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Isolating neural components of threat bias in pediatric anxiety

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Abstract

Background—Attention biases towards threat are often detected in individuals with anxiety disorders. Threat biases can be measured experimentally through dot-probe paradigms, in which individuals detect a probe following a stimulus pair including a threat. On these tasks, individuals with anxiety tend to detect probes that occur in a location previously occupied by a threat (i.e., congruent) faster than when opposite threats (i.e., incongruent). In pediatric anxiety disorders, dot-probe paradigms detect abnormal attention biases towards threat and abnormal ventrolateral prefrontal cortex (vLPFC) function. However, it remains unclear if this aberrant vLPFC activation occurs while subjects process threats (e.g., angry faces) or, alternatively, while they process and respond to probes. This magnetoencephalography (MEG) study was designed to answer this question.

Methods—Adolescents with either generalized anxiety disorder (GAD, $n=17$) or no psychiatric diagnosis ($n=25$) performed a dot-probe task involving angry and neutral faces while MEG data were collected. Synthetic Aperture Magnetometry (SAM) beamformer technique was used to determine whether there were group differences in power ratios while subjects processed threats (i.e., angry vs. neutral faces) or when subjects responded to incongruent vs. congruent probes.

Results—Group differences in vLPFC activation during the response period emerged with a 1-30 Hz frequency band. No group differences in vLPFC activation were detected in response to angry-face cues.

Conclusions—In the dot-probe task, anxiety-related perturbations in vLPFC activation reflect abnormal attention control when responding to behaviorally-relevant probes, but not to angry faces. Given that motor responses to these probes are used to calculate threat bias, this study provides insight into the pathophysiology reflected in this commonly-used marker of anxiety. In addition, this finding may inform the development of novel anxiety-disorder treatments targeting the vLPFC to enhance attention control to task-relevant demands.

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Keywords

magnetoencephalography; ventrolateral prefrontal cortex; attention

INTRODUCTION

Cognitive neuroscience research implicate threat-related attention biases in the etiology and maintenance of anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van, 2007). However, many gaps remain in our knowledge about the pathophysiology of such biases. Indeed, abnormal biases towards threat may result from dysfunction in many processes, including directing attention toward or away from threat and/or directing attention to task demands (Fox, Russo, Bowles, & Dutton, 2001). Attention-bias-modification treatment (ABMT), a treatment that targets threat biases, appears to both reduce anxiety and increase attention control, perhaps via recruitment of frontal cortical regions (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010). As the neural mechanisms underlying abnormal attention biases are elucidated with increasing detail, novel behavioral treatments such as ABMT can be tailored towards these underlying perturbations more effectively, potentially improving therapeutic response.

Dot-probe paradigms are used commonly to measure attention biases by presenting stimulus pairs followed by a probe that requires a response (Figure 1). Threat biases are measured using the reaction time difference between incongruent trials, where the probe replaces a neutral stimulus, and congruent trials, where the probe replaces a threatening stimulus. During dot-probe paradigms, adolescents with generalized anxiety disorder (GAD) exhibited greater ventrolateral prefrontal cortex (vLPFC) activation than healthy adolescents (Monk et al., 2006; Pine & Monk, 2008). Moreover, anxiety levels and vLPFC activation detected with functional magnetic resonance imaging (fMRI) exhibit negative correlations in anxious adolescents (Monk, et al., 2006) and positive correlations in healthy adolescents (Telzer et al., 2008). Together, these findings suggest that vLPFC, through its effects on attention control, facilitates emotion regulation when confronting threats (Corbetta, Patel, & Shulman, 2008; Monk, et al., 2006; Monk et al., 2008).

However, while the vLPFC may play a central role in mediating threat bias and anxiety, the precise role of aberrant vLPFC activation in pediatric anxiety remains unknown. For example, on dot-probe tasks, aberrant vLPFC activation could be associated with difficulties directing attention towards/away from threats (i.e., angry faces vs. neutral faces) or, alternatively, towards the probes that follow these threats (i.e., incongruent vs. congruent probes) (Bar-Haim, et al., 2007). Detecting between-group differences in only one of these contrasts would isolate the aberrant activation to a particular time period. Since motor responses to incongruent vs. congruent probes are used to calculate threat bias, aberrant vLPFC activation in response to probes may demonstrate a central role for this brain region in mediating threat bias in patients with anxiety disorders.

