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Amygdala activation in response to facial expressions in pediatric obsessive-compulsive disorder

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Abstract

Background—Exaggerated amygdala activation to threatening faces has been detected in adults and children with anxiety disorders, compared to healthy comparison subjects. However, the profile of amygdala activation in response to facial expressions in obsessive-compulsive disorder (OCD) may be a distinguishing feature; a prior study found that compared with healthy adults, adults with OCD exhibited less amygdala activation to emotional and neutral faces, relative to fixation (Cannistraro et al., 2004).

Methods—In the current event-related functional magnetic resonance imaging (fMRI) study, a pediatric OCD sample (N=12) and a healthy comparison sample (HC, N=17) performed a gender discrimination task while viewing emotional faces (happy, fear, disgust) and neutral faces.

Results—Compared to the HC group, the OCD group showed less amygdala/hippocampus activation in all emotion and neutral conditions relative to fixation.

Conclusions—Like previous reports in adult OCD, pediatric OCD may have a distinct neural profile from other anxiety disorders, with respect to amygdala activation in response to emotional stimuli that are not disorder-specific.

Keywords

OCD; fMRI; neuroimaging; anxiety disorder; fear; disgust

INTRODUCTION

Models of anxiety disorders, both in adults and children, hypothesize amygdala hyperresponsivity to threat-related stimuli [1,2]. Exaggerated amygdala activation has been observed during symptom provocation using disorder-specific stimuli across a broad array of anxiety disorder populations [3–6], including obsessive-compulsive disorder (OCD) [7,8]. However, the exaggerated amygdala activation seen in anxiety disorders is not limited to

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disorder-specific stimuli. Exaggerated amygdala activation in response to emotional facial expressions has been shown for a subset of adult and childhood anxiety disorders [9–16].

Not all anxiety disorders show exaggerated amygdala activation to both disorder-specific and general emotional stimuli. Activation profiles to these types of stimuli may aid in differentiating among anxiety disorders. Prior studies of adults with specific animal phobia, compared with healthy adults, suggest exaggerated amygdala activation to spiders and snakes [3,5] and an absence of such exaggerated amygdala activation to emotional faces [17]. Although exaggerated amygdala activation has been shown in response to OCD-specific stimuli (e.g., disgusting toilet water) in some studies of adults with OCD [7,8,18], less amygdala activation in response to happy, neutral, and fearful faces has been found in adult OCD subjects, compared to healthy subjects [19], which contrasts with other anxiety disorders showing greater amygdala activation to such stimuli. The current study extends these findings to children by testing the hypothesis that less amygdalar activation in response to facial expressions also characterizes pediatric OCD.

METHODS AND MATERIALS

2. 1. Participants

Individuals were recruited via local outpatient OCD clinics and community advertisements as paid volunteers. All participants were between 10 and 17 years old, English speaking, and had normal or corrected-to-normal vision. Participants denied current or past history of head injury, learning disability, medical illness, or substance abuse/dependence. Prior to enrollment and after the procedures were explained, written informed consent was obtained from a parent/legal guardian and written informed assent was obtained from the child/adolescent participant. All study procedures were performed in accordance with the Human Research Committees at McLean Hospital and Partners Healthcare System.

The Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-PL) was administered to all participants [20]. Individuals included in the OCD group met DSM-IV criteria for this disorder [21]. For feasibility and ethical reasons, entry criteria for the OCD group allowed for the presence of comorbid disorders as well as the use of specified psychotropic medications (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, mood stabilizers). Neuroleptic (e.g., traditional and atypical anti-psychotics) and anti-hypertensive medications were exclusionary. All individuals included in the healthy comparison (HC) group were free from any current Axis I psychiatric disorder and from psychotropic medications. For all participants, symptom severity scores were measured using Child Yale-Brown Obsessive Compulsive Scale (CY-BOCS), Child Depression Inventory (CDI), Spielberger State-Trait Inventory – Child Version (STAIC), the Yale Global Tic Severity Scale (YGTSS) [22–26] and a modified version of the Disgust Sensitivity Scale, eliminating items not suitable for children and adolescents (7, 14, 21, 24, and 27) [27].

The final study sample included 12 individuals with OCD and 17 HC subjects, matched for age, gender and handedness. This final sample was obtained after data from individuals were excluded for excessive head movement (3 OCD, 4 HC), technical problems (4OCD, 1 HC), and poor behavioral responding during post-scan tasks (1 OCD, 1 HC). Group characteristics are outlined in Table 1.

Of note, each participant completed a set-shifting paradigm [28] and a visuospatial priming task [29,30] before this faces task was completed. Results from those fMRI paradigms will be reported separately elsewhere.

2.2. Gender discrimination task

In an event-related fMRI design, participants viewed facial expressions. Participants were instructed to indicate the gender of the face by pressing one of two buttons. The left index finger button was pressed if the face was identified as male and the right index finger button was pressed if the face was identified as female.

