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The Pathology of Social Phobia is Independent of Developmental Changes in Face Processing

Karina S. Blair, PhD[1,*], **Marilla Geraci, MSN**[1], **Katherine Korelitz, BS**[1], **Marcela Otero, BA**[1], **Ken Towbin, MD**[1], **Monique Ernst, MD, PhD**[1], **Ellen Leibenluft, MD**[1], **RJR Blair, PhD**[1], and **Daniel S. Pine, MD**[1]

[1]Mood & Anxiety Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

Abstract

Objective—While social phobia (SP) in adolescence predicts risk for SP in adulthood, no work has directly compared neural responses in SP adults and adolescents. The current study examines neural response to facial expressions in adult and adolescent SP to determine whether the neural correlates of adult SP during face processing also manifest in adolescent SP.

Method—Blood oxygen level-dependent (BOLD) was compared in 39 medication-free individuals with SP (25 adults and 14 adolescents), and 39 healthy comparison individuals (23 adult and 16 adolescent) matched on age, IQ, and gender using functional magnetic resonance imaging (fMRI). During fMRI scans, individuals saw angry, fearful, and neutral expression stimuli while making a gender judgment.

Results—Hypothesized significant diagnosis-by-emotion interactions were observed within the amygdala and rostral anterior cingulate cortex (rACC). In these regions, the adolescent and adult SP patients both showed significantly increased BOLD responses, relative to their respective age-matched comparison groups, with no evidence of age-related modulation of between-group differences. These enhanced responses occurred specifically to angry (rACC) and fearful (amygdala and rACC) but not neutral expressions. In addition, SP severity correlated significantly with this enhanced rACC response in the adults.

Conclusions—The neural correlates of adult SP during face processing also manifest in adolescents. As such, neural correlates observed in adult SP may represent the persistence of profiles established earlier in life, rather than adaptive responses to such earlier perturbations or maturational changes. These cross-sectional observations might encourage longitudinal fMRI studies of adolescent SP.

INTRODUCTION

Adolescent social phobia (SP) predicts adult SP (1, 2). While this might suggest that the neural correlates of SP manifest similarly in adolescents and adults, limited work evaluates this possibility. In particular, no previous imaging study has used identical methods to compare healthy and SP adolescents and adults. It is important to directly compare these groups directly, since the neural correlates of SP can be masked by minor variation in task parameters. Moreover, age-related differences manifest between adolescents and adults in the responsiveness of regions implicated in SP. As a result, neural correlates of adult SP

[*]Correspondence concerning the article should be addressed to Karina S. Blair, Mood & Anxiety Program, National Institute of Mental Health, 15K North Drive, MSC 2670, Bethesda, Maryland 20892; peschark@mail.nih.gov; phone (301) 451-5088 .

could arise from one of two reasonable scenarios. They either could reflect persistence of adolescent perturbations or perturbations that manifest differently in adults than adolescents. A direct comparison of adolescents and adults with and without SP is the first step towards beginning to resolve these two competing scenarios.

The current study evaluates the degree to which adults and adolescents with SP, relative to age-matched comparisons, show similar or dissimilar neural perturbations to morphed expression stimuli. We used facial expression stimuli because they have the advantage that they have been used extensively in studies with healthy individuals and are the most frequently employed stimuli in prior work on SP (3-13). This previous work provides a rich scientific context in which to embed the current study. Facial expression stimuli also engage relatively automatic responses, optimizing their utility in developmental work. More complex stimuli, also used in studies among adults, rely on contextual information to convey emotional cues, which engage less automatic responses (e.g., 14, 15-17). Finally, the use of morphed-face stimuli in such work carries particular advantages, in that the use of subtly varying morphs within an emotion class increases stimulus novelty, a factor previously shown to influence brain response to emotional faces.

The prior work with adult SP finds increased responses across regions involved in facial expression processing in healthy individuals, notably the amygdala, but also anterior cingulate gyrus (ACC), insula, and temporal cortical regions. This increased responsiveness appears emotion-specific, in that it occurs consistently for emotional, and particularly negative-valence, expressions (e.g., 4, 6, 7, 9, 11, 13), but typically not for neutral or positive expressions (e.g., 4, 6, 9, 11) though see (3, 8). Given that perturbed emotion-specific processing has been demonstrated relatively consistently across laboratories in adult SP, we would expect to observe similar emotion-specific findings in adolescent SP if the pathology of the disorder does not vary independently. However, only limited work has examined emotion-specific processing in adolescent SP. Studies have used face-emotion displays in the context of attention-manipulation tasks, and these studies do find increased amygdala responding in various pediatric anxiety disorders (18-20). However, findings in adults suggest that atypical responding in SP can be distinguished from that in other anxiety disorders, which emphasizes the need to examine responding in adolescent SP specifically (11). The only such fMRI study in this particular group (21) focused on psychological processes more relevant to adolescent than adult SP and failed to examine emotion-specific processing. As a result, it remains critical to compare directly neural responding to disorder-specific relevant social stimuli in adolescents and adults with and without SP.