Magnetoencephalography (MEG) can be used to differentiate vLPFC dysfunction to the face presentation vs. to the probes that appear during the response period. Unlike fMRI, which indexes blood flow, MEG directly indexes the brain's electrical activity, with sensitivity to changes occurring over a few milliseconds (Hari, Parkkonen, & Nangini, 2010). This technique is also free of scalp distortions found in event-related potentials (ERPs). Available neuroimaging studies on dot-probe performance in anxious individuals rely on ERP or fMRI (Eldar & Bar-Haim, 2010; Monk, et al., 2006). ERP studies using dot-probe paradigms have identified frontal recruitment following probe onset (Eldar & Bar-Haim, 2010); however, with limited spatial resolution, it is unclear whether the vLPFC is specifically recruited. fMRI

studies depend on a slow hemodynamic-response function, limiting temporal resolution; therefore, aberrant activation found in pediatric anxiety could reflect perturbations to many aspects of a dot-probe trial (Monk, et al., 2006). However, MEG uniquely combines excellent temporal and spatial resolutions. Thus, it is ideally suited to test whether aberrant vIPFC activation occurs when processing threats or responding to the probes used to measure attention biases. Of note, the relationship between fMRI and MEG signals is complex (Winterer et al., 2007), with some data suggesting that fMRI activation correlates with event-related desynchronization (i.e., negative oscillatory power) at frequencies below 25 Hz (Singh, Barnes, Hillebrand, Forde, & Williams, 2002).

Few MEG studies have investigated pediatric populations (e.g., Rich et al., 2011), and to our knowledge, none examine between-group differences in pediatric anxiety disorders or investigate attention biases using the dot-probe task in any age group. The current MEG study compares vIPFC oscillatory power ratios in GAD and healthy adolescents performing a dotprobe task in order to test whether the aberrant vIPFC activation manifests specifically during the response period capturing attention bias following threat cues.

METHODS AND MATERIALS

Participants

This study recruited physically-healthy, medication-free, 8-to-18-year olds with IQ>70 (Wechsler, 1999). Written informed assent/consent was obtained from all participants and parents. All procedures were conducted in accordance with the National Institute of Mental Health (NIMH) Institutional Review Board.

Psychiatric history was assessed by trained clinicians via the Kiddie-Schizophrenia-and-Affective-Disorders-Schedule (K-SADS) (Kaufman et al., 1997). Patients met full criteria for DSM-IV GAD (n=15) or for social phobia (SoPh) (n=2) accompanied by prominent GAD symptoms not sufficiently distinct from social worries to qualify unequivocally for GAD. Children with secondary anxiety diagnoses or major depressive disorder (MDD) were included because these disorders often co-occur, and prior fMRI studies of the dot probe task include them. Healthy comparison (HC) individuals were free of any current or past Axis I psychiatric disorder. Group characteristics are outlined in Table 1.

The final sample included 17 GAD and 25 HC adolescents, matched for age, gender, and IQ. Co-morbid diagnoses included: SoPh secondary to GAD=4, separation anxiety disorder=2, panic disorder=1, specific phobia=3, and MDD=3. This final sample was obtained after excluding individuals for technical reasons (GAD=2, HC=6), excessive movement (GAD=10, HC=8) or poor behavioral performance (<65% accuracy, GAD=2, HC=2). The excluded groups were younger [12.1 ± 2.7 , $t(70)=2.98$, $p<0.004$] than the individuals included in the analysis [14.0 ± 2.6], but did not differ with respect to sex, IQ, and trait anxiety [all $p>0.1$].

Procedures

The dot-probe task—In dot-probe trials (Figure 1), participants viewed a fixation cross. Then, two faces appeared at the sides of the fixation cross. After the face pair disappeared, a dot-probe appeared in one of the previously-occupied face locations. Using left or right button press, participants identified the probe orientation, (:) or (..). The response mapping of the probe orientation was counterbalanced across participants.