2.3. Stimuli

Facial expressions were selected from a stimulus set obtained from Ruben Gur at the University of Pennsylvania [31]. Sixty-four identities each displaying happy, disgusted, fearful and neutral facial expressions were presented. An equal number of male and female individual identities were selected and the identities reflected the minority population distribution within the regional area. These color images were standardized using Photoshop CS2 and placed on a black background. Face stimuli were presented for 1950 milliseconds (ms), with a 50 ms inter-stimulus interval of low-level fixation.

Four functional runs of this faces task were completed in the scanner. Each run lasted 3 minutes and 16 seconds. All 64 individual identities were presented within each run. The different expressions of each identity were distributed evenly across the runs, so that each run had an equal number of happy, disgusted, fearful and neutral facial expressions.

The trial order was determined using an optimization tool for event-related fMRI designs [32], which introduces “jitter” by interspersing 1–5 consecutive fixation trials within each run to maximize the ability to deconvolve the ‘blood oxygenation level dependent’ (BOLD) signal according to trial type. In this task, 32 fixation trials were included in each run. To avoid establishment of response patterns, the identities were distributed such that the same gender would not occur for more than three successive instances.

2.4. Apparatus

Stimuli were centered on a black background via standardized software (E-Prime, Inc, 1.1) and displayed on a rear-projection screen. Responses were collected via a Fiber Optic Response (FORP) straight button-box device (Current Designs, Philadelphia, PA) and recorded via E-prime.

Magnetic resonance images were collected with a Siemens Trio 3.0T syngo MR 2004A whole-body high-speed imaging device equipped for echo planar imaging (EPI) (Siemens Medical Systems, Iselin NJ) and an 8-channel gradient head coil.

2.5. Functional MRI Data Acquisition

An automated scout image was acquired and localized shimming procedures were performed to optimize field homogeneity. A high resolution 3D MPRAGE sequence (TR/TE/flip angle=2530 ms/3.39 ms/7^{o}, 1.3×1.0 mm in-plane resolution, and 1.33 mm slice thickness) was collected for spatial normalization. Prior to each functional scan, 3–5 seconds of acquisition were discarded to allow longitudinal magnetization to reach equilibrium. Functional MRI images were acquired using a gradient echo T2*-weighted sequence (TR/TE/flip angle/FOV=2 s/30 ms/90^{o}/200 mm, orientation=25 axial slices angled approximating the AC-PC line, slice thickness=5mm with no interslice skip, voxel size=3.125 × 3.125 × 5 mm, interleaved excitation order and anterior-to-posterior phase encoding). Four functional runs were completed, yielding 96 acquisition volumes per run.

2.6. Post-scan ratings

Immediately after scanning, all participants viewed a subset of the faces on a computer outside the scanner. Via button press responses, subjects rated the valence (−4 = very negative to +4 = very positive) and reported the emotion displayed on each face using a forced choice task with happy, disgust, fear, and neutral as options.

2.7. Data Analysis

Behavioral—Online (reaction time and accuracy) behavioral data were analyzed using a 2 (group: OCD, HC) × 4 (condition: happy, disgust, fear and neutral) repeated measures ANOVA in SPSS 16.0. Statistical significance was determined using an alpha-level of 0.05. Post-hoc analyses using two-tailed t-tests and multiple comparison correction were performed where indicated.

Neuroimaging—Pre-processing and image analysis was completed in SPM5 [33]. The parameters to motion-correct the functional images to the mean image were calculated using 6-parameter rigid body spatial registration. Any EPI motion-related susceptibility was removed via an unwarping procedure. For each individual, the anatomical MPRAGE image was co-registered to the mean functional image. Segmentation parameters were used to normalize the functional images to the SPM5's MNI T1 2×2×2 template. Finally, the functional images were spatially smoothed with a 6mm full-width-half-maximum (FWHM) Gaussian filter.

A general linear model was created for each individual. The data were modeled using the onsets of happy, fearful, disgust, and neutral as well as fixation trials, convolved with the canonical hemodynamic response function (HRF). Each condition regressor contained scan onset times for correct gender-discrimination trials only. A separate error regressor, across all condition types, was included. Time and dispersion derivatives were included in the model for each condition. A high pass filter with 128 second cut-off was used to eliminate low-frequency drift and AR1 correction was used to remove any temporal autocorrelation. To isolate within-brain voxels, the SPM masking threshold was reduced and an explicit mask representing the combined gray and white matter volume was included. A series of estimated betas, one for each regressor, was generated to minimize the error term within the model. Contrasts were generated by comparing the beta weights associated with BOLD activations in response to each emotion and neutral face relative to baseline (e.g., happy>fixation) and relative to neutral (e.g., happy>neutral) across all runs.