As noted above, given that adult SP typically begins in adolescence, two scenarios could link neural and symptomatic expressions of SP in adolescents and adults. First, similar neural correlates could manifest in adolescents and adults. In this instance, one would expect to find diagnosis-by-emotion interactions in adolescents and adults, with and without SP. Specifically, data in adult SP suggest that adolescents with SP, relative to healthy adolescents, also would show increased responses to the fearful and angry, but not neutral expressions. One might expect these interactions specifically within the amygdala, the region most frequently associated with hyper-responsiveness in adult SP, but also in other regions frequently identified in studies of adults. Second, prior research on face processing indicates differences between adolescents and adults in the response of these same brain regions; see e.g., (22). As a result, findings in adult SP also could reflect either adaptations to perturbations present in adolescence or other maturational changes, yielding different neural correlates of one and the same disorder, as manifest in adolescence and adulthood. In either case, one would expect diagnosis-by-age or diagnosis-by-age-by-emotion interactions, reflecting unique SP correlates in the two age groups. The current study tests these alternative possibilities.

METHODS AND MATERIALS

Subjects

The current study included 78 individuals, comprising 39 patients, including 25 adults and 14 adolescents with current social anxiety disorder, as well as 39 healthy comparisons, including 23 adult and 16 adolescent comparison individuals, group matched with patients in the same age group. This yielded two samples of adult and adolescent patients and comparisons, each of which did not differ in terms of age, gender, or IQ (F range 0.92 to 2.02; ns); see Table 1. In addition, there was no significant gender or IQ difference between the adult (N=48) and adolescent (N=30) cohorts. Among the 48 adults, data from n=32 (15 patients and 17 healthy comparisons) were included in a prior report (11). None of the data from the pediatric group have been reported previously.

Adults

Adults were recruited as described previously (11, 15). Briefly, all patients met criteria for current Generalized Social Phobia according to the DSM-IV (1994) criteria, based on the Structured Clinical interview for DSM-IV Axis I disorders (SCID) (23) and a confirmatory clinical interview by a board-certified psychiatrist (DSP). None had any other Axis 1 diagnosis. All indicated a childhood-onset of symptoms. In addition, all patients were currently medication-free. Comparisons were excluded for any history of mental illness. All subjects were free of any history of substance dependence or current substance abuse, and all provided a negative urine toxicity screen. Severity of social anxiety was assessed with the Liebowitz Social Anxiety Scale. In addition all subjects were in good physical health, as confirmed by a complete physical exam, and provided written informed consent.

Adolescents

Adolescent subjects also were recruited using methods described previously.(24) Briefly, like adult patients, all pediatric patients met criteria for current Generalized Social Phobia, according to DSM-IV. Diagnosis in adolescents is based on the Kiddie-Schedule-for-Affective-Disorders-Present-and-Lifetime version (K-SADS-PL). Pediatric patients were recruited when they sought treatment for social anxiety that persisted during three weeks of supportive therapy. This additional inclusion criterion for adolescents but not adults reflected the fact that some forms of pediatric social anxiety can remit with brief interventions, and we wanted to restrict our samples of adolescents and adults to patients with severe, persistent anxiety. All pediatric patients also demonstrated severe social anxiety on the Pediatric Anxiety Rating Scale (PARS). As with adults, none of the adolescent patients had any other Axis 1 diagnosis and all were medication free. Other inclusion and exclusion criteria are identical to those described previously.

Task

Subjects viewed static grey-scale images of emotionally (fearful, angry) expressive faces in addition to neutral faces from the empirically valid and reliable Pictures of Facial Affect (25). In designing our paradigm, we wanted to maximize statistical power by devoting as much time as possible to precisely estimating neural responses to a relatively select set of stimuli. As such, we felt that we could only present neutral faces, in addition to two classes of emotional stimuli, plus a baseline, while remaining confident that we had maximized power.