Stimuli—Face pairs consisted of two black-and-white images of the same individual presented side-by-side. The face identities included six males and six females from the

NIMstim face set (Tottenham, 2009). Emotional-neutral trials were classified based on the relation between the locations of the emotional face and the probe. In congruent trials, the probe was presented in the location previously occupied by the emotional face. In incongruent trials, the probe was presented in the location opposite the emotional face. The location of the emotional face was counterbalanced across all trials. In neutral trials, two identical neutral facial expressions appeared and the probe location was insignificant.

Angry and happy blocks alternated twice with order counterbalanced across participants. In each block, 24 congruent and 24 incongruent trials according to the emotion of the block (either angry-neutral or happy-neutral trials) and 24 neutral trials were randomly presented. Each 2500 ms trial consisted of a 500 ms fixation, a 500 ms face pair, a 200 ms probe, and a 1300 ms inter-stimulus interval. Based on prior work implicating vIPFC in threat biases (Monk, et al., 2006), analyses only focused on data collected during angry blocks.

Apparatus and Acquisition—A whole-head 275-sensor MEG system (CTF Systems, Inc., kurage.nimh.nih.gov/meglab/Main/MegFacility) was located in a magnetically shielded room. Each sensor was configured as a first-order axial gradiometer, with two 18-mm radius coils separated by 50 mm, spaced 22 mm apart. MEG data were sampled at 600 Hz (bandwidth: 0-150 Hz). Three localization coils were attached to the nasion, left pre-auricular and right pre-auricular sites to measure head position. Using E-Prime 1.1, task stimuli were displayed on a screen approximately 85 mm from the seated subject.

On a separate visit, a T1-weighted magnetic resonance image using a high resolution 3D MPRAGE MRI sequence (TI/TE/flip angle=725 ms/min/6°, 1.2mm in-plane resolution, and 1.2 mm slice thickness) was collected. Vitamin-E capsules served as fiducial points for co-registration. Using this anatomical image, MEG data were co-registered and normalized into Talairach space in AFNI software (Cox, 1996). Two patients did not complete a structural MRI; therefore, a similarly aged and gendered participant's brain was used for co-registration. A multi-sphere head model, based on brain shape was derived for source localization procedures described below.

Data Analysis

Behavior—Trials with incorrect responses and trials with reaction times less than 150 ms or greater than 2.5 standard deviations outside each individual's mean reaction time for each event type were excluded from both behavioral and MEG analyses.

Attention bias scores were calculated by subtracting the mean reaction times on angry congruent trials from angry incongruent trials. Positive bias scores reflect a bias towards threat and negative bias scores reflect a bias away from threat.

Group differences in accuracy rates, reaction times, and bias scores were examined and attention biases were tested within each group separately using t-tests with an $\alpha=0.05$.

Synthetic Aperture Magnetometry (SAM) beamformer MEG analysis—Raw MEG data were filtered using 3rd gradient reference coils with fixed weights. DC offset was removed, and data were filtered with high-pass (0.50 Hz) and 60 Hz notch filters.

In MEG analyses, frequency bands and time periods must be selected. Traditionally, for MEG studies which represent the first attempt to address a particular research question, a broad frequency band has been used (Cornwell et al., 2008; Rich, et al., 2011); therefore, in the current study, a 1-30 Hz frequency band was selected for our primary analyses. This approach facilitates comparisons with previous ERP studies using this frequency band (Eldar, Yankelevitch, Lamy, & Bar-Haim, 2010). Moreover, this approach effectively

balances Type I and Type II errors that can accrue when conducting multiple analyses in many narrow frequency bands. Nevertheless, secondary analyses examined theta (4-8 Hz), alpha (8-14 Hz), beta (14-30 Hz), and gamma (30-90 Hz) bands. Time periods were defined to capture the periods of dot-probe trials and balance the number of times the non-phased locked signal was sampled for each frequency band. The face-presentation period was defined as the 500 ms following face onset and the response period corresponds to the 1000 ms following probe onset, including the dot-probe and subsequent motor response. For 30 Hz signals, the 500 ms time period was sampled 15 times. For signals lower in frequency, fewer samples were obtained.

