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Abstract

1. Context. Amygdala and ventrolateral prefrontal cortex dysfunction manifests in adolescents with anxiety disorders when they view negatively-valenced stimuli in threatening contexts. Such fear-circuitry dysfunction may also manifest when anticipated social evaluation leads socially anxious adolescents to misperceive peers as threatening.

2. Objective. To determine whether photographs of negatively-evaluated smiling peers, viewed during anticipated evaluation, engage the amygdala and ventrolateral prefrontal cortex differentially in adolescents with and without social anxiety.

3. Design. Case-control study.

4. Setting. Government clinical research institute.

5. Participants. Fourteen adolescents with anxiety disorders associated with marked social concerns and 14 diagnosis-free adolescents, matched on sex, age, IQ, and socio-economic status.

6. Main Outcome Measure(s). Blood oxygenation level-dependent signal measured with event-related functional magnetic resonance imaging. Before and during neuroimaging scans, participants anticipating social evaluation completed peer- and self-appraisals. Event-related analyses were tailored to participants' ratings of specific peers.

7. Results. Participants classified 40 pictures of same-age peers as ones they wanted to engage or not engage with for a social interaction. Anxious adolescents showed greater amygdala activation than healthy adolescents when anticipating evaluation from peers rated as undesired for an interaction. Viewing undesired peers engaged stronger positive amygdala-ventrolateral-prefrontal-cortex connectivity in anxious vs. healthy adolescents.

8. Conclusions. Anticipating social evaluation from negatively-perceived peers modulates amygdala and ventrolateral prefrontal cortex engagement differentially in anxious and healthy

adolescents. Amygdala and ventrolateral prefrontal cortex abnormalities in adolescent anxiety disorders are heightened in specific contexts of potential peer evaluation.

Introduction

Dramatic change in social behavior is associated with increased social anxiety during adolescence[1-4]. Social experiences may heighten information-processing biases contributing to anxiety. For example, current theories posit that adolescent social anxiety emerges from excessive fears of judgment and biased appraisals of peers as overly critical[5, 6]. These theories suggest that anticipation of peer evaluation leads anxious adolescents to misperceive peers as overly threatening and uninterested in social interactions with them. Functional neuroimaging provides an opportunity to ground these theories in knowledge of the brain's "fear-circuitry"[7].

Research in animals and adult humans implicates a circuit connecting the amygdala and ventrolateral prefrontal cortex (vlPFC) in social-threat processing[7, 8]. These data suggest that chronic anxiety emerges from early life changes in fear-circuitry and its role in social-threat perception[9]. Specifically, research in non-human primates shows that the developmental timing of amygdala injury profoundly influences social-threat perception[10, 11]. These findings raise key questions about the relations among human amygdala and vlPFC function, social-threat perception, and pediatric anxiety disorders. Understanding these processes in the adolescent is important because this developmental period is associated with an increased focus on peer relationships and increased onset of anxiety disorders, which heightens risk for adult anxiety disorders[2]. While few neuroimaging studies pursue this line of research, preliminary work implicates amygdala-vlPFC circuitry in adolescent anxiety[12-14].

Perturbed amygdala function in anxiety disorders is thought to generate fear responses to innocuous stimuli, misperceived as threatening[15]. Indeed, amygdala hyper-activation consistently differentiates adults with and without anxiety about social situations[16-22]. However, a unique association between amygdala function and social-threat perception may arise in adolescence.

Specifically, amygdala hyper-activation in adult anxiety typically occurs when attention focuses toward *non-threatening*, rather than threatening, aspects of negatively-valenced, social stimuli[19, 20]. In adolescent anxiety, however, amygdala dysfunction manifests specifically when attention focuses toward *threatening* aspects of social cues[12]. Furthermore, vlPFC activation is implicated in threat representation and emotion regulation via influences on the amygdala[21, 23] and dysfunctional amygdala-vlPFC interactions are found to relate to anxiety[24]. A fear of being negatively evaluated leads some adolescents to misperceive peers as overly critical and to anticipate pejorative peer evaluation[6]. Accordingly, high levels of social concern are expected in the anxious adolescent who confronts peers within a reciprocally-evaluative context.

Three issues shaped our current focus on the fear response to social threats in adolescent anxiety. First, although amygdala hyper-activation has been found in response to mild emotional provocations (e.g., pictures of fearful faces)[12, 13], work has yet to assess fear of social evaluation in a salient context for adolescents. Thus, we developed an ecologically-valid paradigm that uses anticipation of peer evaluation within a simulated internet "chatroom" to induce feelings of social threat highly relevant to an adolescent's daily life. Second, in light of prior work that shows powerful contextual effects on adolescent amygdala and vlPFC responsivity[8, 12, 25, 26], we probed amygdala and vlPFC function using prototypically non-threatening social cues—smiling faces of novel peers[27, 28]—within the potentially threatening context of peer evaluation. Finally, recent work suggests that between-group differences in functional connectivity with ventro-lateral expanses of prefrontal cortex parallel differences in amygdala response[12, 29]. However, because only two studies, using mild threats, examined this issue in adolescents[8, 12], extension to ecologically-valid situations was needed. Therefore, we considered the degree to which

amygdala-vlPFC connectivity relates to between-group differences within a real-world, social context.

