ORIGINAL ARTICLE

Amygdala Response to Fearful Faces in Anxious and Depressed Children

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Background: Alterations in amygdala function have been implicated in the pathophysiological characteristics of adult anxiety and depressive disorders. Studies with healthy adults and children, as well as with adults who have amygdala lesions, have found facial expressions of emotion to be useful probes of amygdala activity. Our study examined the amygdala response to fearful and neutral facial expressions in healthy, anxious, and depressed children. We hypothesized that children with anxiety and depression may show atypical amygdala responses to emotional stimuli.

Methods: Twelve children (8-16 years of age) with generalized anxiety or panic disorder and 12 healthy comparison children underwent noninvasive functional magnetic resonance imaging while viewing photographs of fearful and neutral facial expressions. In a second comparison, 5 girls with major depressive disorder were compared with 5 anxious and 5 healthy girls from the previous sample.

Results: Children with anxiety disorders showed an exaggerated amygdala response to fearful faces compared with healthy children, whereas depressed children showed a blunted amygdala response to these faces. In addition, the magnitude of the amygdala's signal change between fearful and neutral faces was positively correlated with the severity of everyday anxiety symptoms.

Conclusions: Our results suggest that amygdala function is affected in both anxiety and depression during childhood and adolescence. Moreover, this disruption appears to be specific to the child's own rating of everyday anxiety.

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THE AMYGDALA and its related structures are thought to play a key role in evaluating the emotional significance of sensory and social stimuli.[1,2] Stimulation of the amygdala produces autonomic reactions associated with the fight or flight response, including increased heart rate and blood pressure, freezing behavior in animals, feelings of fear and anxiety in humans, and increased plasma stress hormone levels.[2-4] Human neuroimaging studies have shown that amygdala activity increases during exposure to fear conditioned[5,6] and other emotionally valenced stimuli.[7-11] In contrast, amygdala lesions result in diminished fear reactions in animals[12,13] and an impaired recognition of negative facial expressions, particularly fearful expressions, in humans.[14]

Abnormal amygdala function has been implicated in adult neuroimaging studies of anxiety and depression.[15,16] Adults with social phobia show increased bilateral amygdala responses to faces judged by healthy controls to be affectively neutral.[17] Hyperreactivity of the amygdala has been observed in adults with posttraumatic stress disorder (PTSD) in response to reminders of traumatic events[18,19] and to general negative stimuli.[20,21] Finally, positron emission tomography (PET) studies of depressed adults report an elevated resting blood flow and glucose metabolism in the amygdala that correlate positively with depression severity.[22,23]

One common probe of human amygdala function has been facial expressions of emotion. Results from several functional neuroimaging studies have suggested that in healthy adults, the amygdala responds more strongly to fearful faces than to other expressions such as neutral or happy faces.[6,9-11,24,25] This pattern of ac-

SUBJECTS AND METHODS

SUBJECTS

Two pediatric patient groups and healthy comparison groups participated. Twelve children and adolescents (mean±SD, 12.8±2.1 years; range, 8-16 years; 7 boys, 5 girls) who met *DSM-IV*[34] criteria for GAD (n=11) and/or panic disorder (n=2) were compared with 12 healthy children (mean±SD, 12.1±2.6 years; range, 8-15 years; 7 boys, 5 girls), some of whose data were reported previously.[32] In a second comparison, 5 girls (mean±SD, 12.3±2.7 years; range, 8-16 years) with *DSM-IV* diagnoses of major depressive disorder (MDD) were compared with the previously studied healthy girls and girls with anxiety disorders. All subjects were right-handed. Groups were similar in pubertal development (range, Tanner stage 1/1 to 5/5 for anxious and depressed children and 1/1 to 5/4 for healthy children) and estimated IQ (mean±SD, 124±16 for anxious subjects, 127±12 for depressed subjects, and 137±14 for healthy subjects). One child with GAD had comorbid social phobia. Two children with MDD had comorbid GAD.

