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Christopher Monk
National Institutes of Health

Eric E. Nelson
National Institutes of Health

Erin McClure
Georgia State University, etone@gsu.edu

Karin Mogg

Brendan P. Bradley
National Institutes of Health

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Authors

Christopher Monk, Eric E. Nelson, Erin McClure, Karin Mogg, Brendan P. Bradley, Ellen Leibenluft, James R. Blair, Gang Chen, Dennis S. Charney, Monique Ernst, and Daniel Pine

Ventrolateral Prefrontal Cortex Activation and Attentional Bias in Response to Angry
Faces in Adolescents with Generalized Anxiety Disorder

Christopher S. Monk, PhD, Eric E. Nelson, PhD, Erin B. McClure, PhD, Karin Mogg,
PhD, Brendan P. Bradley, PhD, Ellen Leibenluft, MD, R. James R. Blair, PhD, Gang
Chen, PhD, Dennis S. Charney, MD, Monique Ernst, MD, PhD, Daniel S. Pine, MD

From the National Institute of Mental Health, National Institutes of Health, U.S.
Department of Health and Human Services, Bethesda, MD, University of Southampton,
Southampton, United Kingdom, and the Mount Sinai School of Medicine, New York,
NY. Address correspondence and reprint requests to Dr. C. S. Monk, NIMH,
NIH/DHHS, Bethesda, MD, 15K North Drive, Bethesda, MD 20892-2670,
christopher.monk@nih.gov. Data from this study were presented at the American
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Abstract

Objective: While adolescent anxiety disorders represent prevalent, debilitating conditions, few studies explore their brain physiology. Using event-related functional MRI (fMRI) and a behavioral measure of attention to angry faces, we evaluated differences in response between healthy adolescents and adolescents with generalized anxiety disorder (GAD).

Method: In the primary trials of interest, 18 adolescents with GAD and 15 comparisons of equivalent age/gender/IQ viewed angry/neutral face pairs during fMRI acquisition. Following the presentation of each face pair, subjects pressed a button to a probe that was either on the same (congruent) or opposite (incongruent) side as the angry face. Reaction time differences between congruent and incongruent face-trials provided a measure of attention bias to angry faces.

Results: Relative to controls, patients with GAD manifested greater right ventrolateral prefrontal cortex (VLPFC) activation to trials containing angry faces. Compared with controls, patients with GAD also showed greater attentional bias *away* from angry faces. VLPFC activation differences were independent of differences in attentional bias.

Conclusions: Adolescents with GAD show greater right VLPFC activation and attentional bias away from angry faces than controls. Enhanced VLPFC engagement may directly relate to anxiety, or may regulate abnormal functioning in another region.

Introduction

Adolescent generalized anxiety disorder (GAD) predicts high risk for adult GAD, social phobia, and major depressive disorder (MDD) (1). While only one study (2) explores neurophysiological correlates of GAD in youth, considerable data both in the basic sciences and adult anxiety disorder literature form the basis for hypotheses about the roles of specific neural structures in adolescent GAD (3-12).

Basic research implicates a neural circuit including the amygdala and ventral prefrontal cortex (VPFC) in threat monitoring and response (5, 9, 10). The VPFC, in particular, the ventrolateral PFC (VLPFC), modulates amygdala engagement to facilitate flexible attention and behavior when responding to environmental threats (3-6, 9).

Anxiety disorders may relate to perturbations in this VPFC-amygdala circuit. The only available study in anxious youth selectively imaged the amygdala in ten patients and ten controls and reported that patients relative to controls showed greater response to threat-related facial expressions (2). Among adults, patients with anxiety disorders showed increased amygdala activation and abnormal VPFC responses (8, 12-15). These neural abnormalities may disrupt the regulatory processes of vigilance and attention to threat-related stimuli.

Increased vigilance and perturbed attention are prominent features of pediatric and adult anxiety disorders (16-23). Thus, brain-based differences between anxious patients and controls may reflect anxiety-related differences in attentional processes. For example, anxious patients relative to controls may shift attention away from threatening stimuli, which could either reflect or affect between-group differences in brain activation. Therefore, when examining between group differences in neural responses, it may be

advantageous to monitor attention and examine effects of attention on between-group differences in activation.