A whole-brain, voxel-wise analysis was conducted using random-effects analysis. Contrast images from each individual were entered into a 2^{nd}-level model. Two-sample t-tests were conducted to determine significant group x condition interaction effects for each emotion. Statistical significance was based on both a peak threshold and as a means to correct for multiple comparisons at $p<0.05$ level, a spatial extent threshold. The spatial extent threshold within anatomically-defined ROIs was determined using Analysis for Functional Neuroimages (AFNI)'s AlphaSim program based on alpha=0.05, 1000 Monte Carlo simulations and smoothness of 10 mm [34]. At a $p<0.005$ peak threshold, a 7-voxel cluster size in the amygdala was needed. Regions implicated in the processing of emotion, facial expressions and disgust (e.g., anterior cingulate, prefrontal cortex, insula cortex) [35–38] were also examined using a $p<0.001$ peak threshold and a 12-voxel cluster size. For completeness, significant activations in additional regions using a $p<0.05$ family-wise error (FWE) corrected threshold were noted. Brain regions were identified by visual inspection and cross-referenced with a Talairach atlas [39]. MNI coordinates are reported throughout the Results sections.

To further investigate the group differences and determine whether the activation patterns were correlated with symptom severity or age, one-sample t-tests and ANCOVAs models in each group were examined in regions showing group difference using whole-brain analysis with similar thresholds as described above.

RESULTS

Behavioral

The accuracy rates for determining gender of the happy faces (OCD: 90.4%±7.2, HC: 92.9% ±4.7), disgusted faces (OCD: 89.7%±6.8, HC: 91.5%±6.2), fearful faces (OCD: 89.5%±6.4, HC: 91.8%±5.8), and neutral faces (OCD: 90.4%±4.8, HC: 92.9%±3.9) were not significantly different between OCD and HC groups [$p>0.4$]. No group or group x condition effects were noted [$p>0.2$].

The post-scan ratings indicated that the faces were appropriately valenced. The happy faces were rated more positively (OCD: 1.3±1.5, HC: 1.9±0.8) than the neutral faces (OCD: −0.3±0.4, HC: 0.1±0.8). The disgusted faces (OCD: −1.7±0.8, HC: −1.1±1.1) and fearful faces (OCD: −1.2±0.6, HC: −0.7±1.0) were rated more negatively than the neutral faces (condition effect: $F(3,81)=69.8$, $p<0.001$). No condition x group interaction was noted [$p>0.9$]; however, the OCD group rated the faces overall more negatively than did the HC group [group effect: $F(1,27)=5.1$, $p<0.03$].

The post-scan ratings of emotion recognition indicated that happy faces (OCD: 97.9%±4.1, HC: 97.8±3.1) were rated with greater accuracy than neutral faces (OCD: 90.1%±9.0, HC: 92.6±9.7) and disgusted faces (OCD: 89.1%±10.0, HC: 83.8.6±12.5). Fearful faces were recognized with the lowest accuracy (OCD: 58.9%±15.6, HC: 67.3±13.2) [condition effect: $F(3,81)=71.9$, $p<0.001$]. The group effect was not significant [$p>0.6$].

FMRI

Amygdala—When comparing the activation to facial expressions versus fixation, the OCD group showed reduced activation at the amygdala/hippocampal border compared to the HC group in all emotion and neutral facial expression conditions (Table 2 and Figure 2). No group differences in amygdala activation relative to neutral facial expressions were found (Table 3).

After accounting for CDI depression scores and age, the group differences in amygdala response to faces relative to fixation remained significant. Of note, across both groups, age positively correlated with amygdala [(20,6, −24), $Z=3.17$, $k=18$] and hippocampus [(−30,−2, −30), $Z=3.06$, $k=24$] activation in response to happy vs. fixation.

The amygdala activation did not correlate with CY-BOCS, state anxiety scores or disgust sensitivity scores in either group.

Cortical regions—Group differences were detected in cortical regions in response to emotional conditions relative to neutral facial expressions (Table 3).

No significant group differences in cortical regions in response to faces relative to fixation or in the insula cortex activation in any contrast were found. No additional regions were significant using a $p<0.05$ FWE corrected threshold.

DISCUSSION

This study is the first to examine the neural response to general emotional stimuli in a pediatric OCD sample. In this study, less amygdala/hippocampus activation to facial expressions relative to fixation was found in a pediatric sample with OCD compared to healthy comparison subjects, replicating previous work in adult OCD [19]. Due to the spatial resolution of fMRI, it is difficult to pinpoint the exact location of the group difference found at the border of the amygdala and hippocampus; however, based on the previous literature in adult OCD as well as studies of emotional face processing, this group difference likely emanates from the amygdala.

As in the previous study in adult OCD, the pediatric OCD group exhibited less amygdala activation to multiple facial expressions compared to the HC group. The amygdala activation is less in response to positive (i.e., happy), negative (i.e., fearful) and neutral facial expressions. In addition, this study provides evidence that the less amygdala activation in OCD patients extends to other negative emotions, i.e., disgust. In the literature, the amygdala has been shown to respond to all of these different types of emotion [40–43] and given the lack of specificity in a previous study [19], identifying less amygdala activation to multiple emotions is not surprising. While OCD may be similar to other anxiety disorders with respect to greater amygdala activation during symptom provocation [7], the finding of less amygdala activation to facial expressions, general emotional stimuli, may distinguish OCD from other anxiety disorders.