The present study tested two hypotheses. First, based on past work in anxious adolescents[8, 12, 13], relative to healthy adolescents, adolescents with anxiety disorders would exhibit amygdala hyper-activation when anticipating judgment from smiling peers in a context that induces social concerns, i.e., fear of negative evaluation. Participants were asked to rate how peers would evaluate them for an interaction to elicit anticipation of social evaluation. We chose the cognitive task of considering how others judge one's self to tap into self-esteem, a psychological construct related to anxiety[30]. Second, as in prior studies in healthy adults and anxious adolescents[8, 12, 31], we hypothesized that amygdala-vlPFC connectivity would emerge in this context of social concern. We hypothesized that these activations would vary based on their initial evaluations of peers. We contrasted two instances of anxious adolescents' expectations concerning unfamiliar peers: those where peers had been rated as either undesirable or desirable for anticipated interaction. As part of the paradigm, participants were led to believe that their peer-ratings would be revealed to the other participants. Hence, appraising how undesirable peers would evaluate them was expected to elicit amygdala hyperactivation and positive amygdala-vlPFC connectivity in the anxious relative to non-anxious adolescent, due to fears of social retaliation when anticipating evaluation from a peer previously rated as undesirable. In addition, because prior data suggest that anxious adolescents exhibit greater amygdala activation[8, 12, 13] and biased expectation of being negatively evaluated[6, 32], both anxiety severity and self-esteem ratings were expected to vary with engagement of amygdala-vlPFC circuitry[9, 15].

Methods

Participants. Fourteen medication-free adolescents with a current DSM-IV anxiety diagnosis (age 8-17 years; 5 males; IQ=113; socio-economic status [SES]=7.4), and 14 psychiatrically healthy control adolescents (age 8-16 years; 5 males; IQ=117; SES=8.3) participated. *T*-test and chi-square analyses confirmed the groups were matched on age, sex, IQ, and SES (Table 1).

Diagnoses were determined using the Kiddie-Schedule-for-Affective-Disorders–Present-and-Lifetime-version (K-SADS-PL)[33]. All patients were recruited when they sought treatment for anxiety about social situations, and thus, had current, impairing, clinically significant anxiety (Table 1). Patients not diagnosed with current SP (*n*=6) demonstrated clinically significant fear of social interaction/performance) on the Pediatric Anxiety Rating Scale (PARS) [34] and/or K-SADS-PL. This sample selection approach extends Rapee & Heimberg's model[6], which posits that social evaluation concerns exist along a continuum, with SP at the extreme, immediately proximal to other anxiety disorders with high social concerns. We included both patient groups, as Rapee and Heimberg argue that the same cognitive biases manifest in both groups, though to varying degrees.

Other inclusion criteria for patients comprised: clinically significant anxiety on the PARS (score >=10); significant impairment on the Child Global Assessment Schedule (CGAS; score <60) [35]; and persistent anxiety during 3 weeks of supportive psychotherapy. Exclusion criteria comprised: current major depressive disorder, obsessive compulsive disorder, Tourette's syndrome, oppositional defiant disorder, or conduct disorder (CD); exposure to trauma; suicidal ideation; lifetime history of mania, psychosis, or pervasive developmental disorder (PDD); IQ<70; contraindications for magnetic resonance imaging (e.g. pacemaker, pregnancy, braces), and use of any psychoactive substance. Participants and their parent completed the Screen for

Child Anxiety Related Emotional Disorders (SCARED), an anxiety severity measure with excellent reliability and validity[36]. Both SCARED scores were averaged to index anxiety severity.

fMRI Procedures. Study procedures were approved by the NIMH institutional review board. All participants provided written assent; parents/legal guardians provided written informed consent. Participants were informed that they would receive misinformation at some point during the course of their testing; all participants were debriefed. No adverse reactions occurred.

We developed an ecologically-valid neuroimaging paradigm, the "Chatroom," to simulate adolescent social interactions in two phases. In phase one, participants were led to believe we were implementing a nationwide investigation of internet-based communication through chatrooms among teenagers. They were told that after an fMRI scan, they would chat online with another teenager from a collaborating institution. Participants then viewed 40 photographs of peers (20 males) allegedly participating in the study and rated, on a 100-point scale, their interest in chatting with each peer (Figure 1a). These ratings provided a way to sort events during scanning based on participants' impressions of peers (i.e., desirable or undesirable). Participants were also photographed, told that the "participants" they had rated would similarly evaluate their pictures and view the ratings they had received, and would later chat with a mutually high-interest "participant," based on their ratings, interests, and hobbies. As part of our hypothesis, knowing that the "peer" would learn how the participant rated him or her was thought to elicit fear about being evaluated in return. This deceptive approach was intended to increase task sensitivity for engaging symptom-relevant cognitions.

