standard" definitively indexes how closely subjective ratings of fear relate to actual experience of fear.

However, considerable data support the validity of the present paradigm. Previous studies show that this attention manipulation differentiates adolescents who have acute anxiety or who are at risk for anxiety from unaffected and low-risk adolescents.[5] The present data add to existing findings by demonstrating an anxiety-related association between elevated amygdala activity and attention to one's own fear. Although these data suggest that our introspective attention manipulation engaged neural processes that reliably relate to clinical anxiety disorders, further study is needed to more precisely specify the cognitive processes that occur during this type of introspection and their neural correlates.

Submitted for Publication: October 19, 2005; final revision received March 31, 2006; accepted April 19, 2006.
Author Affiliations: Emotional Development and Affective Neuroscience Branch (Drs McClure, Nelson, Ernst, and Pine and Mss Parrish and Adler) and Unit on Affective Disorders, Pediatrics and Developmental Neuropsychiatry Branch (Dr Leibenluft), Mood and Anxiety Disorders Program (Drs Blair and Fromm), National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Md; Department of Psychology, Georgia State University, Atlanta (Dr McClure); Department of Psychology and Center for Human Growth and Development, University of Michigan at Ann Arbor (Dr Monk); and Departments of Psychiatry, Neuroscience, and Pharmacology and Biological Chemistry, Mount Sinai School of Medicine, New York, NY (Dr Charney).
Correspondence: Erin B. McClure, PhD, Department of Psychology, Georgia State University, PO Box 5010, Atlanta, GA 30302-5010 (emcclure@gsu.edu).
Financial Disclosure: Dr Charney had consulting agreements with Abbott Laboratories, Astra Zeneca, Bristol-Myers Squibb Company, Cyberonics, GeneLogic, Inc, the Institute of Medicine, Neurogen Corp, the Neuroscience Education Institute, Novartis Pharmaceuticals Corporation, Orexigen Therapeutics, Inc, Organon International, Inc, Otsuka America Pharmaceutical, Inc, Quintiles, Inc, and Sepracore, Inc, and confidentiality agreements with Forest Laboratories, Inc, and Novartis Pharmaceuticals Corporation.
Funding/Support: This study was supported by the Intramural Research Program of the National Institute of Mental Health, National Institutes of Health.

REFERENCES

1. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry*. 1998;55:56-64.
2. Stein MB, Goldin PR, Sareen J, Zorrilla LTE, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry*. 2002;59:1027-1034.
3. Straube T, Kolassa I-T, Glauer M, Mentzel H-J, Miltner WHR. Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study. *Biol Psychiatry*. 2004; 56:921-930.
4. Clark DM, McManus F. Information processing in social phobia. *Biol Psychiatry*. 2002;51:92-100.
5. Pine DS, Klein RG, Mannuzza S, Moulton JL III, Lissek S, Guardino M, Woldehawariat G. Face-emotion processing in offspring at risk for panic disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44:664-672.
6. Vasey MW, Daleiden EL, Williams LL, Brown LM. Biased attention in childhood anxiety disorders: a preliminary study. *J Abnorm Child Psychol*. 1995;23:267-279.
7. Bishop S, Duncan J, Brett M, Lawrence AD. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nat Neurosci*. 2004;7:184-188.
8. Bishop SJ, Duncan J, Lawrence AD. State anxiety modulation of the amygdala