Although speculative, the hyperactivity of the frontal cortical regions found in OCD may dampen the amygdala activation to disorder-irrelevant stimuli, such as facial expressions. The increased cortical activity may, in turn, suppress the subcortical and autonomic systems [10,44,45]. Although no differences in frontal cortical activation in response to emotional faces relative to fixation were noted in this study, resting state studies have consistently reported enhanced activity in orbitofrontal-striatal regions in OCD [46,47]. The tonic hyperactivity of the orbitofrontal regions in OCD may have prevented the detection of phasic changes in the amygdala and/or frontal cortical regions to general emotional stimuli in this study. This finding is consistent with the demonstrated blunted peripheral autonomic response to general stressors not relevant to OCD symptoms. Compared to HC subjects and other anxiety disorder groups, patients with OCD had lower levels of physiological responding to non-disorder related stressors (i.e., decreased physiological flexibility) [48]. On the other hand, disorder-specific stimuli or increased disorder-related anxiety may elicit amygdala activation and hyperarousal symptoms in adult OCD [7,8], like other anxiety disorders. It is unclear whether the different pattern of amygdala activation in response to symptom provocation versus general emotional stimuli applies to both adult and pediatric OCD. Only one published study has examined symptom provocation in pediatric OCD [49]. In that study, reduced activation in the cortico-striatal-thalamic circuit as well as the insula was detected in the pediatric OCD group relative to healthy controls; however, no group differences were noted in the amygdala. Future studies will need to determine the pattern of amygdala activation to disorder-specific and general emotional stimuli.

Less amygdala activation in pediatric OCD in response to facial expressions could potentially be explained by group differences in amygdala structure. Previous literature has shown both decreased [50,51] and increased amygdala volumes in OCD [52]. To address this potential issue regarding amygdala structure, two separate structural analyses, including intracranial volume as a covariate, were completed to investigate any structural differences in the amygdala. A voxel based-morphometry (VBM) analysis assessed grey matter density in a whole-brain analysis and an automated segmentation method assessed anatomically-

defined amygdala and hippocampus volumes [53]. No group differences in amygdala or hippocampus structure were noted using either method.

No between-group behavioral differences were observed that would help explain the group differences in regional brain activation. The on-line performance of gender discrimination was similar in OCD subjects and comparison subjects and regressors coding accurate trials were used in the analysis. However, the OCD group did rate the faces more negatively after the fMRI session. Lower amygdala activation in the face of increased ratings of negative emotion is contrary to what might be expected. Amygdala activation has been shown to be modulated by arousal [54] and is greater with higher emotional intensity in anxious individuals [55]. Therefore, one might have hypothesized greater amygdala activation with greater negative ratings rather than less activation.

The current finding in a pediatric sample extends prior work in adult OCD, despite methodological differences. In the adult study, individuals passively viewed facial expressions in a block design [19]. In the current study in youth, individuals completed a gender discrimination task in an event-related design. Previous studies have used block designs to illustrate exaggerated amygdala activation to facial expressions [9–12,56]. The amygdala response to repeatedly presenting faces in a blocked fashion is subject to unfavorable habituation effects [57,58]. Habituation effects are reduced by using an event-related design. With respect to the differences in task, it is well-known that amygdala activity is modulated by task demands. In healthy subjects, cognitive tasks (e.g., rating and reappraising) tend to increase mPFC activation and consequently reduce amygdala activation [44,59], and threat appraisal tasks tend to be associated with increased amygdala activation [60]. In most anxiety disorders, the exaggerated amygdala activation to facial expressions is task-independent. For example, exaggerated amygdala activation has been noted in anxiety disorders using passive viewing [9,10,56], using emotion appraisal tasks such as emotional labeling [11], and using incidental processing tasks such as gender discrimination [12,13].

Several limitations of this study should be noted. First, the sample size of our pediatric OCD group is modest, though comparable to that of other pediatric functional neuroimaging studies. Despite the small sample size, significant group differences in amygdala activation were detected. Future studies examining emotional activation patterns in pediatric populations with increased numbers are needed. Second, our OCD sample had higher depression symptoms compared with the healthy controls. To address this in the current study, when CDI depression scores were included as a covariate of non-interest, the group differences in amygdala/hippocampus remained significant. Additional analyses were also conducted by excluding individuals with a comorbid diagnosis of MDD or Depression NOS and the study results were not altered. Finally, our pediatric OCD sample consisted mostly of medicated individuals. Treatment effects on amygdala activation have been previously reported in adults with depression. Following anti-depressant treatment in depressed adults, exaggerated amygdala activation to emotional faces was reduced [61,62] and the coupling between frontal cortical regions and the amygdala during incidental face processing was increased [63]. Rather than changes in amygdala activation [64], anti-depressant treatment effects reported in adult OCD show reduced frontal hyperactivity [65,66]. It is unclear what the effects of anti-depressant medication are in pediatric OCD. Although we cannot exclude the possibility that medication may contribute to our findings, the adult OCD subjects in a previous study that demonstrated a comparable amygdala activation pattern to emotional faces were medication-free [19]. Future studies should examine medication effects on amygdala function in both adult and pediatric OCD.