Children with anxiety or depression were recruited from the Child and Adolescent Anxiety and Depression Program of the Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, Pa. Children were evaluated by trained research physicians blind to the subject's clinical status and with the supervision of child psychiatrists using a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)[35] with the participation of both the child and parent(s). A psychiatrist then heard the case to confirm the presence of a psychiatric disorder. Healthy control children were required to have a low familial risk for depression as defined by the absence of any current or past psychiatric disorders, no first-degree relatives with mood or psychotic disorders, no second-degree relatives with childhood-onset recurrent psychotic or bipolar depression, schizoaffective disorder, or schizophrenic disorder, and no more than 20% of second-degree relatives with a single episode of major depression. All children were screened using the vocabulary, digit span, block design, and object assembly subtests of the Wechsler Intelligence Scale for Children–Third Edition (WISC-III),[36] the 12 handedness items from the Revised Physical and Neurological Examination for Soft Signs (PANESS) Inventory,[37] the Tanner Scales of Pubertal Development,[38] and the Screen for Child Anxiety Related Emotional Disorders (SCARED).[39,40] The SCARED is a 41-item parent report and child self-report instrument. It consists of 5 factors that parallel the *DSM-IV* classification of anxiety disorders: somatic/panic, generalized anxiety, separation anxiety, social phobia, and school phobia. This measure was used to assess the severity of the anxiety symptoms. Exclusionary criteria for all participants included (1) a positive urine screen for cigarette, alcohol, or illicit drug use; (2) the use or presence of medication with central nervous system effects within the prior 2 weeks; (3) the presence of a significant medical or neurological illness; (4) extreme obesity (weight > 150% of the subject's ideal body weight) or growth failure (height or weight < the third percentile for the child's age); (5) an IQ lower than 80; (6) anorexia nervosa, autism, or schizophrenia by *DSM-IV* criteria; (7) GAD chronologically secondary to conduct disorder; (8) specific learning disabilities; (9) a current diagnosis of PTSD; or (10) any contraindication for an MRI.

The study was approved by the institutional review board of the University of Pittsburgh Medical Center. Written parental consent and child assent were acquired prior to the study, and subjects were compensated $50 for their participation in the MRI portion of the study.

PROCEDURES

Stimuli and Task

The task consisted of the rapid (1 Hz) and successive presentation of a standard photographic set of faces[41] in blocks of neutral and emotional expressions. A total of 8 different actors (4 men, 4 women) demonstrating both fearful and neutral expressions were used (**Figure 1**). Hair was stripped from the images to remove any nonfacial features, and both fear and exaggerated fear poses were used for each actor.[42] Facial stimuli were presented

tivity is generally lateralized, with a greater amygdala response in the left hemisphere than in the right for standard face presentations. However, when the facial expressions are masked so that the initial emotion is not consciously perceived, the right amygdala shows greater activity than the left.[6,10,25] This unconscious amygdala response to fearful vs happy faces has been shown to be enhanced in adults with PTSD.[21] In addition, adults with amygdala lesions exhibit deficits in the ability to recognize certain facial expressions, especially fear.[14,26-29]

There is an increasing recognition of the importance of understanding mechanistic changes in emotional processing that are evident early in the development of anxiety and depression, in ways that may ultimately lead to more effective early interventions. A recent anatomical magnetic resonance imaging (MRI) study observed an increased volume of the right amygdala but not of other brain regions in children with generalized anxiety disorder (GAD), suggesting that amygdala abnormalities may be associated with childhood-onset as well as adult anxiety disorders.[30] However, few functional imaging studies have examined amygdala responses in children. Baird et al[31] found that healthy adolescents showed bilateral amygdala activity in response to unmasked fearful faces when compared with neutral nonface scrambled images. Recently we reported that although children exhibited amygdala increases with fearful faces compared with a nonface baseline stimulus, they actually showed less amygdala activity with fearful faces than with neutral faces.[32] The implications of this continued development in the processing and understanding of facial expressions are not entirely clear but have been attributed to ambiguity in the emotional significance of a neutral face.[32,33] In our study, we use fearful and neutral facial expressions to examine amygdala responsiveness in children with anxiety and depression, keeping in mind that the normal pat-