A three-way group (GAD, HC)-by-period-(face-presentation, response)-by-condition interaction examined differences between anxious and healthy groups in *oscillatory power activity* (i.e., non-phase locked activity). The condition term in this interaction varies based on period because congruent and incongruent trials are not defined until the probe appears. Specifically, the face-presentation period included angry (i.e., angry congruent and angry incongruent trials) and neutral trials to capture emotion processing. The response period included the two trial types used to calculate behavioral threat bias, angry-incongruent and angry-congruent (see Figure 1). This comparison captures differential attention shifts towards or away from a spatial location previously occupied by an angry-threat cue.

Separate group-by-condition interactions within each period, face-presentation and response, were used to decompose the 3-way interaction. To fully characterize the between-group difference, subsequent analyses examined the face presentation period, relative to baseline fixation (i.e., the 500 ms preceding the face). In addition, angry-congruent and angry-incongruent trials were examined relative to neutral trials and baseline (i.e., 1000 ms immediately preceding the face onset).

The synthetic aperture magnetometry (SAM) beamformer technique was used to calculate the electromagnetic source power distribution for individual voxels (Vrba & Robinson, 2001). SAM produces a 3D representation of brain activity by using the recorded magnetic field across the sensor array to compute a set of beamformer weights to estimate activation at individual voxels. At each voxel, an optimal spatial filter is determined through a minimum variance procedure that reduces extraneous power sources but preserves signal from that particular voxel; therefore, it minimizes potential artifacts (e.g., eye blinks or muscle contractions). The orientation of the source dipole is estimated by a vector-based approach. This SAM analysis requires no *a priori* specification of the number of active sources and provides source power images in 3D space within specific frequency bands.

For each individual participant, SAM analyses were performed on the MEG data using 7 mm voxel spacing. The SAM procedure calculates pseudo F-values, ratio of power differences (i.e., activation). Positive power ratios indicate greater power in the active state (e.g., angry incongruent) than the comparison state (e.g., angry congruent). (Vrba & Robinson, 2001). After estimating pseudo F-ratios at each voxel, SAM volumes were normalized to Z-scores. The normalized data were transformed into common Talairach coordinate space.

Group analyses of the whole-brain normalized pseudo F-ratios were conducted using AFNI software. The vIPFC was chosen as the *a priori* region for our main hypothesis, as tested in a three-way group-by-period-by-condition interaction. For completeness, between-group differences in other cortical regions are also reported. To correct for multiple comparisons in fMRI studies, a whole-brain-derived false discovery rate (FDR) threshold of 0.05 is the current standard and can be approximated using a $p < 0.005$ intensity threshold and 20 $3.5 \times 3.5 \times 5$ mm voxel threshold (Lieberman & Cunningham, 2009). Given the larger voxel

size (7mm)³ in this MEG study, we report regions that survived a $p < 0.005$ uncorrected threshold with a minimum of 4 voxels to approximate 0.05 FDR.

Correlational analysis—Within each group, Pearson correlations examined the association between anxiety, age and measures of threat bias. To examine the association between anxiety measures and MEG data, a functionally-defined region-of-interest (ROI) was created using an 8-mm radius sphere centered at the right vIPFC peak (35,34,-8) identified by the group-by-condition interaction during the response period. Significant correlations between the extracted pseudo-F values from this ROI and anxiety measures were tested. In addition, group differences in correlation were examined using a Fisher's r -to- Z -transformation. A significance level of $\alpha = 0.05$ was used.

RESULTS

Behavioral Results

Table 1 summarizes the behavioral data. There were no between-group differences in accuracy, bias, or reaction-time indices [all $p > 0.1$]. No significant attention biases towards or away from angry faces were detected in either group [all $p > 0.5$].