Given that the neural pattern in response to emotional faces observed in adults with OCD appears to arise at an early age, the lower amygdala activation to emotional faces in pediatric OCD found in this study may precede symptom onset. Several findings suggest that amygdala activation to facial expressions may represent a risk factor for anxiety and depression; however, the results are not straightforward due to variations in the definition of risk and in task demands. In concordant twin pairs at risk for anxiety and depression determined by neuroticism, anxiety, and depression surveys, the high-risk adults showed reduced amygdala activation compared with the low-risk adults when identifying gender on emotional faces [67]. Adolescents with behavioral inhibition, an early-appearing personality temperament and anxiety-disorder risk factor, have shown lower amygdala activation in response to facial expressions during passive viewing and greater amygdala activation during emotion appraisal compared to behaviorally-uninhibited adolescents [68]. In contrast, adolescent offspring of parents with major depression show exaggerated amygdala activation while passively viewing facial expressions [69]. Across all individuals, only amygdala activation to happy faces relative to fixation was positively correlated with age in the current study, which may indicate that this group difference may be the final one to develop. Longitudinal studies of individuals at-risk for developing OCD and cross-sectional studies in unaffected relatives should examine amygdala activation in response to facial expressions to determine if this reduced amygdala activation may predict onset and/or be an endophenotype of OCD.

In summary, the amygdala/hippocampus activation to facial expressions was lower in a pediatric OCD sample when compared to healthy age-matched individuals. This finding replicates previous work in adult OCD [19]. Future studies are required to investigate whether this reduced amygdala activation to facial expressions predicts symptom onset and is present in unaffected relatives of OCD probands.

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References

1. LeDoux. The Emotion Brain. New York: Simon and Schuster; 1996.
2. Rauch SL, Shin LM, Wright CI. Neuroimaging studies of amygdala function in anxiety disorders. Ann N Y Acad Sci. 2003; 985:389–410. [PubMed: 12724173]
3. Dilger S, Straube T, Mentzel HJ, et al. Brain activation to phobia-related pictures in spider phobic humans: an event-related functional magnetic resonance imaging study. Neurosci Lett. 2003; 348(1):29–32. [PubMed: 12893418]
4. Liberzon I, Taylor SF, Amdur R, et al. Brain activation in PTSD in response to trauma- related stimuli. Biol Psychiatry. 1999; 45(7):817–26. [PubMed: 10202568]
5. Straube T, Mentzel HJ, Miltner WH. Neural mechanisms of automatic and direct processing of phobogenic stimuli in specific phobia. Biol Psychiatry. 2006; 59(2):162–70. [PubMed: 16139812]
6. Tillfors M, Furmark T, Marteinsdottir I, et al. Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET study. Am J Psychiatry. 2001; 158(8):1220–6. [PubMed: 11481154]
7. Breiter HC, Rauch SL, Kwong KK, et al. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. Arch Gen Psychiatry. 1996; 53(7):595–606. [PubMed: 8660126]

8. van den Heuvel OA, Veltman DJ, Groenewegen HJ, et al. Amygdala activity in obsessive-compulsive disorder with contamination fear: a study with oxygen-15 water positron emission tomography. Psychiatry Res. 2004; 132(3):225–37. [PubMed: 15664794]
9. Rauch SL, Whalen PJ, Shin LM, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry. 2000; 47(9):769–76. [PubMed: 10812035]
10. Shin LM, Wright CI, Cannistraro PA, et al. 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(3):273–81. [PubMed: 15753240]
11. Phan KL, Fitzgerald DA, Nathan PJ, et al. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. Biol Psychiatry. 2006; 59(5):424–9. [PubMed: 16256956]
12. Stein MB, Goldin PR, Sareen J, et al. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. Arch Gen Psychiatry. 2002; 59(11):1027–34. [PubMed: 12418936]
13. Straube T, Kolassa IT, Glauer M, et al. 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(12):921–30. [PubMed: 15601601]
14. Thomas KM, Drevets WC, Dahl RE, et al. Amygdala response to fearful faces in anxious and depressed children. Arch Gen Psychiatry. 2001; 58(11):1057–63. [PubMed: 11695953]
15. Beesdo K, Lau JY, Guyer AE, et al. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry. 2009; 66(3):275–85. [PubMed: 19255377]
16. McClure EB, Monk CS, Nelson EE, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. Arch Gen Psychiatry. 2007; 64(1):97–106. [PubMed: 17199059]
17. Wright CI, Martis B, McMullin K, et al. Amygdala and insular responses to emotionally valenced human faces in small animal specific phobia. Biol Psychiatry. 2003; 54(10):1067–76. [PubMed: 14625149]
18. Adler CM, McDonough-Ryan P, Sax KW, et al. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. J Psychiatr Res. 2000; 34(4–5):317–24. [PubMed: 11104844]
19. Cannistraro PA, Wright CI, Wedig MM, et al. Amygdala responses to human faces in obsessive-compulsive disorder. Biol Psychiatry. 2004; 56(12):916–20. [PubMed: 15601600]
20. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997; 36(7):980–8. [PubMed: 9204677]
21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders - Fourth Edition. Washington D.C: American Psychiatric Association; 1994.
22. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. II. Validity. Arch Gen Psychiatry. 1989; 46(11):1012–6. [PubMed: 2510699]
23. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989; 46(11):1006–11. [PubMed: 2684084]
24. Kovacs, M. Child Depression Inventory. 1992.
25. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry. 1989; 28(4):566–73. [PubMed: 2768151]
26. Spielberger, CD.; Edwards, CD.; Montuori, J., et al. STAI-C.
27. Olatunji BO, Williams NL, Tolin DF, et al. The Disgust Scale: item analysis, factor structure, and suggestions for refinement. Psychol Assess. 2007; 19(3):281–97. [PubMed: 17845120]
28. Casey BJ, Davidson MC, Hara Y, et al. Early development of subcortical regions involved in non-cued attention switching. Dev Sci. 2004; 7(5):534–42. [PubMed: 15603286]