The visual probe task provides an index of threat-related perturbations in attention (16, 17, 20-22). In the visual probe task, adult patients with GAD and other anxiety disorders orient attention towards angry “threat” faces more strongly than healthy adults (21-23). Interestingly, in a visual probe study of children with post-traumatic stress disorder (PTSD), findings were opposite to those in adults: pediatric patients displayed a greater attentional bias *away* from threat, in comparison with healthy children (16). While preliminary, these findings suggest that anxiety disorders may involve systematic disruptions in threat biases that vary across development.

For the present fMRI investigation, we used the visual probe task to examine differences between adolescents with GAD and healthy adolescents. Consistent with prior studies, we hypothesized that adolescents with GAD would show abnormal VPFCA activation and increased amygdala activation relative to controls in response to angry faces. We also hypothesized that adolescents with GAD would exhibit abnormal attentional bias to angry faces.

Methods

Participants

Thirty-three adolescents participated in this study. Health and cognitive status of all participants was determined with a physical examination and an IQ test. The Kiddie Schedule for Affective Disorders and Schizophrenia (24) was administered by trained clinicians. Based on an independent study, each clinician had been shown to have

excellent reliability ($\kappa > .75$) with senior clinicians for all diagnoses. Group demographics are provided in Table 1. The NIMH IRB approved all procedures, and all adolescents/parents provided written assent/consent.

The primary inclusion criterion was a diagnosis of GAD in an adolescent (9-17 years of age); the GAD diagnosis had to be the explicit focus of treatment. Other inclusion criteria were similar to those in published studies of pediatric anxiety disorders (25-27). Specifically, these included: (1) clinically significant symptoms of anxiety based on a Pediatric Anxiety Rating Scale score (PARS) ≥ 10 (28); (2) Children's Global Assessment Scale score < 60 (29); (3) desire for outpatient treatment; (4) persistent anxiety based on the PARS over a 3-week period during which supportive psychoeducational therapy was provided

Exclusion criteria included: (1) current use of any psychoactive substance; for patients, usage of any psychoactive substance since the onset of the anxiety disorder; (2) current Tourette's syndrome, obsessive-compulsive disorder, PTSD, conduct disorder, exposure to extreme trauma, or suicidal ideation; (3) lifetime history of mania, psychosis, or pervasive developmental disorder; (4) IQ less than 70. MDD was not considered exclusionary, since longitudinal and family-based studies note strong relationships between adolescent GAD and MDD. Secondary fMRI analyses compared activation between groups with and without MDD as well as social phobia to determine the degree to which comorbidity moderated findings in patients with GAD.

Visual Probe Task

We used the same procedures and stimuli as previously described (30) (See Figure 1). Briefly, trials began with a 500 ms central fixation point. Two faces then appeared for 500 ms. These were replaced by an asterisk-probe in one hemi-field for 1100 ms. Participants were instructed to press one button with their thumb if the probe appeared on the left and a second button with their index finger if the probe appeared on the right. The inter-trial interval was 1900 ms. Before scanning, participants were trained on the task.

Participants saw 80 actors, each presented twice, for a total of 160 trials (Figure 1). An additional 40 blank trials (no faces and no probes) were presented to serve as the primary comparison for documenting between-group differences in activation to the angry faces.

For the behavioral measure of attention, there were two conditions of interest: (1) congruent trials – an angry/neutral face-pair, followed by a probe replacing the angry face; and (2) incongruent trials -- an angry/neutral face-pair followed by a probe replacing the neutral face. Three other conditions were included as controls: congruent happy-neutral pairs, incongruent happy-neutral pairs, and neutral-neutral pairs. There were 32 trials for each of the five conditions. Trial presentation order was randomly determined for each subject. Equal numbers of replicates displayed the emotional face on right and left hemi-fields.

The task was programmed using E-Prime versions 1.0 and 1.1 by Psychological Software Tools (Pittsburgh, PA) and displayed on Avotec Silent Vision Glasses (Stuart, FL). The button response system was developed by MRI Devices (Waukesha, WI).