We selected fearful expressions because we entered the study with a particular interest in amygdala function and selected the expression most consistently shown to elicit amygdala responses in healthy individuals: fearful expressions (26-28). This expression is of particular interest since few studies of SP have specifically examined responsiveness to this

expression. We selected angry faces because they represent the stimulus class that most consistently has elicited increased responsiveness in SP (4, 6, 7, 13).

Of note, inclusion of happy expressions would allow us to dissociate valence and arousal effects, since both angry and fearful faces are high-arousal negative stimuli, whereas happy expressions are high-arousal positive stimuli. However, prior work is inconsistent regarding amygdala responding to happy faces in healthy individuals (28). Moreover, while two studies found increased amygdala responses to happy expressions in adult SP (6, 13), three others reported normal responding (3, 4, 9). As such, we chose to include angry and fearful but not happy expressions.

A gender judgment task was selected for a few reasons. First, since considerable prior work relies on this task (11, 29-31), its use in the current study allows the current data to be placed within a rich research context. Second, prior work shows that task instructions focusing attention on emotional features influences the neural response to emotional stimuli (see e.g., 29, 31). Gender rating was selected to minimize the possibility of muting between-group differences, through a focusing of attention on non-emotional aspects of stimuli. Finally, gender judgment has the advantage of being easily applicable with a younger subject population due to its limited number of response options, and conceptual simplicity.

For our stimuli set, ten different actors were used, each digitally morphed to represent seven different expressions: 50% fear, 100% fear, 150% fear, 50% anger, 100% anger, 150% anger and 25% happy. Since it is conventional to signal approval in normal social interaction, 100% neutral faces can appear slightly cold and threatening. As a result, the 25% happy face-emotion was used to indicate neutral non-emotional facial displays. This generated 70 stimuli (10 actors by seven expressions). The decision to use morphed faces reflected our desire to increase variability in emotion displays beyond that in tasks relying only on prototypical 100% face-emotion displays. This aims to reduce the habituation associated with repeated viewing of identical face-emotions. In the data analysis, face-viewing events were categorized using weights reflecting these levels of emotion. This model, weighing the variability in emotion displays according to intensity, was chosen on the basis of our previous experience analyzing data from this paradigm; power is maximized by modeling the intensity rather than treating each intensity indicator as a separate regressor.

Each face stimulus was presented for 2500ms with a 500ms inter-stimulus interval. An event-related design whereby all events occurred randomly throughout the task was used. Subjects made the gender judgments by pressing left or right response buttons. Responses were monitored via two means: by computer recording of the motor response and by observation in real time of performance, as indicated by a light display on a monitor in the scanning room. Subjects completed four runs of the task, and each run consisted of 29 3000ms fixation-point trials, 20 neutral-face trials and 10 face-emotion trials of each intensity for anger and fear expressions. This resulted in 80 distinct face stimuli and 109 total trials per run.

fMRI Parameters

Whole-brain blood oxygen level dependent (BOLD) fMRI data were acquired using a 1.5 Tesla Siemens MRI scanner. Following sagital localization, functional T2* weighted images were acquired using an echo-planar single-shot gradient echo pulse sequence with a matrix of 64 × 64mm, repetition time (TR) of 3000ms, echo time (TE) of 30ms, field of view (FOC) of 240mm, and voxels of 3.75×3.75 4mm. Images were acquired in 31 contiguous 4mm axial slices per brain volume. The functional data were acquired over four runs, each lasting 5 minutes 27 seconds. In the same session, a high-resolution T1-weighed anatomical image was acquired to aid with spatial normalization (three-dimensional Spoiled GRASS;

TR=8.1 ms; TE=3.2 ms, flip angle=20°; field of view=240mm, 124 axial slices, thickness=1.0mm; 256×256 acquisition matrix).

fMRI Analysis

Data were analyzed using Analysis of Functional Neuroimages (AFNI) (32). Motion correction was performed, data were spatially smoothed, and time series data were normalized by dividing the signal intensity of a voxel at each time point by the mean signal intensity of that voxel for each run so that regression coefficients represented percent signal change. Regressors for each emotion were created through convolution with gamma-variate haemodynamic response functions for weighted estimates of angry and fearful expressions, reflecting proportions of the emotional prototypes. With this approach, the regressor for each face-emotion type effectively models activation associated with all of the gradations of one or another face-emotion type, generating for each voxel and each regressor, a beta coefficient and its associated t-statistic.