for 200 milliseconds followed by an 800-millisecond interstimulus interval containing a flashing central asterisk (fixation point). In each behavioral run, a block of fixation trials was presented for 45 seconds followed by alternating 42-second blocks of either neutral or fearful expressions and a final 45-second epoch of fixation. This procedure was repeated in 3 runs of trials with the presentation order counterbalanced across runs and across subjects (ie, F-N-F-N-F or N-F-N-F-N, where *F* indicates fearful expressions and *N* indicates neutral expressions). No overt response was required. Subjects were instructed to fixate centrally and to try to get an overall sense of the faces.[11,32] The stimulus parameters and task design were specifically selected to replicate previous studies of the amygdala response to facial expressions.

MRI Methods

Structural and functional MRI scans were acquired on a 1.5 Tesla General Electric (Milwaukee, Wis) Signa scanner with an Advanced NMR (Wilmington, Mass) system for echo-planar imaging (EPI) and a quadrature head coil. A T1-weighted sagittal localizer image was used to identify the position of the head and to prescribe the subsequent slice locations (repetition time [TR], 400 milliseconds; echo time [TE], 25 milliseconds; 15 slices; thickness, 5 mm; spacing, 2.5 mm; field of view [FOV], 200 mm; matrix, 256 × 256 pixels). T1-weighted structural images were acquired in 4-mm contiguous coronal slices across the whole brain (TR, 500 milliseconds; TE, 14 milliseconds; matrix, 256 × 256 pixels; FOV, 200 mm) for purposes of localizing the functional activity and aligning images to a reference brain. Functional images (T2*-weighted) were acquired at 12 of these slice locations (approximately A20 to P24 in Talairach[43] coordinates) spanning the amygdala and portions of the posterior orbitofrontal cortex using a gradient EPI sequence (TR, 3000 milliseconds; TE, 40 milliseconds; flip angle, 90° matrix, 64 × 64 pixels; FOV, 200 mm; slice thickness, 4 mm contiguous). Each participant completed 3 runs of 100 images totaling 300 images per slice. Each subject's images were motion corrected and aligned to the corresponding structural data set using AIR software.[44] All subjects had less than 0.5 voxels of in-plane motion. An additional 6 children (4 healthy, 2 anxious) were tested but excluded from the analysis because of excessive movement (>0.5 voxels). Individual structural and functional images were cross-registered with a representative subject's brain, smoothed (8-mm full width at half-maximum kernel), and pooled across subjects to improve the signal-to-noise ratio. Resulting group data were transformed into Talairach space for comparison with previous functional imaging studies.

STATISTICAL ANALYSES

Voxelwise diagnosis × condition analyses of variance (ANOVAs) were conducted on pooled functional MRI data for all voxels in the acquired slices using normalized signal intensity as the dependent variable. Statistical maps of F ratios for each voxel were calculated using a cluster-size algorithm[45] that takes into account the spatial extent of activation to correct for multiple comparisons. Significant activations were defined by at least 3 contiguous voxels (120 mm^3) and $\alpha = .05$. Separate analyses were conducted comparing anxious and healthy children (n = 12 per group) and anxious, healthy, and depressed girls (n = 5 per group) across pairs of conditions (fearful vs neutral faces, fearful faces vs fixation, and neutral faces vs fixation). Post-hoc Tukey Honestly Significant Difference tests were used to identify significant mean differences among groups and within interaction effects. Amygdala activation was confirmed on a reference brain using standard atlases[43,46] and consensus among 3 raters (B.J.C., K.M.T., and P.J.W.). Significant activations extending outside the brain or with large standard deviations were excluded. Discussion was limited to significant activation in mesotemporal brain regions given the implication of these structures in previous neuroimaging studies of facial expressions of emotion.[10,11]

Following the identification of significant regions of activity showing a diagnosis × condition interaction, correlation analyses were performed relating the percent change in magnetic resonance signal intensity in those regions to behavioral SCARED scores. Separate correlations were conducted for the larger sample of anxious and healthy children and for the smaller sample of depressed, anxious, and healthy girls. Scores from the SCARED were not available for some of the healthy and anxious children. The reported correlations reflect an analysis for the subset of children with behavioral data.

tern of amygdala activity appears to differ between adults and children.