In phase two, two weeks later, participants were scanned while reviewing the photographs they had rated previously and asked to indicate how interested they thought each depicted peer would be in chatting with them (Figure 1b). This cognitive task, involving appraisal of expected peer evaluation, was designed to engage concerns about social evaluation, expected to differ in anxious and healthy adolescents, following Rapee and Heimberg's social-anxiety model[6]. Our hypothesis and analysis focused on neural activation during these appraisal events of anticipated social evaluation by each peer, sorted by the peer desirability groupings. Post-scan, participants completed a series of questions to validate the degree to which they believed the task and were then debriefed one-on-one and told that no real interactions would occur. Only data from successfully-deceived participants (80% of participants), those that believed others would rate them, see their ratings, and would chat with a peer post-scan, were included.

The Chatroom task used a rapid, event-related design presented in one 7-min run. Each event was 9-s, consisting of stimulus face presentation (4-s) and rating response (5-s). These two event sub-components were considered a single psychological process because, upon picture presentation, which occurs in tandem with presentation of a question, the adolescent likely begins assessing the picture before actually making their rating. Additionally, our hypotheses were directed to activation differences due to stimuli valence as determined by the adolescent rather than to each event sub-component. Task stimuli were 40 digital head shots of 11-17 year-old actors of varied ethnicities[37] posing happy expressions under the direction of an acting coach. Fixation crosses were displayed (4-s) randomly throughout the task to serve as a baseline. Interstimulus interval was 1-s.

fMRI Data Acquisition and Preprocessing. Scanning occurred in a General Electric (Waukesha, WI) Signa 3T magnet. Task stimuli were viewed with a head- coil-mounted mirror. Participants rated task stimuli using a hand-held two-button response box (Research Services Branch, NIMH, Bethesda, MD).

Functional scans were preceded by a localizer and a manual shim procedure. For functional image acquisition, each brain volume contained 29 contiguous 3.3 mm axial slices acquired parallel to the AC/PC line using a single shot gradient echo with T2* weighting with a repetition time (TR) of 2300 ms and echo time (TE) of 23 ms. Voxel dimension was 3.3x3.75x3.75 mm. Matrix size was 64x64mm and field of view (FOV) was 24 cm. A high resolution anatomical image was also acquired per subject using a T1-weighted standardized magnetization prepared spoiled gradient recalled echo sequence to aid with spatial normalization using the following parameters: 124 1 mm axial slices, TR of 8100 ms, TE of 32 ms, flip angle of 15°, NEX=1, matrix size of 256x256 mm, bandwidth=31.2 KHz, and FOV of 24 cm.

Data Analysis. Behavioral rating data collected before and during the scan were analyzed using SPSS 14.0 (Chicago, IL). FMRI data were analyzed using Analysis of Functional and Neural Images (AFNI) software version 2.56b[38]. Standard preprocessing of echo-planar imaging (EPI) data included slice time correction, motion correction, reslicing to a 1mm isotropic voxel (1x1x1), spatial smoothing (6 mm full-width half-maximum Gaussian kernel), removal of large signal deviations > 2.5 SD from the mean using an AFNI de-spiking algorithm applied on a voxelwise basis, a bandpass filtering algorithm to smooth cyclical fluctuations (>.011 or <.15 s), and normalization of blood oxygen level-dependent (BOLD) signal intensity to percentage signal change using each subject's voxel-wise time series mean as a baseline. Motion correction

parameters were included as nuisance covariates along with a covariate for mean intensity and linear drift. In addition, subjects moving more than 2.5 mm were excluded.

Amygdala Activation: The statistical model was a gamma variate basis function convolved with the hemodynamic response function contained in AFNI. The basis function was set to the onset of each event type. Event types consisted of two expected-peer-appraisal events: when expecting reactions from peers previously judged as (1) low or (2) high in desirability. These events were determined using a median split of each participants' pre-scan appraisal ratings of peers. A general linear model was then used to determine the beta value and *t*-statistic for each event type at each voxel. Contrasts of whole-brain BOLD activation were created for each individual for each event type, followed by a second group-level, random-effects analysis of individual contrast values.

Based on past data and our *a priori* hypothesis, group-level analyses focused on the left and right amygdala regions of interest (ROI). Talairach anatomical boundaries in AFNI defined voxels within each ROI[39]. Mean contrast values were generated for all voxels within the left and right amygdala separately and analyzed with *t*-tests. We tested between-group differences in the low-versus-high-desirability contrast during rating of expected-peer-appraisal. Statistical significance was based on both height intensity and spatial extent in ROIs, using AFNI *AlphaSim* to correct for multiple comparisons within the ROIs based on 1000 Monte Carlo simulations for the right and left amygdala. With this algorithm, significant voxels had to exceed $p<.005$ whole-brain uncorrected with a 92-voxel cluster size, corresponding to an ROI-corrected $p<.05$.