Functional MRI Procedures and Analyses

Imaging used a GE 3T scanner to acquire images with 29 contiguous 3.3 mm axial slices, parallel to the AC/PC line. We used an echo-planar single shot gradient echo T2* weighting (TR=2300 ms; TE=23 ms; FOV= 240 mm; 64 x 64 matrix; 3.3 x 3.75 x 3.75 mm voxel). High-resolution T1-weighted volumetric scans used a magnetization prepared gradient echo sequence (MP-RAGE) [180 1.0 mm axial slices; FOV=256 mm, NEX = 1, TR = 11.4 ms, TE = 4.4 ms; matrix = 256 x 256; TI = 300 ms, bandwidth 130 Hz/pixel =33 kHz for 256 pixels in-plane resolution = 1 mm³].

Functional imaging data were analyzed using AFNI software version 2.56b (available at <http://afni.nimh.nih.gov/afni>) (31). Participants were excluded if there was movement greater than 2.5 mm in any direction. Movement was mitigated by registering the images to one volume in each run. Individuals' data were smoothed with a 6 mm full-width at half-maximum isotropic Gaussian filter. Incorrect trials and trials in which the reaction time for the button response was < 200 ms or > 800 ms were removed from the fMRI analysis.

A random effects fMRI data analysis was conducted using a two level procedure. At the first (subject) level, data from each subject were separately submitted to multiple regression analyses using the 3dDeconvolve module in AFNI. For the five conditions (angry congruent, angry incongruent, happy congruent, happy incongruent, and neutral), five vectors were created containing the onset time of each trial for each condition. (blank trials were modeled as an implicit baseline.) Time points for trials in which the subject responded incorrectly or did not respond were placed in a separate vector included in the multiple regression model as a nuisance covariate. Using a gamma

variate (32), vectors of stimulus timing were transformed into reference waveforms of response function for multiple regression, and coefficients were produced for each condition from each subject. Comparison of coefficients for given conditions yielded contrast values. The primary effect of interest for the fMRI analysis was response to angry faces. Therefore, contrasts were established to examine activation to angry faces relative to baseline. Before individual subject data sets were subjected to a group level analysis, individual anatomical data sets were converted to Talairach space (33). The underlying transformation was then applied to that same individual's functional data in order to convert those images as well. The second (group) level analysis involved conducting a regression analysis using the AFNI module 3DregAna on the main contrast of interest: angry vs. baseline trials to evaluate the neurophysiological response with age as a covariate following previous work (16). For comparison, we used the same procedures to examine responses to happy faces vs. baseline and neutral faces vs. baseline.

We employed two thresholds to evaluate the fMRI results. For the first threshold, we used the standard whole-brain $p < .001$ 2-tailed t-test uncorrected for multiple comparisons throughout the brain (34). As a second step if activation in an area was significant at $p < .001$, we also used a Monte Carlo simulation (35) to control for multiple comparisons within the primary areas of interest, the ventral frontal area (anterior to anterior commissure and ventral to genu of corpus callosum) and the amygdala. In the Monte Carlo simulation, each voxel surpassed a threshold of $p < .01$.

Behavioral Data Analysis

The same deviant trials were removed as in the fMRI analysis. Participants were excluded from data analysis if fewer than 75% of the responses were correct or within the accepted reaction time range.

Attentional bias scores reflected the difference between mean reaction times for incongruent and congruent trials, such that positive values indicate bias toward angry faces and negative values indicate bias away from angry faces (16, 22). A comparable analysis examined bias for happy faces. An analysis of variance with age entered as a covariate was used to compare group differences in attentional bias, following previous work (16) and to be consistent with the fMRI analysis.

Results

The primary fMRI and behavioral analyses examined whether there were fMRI activation and reaction time differences between the GAD and control groups in response to angry faces. In addition, we compared activation between groups for responses to happy and neutral faces. Secondary analyses evaluated the degree to which differences in the primary analysis were influenced by either task performance or comorbidity.

fMRI Results

Differential activation between the groups was examined for the contrast of angry faces vs. baseline. In this analysis, GAD adolescents showed greater activation in the right VLPFC, $t(30) 3.91, p < .001$ (Figure 2). The Monte Carlo simulation was significant at $p < .05$ corrected for multiple comparisons of the region of interest. No

effects in the amygdala were found. No significant differences in activation were found between the two groups in response to either happy or neutral faces relative to baseline.