Voxel-wise group analyses involved transforming single subject beta coefficients into standard space (33) and submitted these to a 2(Diagnosis: Social Phobia, Healthy) by 2(Age: Adult, Adolescent) by 3(Emotion: Angry, Fearful, Neutral) mixed ANOVA. This analysis produced statistical maps of the main effects and interactions. One main interest was in testing the diagnosis-by-emotion interaction. The other was in the three-way diagnosis-by-age-by-emotion interaction as well as the two way diagnosis-by-age interaction. These interactions test the degree to which any potential diagnostic-specific responses to faces appear similar or different in the two age groups.

As in our prior work, threshold was set through a two-stage procedure. In the initial stage, group-maps were generated at a two-tailed $p<0.005$ threshold. In the second stage, to correct for multiple comparisons, a spatial-clustering operation was performed using AlphaSim (Ward http://afni.nimh.nih.gov/afni/docpdf/AlphSim.pdf) with 1,000 Monte Carlo simulations, to generate a map-wise false-positive probability of $p<0.05$, corrected for multiple comparisons and subsequent ROI-based data. These data then were used in two sets of analyses. First, to facilitate interpretation of results from our main ANOVA-based analysis, the average percent signal change was measured within each ROI. This generated mean values for each event type in each subject, which could be extracted and submitted to post-hoc group-level statistics performed within SPSS. This clarified the degree to which findings in the ANOVA reflected particularly large or small responses to one or another face-emotion type in one or another subject group. Second, to examine the relationship between symptom severity and neural responses in SP, we examined the correlations between the increased responses to emotional expressions identified by the group-by-emotion interaction and the anxiety ratings reported in Table 1.

RESULTS

Table 1 provides data on the subject characteristics. As shown in the table, subjects were appropriately matched on age, gender, and IQ. Task performance was adequate in the four groups, with low errors. Although the adolescent groups overall committed more errors than the adults ($F=17.55$; $p<0.005$), there was no significant difference in error rates between the two adolescent groups ($F=1.98$; ns) or between the patients with SP (adults + adolescent) and the healthy comparison individuals (adults + adolescent) ($F<1$; ns); Table 1. Of note, due to equipment malfunction, data were not saved for behavioral performance in five adolescents.

No regions survived correction for multiple comparisons from the diagnosis-by-emotion-by-age, diagnosis-by-age, or emotion-by-age interaction statistical maps. As also noted above,

our main interest was in statistical tests of diagnosis-by-emotion interactions. We provide results in Table 2 for regions showing a significant diagnosis-by-emotion interaction and main effects of diagnosis, age group and emotion.

Diagnosis-by-emotion interaction

In line with our predictions, the diagnosis-by-emotion interaction identified the amygdala and rostral ACC (see Table 2 and Figure 1). Within both regions, patients showed greater activation to fearful expressions relative to the healthy comparisons ($F=6.31$ & 10.88 respectively; $p<0.005$). In addition, within rostral ACC they showed greater activation to angry expressions relative to the comparison individuals ($F=4.77$; $p<0.05$). However, importantly, there were no significant group differences in BOLD responses to the neutral stimuli within either the amygdala or the ACC; Figure 1.

Main effects

The group main effect identified one large temporo-occipital area (see Table 2). In this region, the healthy comparison individuals showed a significantly greater BOLD response compared to SP patients ($F=13.31$; $p<0.001$).

Regions identified by the age main effect included inferior and medial frontal gyrus; see Table 2 for full list. In all regions identified by this main effect, adult subjects showed a significantly greater BOLD response compared to the adolescent subjects (F range = 9.63 to 24.52; $p<0.001$ to 0.005). None of these regions interacted with SP status.

Regions identified by the emotion main effect included bilateral amygdala, and inferior, middle and medial frontal regions; Table 2. In all regions identified by this main effect, subjects showed significantly greater BOLD responses to the fearful relative to neutral (F range = 6.31to 31.74; $p<0.05$ to 0.001) and angry relative to neutral (F range = 9.08 to 83.66; $p<0.005$ to 0.001) expressions.