Secondary analyses were conducted by converting each participant's data to percentage signal change using their voxelwise time series mean as a baseline. The AFNI *3dmaskave* procedure was used to compute and extract for each participant average activation of all voxels

within a functionally-defined ROI mask of the low-high desirability contrast[40]. Threshold parameters for the mask were based on the results from the primary ROI analyses, using t=2.78, p<.005, and cluster size=92. Mean activation values within left and right amygdala clusters were extracted to decompose the pattern of results using SPSS. Two repeated measures analysis of variance (ANOVA) models included group (patient, control) as a between-subjects factor and peer desirability (low, high) as a within-subjects factor; average left and right amygdala activation during appraisal of expected peer evaluation were the dependent variables. The group-by-peer-desirability interaction on amygdala response was of primary interest. Using extracted values, secondary analyses evaluated the influence of between-group differences in task-performance on between-group differences in amygdala activation. Finally, analyses examined correlations among amygdala activation, task performance (e.g., self-esteem ratings), and anxiety severity.

Functional Connectivity: We conducted a psychophysiological interaction analysis to examine connectivity between the amygdala and the ventrolateral prefrontal cortex during the "low vs. high" peer desirability contrast with the between-group differences in the left and right amygdala. We used established procedures adapted for use with AFNI [8, 41, 42]. BOLD signal was deconvolved using an assumed form of the hemodynamic response function prior to creating the interaction term[42]. Each participant's EPI time series was converted to Talairach space. The first eigenvariate time series was extracted from each of two "seed" voxels for each participant. The seeds came from the peak t-value for the left and right amygdala where between-group differences emerged on the low vs. high peer desirability contrast. To selectively examine activation related to the events of interest, we entered the low and high peer desirability conditions as covariates. The correlation coefficient of the interaction term between the

amygdala seed and the low vs. high contrast was converted using Fisher's Z-score transformation to reduce skew and normalize sampling distribution. *T*-tests compared groups on co-activation between each amygdala seed and other brain regions. The results of this procedure show event-related changes in the interaction of the right amygdala seed and left ventrolateral prefrontal cortex. A spatial clustering procedure again determined statistical significance with a $p<.005$ height threshold and a spatial extent correction ($n=216$ voxels) based on 1000 Monte Carlo simulations taking into account the entire EPI map, corresponding to a whole-brain corrected $p<.01$. Secondary analyses decomposed initial findings. Co-activation correlation values were extracted from the vlPFC region that survived statistically and graphed for presentation purposes. For the amygdala-vlPFC co-activation that differed between groups, we examined its association with task performance (i.e., interest in peers and expected evaluation/self-esteem ratings) and anxiety severity.

Results

Behavioral Responses. Patients and controls reported similar levels of interest in peers (i.e., peer desirability) based on their pre-scan ratings, but data collected during scanning revealed expected between-group differences (Table 1). Specifically, relative to controls, patients expected peers to rate them as less desirable, reflecting between-group differences in self-esteem. There was also a positive significant correlation between peer desirability ratings and expected peer evaluation ratings (Table 2).

It is possible that peer desirability ratings varied with the sex of the peer. A repeated measure ANOVA yielded no between-group differences in the proportion of same-sex vs. opposite-sex peers nominated into low vs. high peer desirability conditions. As expected, both

groups reported higher interest in chatting with same-sex than opposite-sex peers (peer-desirability-by-peer-sex interaction, $F[1, 26]=51.47$, $p<.001$). Most importantly, however, no significant main effects or interactions with group emerged.

Amygdala Activation. Our *a priori* hypothesis that the "low vs. high" peer desirability contrast would elicit more amygdala activation in patients vs. controls was confirmed by significant group-by-peer desirability interactions. Patients showed significantly greater bilateral amygdala activation while appraising potential peer evaluation; this effect occurred specifically while viewing undesirable peers. After correcting for multiple comparisons in the amygdala regions, the maximum intensity value in the left amygdala was $t(26)=3.62$ (x=-23, y=3, z=-20) and for the right amygdala was $t(26)=3.53$; (x=27, y=-3, z=-21). Figure 2a presents the topography of the maximum intensity *t*-value in the right amygdala, where one interaction emerged.

The group-by-peer desirability interactions were decomposed through post-hoc analyses of extracted percent signal change for each event, relative to a null-event baseline. Repeated measures ANOVAs revealed group-by-peer-desirability interactions (left amygdala: $F(1,26)=13.26$, $p=.001$; right amygdala: $F(1,26)=12.91$, $p=.001$), consistent with AFNI analyses (Figure 2b). Amygdala activation was greatest among patients specifically when appraising predicted evaluation from undesirable peers as compared to desirable peers ($p<0.001$). By contrast, controls showed no difference in amygdala activation when viewing undesirable vs. desirable peers. A significant positive correlation also emerged between anxiety severity ratings and right amygdala activation (Spearman $r=0.42$, $p<.05$; Table 2).