RESULTS

ANXIOUS VS HEALTHY CHILDREN

The 2 × 2 (diagnosis × condition) ANOVAs comparing anxious and healthy children showed a main effect of condition for the comparisons of fearful faces and fixation and of neutral faces and fixation, as well as a significant interaction between groups for fearful compared with neutral faces. Both anxious and healthy children showed bilateral increases in the blood oxygen level–dependent (BOLD) signal in the amygdala for fearful faces compared with fixation. The maximum activation in the right amygdala was centered at $x = 18$, $y = -8$, $z = -20$ (maximum F = 9.56; 29 voxels); that in the left amygdala was centered at $x = -14$, $y = -8$, $z = -11$ (maximum F = 10.27; 9 voxels). A similar signal increase was observed in the left amygdala for neutral faces compared with fixation ($x = -18$, $y = -4$, $z = -19$; maximum F = 5.86; 9 voxels). However, anxious children differed from healthy children when fearful expressions were compared with neutral expressions. **Figure 2**A shows the significant region of activity in the right amygdala for this diagnosis × condition interaction ($x = 11$, $y = -7$, $z = -14$; maximum F = 8.10; 8 voxels). Post hoc *t* tests indicate that anxious children demonstrated larger responses in the right amygdala for fearful faces than for neutral faces, whereas healthy children did not (Figure 2B). In addition, the magnitude of this signal change (fearful vs neutral) was positively correlated with child self-reported anxiety symptoms as measured by the SCARED ($r_{17} = 0.62$; $P = .004$) (Figure 2C). This correlation remained significant even when potential outliers were removed ($r_{16} = 0.56$; $P = .02$; $r_{15} = 0.55$; $P = .02$).

DEPRESSED VS ANXIOUS VS HEALTHY CHILDREN

The 3×2 (diagnosis × condition) ANOVAs among the depressed, anxious, and healthy girls showed significant interactions for fearful faces compared with neutral faces and for fearful faces compared with fixation. Anxious children showed more activity in the right amygdala for fearful faces than for neutral faces (**Figure 3**A). In contrast, depressed children did not exhibit significant differences in the BOLD response to fearful and neutral faces in the right amygdala. Child self-reported anxiety symptoms as measured by the SCARED were positively correlated with the signal difference between fearful and neutral facial expressions (r_9=0.79; P<.001) (Figure 3B). Depressed children showed a reduction in the BOLD signal in the left amygdala for fearful expressions vs fixation, whereas anxious and healthy children did not (x=−13, y=−4, z=−16; maximum F=5.07; 6 voxels) (Figure 3C-D).

COMMENT

Our findings suggest functional differences in the amygdala for children with anxiety and depressive disorders relative to healthy children. To our knowledge, this study is among the first to relate clinical symptoms to the neurophysiological response to social stimuli, as evidenced by the correlation between severity of everyday anxiety and BOLD signal change. Furthermore, this study exemplifies the ability to assess functional brain responses to emotional stimuli at the onset of a childhood disorder rather than in adulthood after the disorder has progressed and/or been treated.

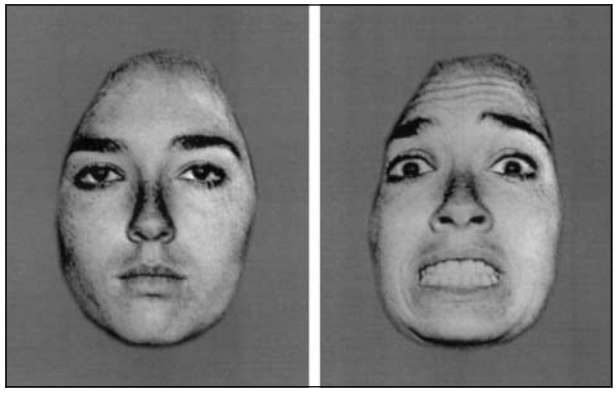

Figure 1. Examples of neutral and fearful expressions used in the passive-viewing task.[41]