Across both groups, STAI trait anxiety scores were negatively correlated with threat bias [$R = -0.35$, $p < 0.03$] (Figure 2A). In the HC group, individuals with higher trait anxiety had greater negative threat bias scores (i.e., greater avoidance) [$R = -0.49$, $p < 0.02$]. A non-significant negative correlation manifested in the patient group [$R = -0.30$, $p > 0.3$], with no significant between-group difference [$p > 0.5$]. No correlation between age and threat bias was detected across both groups or within each group separately [all $p > 0.7$].

SAM beamformer analysis

The primary analysis compared the un-averaged MEG activity (i.e., oscillatory power ratios) in the 1-30 Hz frequency band between groups, focusing on the three-way group-by-period-by-condition interaction. A significant three-way interaction was detected in the right vIPFC BA47, [(35,41,-8), $F = 15.00$, $k = 15$]. To decompose this interaction, group differences between conditions were examined in the face-presentation and response period separately. No group differences were found between conditions during the face-presentation period. However, as shown in Figure 3, during the response period between angry-incongruent and angry-congruent trials, a group-by-condition interaction was detected in the right vIPFC BA47, [(28 20,-8), $t = 3.17$, $k = 10$, (35,34,-8), $t = 3.13$, $k = 5$]. Compared to the HC group, the patient group exhibited a greater negative power ratio when contrasting the response periods assessing attention bias (i.e., angry incongruent vs. angry congruent). Specifically, in patients, a significant negative power ratio manifested, suggesting greater power in the angry-congruent, relative to the angry-incongruent condition [(42,41,-8), $t = 3.77$, $k = 6$]. In contrast, the HC group showed similar activity in the two conditions (Table 2). This pattern is also illustrated using extracted data from the vIPFC ROI (Figure 3).

To characterize this finding further, group differences in each condition were examined relative to baseline fixation. Patients exhibited greater right vIPFC activation (i.e., positive power ratio) [(35,48,-8), $t = 3.10$, $k = 14$] during angry-congruent trials, relative to baseline, than the HC group. No between-group differences were noted for the angry-incongruent trials. Both groups exhibited vIPFC activation in both the angry-incongruent [GAD: (-21,55,-8), $t = 5.65$, $k = 921$, HC: (28,48,-15), $t = 5.33$, $k = 2128$] and angry-congruent trials relative to baseline [GAD: (28,55,0), $t = 5.64$, $k = 771$, HC: (28,48,-15), $t = 5.88$, $k = 1897$]. Although the peak was lateralized, the activation extended bilaterally in all cases.

Correlational analysis

Across both groups, a negative correlation was found between STAI trait anxiety scores and vIPFC activation during the response period for the threat bias contrast [$R=-0.40$, $p<0.01$] (Figure 2B). However, the correlations differed significantly between groups [Fisher's r -to- $Z=-2.05$, $p<0.05$]. In the HC group, trait anxiety scores and vIPFC activation were negatively correlated [$R=-0.44$, $p<0.04$]; HC individuals with greater trait anxiety scores had greater negative power. This relation was explained by a negative correlation between trait anxiety and the vIPFC activation in response to angry-incongruent trials relative to baseline [$R=-0.42$, $p<0.05$]. However, in patients, vIPFC activation to threat bias was not significantly correlated with trait anxiety [$R=0.23$, $p>0.4$] or PARS scores [$p>0.9$].

No correlations between age, threat bias, and vIPFC activation during the response period for threat bias were noted across both groups or within each group separately [all $p>0.2$].

Additional analyses

For completeness, secondary analyses considered narrower frequency bands. Although the HC group showed no difference in power between angry-incongruent and congruent conditions in the 1-30 Hz frequency band, the HC group did exhibit vIPFC activation [(35,20,-8), $t=4.01$, $k=14$] when analyses were restricted to the 14-30 Hz frequency band.

Group differences were also detected in the other regions in narrower frequency bands for the angry bias contrast. In the 30-90 Hz band, the patient group exhibited greater negative power in the fusiform gyrus than the HC group [(-21,-50,-8), $t=-3.33$, $k=7$]. In the 8-12 Hz band, compared to the patient group, the HC group had greater activation in the putamen [(21,13,13), $t=-3.20$, $k=11$] and greater negative power in the parahippocampus [(-14,-29,-15), $t=3.25$, $k=9$].