The AFNI *3dRegAna* procedure was used to conduct a regression analysis of the effects of group and peer desirability level on amygdala activation with expected peer evaluation (i.e.,

self-esteem) ratings included as a covariate. These analyses showed that the group differences in bilateral amygdala activation remained significant (left amygdala: $t[26]=3.72$, $p<.005$; right amygdala: $t[26]=2.53$, $p<.01$).

We also examined differences between participants with social phobia, (n=8), those with other anxiety disorders plus elevated social concerns on the PARS (n=6), and controls (n=14). As expected, a significant between-group difference was found in left ($F[2, 25]=7.16$, $p=.003$) and right ($F[2, 25]=5.93$, $p=.008$) amygdala activation while appraising evaluation from low vs. high desirable peers. Both social phobia and other anxiety patients had significantly greater amygdala activation than controls, but did not differ from each other. Social phobia patients had the highest mean amygdala activation values (Left amygdala: $M=.88\pm.91$; Right amygdala: $M=.76\pm.94$), followed by other anxiety patients (Left amygdala: $M=.58\pm.54$; Right amygdala: $M=.68\pm.83$), and controls (Left amygdala: $M=-.21\pm.59$; Right amygdala: $M=-.15\pm.35$).

We entered the study with specific *a priori* hypotheses concerning greater amygdala activation in patients than in healthy adolescents. Nevertheless, we considered other areas where patients might exhibit greater activation based on peer desirability, using the Monte Carlo-based ROI-corrected threshold (Table 3). At this threshold, greater activation in patients vs. controls also emerged within the cerebellum (x=-5, y=-70, z=-29; t=3.66). Greater activation in controls vs. patients emerged in the left anterior cingulate (x=-15, y=30, z=-8; t=-3.53) and the left middle frontal gyrus/Brodmann Area 46 (x=-41, y=43, z=5).

Functional Connectivity. Table 4 summarizes all group differences that surpassed the whole-brain-corrected statistical threshold. Between-group comparisons of the correlative strength between significantly co-activated regions showed that, relative to controls, patients demonstrated a positive correlation between the right amygdala seed and left vlPFC

encompassing bilateral Brodmann's Area (BA) 47 (Figure 3a) while appraising low vs. high desirable peers. This difference was driven by positive amygdala-vlPFC connectivity in patients and negative amygdala-vlPFC connectivity in controls during appraisal of low desirable peers (Figure 3b). Consistent with these findings, anxiety severity and self-esteem ratings correlated significantly with amygdala-vlPFC co-activation, such that lower self-esteem (Table 2) and higher anxiety severity (Table 2; Figure 3c) were related to positive amygdala-vlPFC connectivity.

Comment

This is the first study to map neural processing engaged in real-world social interactions among adolescents, using a novel paradigm to simulate social judgments in which adolescents participate routinely. Two main fMRI findings emerged. First, group differences in bilateral amygdala activation varied with participants' ratings of unfamiliar peers. Anxious adolescents showed greater activation than healthy adolescents when viewing photographs of smiling peers they rated as not interesting to chat with, relative to those deemed interesting to chat with. Second, these between-group differences were paralleled by differing patterns of co-activation in a distributed neural circuit connecting the amygdala with the vlPFC. Accordingly, these findings suggest a stronger relationship in anxious adolescents than controls between amygdala activity and responses in prefrontal regions implicated in evaluating salient social events and modulating responses to such events.

These findings emerged against a backdrop of behavioral findings. Compared to controls, anxious adolescents perceived unfamiliar peers as less likely to want to chat with them. This resonates with prior findings that anxious youth view themselves as socially unaccepted and

report low self-esteem[30]. Thus, by design, the current task engages expected between-group differences in psychological processes. Indeed, social stimuli typically considered non-threatening (i.e., smiling peers), elicited robust amygdala responses in patients with extreme worry about potential social evaluation, particularly when viewing peers whom they rated negatively. Because participants were told the "peers" would learn of their ratings, having rated certain peers as undesirable was expected to generate concern about negative peer evaluation in anxious patients. A strong relationship was also noted between participants' initial ratings of each peer's desirability and later ratings of expected peer evaluation; this provides some evidence that participants' initial impressions of peers relate to psychological processes engaged in the participants when they view these same peers, two weeks later.