Abnormalities in the response of the right amygdala to fear stimuli in anxious children are consistent with previous anatomical and functional studies of children and adults. A morphometric MRI study of childhood anxiety that included some of the same children tested in our functional study reported a significantly larger volume of the right amygdala in children and adolescents with generalized anxiety compared with healthy children,[30] suggesting the possibility of a relationship between structure and function. Our results complement findings of an exaggerated amygdala response to fearful faces in adults with PTSD,[21] as well as PET studies suggesting that adults with high trait anxiety scores show greater right vs left cerebral metabolism than adults with low trait anxiety.[47] The correlation between amygdala responsiveness and severity of everyday anxiety in the current study was robust even with a sample size of 5 subjects per group, arguing that the differential amygdala response in anxious children is likely related to chronic or persistent anxiety symptoms rather than anxiety specific to the scanning environment. The hyperreactivity of the amygdala appears to be a characteristic of anxiety disorders and may reflect a trait rather than a state effect.

In contrast to the anxious children, girls with MDD demonstrated a decreased response in the left amygdala to all facial stimuli regardless of the emotional content, perhaps reflecting a general blunted response to social stimuli or emotional probes. Alternatively, given previous reports of elevated resting blood flow in the left amygdala in depressed adults,[23] our findings may reflect primarily increased baseline activation or be specific to the emotional categories used in this study (fearful and neutral expressions). Additional research with larger sample

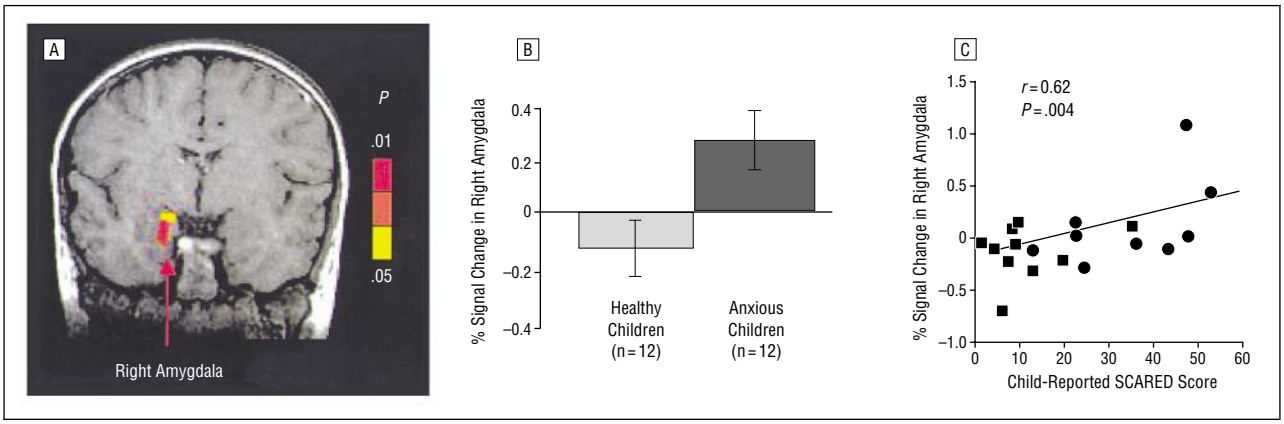

Figure 2. A, Significant region of the right amygdala (x=11, y=−7, z=−14) observed in the diagnosis (anxious vs healthy children) × condition (fearful vs neutral faces) interaction. B, Percent change in normalized magnetic resonance signal intensity in the right amygdala for the comparison between fearful and neutral faces for anxious and healthy children. Bars reflect the SEM. C, Correlation between the percent change in normalized magnetic resonance signal intensity in the right amygdala and the child-reported score from the Screen for Child Anxiety Related Emotional Disorders (SCARED). Squares reflect healthy children (n=9); circles reflect children with generalized anxiety and/or panic disorder (n=10).