During the face presentation period, no significant group differences in vIPFC were noted for 1-30 Hz; however, a group difference was detected in the precuneus for this broad frequency band. Compared to the HC group, the patients had greater negative power in response to angry relative to neutral faces [(-14,-78,49), $t=3.84$, $k=7$]. In addition, in the 14-30 Hz frequency band, the HC group exhibited greater activation in the parahippocampus than the patients [(21,-36,0), $t=3.57$, $k=9$].

DISCUSSION

To our knowledge, this is the first MEG study in pediatric anxiety. Previous dot-probe work using fMRI found group differences between GAD and healthy adolescents in vIPFC activation (Monk, et al., 2006). However, the limited temporal resolution of fMRI prevents conclusions regarding whether processing of threat faces or responses to the dot-probes induces abnormal vIPFC engagement in GAD. Using MEG, with both excellent temporal and spatial resolutions, a group difference in right vIPFC activation on the dot-probe task was isolated to the response period. This difference manifested for the same contrast used to calculate threat bias (angry-incongruent vs. angry-congruent). Patients exhibited greater negative oscillatory power in right vIPFC during this period compared to the HC group; trait anxiety scores in the HC group negatively correlated with this vIPFC activation. No group differences in vIPFC activation were detected in response to the angry face stimuli. Isolating the aberrant activation to the response period, rather than the face presentation period, clarifies the nature of attention-related perturbations in pediatric anxiety disorder. Novel treatments, such as attention training regimens or psychopharmacologic treatments, might be developed based on their specific ability to shape vIPFC function and direct attention toward task-relevant behaviors, rather than more general approaches.

The group difference in the threat bias contrast during the response period was explained by greater activation during the angry-congruent condition in patients than HC (Figure 3). In this condition, the probe occurs in the location previously occupied by the angry face. In the current study, individuals with high anxiety levels tended to avoid the threat cue (i.e., negative threat bias). Thus, greater power in response to congruent probes in the patient group may reflect difficulties disengaging attention from the location used to avoid the threat (i.e., neutral cue). Because activation in the current study was isolated to the response period, the vIPFC activation may serve to redirect attention, facilitating shifts of attentional resources away from threats in the service of probe identification. Therefore, vIPFC is needed to mobilize attention away from a stimulus pair that includes a threat to enable a response to the task-relevant probe.

The current dot-probe study revealed no between-group differences in behavior based on diagnosis. This raises questions on the functional significance of vIPFC findings, occurring in the absence of behavioral differences. Nevertheless, the significant correlation between threat bias and levels of anxiety on the STAI generally replicates the patterns found in previous research. Moreover, a lack of behavioral differences between anxious and healthy adolescents also clarifies interpretations because between-group differences in vIPFC engagement cannot be attributed to so-called performance confounds.

Typically, anxious individuals studied in low-stress environments exhibit behavioral responses biased towards threat on the dot-probe task (Bar-Haim, et al., 2007; Waters, Mogg, Bradley, & Pine, 2008). However, as in the current study, (Bar-Haim, et al., 2007) threat biases are altered in stressful environments. Anxious adults in mildly stressful (Constans, McCloskey, Vasterling, Brailey, & Mathews, 2004) or life-threatening situations often show avoidance, rather than vigilance towards threat. Moreover, in these situations, the level of anxiety often shows an association with threat avoidance as opposed to vigilance (Bar-Haim et al., 2010), as was found in the current study with anxiety on the STAI. Consistent with prior work, imaging environments may be mildly stressful and may influence attention bias (Monk, et al., 2006). Finally, it is common to observe between-group differences in neural activation in the absence of behavioral differences, possibly because imaging measures are more sensitive to group differences compared to behavioral indices. Larger studies may clarify these possibilities.

Caution is needed when considering the lateralization of group difference. Such findings could reflect Type II errors. However, in subsequent analyses using more liberal statistical thresholds, findings remained unilateral. Lateralization of group differences may indicate a distinction of function in the right and left vIPFC. Group differences in the right vIPFC activation during the response period for angry-congruent conditions may reflect response inhibition or reflexive orienting (Levy & Wagner, 2011). In other words, the right vIPFC activation may either reflect withholding a response until the dot-probe appears or reorienting attention to the appearance of task-relevant dot-probes. More research is needed to clarify these possibilities.