Behavioral Results

Adolescents with GAD, relative to controls, showed a greater attentional bias away from angry faces, $F(1, 30) = 4.90, p < .05$. For patients, attentional bias was -6.93 ms (32.3), and for the controls the bias was 10.41 ms (21.0). Mean \pm sd reaction times (ms) were: 562.4 (55.0) for patients to congruent angry-face trials; 523.8 (89.9) for healthy controls to congruent angry-face trials; 555.5 (53.2) for patients to incongruent angry-face trials; and 534.1 (91.4) for healthy controls to incongruent angry-face trials. No between-group differences were found in reaction time overall to trials containing angry faces. Furthermore, there were no between group differences in attention bias to happy faces and there were no between group differences in reaction time overall to trials with happy faces.

Secondary fMRI Results

Given that there were behavioral differences in attentional bias between groups, a secondary fMRI analysis included the attentional bias measure as a covariate. In this analysis, the GAD group continued to show greater activation in the previously identified right VLPFC region $t(29) = 3.78, p < .001$.

Nine GAD patients had MDD, and nine had no history of MDD. We examined differences in VLPFC activation from controls separately in these two groups and relative to one another. In order to maximize the likelihood that differences would be detected

between the GAD and GAD/MDD groups, we used uncorrected t tests and the values from the VLPFC cluster analysis presented in Figure 2b. Both adolescents with GAD/no MDD and adolescents with GAD/MDD showed greater VLPFC activation relative to controls (GAD/no MDD vs. controls $t(22)=2.89, p<.01$; GAD/MDD vs. controls $t(22)=4.22, p<.001$), with no differences in VLPFC activation found between the two patient groups ($t(16) = .59, p=.57$).

Furthermore, ten of the 18 GAD patients had social phobia. To evaluate the effect of social phobia on VLPFC activation, we employed the same liberal cluster analysis as described with MDD to maximize the likelihood of finding differences. Adolescents with GAD/no social phobia and adolescents with GAD/social phobia showed greater VLPFC activation relative to controls (GAD/no social phobia vs. controls $t(23)=3.70, p<.01$; GAD/social phobia vs. controls $t(21)=3.22, p<.01$), with no differences in VLPFC activation found between the two patient groups ($t(16) = .35, p=.73$).

Finally, to examine the relationship between severity of anxiety symptoms and brain activation, we entered the patients' PARS scores in a covariate analysis. Results revealed a significant activation in the right VLPFC, $t(16) = 3.98, p= .001$ (Figure 2C). As severity of symptoms increased across patients, activation in the VLPFC diminished.

Discussion

In response to angry faces, adolescents with GAD, relative to healthy adolescents, exhibit greater activation in the right VLPFC. Furthermore, adolescents with GAD show an attentional bias away from angry faces relative to healthy adolescents. When the difference in attention was treated as a covariate in the fMRI analysis, the GAD patients

continued to show greater VLPFC activation relative to controls, suggesting that differences in attention do not account for differences in VLPFC engagement. Contrary to our hypothesis, patients with GAD did not evidence greater amygdala activation than controls in response to angry faces. Finally, there were no differences in response to happy or neutral faces.

Abnormal activation in GAD adolescents' VLPFC in the current study is consistent with previous neuroimaging work on adults with various anxiety disorders, including social phobia, PTSD, and panic disorder (7, 12, 13, 36), although the direction of the effects in previous studies is inconsistent. In the present study, the enhanced GAD VLPFC activation suggests one of two possibilities: 1) a disturbance in functioning that may be a direct neural correlate of increased anxiety; or 2) a compensatory response designed to regulate abnormal function in another region.

Support for the first possibility comes from a study of pediatric patients with traumatic brain injury (37). This work revealed that greater damage to the VPFC was associated with reduced anxiety, suggesting that this region is involved in the manifestation of anxiety symptoms. In the present study, angry faces may induce a modicum of anxiety among patients, and this is manifested as increased VLPFC activation.

Concerning the second possibility, the VPFC is involved in various regulatory processes (9, 38, 39). In particular, animal work demonstrates extensive connections between the VPFC and subcortical structures, including the striatum, amygdala and hippocampus, which are implicated in processing emotion-based information (40-42). Moreover, these connections facilitate VPFC regulation of subcortical structures (39, 40).