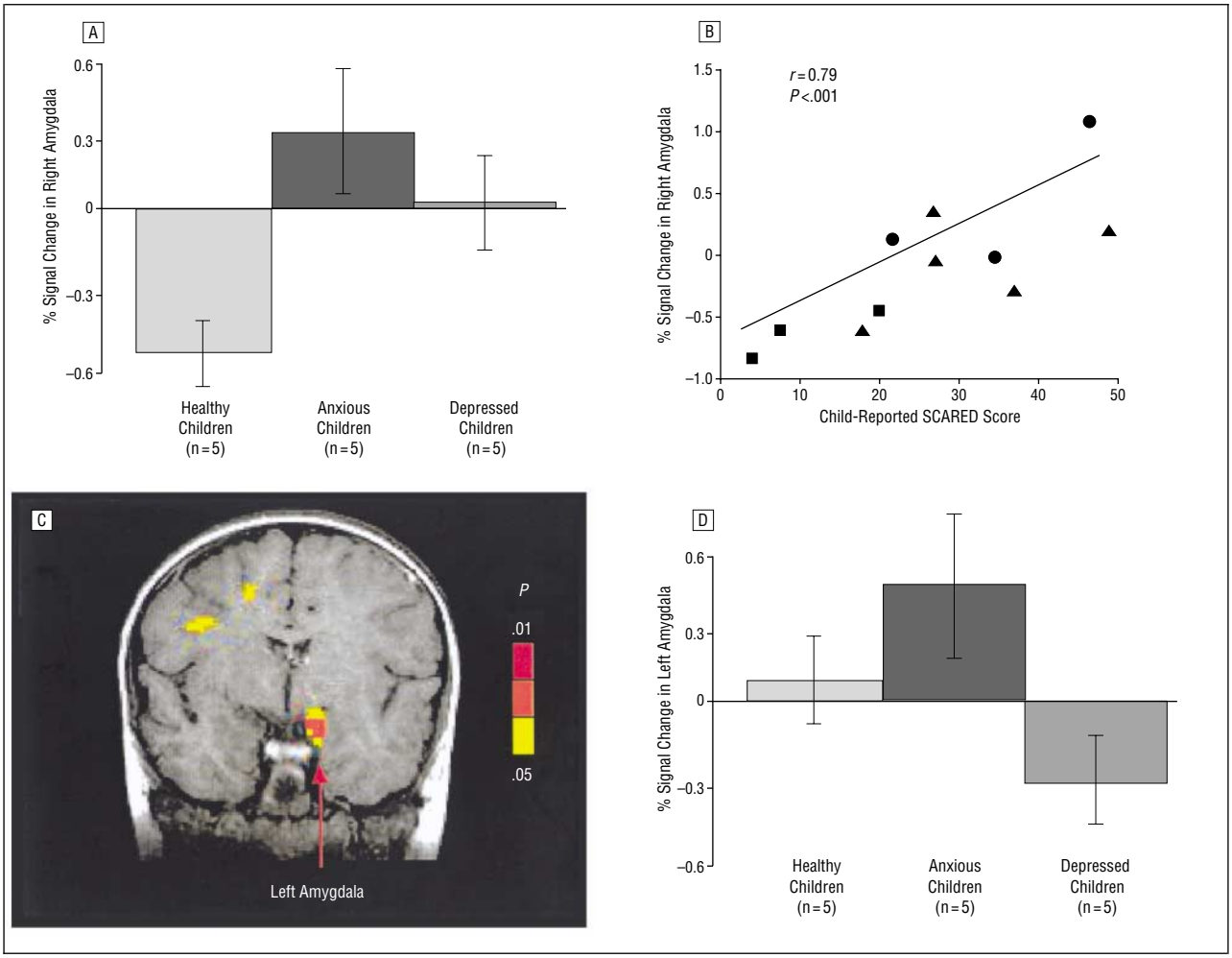

Figure 3. A, Percent change in normalized magnetic resonance signal intensity in the right amygdala for the diagnosis (anxious vs depressed vs healthy children) × condition (fearful vs neutral faces) interaction. B, Correlation between the child-reported score from the Screen for Child Anxiety Related Emotional Disorders (SCARED) and the normalized magnetic resonance signal change in the right amygdala for the comparison between fearful and neutral faces. Squares reflect healthy children (n=3), circles reflect anxious children (n=3), and triangles reflect depressed children (n=5). C, Diagnosis × condition interaction in the left amygdala ($x=-13$, $y=-4$, $z=-16$) for the comparison between fearful faces and fixation. D, Percent change in normalized magnetic resonance signal intensity in the left amygdala for fearful faces vs fixation by diagnosis (healthy vs anxious vs depressed children). Bars reflect the SEM.

sizes and multiple emotional categories will be required to address the generalizability of this response. However, our results are generally consistent with those of recent reports suggesting decreased volume and histopathological changes in the amygdala, predominantly on the left side, in imaging and postmortem studies of adult MDD.[48,49]

There is evidence to suggest that relative laterality differences in the amygdala response to facial expressions in healthy adults may reflect top-down vs bottom-up processing of the emotional stimuli. Studies of rapidly presented masked facial expressions have typically shown greater right than left activation to fearful faces, whereas longer stimulus presentations generally result in greater activity of the left amygdala.[6,10] The exaggerated right amygdala response observed in anxious children may reflect increased automatic or unconscious processing of the fear stimuli, as suggested for adult subjects.[21] However, this hypothesis is clearly speculative; the current stimuli were consciously perceived, and the paradigm was not designed to compare conscious and unconscious processing. Alternatively, laterality differences in cortical activity have been hypothesized to reflect activation of approach and withdrawal-related networks, respectively.[50,51] Studies of electroencephalogram (EEG) asymmetry in the frontal cortex suggest that depressed adults demonstrate a decrease in left frontal activity that maps onto a behavioral decrease in approach behaviors. In contrast, individuals with anxiety or with a socially inhibited temperament tend to show increased right compared with left frontal baseline EEG activity, perhaps indicating greater activation of a withdrawal or avoidance network.