Several study limitations should be noted. First, patients included individuals with MDD and other comorbid illnesses. This approach was adopted to most directly extend prior fMRI research, which had used similar inclusion criteria. Moreover, after excluding MDD cases, the vIPFC group difference remained significant [$t(37)=2.62, p<0.01$]. Second, since the frontal cortex matures throughout adolescence, the broad age range may be a limitation. Again, we considered this age range to directly extend prior work (Monk, et al., 2006). Moreover, anxious and HC groups were age-matched to control for these developmental effects. Regardless, future longitudinal and cross-sectional studies examining more refined age-ranges may be able to identify developmentally-sensitive changes in the vIPFC and their

impact on anxiety disorders. Third, like other MEG studies attempting to balance Type I and Type II errors, a broad frequency band, 1-30 Hz, was used to detect group differences in vIPFC activation. When individual frequency bands were examined, few yielded clear results, possibly due to a relatively small number of experimental trials. Future studies need to isolate the contributions from individual frequency bands. Finally, while our hypotheses were generated from fMRI studies, it is difficult to compare directly findings based on BOLD signal and MEG power due to complex relations between these two signals. To do so, the same group of subjects should be studied using both imaging modalities. Although the current study cannot answer questions that arise due to differences between MEG and fMRI, group differences in vIPFC activation during the response period were detected, suggesting the role of the vIPFC in orienting to task demands.

Despite these limitations, connecting aberrant vIPFC activation to aberrant attention control in individuals with pediatric anxiety is an important step toward improving treatments. Attention biases are often detected in individuals with anxiety and there is increasing interest in novel behavioral treatments (e.g., ABMT). Understanding the neural architecture engaged on attention orienting tasks, like the dot-probe task, may inform the further development of ABMT and other novel treatments. The current and prior imaging work suggests that an appropriate treatment target would be vIPFC activation when anxious patients must direct their attention to task-relevant behaviors following a distracting threat cue. In contrast, a less promising treatment target would be vIPFC function during initial attention orienting to threat; other structures (e.g., amygdala) may play a larger role in such abnormalities. Future neuroimaging work may provide further evidence that ABMT enhances both vIPFC function and attention control. Identifying vIPFC-mediated changes in attentional bias with training may support the use of ABMT as a prevention strategy in adolescents at-risk for developing anxiety disorders.

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KEY POINTS

- Pediatric anxiety is associated with abnormal ventrolateral prefrontal cortex (vlPFC) function.
- Attention biases towards threat are often detected in individuals with anxiety using dotprobe paradigm.
- Group differences in vlPFC activation were isolated to the response period using magnetoencephalography (MEG).
- Aberrant ventrolateral PFC activation may reflect difficulties directing attention to task-relevant behaviors following threats.
- Targeting treatment to behavioral and neural dysfunction may yield better long-term outcome.

Figure 1.

Dot-probe paradigm and time period definitions.

In dot-probe trials, participants view a fixation cross (500 ms). Then, two facial expressions of a single individual appear (500 ms). Following the face pair, a dot-probe appears (200 ms) and participants indicate via button press the orientation of the dot probe, horizontal (..) or vertical (:). A 1300 ms inter-stimulus interval separates trials. Two trial types, are used to assess attention bias (incongruent vs. congruent). In congruent trials, the dot probe appears in the same location that the emotional face (e.g., angry) had previously appeared. In incongruent trials, the dot probe appears in the opposite location. For the oscillatory power analysis, face presentation (red/dark gray arrow), response (blue/light gray arrow), and baseline control periods (black arrows) were examined. A 500 ms face presentation and a 1000 ms response period served as active periods. Active periods and corresponding baseline periods were of equal length.

Figure 2.

Correlations between trait anxiety measures, threat bias and vIPFC power.