The current findings suggest that amygdala abnormalities in adolescent anxiety disorders reflect the contexts in which salient stimuli appear. Here, anticipating social judgment from peers rated negatively differentially modulated amygdala engagement in socially anxious and healthy adolescents. However, these findings do not clarify the degree to which amygdala activation produces or results from the initial low interest response. The current study also leaves open questions concerning specific factors about peers (i.e., age, appearance, sex) that may influence participants' desirability ratings. Regardless, the present findings suggest that psychological interpretations initiate or maintain social information-processing biases associated with neural function, extending prior work in anxious adults and adolescents, as well as adolescents at-risk for social anxiety, that documents pronounced amygdala response to facial expressions viewed in various conditions (e.g., emotional vs. non-emotional)[12, 19, 20, 22, 26]. Together, the current and prior findings suggest that psychological interpretations, shaped by the context in which stimuli are viewed, influences brain circuitry implicated in adolescent anxiety disorders.

The present study also underscores the powerful influence of attention on amygdala reactivity. Past work shows that adult social phobia involves a pronounced amygdala response to socially threatening faces when attention is constrained to a non-emotional context[20]. Further, like the current study, our previous research demonstrated that focusing attention on disorder-relevant cognitions elicits amygdala hyper-activation in adolescents either at-risk for or suffering from anxiety[12, 26]. The current study shows that appraisal variations influence amygdala response even for social stimuli that prototypically appear non-threatening. This again suggests that viewing context powerfully modulates neural and cognitive correlates of anxiety. The lack of amygdala engagement during appraisal of peer evaluation in controls suggests that adolescents without social anxiety do not engage in the same cognitive biases and associated neural response that reflect fear of social evaluation, regardless of the desirability of the peer.

Group differences in amygdala response were paralleled by differential co-activation in circuitry connecting the amygdala and vlPFC implicated in attention-modulation[43]. These results complement prior findings in adult health and disease[12, 14, 20, 22, 43] and patterns of dysfunctional circuitry involving amygdala regions and the vlPFC. Like prior studies[29], our measures of anxiety severity and task performance correlated with amygdala-vlPFC connectivity. Of note, considerable previous work in both adult humans and in animal models also implicates expanses of the medial PFC (mPFC) in amygdala regulation[44-46]. Accordingly, one may also expect between-group differences in mPFC-amygdala connectivity in the current study. However, prior work from our group more consistently implicates the vlPFC than the mPFC in adolescent anxiety; across four different studies, including the current one, we find consistent evidence of perturbed vlPFC function but no evidence of perturbed mPFC function in adolescent anxiety[8, 12, 14].

Findings across prior studies in adolescents suggest that distinct perturbations in amygdala-vlPFC circuitry manifest in distinct psychological contexts. In the context of an attention-orienting task, vlPFC appears to regulate amygdala engagement, when briefly-presented threats serve as implicit distracters from task-related goals. In this instance, negative amygdala-vlPFC connectivity occurs in healthy adolescents but not in adolescent GAD[8], where increased amygdala activation occurs in the context of positive correlations between amygdala engagement and anxiety severity. In other psychological contexts, however, including the current study, task parameters lead attention to focus on explicit aspects of threat content. In this instance, increased amygdala activation in anxiety patients occurs in tandem with increased vlPFC and amygdala activation[12]. As in prior work[12], the current finding of positive amygdala-vlPFC connectivity in patients but not healthy adolescents suggests that positive connectivity serves to represent threat-related information in contexts where task parameters lead attention to focus explicitly on threat content. The positive correlation between anxiety severity and amygdala-vlPFC connectivity supports this view, as well as prior lesion-based work in children suggesting that brain injury to the vlPFC protects from trauma-related anxiety[47].

Specifically, we found stronger positive connectivity in patients than controls between the right amygdala and the left vlPFC, encompassing BA47, in response to evaluating low vs. high desirable peers. This finding is consistent with past clinical neuroimaging work documenting strong relations between the vlPFC and amygdala function[12, 14, 22, 48, 49] and with prior basic research suggesting that the vlPFC exerts regulatory influences over the amygdala[23, 50, 51]. Thus, greater amygdala-vlPFC connectivity in patients might reflect a lower threshold in patients for engaging vlPFC-based representations of threat-relevant schemas. This is consistent with the role of amygdala-vlPFC circuitry in decision-making and behavioral response, in

various contexts, demonstrated in animal models and anxious adolescents[12, 23]. Moreover, work in animal models finds that developmental events impact amygdala-vlPFC function and shape individual differences in emotional processes throughout life[9]. Thus, the similarities in dysfunctional circuitry documented in both adult and adolescent samples may provide a developmental link between childhood anxiety and adult psychopathology.

An individual's ability to regulate emotion contributes to anxiety. Indeed, recent neurobiological frameworks suggest that bi-directional communication between vlPFC and subcortical regions orchestrates cognition-emotion interaction[52, 53]. For example, cognitive inhibition of emotional responses engages the vlPFC, whereas experienced emotional reactions engage the amygdala[54]. Deficits or imbalances in fear circuitry may lead to dysfunction and psychopathological states such as anxiety. In the current study, enhanced amygdala-vlPFC coactivation in patients suggests that perturbations in both regions may regulate heightened anxiety in a social context.