Similarly, imaging studies suggest that the VLPFC regulates activation in subcortical structures in adult humans as well (9, 43, 44). Thus, it is possible that the VLPFC in the patients modulates abnormal activation in another region. Differential between-group activation in the other region is not detected possibly because the VLPFC is effectively modulating the abnormal response. The finding that increased VLPFC activation is associated with fewer anxiety symptoms is consistent with the possibility that the activation is compensatory. Enhanced VLPFC activation may help GAD patients more effectively regulate initial responses to anxiety provoking stimuli, thereby reducing severity of symptoms.

The observation of greater attentional bias away from threat in adolescent anxiety disorders replicates previous work in children with PTSD (16). Both the current and the prior study document findings opposite from those found in adults. Specifically, in adults studied with the same task, anxiety disorder patients exhibit a bias *towards* threat faces relative to neutral faces, compared with healthy adults (21, 22). Thus, the relationship between anxiety and threat bias assessed with this task varies across development. An important direction for future work will be to uncover the mechanisms that explain the developmental variation. Monitoring eye gaze, varying intensity of threat and manipulating presentation duration may illuminate the variables that contribute to the developmental differences.

The current findings illustrate the importance of behavioral measures and event-related analyses in neuroimaging investigations of between-group differences. We restricted our analyses to events where participants performed the task properly. Thus, only trials in which participants were engaged in the task were included in the analyses.

Furthermore, because this task provides a measure of attention to angry faces, it was possible to evaluate whether the fMRI results were influenced by group differences in attention allocation to the angry faces. When the attentional bias measure was included in the fMRI analysis as a covariate, the between group difference in VLPFC activation remained significant, indicating that attention differences do not account for these findings.

A potential limitation of this study is that the clinical sample included GAD patients who were comorbid with MDD and/or social phobia. To examine whether effects were differentially influenced by these other conditions, we examined the VLPFC activation within each of the clinical groups. Whereas both clinical subgroups showed significantly increased VLPFC activation relative to controls in response to angry faces, the VLPFC activation did not differ between clinical subgroups. These analyses suggest that the VLPFC activation was not disproportionately influenced by MDD or social phobia.

A second limitation of the study is the broad age range in our relatively small sample, which precluded performance of an adequately powered analysis of effects across development within adolescents. Replication in larger sample of younger and older adolescents will help to clarify the developmental progression of these findings and how they relate to anxiety.

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Table 1. Demographics of the control and GAD samples. Diagnoses refer to current or ongoing conditions.

Variable	Healthy Group	Patient Group	Statistical Comparison
Sample Size	15	18	
Gender	7 males; 8 females	10 males; 8 females	$X^2(1) = .26 p > 1.0$
Age	13.53 (2.41)	12.28 (2.05)	$t(31) = 1.62 p > 1.0$
IQ	115.13 (9.77)	109.00 (12.65)	$t(31) = 1.53 p > 1.0$
MDD	0	9	
Soc Phob	0	10	
SAD	0	8	

Figure 1. The two principal trial types in the task. In the left column, a sample trial displays the angry face and probe on different sides of the screen. The same actor always models the two expressions. The middle two columns display the duration of each event and the event name for both trial types. The right column shows a sample trial when the angry face and probe are on the same side. The only difference between the two trials is the location of the probe relative to the threat. Happy/neutral and neutral/neutral trials were also displayed.