Correlational Analysis

Using correlational analysis, we examined whether the increased neural responses to angry and fearful expressions within the ACC and to fearful expressions within the amygdala shown by the patients with SP related to the level of anxiety reported in Table 1. For the adult patients, there was a positive correlation between the BOLD response to both angry and fearful expressions and symptom severity score within the ACC (Pearson's $r=0.453$ & 0.383; $p<.05$ and $p<0.10$ respectively); see Figure 2. However, the result for neutral expressions was not significant (Pearson's $r = 0.141$; $p=0.500$). In contrast, no significant correlation emerged between the BOLD response to fearful expressions and symptom severity within the amygdala (Pearson's $r=0.247$; $p=0.234$). We observed no significant correlations involving adolescents with SP (Pearson's r range=0.098 to 0.345; p range =0.739 to 0.0.228).

DISCUSSION

The current study compares BOLD responses to fearful, angry, and neutral expressions among adults and adolescents with and without SP. The findings appear clear: relative to their respective age-matched comparison groups, both adolescents and adults with SP showed a significantly increased response to emotional, but not neutral, facial expressions within the amygdala and rostral ACC. Data from some adults examined in the current study had been reported previously, and our primary goal was to extend these data to adolescents. The observation of significant diagnosis-by-emotion interactions but not diagnosis-by-age or diagnosis-by-age-by-emotion interactions suggests that neural perturbations in adult SP, at

least to emotional facial expressions, may represent persistent manifestations of abnormalities present in adolescence, rather than the end result of perturbed development. Longitudinal work should evaluate this possibility more critically.

The results with respect to adult SP are broadly consistent with the previous literature. Thus, while studies have implicated a network of emotion-relevant regions in the increased response to emotional facial expression stimuli in adult patients with SP, the regions most consistently identified in that work include the amygdala and ACC (5, 11, 34), the two regions identified in the current work. With respect to pediatric anxiety disorders, several studies have reported increased amygdala responses (18-20) and one found increased amygdala responses in adolescent SP specifically to peers previously rated as undesirable (21). However, no prior study in adolescent SP had used procedures employed in prior studies among SP adults. Importantly, the current data extend the previous literature by demonstrating comparable neural signatures of SP in adolescents and adults. It is worth considering our finding in light of prior findings on emotion-specific responding in SP. Two studies have reported enhanced amygdala responding to neutral expressions in adult SP, emphasizing the importance of contrasting response to emotional and neutral face-event types (3, 8). However, a further four studies (4, 6, 9, 11), like the current study, did not, suggesting that SP is not associated with heightened responsiveness to face stimuli generally. In contrast, hyper-responsiveness to angry expressions has been found with more consistency (4, 6, 7, 9, 13), though see (11). Finally, only two previous studies of SP (4, 11) used fearful faces, the stimulus class most consistently shown to engage the amygdala of healthy adolescents and adults (28), and these generated inconsistent findings. However, amygdala hyper-responsiveness to fearful stimuli was seen in the current study, both in adults and in *adolescents* with SP. Importantly, more work in both adult and adolescent SP is needed to evaluate the degree to which these findings extend to other emotions, such as high-arousal, positive-valence happy faces.

From a developmental perspective, two important features emerge with the current data. First, there were significant main effects of age within many regions, where main effects of age, rather than age-by-emotion or age-by-group-by-emotion interactions, emerged. This is consistent with prior imaging (22) and behavioral (35) data. Second, regions related to age did not overlap with regions implicated in SP. This suggests that the pathophysiology in SP operates in adolescence in a relatively functional independent manner from developmental aspects of face processing.

We found that the increased neural responses to angry and fearful expressions within the ACC, though not the amygdala, related to the level of symptomatology as indexed by the Liebowitz Social Anxiety Scale (LSAS) in the adult patients with SP. With respect to the adult data, this is consistent with the only previous study to examine the relationship between symptom severity and ACC responsiveness (5). This did not manifest in adolescent SP. This negative finding either could reflect developmental differences in brain-behavior relationships or to differing standards for assessing adult and adolescent anxiety. Whereas the LSAS is the accepted standard symptom severity scale for the adults, for adolescents, the Pediatric Anxiety Rating Scale (PARS) is the clinician-rated scale used in most prior imaging and treatment outcome studies (36-38).