The present study has several limitations. First, the sample size is relatively small. However, because results derived from small samples are associated more commonly with type II rather than type I error, there is increased potential for masking true effects and our significant findings reduce this possibility. Given limitations in statistical power associated with small sample size, particular caution is needed when interpreting negative findings emerging in the current study. Second, roughly half of the anxiety group did not meet full criteria for SP. However, all anxiety patients reported significant concerns about social interactions and evaluation during the psychiatric assessment. Limiting our proband sample to those who met criteria for social phobia could provide a more homogenous sample, reduce variance, and increase statistical power; again, this limitation is also likely to contribute more to Type II than

Type I errors, further suggesting the need to emphasize the positive findings more than the negative findings in the current study. In this respect, it is important to note that our sample selection approach did not hinder our ability to detect the main hypothesized group differences. An important future step would be to conduct a larger study that examines participants with varying levels of social anxiety across the full range of the social anxiety continuum. Third, the social evaluation task has some limitations. Although we did not find evidence of differential sex preferences by group, adolescents showed a greater preference to interact with same-sex peers. Including more task trials would allow the binning of stimuli to sex-match subjects by each picture and would likely increase the task sensitivity to detect between-group differences. Finally, task sensitivity to group differences may have been reduced because our key event incorporated two sub-components rather than examining each component separately and additional "jitter" time was not interspersed between sub-components. This limitation may have been offset, however, by the advantages gained in task feasibility and psychological fidelity that was maintained, particularly given confirmation of our expected findings. Nonetheless, future studies should attempt to decompose neural response to picture-presentation and to rating.

Despite these limitations, the present study has several strengths. First, the task paradigm is unique in that it simulates social interactions and judgments that adolescents engage in routinely. Indeed, the task engaged psychological processes central to clinical adolescent anxiety concerning social events. Of note, the current task differs from our previously-used tasks. In past studies, we used photographs of adults and amygdala hyper-activation emerged in response to fearful faces[12, 14, 26]. In the present study, we used photographs of adolescents and included only happy faces. Despite these task differences, a consistent theme across several neuroimaging studies of adolescent and adult anxiety is that variations in attention exert powerful influences on

amygdala reactivity in anxiety and risk for anxiety. Second, the present findings support theoretical models of cognitive biases in social anxiety. Anxious adolescents demonstrated neural abnormalities when assessing how peers whom they rated negatively would evaluate them in return. This effect occurred despite the positive, accepting cues depicted in the photographed peers. By using a neuroimaging paradigm that accounted for variation in participants' psychological interpretations of stimuli, we found differential effects related to both brain-emotion circuitry and adolescent psychopathology. Third, the functional connectivity patterns in the present study support work on regulatory processes involved in neural networks that modulate relationships between cognition and emotion. Future connectivity analyses may be useful for investigating theories of cognitive modulation of emotion, and extending to the design of cognitive-behavioral treatments. By simulating a real-life experience involving peer evaluation, we are able to tap into core, symptom-specific cognitions related to social anxiety. Clinicians could use such specific cognitive features as a guide in psychotherapy. These results also inform a more precise model of the brain's response to complex social interactions, which quite important during adolescence and relate to psychopathological outcomes. Thus, the current findings can allow for precision in understanding the neurophysiological and cognitive mechanisms that can serve as a basis in models of adolescent social anxiety.

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References

1. Nelson EE, Leibenluft E, McClure EB, Pine DS. The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychological Medicine.* 2005;35:163-174.

2. 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. *Arch Gen Psychiatry.* Jan 1998;55(1):56-64.

3. Costello EJ, Pine DS, Hammen C, et al. Development and natural history of mood disorders. *Biol Psychiatry.* Sep 15 2002;52(6):529-542.

4. Steinberg L, Morris AS. Adolescent development. *Annual Review of Psychology.* 2001;52:83-110.

5. Clark DM, Wells A. A cognitive model of social phobia. *Heimberg, Richard G (Ed); Liebowitz, Michael R (Ed); Hope, Debra A (Ed); Schneier, Franklin R (Ed).* 1995;(1995). Social phobia: Diagnosis:and treatment.

6. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. *Behav Res Ther.* Aug 1997;35(8):741-756.

7. Adolphs R. Is the human amygdala specialized for processing social information? *Ann N Y Acad Sci.* Apr 2003;985:326-340.

8. Monk CS, Telzer EH, Mogg K, et al. Amygdala and ventrolateral prefrontal cortex actvivation to masked angry faces in children and adolescents with generalized anxiety disorder. *Arch Gen Psychiatry.* in press.

9. Gross C, Hen R. The developmental origins of anxiety. *Nat Rev Neurosci.* Jul 2004;5(7):545-552.

10. Amaral DG. The amygdala, social behavior, and danger detection. *Ann N Y Acad Sci.* Dec 2003;1000:337-347.

11. Sabatini MJ, Ebert P, Lewis DA, Levitt P, Cameron JL, Mirnics K. Amygdala gene expression correlates of social behavior in monkeys experiencing maternal separation. *J Neurosci.* Mar 21 2007;27(12):3295-3304.