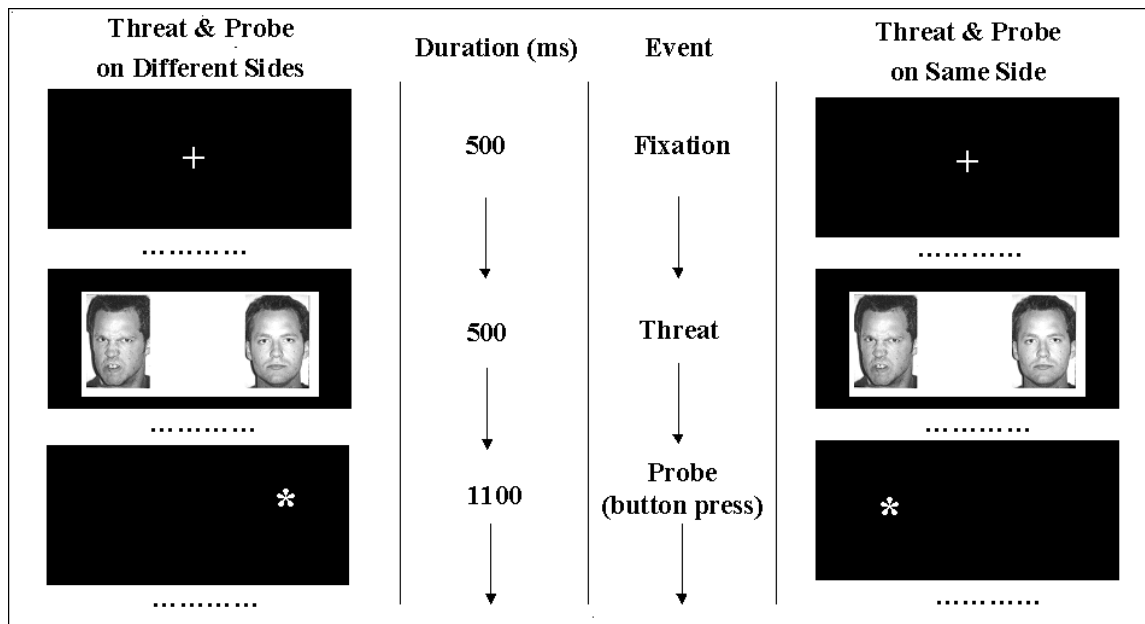
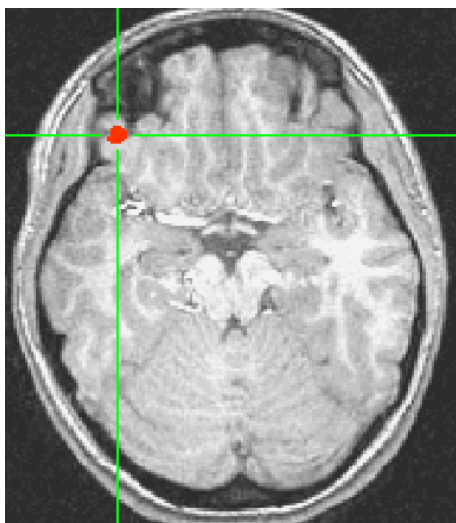
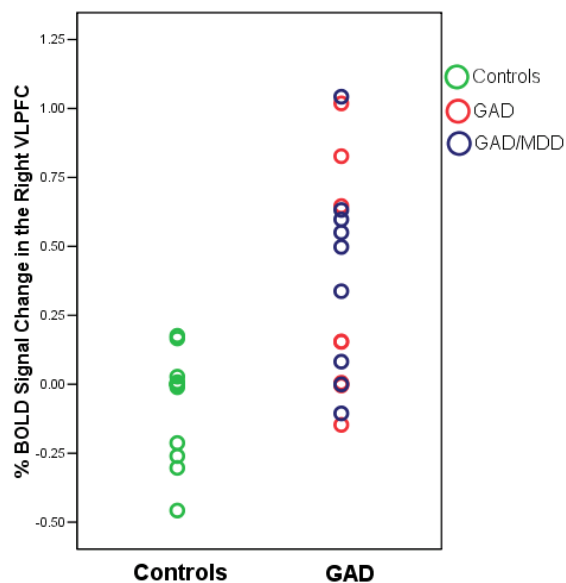


Figure 2. a. In the comparison of trials in which the angry face appeared relative to the baseline condition (fixation followed by black screen), adolescents with GAD show greater activation than controls in the right VLPFC (right is left and left is right). Coordinates (x y z) are 40 34 -12. B. Mean blood oxygenation level-dependent (BOLD) response for adolescent controls and patients with GAD for the same contrast in the voxel cluster encompassing the activation in the right VLPFC. C. BOLD response for patients in right VLPFC covaried by severity of anxiety symptoms (PARS), Pearson $r = -.55, p < .05$. The location of the VLPFC cluster of activation (x y z coordinates 52 37 -9) is slightly different from the cluster in B. GAD patients with and without MDD are differentiated in B and C.

a.



b.



c.