response to unattended threat-related stimuli. *J Neurosci*. 2004;24:10364-10368.
9. Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry*. 2003;53:494-501.
10. Amaral DG. The amygdala, social behavior, and danger detection. *Ann N Y Acad Sci*. 2003;1000:337-347.
11. Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, Axelson D, Whalen PJ, Casey BJ. Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry*. 2001;58:1057-1063.
12. Wager TD, Phan KL, Liberzon I, Taylor SF. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage*. 2003;19:513-531.
13. Monk CS, McClure EB, Nelson EE, Zarahn E, Bilder RM, Leibenluft E, Charney DS, Ernst M, Pine DS. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage*. 2003;20:420-428.
14. Pessoa L, McKenna M, Gutierrez E, Ungerleider LG. Neural processing of emotional faces requires attention. *Proc Natl Acad Sci U S A*. 2002;99:11458-11463.
15. Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, Blair RJ, Chen G, Charney DS, Ernst M, Pine DS. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *Am J Psychiatry*. 2006;163:1091-1097.
16. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36:980-988.
17. Masi G, Millepiedi SS, Mucci MM, Poli PP, Bertini NN, Milantoni LL. Generalized anxiety disorder in referred children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2004;43:752-760.
18. RUPP Group. The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. *J Am Acad Child Adolesc Psychiatry*. 2002;41:1061-1069.
19. Shaffer D, Gould M, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry*. 1983;40:1228-1231.
20. Ekman P, Friesen WV. *Pictures of Facial Affect*. Palo Alto, Calif: Consulting Psychologists Press; 1976.
21. Gur RC, Ragland JD, Moberg PJ, Turner TH, Bilker WB, Kohler C, Siegel SJ, Gur RE. Computerized neurocognitive scanning, I: methodology and validation in healthy people. *Neuropsychopharmacology*. 2001;25:766-776.
22. Tottenham N, Borscheid A, Ellertsen K, Marcus DJ, Nelson CA. Categorization of facial expressions in children and adults: establishing a larger stimulus set. Paper presented at: Cognitive Neuroscience Society Annual Meeting; April 15, 2002; San Francisco, Calif.
23. Zarahn E, Aguirre GK, D'Esposito M. Empirical analyses of BOLD fMRI statistics, I: spatially unsmoothed data collected under null-hypothesis conditions. *Neuroimage*. 1997;5:179-197.
24. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005;8:828-834.
25. Holmes AP, Friston KJ. Generalisability, random effects and population inference [abstract]. *Neuroimage*. 1998;7:s754.
26. Szeszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M, Wu H, Bogerts B. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1999;56:913-919.
27. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry*. 2001;50:651-658.
28. Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, Williams SC, Phillips ML. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol Psychiatry*. 2005;57:201-209.
29. Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry*. 2003;160:2209-2215.
30. Wilkinson D, Halligan P. The relevance of behavioural measures for functional-imaging studies of cognition. *Nat Rev Neurosci*. 2004;5:67-73.
31. Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger DR. A susceptibility gene for affective disorders and the response of the human amygdala. *Arch Gen Psychiatry*. 2005;62:146-152.
32. Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR. The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage*. 2002;17:317-323.
33. Whalen PJ. Fear, vigilance and ambiguity: initial neuroimaging studies of the human amygdala. *Curr Dir Psychol Sci*. 1998;7:177-188.
34. Whalen PJ, Shin LM, McInerney SC, Fischer H, Wright CI, Rauch SL. A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion*. 2001;1:70-83.
35. Shmuel A, Augath M, Oeltermann A, Logothetis NK. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nat Neurosci*. 2006;9:569-577.
36. Pessoa L, Padmala S, Morland T. Fate of unattended fearful faces in the amygdala is determined by both attentional resources and cognitive modulation. *Neuroimage*. 2005;28:249-255.
37. Fu CH, Williams SCR, Cleare AJ, Brammer MJ, Walsh ND, Kim J, Andrew CM, Pich EM, Williams PM, Reed LJ, Mitterschiffthaler MT, Suckling J, Bullmore ET. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatry*. 2004;61:877-889.
38. Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, Macklin ML, Lasko NB, Cavanagh SR, Krangel TS, Orr SP, Pitman RK, Whalen PJ, Rauch SL. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiatry*. 2005;62:273-281.
39. Cannistraro PA, Wright CI, Wedig MM, Martis B, Shin LM, Wilhelm S, Rauch SL. Amygdala responses to human faces in obsessive-compulsive disorder. *Biol Psychiatry*. 2004;56:916-920.
40. Paulus MP, Feinstein JS, Castillo G, Simmons AN, Stein MB. Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Arch Gen Psychiatry*. 2005;62:282-288.
41. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002;297:400-403.
42. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol*. 2001;11:240-249.
43. Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, Mayberg H. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. *Arch Gen Psychiatry*. 2004;61:34-41.
44. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, Rafi-Tari S. Limbic-frontal circuitry in major depression: a path modeling metanalysis. *Neuroimage*. 2004;22:409-418.
45. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. 2001;24:167-202.
46. Damasio A. Feelings of emotion and the self. *Ann N Y Acad Sci*. 2003;1001:253-261.
47. Kosson DS, Budhani S, Nakic M, Chen G, Saad ZS, Vythilingam M, Pine DS, Blair RJ. The role of the amygdala and rostral anterior cingulate in encoding expected outcomes during learning. *Neuroimage*. 2006;29:1161-1172.
48. Verduin TL, Kendall PC. Differential occurrence of comorbidity within childhood anxiety disorders. *J Clin Child Adolesc Psychol*. 2003;32:290-295.
49. Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med*. 2001;344:1279-1285.
50. Kendler KS. Toward a philosophical structure for psychiatry. *Am J Psychiatry*. 2005;162:433-440.