Three caveats should be noted. First, while comparable to other studies involving clinical populations, our sample size for the adolescent groups (N=14 and 16) was relatively small, which could limit power on tests of interactions with age. Thus, it is possible that a larger sample size would reveal developmental changes to facial expression processing in SP not revealed by our current sample size. Second, while the focus of the current study was between-group differences, it is worthwhile noting that the healthy comparison individuals

did not show increased amygdala responses to the emotional stimuli in the region of activation identified by our group-by-emotion interaction. However, secondary analyses conducted on only the healthy individuals' data did demonstrate the expected increased BOLD responses within other portions of the amygdala to fearful and angry expressions relative to neutral expressions, affirming the paradigm's suitability for indexing the emotional response in healthy cognition. Third, as noted above, the current findings are preliminary due to the use of a cross-sectional comparison augmented by retrospective data in adults. SP typically begins by adolescence, and review of the onset information provided by adult patients participating in the current study showed that symptoms had uniformly begun by adolescence. However, using such a retrospective approach, it is not possible to precisely and accurately date in these adults the precise developmental point during which full SP diagnostic criteria were met. Future longitudinal studies will be important in providing definite answers concerning relationships among adolescent SP onset, brain function, and symptomatic expressions of SP in adulthood.

It is also worthwhile noting that we employed basic social stimuli, associated with a relatively automatic emotional response, focused on a narrow, specific stimuli class: facial expressions. Work with adult SP has shown that the disorder is not only associated with heightened responsiveness to the more automatic social stimuli but also with heightened medial prefrontal cortex (MPFC) responsiveness to "constructed" social stimuli, such as self-referential social threats and embarrassing situations (15, 39, 40). However, no work has examined whether adolescents with SP show anomalously increased MPFC responses to self-referential social threats. If this increased MPFC sensitivity to self-referential social threats is a primary component of the pathology of SP, we would predict that it will also be seen in adolescents with SP. Alternatively, it could be a secondary, developmental consequence of the amygdala/ ACC hyper-responsiveness seen in SP. In this case, MPFC hyper-responsiveness to self-referential information could be reduced, or absent, in adolescent SP. Future work will need to examine, within a developmental perspective, the relative neural response to more complicated social stimuli, such as self-referential praise and criticism, to determine whether the areas implicated in the processing of such constructed stimuli are also developmental stable.

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REFERENCE LIST

1. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Archives of General Psychiatry. 1998; 55(1):56–64. [PubMed: 9435761]
2. Bittner A, Egger HL, Erkanli A, Jane Costello E, Foley DL, Angold A. What do childhood anxiety disorders predict? J Child Psychol Psychiatry. 2007; 48(12):1174–83. [PubMed: 18093022]
3. Cooney RE, Atlas LY, Joormann J, Eugene F, Gotlib IH. Amygdala activation in the processing of neutral faces in social anxiety disorder: is neutral really neutral? Psychiatry Research. 2006; 148(1): 55–9. [PubMed: 17030117]
4. Stein MB, Goldin PR, Sareen J, Zorrilla LT, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. Archives of general psychiatry. 2002; 59(11): 1027–34. [PubMed: 12418936]
5. Amir N, Klumpp H, Elias J, Bedwell JS, Yanasak N, Miller LS. Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. Biological psychiatry. 2005; 57(9):975–81. [PubMed: 15860337]