(a) Across both groups, Spielberger State Trait Anxiety Inventory-Children (STAI) trait anxiety scores were negatively correlated with threat bias [$R=-0.35$, $p<0.03$]. No group differences in the correlation were noted [$p>0.5$, patient: $R=-0.30$, $p>0.3$; healthy adolescents: $R=-0.49$, $p<0.02$]. (b) The correlation between trait anxiety and vIPFC activation during the response period for threat bias contrast was significantly different between groups [Fisher's r -to- $Z=-2.05$, $p<0.05$]. Trait anxiety negatively correlated with vIPFC activation only in the healthy group [patient: $R=0.23$, $p>0.4$, healthy: $R=-0.44$, $p<0.04$].

Figure 3.

Between-group difference in *oscillatory power* during response period of threat bias in the 1-30 Hz frequency band, compared with healthy adolescents, adolescents with generalized anxiety disorder exhibited greater negative power in ventrolateral prefrontal cortex (vIPFC, [(28,20,-8), $t=-3.17$, $k=10$; (35,34,-8), $t=-3.13$, $k=5$]) during the response period between incongruent and congruent conditions. Significance was detected using $p<0.005$ threshold and cluster size $k>4$, approximating a $p<0.05$ False Discovery Rate correction. For illustrative purposes, the graph represents extracted normalized power values in the functionally-defined vIPFC cluster highlighted by the crosshairs. Left-Posterior-Inferior coordinates reported. t =t-score, k =cluster size.

Table 1

Group characteristics and behavioral results (mean and standard deviation) of the study patients and health comparison groups

	Patient	Healthy
Demographics		
Number of Participants (males)	17 (8)	25 (16)
Age, years	13.3 (2.9) Range: 8-18	14.4 (2.3) Range: 9-17
IQ	112.7 (10.7) Range: 96-127	108.7 (12.1) Range: 85-131
PARS	15.9 (4.5)	-
SCARED-child *	39.1 (11.7)	11.0 (9.2)
STAI-trait *	43.7 (6.1)	28.7 (5.8)
CDI *	14.9 (7.7)	2.8 (3.2)
Behavioral Data		
% Accuracy	84.8 (8.8)	89.2 (8.9)
Threat Bias Score	-2.2 (32.6)	5.4 (39.6)
Reaction Time (ms)		
Angry-congruent	665.9 (149.1)	672.5 (84.8)
Angry-incongruent	663.7 (147.1)	677.9 (84.5)
Neutral	653.6 (139.5)	671.5 (89.7)

* Significant group difference ($p < 0.001$). PARS: Pediatric Anxiety Rating Scale (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002), SCARED: Screen for Child Anxiety Related Emotional Disorders (Birmaher et al., 1997), STAI: Spielberger State Trait Anxiety Inventory (Spielberger et al., 2009), CDI: Child Depression Inventory (Kovacs, 1992).

Table 2
Differences in 1–30 Hz oscillatory power in ventrolateral prefrontal cortex (vLPFC) during the response period.

Contrast	Patients vs. Healthy			Patients			Healthy		
	Coordinates	t	k	Coordinates	t	k	Coordinates	t	k
Angry Bias (Angry Incongruent vs. Congruent)	28, 20, –8	–3.17	10	42, 41, –8	–3.77	6	-	-	-
	35, 34, –8	–3.13	5				-	-	-
Angry Incongruent vs. Neutral	-	-	-	42, 34, –8	–3.72	4	-	-	-
Angry Congruent vs. Neutral	35, 48, –8	3.10	14	-	-	-	-	-	-
Angry Incongruent vs. Baseline	-	-	-	28, 55, 0	5.64	771 *	28, 48, –15	5.88	1897 *
Angry Congruent vs. Baseline	–35, 48, –8	3.10	10	–21, 55, –8	5.65	921 *	28, 48, –15	5.33	2128 *

Significant between-group and within-group power differences using $p < 0.005$ threshold and cluster size $k > 4$, approximating a $p < 0.05$ False Discovery Rate (FDR) correction. Response period corresponded to 1000 ms following probe onset. Baseline corresponds to 1000 ms preceding the face onset. LPI coordinates reported. t=t-score, k=cluster size.

* Activation extends bilaterally.