[51,52] Our results suggest that the amygdala may respond in a parallel manner. Depressed girls showed a decrease in activity of the left amygdala for faces compared with fixation, which could be interpreted as decreased activity in an approach network. Similarly, anxious children exhibited an increase in activity of the right amygdala for fearful faces, perhaps reflecting increased activity in a withdrawal or avoidance network. With either hypothesis, such laterality findings should be viewed with caution because they are not always replicated.

LIMITATIONS

Our data do not address the etiology of the observed group differences. It is unclear whether an abnormal amygdala response reflects a neurobiological vulnerability to childhood emotional disorders, or whether the presence of these disorders leads to the development of an abnormal amygdala response. Imaging studies of the amygdala response before and after effective treatment for anxiety or depression may help address whether the size and function of this structure become more similar to the pattern in healthy children when the symptoms are no longer present. Future studies will need to address several limitations in this work. In particular, the specificity of the differential amygdala responses must be addressed by including positive stimuli in addition to other types of negative emotional stimuli, and by comparing more homogeneous diagnostic groups with larger sample sizes and equal sex representation. Similarly, the lack of online behavioral data regarding recognition and evaluation of both the portrayed emotions as well as any emotion elicited in the child make cognitive interpretations speculative. In future work, such behavioral data may be useful in determining whether the exaggerated response observed in anxious children correlates with a form of top-down processing of the emotion or reflects a fairly automatic response.

CONCLUSIONS

Our results suggest that amygdala function is affected in both anxiety and depression during childhood and adolescence. Children with anxiety disorders showed an exaggerated amygdala response to fearful faces compared with healthy children, whereas depressed children demonstrated a blunted amygdala response to faces. This disruption appears to be specific to the child's own rating of everyday anxiety.

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