6. Straube T, Mentzel HJ, Miltner WH. Common and distinct brain activation to threat and safety signals in social phobia. Neuropsychobiology. 2005; 52(3):163–8. [PubMed: 16137995]
7. Straube T, Kolassa IT, Glauer M, Mentzel HJ, Miltner WH. Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study. Biological Psychiatry. 2004; 56(12):921–30. [PubMed: 15601601]
8. Birbaumer N, Grodd W, Diedrich O, Klose U, Erb M, Lotze M, et al. fMRI reveals amygdala activation to human faces in social phobics. Neuroreport. 1998; 9(6):1223–6. [PubMed: 9601698]
9. Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. Biological Psychiatry. 2006; 59(5):424–9. [PubMed: 16256956]
10. Yoon KL, Fitzgerald DA, Angstadt M, McCarron RA, Phan KL. Amygdala reactivity to emotional faces at high and low intensity in generalized social phobia: A 4-Tesla functional MRI study. Psychiatry Research: Neuroimaging. 2007
11. Blair KS, Shaywitz J, Smith BW, Rhodes R, Geraci M, Jones M, et al. Response to emotional expressions in Generalized Social Phobia (GSP) and Generalized Anxiety Disorder (GAD): Evidence for separate disorders. Am J Psychiatry. 2008; 165(9):1193–202. [PubMed: 18483136]
12. Gentili C, Gobbini MI, Ricciardi E, Vanello N, Pietrini P, Haxby JV, et al. Differential modulation of neural activity throughout the distributed neural system for face perception in patients with Social Phobia and healthy subjects. Brain Res Bull. 2008
13. Evans KC, Wright CI, Wedig MM, Gold AL, Pollack MH, Rauch SL. A functional MRI study of amygdala responses to angry schematic faces in social anxiety disorder. Depress Anxiety. 2008; 25(6):496–505. [PubMed: 17595018]
14. Blair KS, Geraci M, Hollon N, Otero M, DeVido J, Majestic C, et al. Social norm processing in adult Social Phobia: Atypically increased ventromedial frontal cortex responsiveness to unintentional (embarrassing) transgressions. The American Journal of Psychiatry. 2010; 167(12): 1526–32. [PubMed: 20889651]
15. Blair KS, Geraci M, Devido J, McCaffrey D, Chen G, Vythilingam M, et al. Neural response to self- and other referential praise and criticism in generalized social phobia. Archives of General Psychiatry. 2008; 65(10):1176–84. [PubMed: 18838634]
16. Goldin PR, Manber-Ball T, Werner K, Heimberg R, Gross JJ. Neural Mechanisms of Cognitive Reappraisal of Negative Self-Beliefs in Social Anxiety Disorder. Biol Psychiatry. 2009
17. Blair KS, Geraci M, Otero M, Majestic K, Odenheimer S, Jacobs M, et al. Atypically reduced modulation of medial prefrontal cortex to self-referential comments in Generalized Social Phobia. Psychiatry Research: Neuroimaging. 2011; 193(1):38–45.
18. Monk CS, Nelson EE, McClure EB, Mogg K, Bradley BP, Leibenluft E, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. Am J Psychiatry. 2006; 163(6):1091–7. [PubMed: 16741211]
19. McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJ, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. Arch Gen Psychiatry. 2007; 64(1):97–106. [PubMed: 17199059]
20. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. Amygdala and ventromedial prefrontal cortex activation to masked angry faces in children and adolescents with Generalized Anxiety Disorder. Arch Gen Psychiatry. 2008
21. Guyer AE, Lau JY, McClure-Tone EB, Parrish J, Shiffrin ND, Reynolds RC, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. Arch Gen Psychiatry. 2008; 65(11):1303–12. [PubMed: 18981342]
22. Guyer AE, Monk CS, McClure-Tone EB, Nelson EE, Roberson-Nay R, Adler AD, et al. A developmental examination of amygdala response to facial expressions. J Cogn Neurosci. 2008; 20(9):1565–82. [PubMed: 18345988]
23. First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV. American Psychiatric Press; Washington, DC: 1997.
24. Beesdo K, Lau JY, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, et al. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry. 2009; 66(3):275–85. [PubMed: 19255377]

25. Ekman, P.; Friesen, WV. Pictures of Facial Affect. Consulting Psychologists Press; Palo Alto: 1976.
26. Blair RJR, Morris JS, Frith CD, Perrett DI, Dolan R. Dissociable neural responses to facial expressions of sadness and anger. Brain. 1999; 122:883–93. [PubMed: 10355673]
27. Whalen PJ, Shin LM, McInerney SC, Fischer H, Wright CI, Rauch SL. A functional MRI study of human amygdala responses to facial expressions of fear versus anger. Emotion. 2001; 1(1):70–83. [PubMed: 12894812]
28. Murphy FC, Nimmo-Smith I, Lawrence AD. Functional neuroanatomy of emotions: a meta-analysis. Cogn Affect Behav Neurosci. 2003; 3(3):207–33. [PubMed: 14672157]
29. Critchley H, Daly E, Phillips M, Brammer M, Bullmore E, Williams S, et al. Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study. Hum Brain Mapp. 2000; 9(2):93–105. [PubMed: 10680766]
30. Marsh AA, Finger EC, Mitchell DG, Reid ME, Sims C, Kosson DS, et al. Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. Am J Psychiatry. 2008; 165(6):712–20. [PubMed: 18281412]
31. Keightley ML, Winocur G, Graham SJ, Mayberg HS, Hevenor SJ, Grady CL. An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. Neuropsychologia. 2003; 41(5):585–96. [PubMed: 12559151]
32. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research. 1996; 29:162–73. [PubMed: 8812068]
33. Talairach, J.; Tournoux, P. Co-planar stereotaxic atlas of the human brain. Thieme; Stuttgart: 1988.
34. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007; 164(10):1476–88. [PubMed: 17898336]
35. Thomas LA, De Bellis MD, Graham R, LaBar KS. Development of emotional facial recognition in late childhood and adolescence. Developmental science. 2007; 10(5):547–58. [PubMed: 17683341]
36. RUPP; The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. N Engl J Med. 2001; 344(17): 1279–85. [PubMed: 11323729]
37. RUPP. The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. J Am Acad Child Adolesc Psychiatry. 2002; 41(9):1061–9. [PubMed: 12218427]
38. Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med. 2008; 359(26):2753–66. [PubMed: 18974308]
39. Blair, KS.; Geraci, M.; Hollon, N.; Otero, M.; DeVido, J.; Majestic, C., et al. Social norm processing in Social Phobia: Atypically increased ventromedial frontal cortex responsiveness to unintentional (embarrassing) transgressions. submitted
40. Blair, KS.; Geraci, M.; Majestic, K.; Odenheimer, S.; Jacobs, M.; Blair, KS., et al. Reduced modulation of medial prefrontal cortex to self-referential comments in Generalized Social Phobia. submitted