29. Wright CI, Keuthen NJ, Savage CR, et al. Brain correlates of negative and positive visuospatial priming in adults. Neuroimage. 2006; 30(3):983–91. [PubMed: 16300966]
30. Wright CI, McMullin K, Martis B, et al. Brain correlates of negative visuospatial priming in healthy children. Psychiatry Res. 2005; 139(1):41–52. [PubMed: 15932793]
31. Gur RC, Schroeder L, Turner T, et al. Brain activation during facial emotion processing. Neuroimage. 2002; 16(3 Pt 1):651–62. [PubMed: 12169250]
32. Greeve, D. Freesurfer optseq program.
33. Friston, K. Statistical Parametric Mapping.
34. Ward, BD. AlphaSim. 2000.
35. Phan KL, Wager T, Taylor SF, et al. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage. 2002; 16(2):331–48. [PubMed: 12030820]
36. Schienle A, Schafer A, Stark R, et al. Neural responses of OCD patients towards disorder-relevant, generally disgust-inducing and fear-inducing pictures. Int J Psychophysiol. 2005; 57(1):69–77. [PubMed: 15935263]
37. Shapira NA, Liu Y, He AG, et al. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. Biol Psychiatry. 2003; 54(7):751–6. [PubMed: 14512216]
38. Stein DJ, Arya M, Pietrini P, et al. Neurocircuitry of disgust and anxiety in obsessive-compulsive disorder: a positron emission tomography study. Metab Brain Dis. 2006; 21(2–3):267–77. [PubMed: 16850255]
39. Talairach, J.; Tournoux, P. Co-Planar Stereotactic Atlas of the Human Brain. Thieme; Stuttgart: 1988.
40. Breiter HC, Etcoff NL, Whalen PJ, et al. Response and habituation of the human amygdala during visual processing of facial expression. Neuron. 1996; 17(5):875–87. [PubMed: 8938120]
41. Morris JS, Frith CD, Perrett DI, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature. 1996; 383(6603):812–5. [PubMed: 8893004]
42. Whalen PJ, Shin LM, McInerney SC, et al. A functional MRI study of human amygdala responses to facial expressions of fear versus anger. Emotion. 2001; 1(1):70–83. [PubMed: 12894812]
43. Fitzgerald DA, Angstadt M, Jelsone LM, et al. Beyond threat: amygdala reactivity across multiple expressions of facial affect. Neuroimage. 2006; 30(4):1441–8. [PubMed: 16368249]
44. Ochsner KN, Bunge SA, Gross JJ, et al. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 2002; 14(8):1215–29. [PubMed: 12495527]
45. Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex. 2000; 10(3):206–19. [PubMed: 10731217]
46. Baxter LR Jr, Phelps ME, Mazziotta JC, et al. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and in normal controls. Arch Gen Psychiatry. 1987; 44(3):211–8. [PubMed: 3493749]
47. Swedo SE, Schapiro MB, Grady CL, et al. Cerebral glucose metabolism in childhood- onset obsessive-compulsive disorder. Arch Gen Psychiatry. 1989; 46(6):518–23. [PubMed: 2786402]
48. Hoehn-Saric R, McLeod DR, Hipsley P. Is hyperarousal essential to obsessive-compulsive disorder? Diminished physiologic flexibility, but not hyperarousal, characterizes patients with obsessive-compulsive disorder. Arch Gen Psychiatry. 1995; 52(8):688–93. [PubMed: 7632122]
49. Gilbert AR, Akkal D, Almeida JR, et al. Neural correlates of symptom dimensions in pediatric obsessive-compulsive disorder: a functional magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry. 2009; 48(9):936–44. [PubMed: 19625980]
50. Szeszko PR, Robinson D, Alvir JM, et al. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. Arch Gen Psychiatry. 1999; 56(10):913–9. [PubMed: 10530633]
51. Szeszko PR, MacMillan S, McMeniman M, et al. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. Neuropsychopharmacology. 2004; 29(4):826–32. [PubMed: 14970831]
52. Kwon JS, Shin YW, Kim CW, et al. Similarity and disparity of obsessive-compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus-amygdala complex. J Neurol Neurosurg Psychiatry. 2003; 74(7):962–4. [PubMed: 12810792]

53. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 1999; 9(2):179–94. [PubMed: 9931268]
54. Phan KL, Taylor SF, Welsh RC, et al. Activation of the medial prefrontal cortex and extended amygdala by individual ratings of emotional arousal: a fMRI study. Biol Psychiatry. 2003; 53(3): 211–5. [PubMed: 12559653]
55. Yoon KL, Fitzgerald DA, Angstadt M, et al. Amygdala reactivity to emotional faces at high and low intensity in generalized social phobia: a 4-Tesla functional MRI study. Psychiatry Res. 2007; 154(1):93–8. [PubMed: 17097275]
56. Whalen, PJ.; Pollack, MH.; Shin, LM., et al. Amygdala response to masked faces in panic disorder. 2001. unpublished work
57. Britton JC, Shin LM, Barrett LF, et al. Amygdala and fusiform gyrus temporal dynamics: responses to negative facial expressions. BMC Neurosci. 2008; 9:44. [PubMed: 18474111]
58. Wright CI, Fischer H, Whalen PJ, et al. Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. Neuroreport. 2001; 12(2):379–83. [PubMed: 11209954]
59. Taylor SF, Phan KL, Decker LR, et al. Subjective rating of emotionally salient stimuli modulates neural activity. Neuroimage. 2003; 18(3):650–9. [PubMed: 12667842]
60. Habel U, Windischberger C, Derntl B, et al. Amygdala activation and facial expressions: explicit emotion discrimination versus implicit emotion processing. Neuropsychologia. 2007; 45(10): 2369–77. [PubMed: 17408704]
61. Fu CH, Williams SC, Cleare AJ, et al. 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(9):877–89. [PubMed: 15351766]
62. Sheline YI, Barch DM, Donnelly JM, et al. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry. 2001; 50(9):651–8. [PubMed: 11704071]
63. Chen CH, Suckling J, Ooi C, et al. Functional coupling of the amygdala in depressed patients treated with antidepressant medication. Neuropsychopharmacology. 2008; 33(8):1909–18. [PubMed: 17987064]
64. Saxena S, Brody AL, Ho ML, et al. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. Am J Psychiatry. 2003; 160(3):522–32. [PubMed: 12611834]
65. Swedo SE, Pietrini P, Leonard HL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. Arch Gen Psychiatry. 1992; 49(9):690–4. [PubMed: 1514873]
66. Baxter LR Jr, Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry. 1992; 49(9): 681–9. [PubMed: 1514872]
67. Wolfensberger SP, Veltman DJ, Hoogendijk WJ, et al. Amygdala responses to emotional faces in twins discordant or concordant for the risk for anxiety and depression. Neuroimage. 2008; 41(2): 544–52. [PubMed: 18396414]
68. Perez-Edgar K, Roberson-Nay R, Hardin MG, et al. Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. Neuroimage. 2007; 35(4):1538–46. [PubMed: 17376704]
69. Monk CS, Klein RG, Telzer EH, et al. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. Am J Psychiatry. 2008; 165(1):90–8. [PubMed: 17986682]
70. Leckman JF, Grice DE, Boardman J, et al. Symptoms of obsessive-compulsive disorder. Am J Psychiatry. 1997; 154(7):911–7. [PubMed: 9210740]
71. Stewart SE, Rosario MC, Baer L, et al. Four-factor structure of obsessive-compulsive disorder symptoms in children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2008; 47(7): 763–72. [PubMed: 18520961]

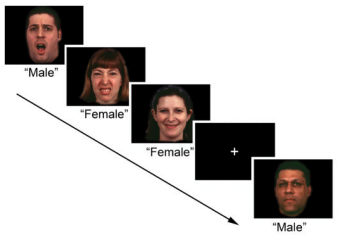

Figure 1. Gender Discrimination Task

Fearful, disgusted, happy, and neutral faces were displayed randomly. Subjects were required to identify the gender of the face by button-press (1=male, 2=female).

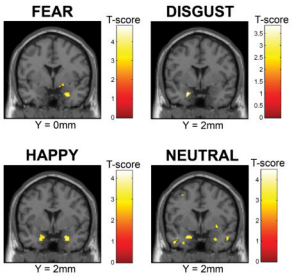

Figure 2. Less amygdala/hippocampus activation in response to emotional and neutral faces in OCD compared to healthy controls

The amygdala/hippocampus activation in response to emotional faces vs. fixation conditions [(−24, 2, −26), Z=3.22, k=47; (24, 2, −26), Z=3.48, k=85] was lower in the OCD group compared to the healthy comparison group (Not shown). Group differences (Healthy comparison>OCD) were detected in response to all emotions (fear: [(28, 0, −28), Z=3.61, k=131], disgust: [(−22, 2, −24), Z=3.25, k=24], happy: [(−20, −12, −20), Z=3.27, k=112; (26, 4, −28, Z=3.28, k=66]) and neutral [(−22, 2, −24), Z=3.39, k=69; (28, 0, −28), Z=3.07, k=19], relative to fixation. Significant group differences within the amygdala/hippocampus are displayed at $p<0.005$. These activations are corrected to $p<0.05$ given the cluster level (>7 voxels). The left amygdala is shown on the left side of the image.