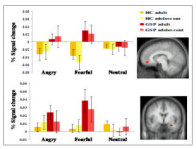

Figure 1.
Interactions of diagnosis-by-emotion. BOLD responses within **(a)** right ACC (7, 44, −6) to angry, fearful, and neutral facial expressions; and **(b)** left amygdala (−28, −2, −18) to angry, fearful, and neutral facial expressions.

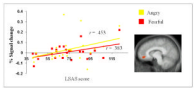

Figure 2.
Symptom severity and BOLD response. Correlations between severity of symptomatology in the adult SP group and BOLD response to angry and fearful expressions within the ACC.

Table 1

Subject demographics; S.D. in brackets.

	Adult social phobia (N = 25)	Adolescent social phobia (N = 14)	Adult healthy comparison (N = 23)	Adolescent healthy comparison (N = 16)
Age	32.2 (9.14)	13.3 (3.42)	29.7 (8.30)	14.9 (2.03)
Gender	10 M/ 15 F	7 M/ 7 F	13 M/ 10 F	9 M/ 7 F
Race				
Caucasian	15	12	18	12
African-American	6	2	3	2
Asian	4	-	2	1
Mixed	-	-	-	1
IQ	118.8 (11.56)	113.0 (14.67)	115.8 (13.55)	112.1 (16.07)
LSAS*	73.2 (20.40)	-	-	-
PARS*	-	21.7 (4.84)	-	-
Accuracy performance: % incorrect responses	1.7% (2.29)	9.9% (12.25)	1.6% (1.67)	5.2% (5.15\6)

Key to Table 1. M = male; F = female; LSAS = Liebowitz Social Anxiety Scale; PARS = Pediatric Anxiety Rating Scale.

*These scores are consistent with moderate levels of anxiety in both groups.

Table 2

Significant areas of activation for the diagnosis-by-em otion interaction and the diagnosis, age, and emotion main effects †

REGION	BA	Mm^3	X	Y	Z	F-value
Diagnosis-by-emotion interaction						
R anterior cingulate gyrus	32	536	7	44	−6	8.23
L amygdale		147	−28	−2	−18	5.55
Diagnosis main effect						
R occipital/temporal gyrus	18/19/37	14206	10	−95	3	16.36
Emotion main effect (angry=fearful > neutral for all)						
R middle frontal gyrus	6	32201	57	9	38	16.76
R medial frontal gyrus	6/32	4004	5	6	49	9.86
L amygdala/ parahippocampal gyrus		2729	−17	0	−10	9.44
R amygdala		29	26	1	−14	5.93
R thalamus		3457	16	−28	0	10.04
R middle occipital gyurs	18	59545	35	−82	−7	55.73
L inferior occipital gyrus	18	47082	−32	−87	−5	53.23
R precuneus	7	526	27	−64	32	6.41
Age main effect (adult > adolescent for all)						
L medial frontal gyrus/ OFC	11	1169	−7	24	−14	20.86
L inferior frontal gyrus	45	1775	−49	34	7	12.82
L inferior frontal gyrus	6	4376	−54	3	35	19.32
R inferior frontal gyrus	9	1109	60	9	28	14.81
R cingulate gyrus	24	508	0	4	37	11.28
R postcentral gyrus	1/3	14206	52	−15	49	21.28
R middle occipital gyrus	19	6115	50	−80	3	23.58
L middle temporal gyrus	19/37	3970	−63	−68	3	18.78
L culmen		812	−15	−50	−12	13.96