Table 1

Group Characteristics.

Characteristic	OCD	Healthy Comparison
Number	12 (7 males)	17 (11 males)
Age (years)	13.8±2.4	13.2±2.3
Handedness	9R, 3L	15R, 2L
Duration of illness (years)	4.2±2.3	NA
CYBOCS, total	17.8±7.4*	0
CYBOCS, obsessions	8.3±4.6*	0
CYBOCS, compulsions	9.5±3.7*	0
CDI	10.8±7.6*	3.5±3.8
STAIC – trait	36.9±8.7*	28.0±7.0
STAIC – state	31.5±3.1*	27.8±3.1
YGTSS	2.2±5.3	0
Modified DS-R	38.8±16.7	36.4±11.1

Mean and Standard Deviation.

*Significant group difference $p<0.05$. Child Yale Brown Obsessive Compulsive Scale (CYBOCS), Child Depression Inventory (CDI), Spielberger State-Trait Inventory – Child Version (STAIC), Yale Global Tic Severity Scale (YGTSS), and modified Disgust Sensitivity-Revised (DS-R). R=Right, L=Left.

The OCD group endorsed the following current symptoms within previously identified symptom dimensions: (1) aggression, sexual, religious, somatic obsessions/checking compulsions (N=7); (2) symmetry/ordering/repeating (N=7); (3) contamination/washing (N=5), and (4) hoarding (n=2) [70,71]. Of note, several individuals endorsed symptoms of multiple subtypes; therefore, the totals exceed the number of subjects in the OCD sample. In keeping with the expected rates for pediatric OCD, the following comorbid illnesses were present in the OCD group: generalized anxiety disorder (N=2), simple phobia (N=2), agoraphobia (N=1), major depression (N=2)/depression-NOS (N=1), Tourette disorder (N=1) and attention-deficit hyperactivity disorder (N=2). Primary medications taken by OCD subjects included selective serotonin reuptake inhibitors (N=9) and tricyclic anti-depressants (N=3). In addition, several individuals were taking secondary medications: mood stabilizers (N=3), stimulants (N=4), desyrel (N=1), memantine (N=1), atomoxetine (N=1), zolpidem (N=1) and lorazepam (N=1).

Table 2

Activation patterns in response to facial expressions relative to fixation in pediatric OCD subjects and healthy comparison subjects (HC)

	Emotion			Fear			Disgust			Happy			Neutral		
	XYZ	Z	k	XYZ	Z	k	XYZ	Z	k	XYZ	Z	k	XYZ	Z	k
HC>OCD															
Amygdala	−24, 2, −26	3.22	47				−22, 2, −24	3.25	24	−20, −12, −20	3.27	112	−22, 2, −24	3.39	69
	24, 2, −26	3.48	85	28, 0, −28	3.61	131				26, 4, −28	3.28	66	28, 0, −28	3.07	19
HC Activations															
Amygdala													16,−2, −12	2.84	11
Insula				38, 18, −6	3.94	64							42, 18, −4	4.23	114
HC Deactivations															
Insula							−38, 18, 2	3.38	28						
OCD Deactivations															
Amygdala	−26, 0, −28	3.01	11							−24,0,−28	3.13	431	−26, 0, −28	2.80	12
	28,2,−22	2.85	13										30,0,−28	3.64	46

Significant clusters at $p<0.05$ corrected using a cluster level (>7 voxels) for the amygdala and (>12 voxels) for the insula.

MNI coordinates provided. k=cluster values at $p<0.005$ peak threshold for amygdala and $p<0.001$ peak threshold for insula.

Table 3

Activation patterns in response to facial expressions relative to neutral in pediatric OCD subjects and healthy comparison subjects (HC)

	All Emotion			Fear			Disgust			Happy		
	XYZ	Z	k	XYZ	Z	k	XYZ	Z	k	XYZ	Z	k
HC > OCD												
OFC				−16, 10, −16	3.12	31						
OCD>HC												
VLPFC				−32, 30, −6	3.85	30						
DACC										−2, 44, 24	3.38	20
HC Activations												
Amygdala	28,6, −22	3.74	40	28, 6, −24	3.19	23						
	−16,−6, −24	3.12	11									
Insula	−22, 28, −10	4.19	12									
OCD Activations												
Amygdala				−32, 2, −24	3.25	14						
HC Deactivations												
VLPFC	−42, 42, −4	3.64	24	−40, 40, −6	4.47	65				−42, 28, −12	3.58	221

Significant clusters at p<0.05 corrected using a cluster level (>7 voxels) for the amygdala and (>12 voxels) for the orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (VLPFC), dorsal anterior cingulate (dACC), and insula.

MNI coordinates provided. k=cluster values at p<0.005 peak threshold for amygdala and p<0.001 peak threshold for all other regions.