12. McClure EB, Monk CS, Nelson EE, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder *Arch Gen Psychiatry.* 2007;64:97-106.

13. Thomas KM, Drevets WC, Dahl RE, et al. Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry.* Nov 2001;58(11):1057-1063.

14. Monk CS, Nelson EE, McClure EB, et al. Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *Am J Psychiatry.* Jun 2006;163(6):1091-1097.

15. Pine DS. Research Review: A neuroscience framework for pediatric anxiety disorders. *J Child Psychol Psychiatry.* 2007.

16. Birbaumer N, Grodd W, Diedrich O, et al. fMRI reveals amygdala activation to human faces in social phobics. *Neuroreport.* Apr 20 1998;9(6):1223-1226.

17. Lorberbaum JP, Kose S, Johnson MR, et al. Neural correlates of speech anticipatory anxiety in generalized social phobia. *Neuroreport.* Dec 22 2004;15(18):2701-2705.

18. Veit R, Flor H, Erb M, et al. Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. *Neurosci Lett.* Aug 16 2002;328(3):233-236.

19. Stein MB, Goldin PR, Sareen J, Zorrilla LT, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry.* Nov 2002;59(11):1027-1034.

20. 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. *Biol Psychiatry.* Dec 15 2004;56(12):921-930.

21. Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry.* Mar 1 2006;59(5):424-429.

22. 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.* Aug 2001;158(8):1220-1226.

23. Baxter MG, Parker A, Lindner CC, Izquierdo AD, Murray EA. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J Neurosci.* Jun 1 2000;20(11):4311-4319.

24. Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry.* Mar 15 2003;53(6):494-501.

25. Monk CS, McClure EB, Nelson EE, et al. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage.* Sep 2003;20(1):420-428.

26. Perez-Edgar K, Roberson-Nay R, Hardin MG, et al. Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. *Neuroimage.* May 1 2007;35(4):1538-1546.

27. Yang TT, Menon V, Eliez S, et al. Amygdalar activation associated with positive and negative facial expressions. *Neuroreport.* Oct 7 2002;13(14):1737-1741.

28. Breiter HC, Etcoff NL, Whalen PJ, et al. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron.* Nov 1996;17(5):875-887.

29. Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci.* Jun 2005;8(6):828-834.

30. La Greca AM, Stone WL. Social Anxiety Scale for Children--Revised: Factor structure and concurrent validity. *J Clin Child Psychol.* Mar 1993;22(1):17-27.

31. Nomura M, Ohira H, Haneda K, et al. Functional association of the amygdala and ventral prefrontal cortex during cognitive evaluation of facial expressions primed by masked angry faces: an event-related fMRI study. *Neuroimage.* Jan 2004;21(1):352-363.

32. La Greca AM, Lopez N. Social Anxiety Among Adolescents: Linkages with Peer Relations and Friendships. *J Abnorm Child Psychol.* Apr 1998;26(2):83-94.

33. 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.* Jul 1997;36(7):980-988.

34. RUPP G. The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. *J Am Acad Child Adolesc Psychiatry.* Sep 2002;41(9):1061-1069.

35. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry.* Nov 1983;40(11):1228-1231.

36. Birmaher B, Khetarpal S, Brent D, et al. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. *J Am Acad Child Adolesc Psychiatry.* Apr 1997;36(4):545-553.

37. Nelson EE. Adolescent Facial Expressions Stimuli Database: Section on Development and Affective Neuroscience, National Institute of Mental Health; 2004.

38. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* Jun 1996;29(3):162-173.

39. Talairach J, Tournoux P. *Co-planar Stereotaxic Altas of the Human Brain*. Stuttgart: Georg Thieme Verlag; 1988.

40. Clark A. http://afni.nimh.nih.gov/afni/doc/misc/afni_roi/index_html/view?searchterm=3dmaskave. 2005.

41. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage.* Oct 1997;6(3):218-229.

42. Gitelman DR, Penny WD, Ashburner J, Friston KJ. Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. *Neuroimage.* May 2003;19(1):200-207.

43. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* 2001;24:167-202.

44. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron.* Sep 16 2004;43(6):897-905.

45. Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron.* Oct 20 2005;48(2):175-187.

46. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature.* Nov 7 2002;420(6911):70-74.

47. Vasa RA, Grados M, Slomine B, et al. Neuroimaging correlates of anxiety after pediatric traumatic brain injury. *Biol Psychiatry.* Feb 1 2004;55(3):208-216.

48. Bystritsky A, Pontillo D, Powers M, Sabb FW, Craske MG, Bookheimer SY. Functional MRI changes during panic anticipation and imagery exposure. *Neuroreport.* Dec 21 2001;12(18):3953-3957.

49. Rauch SL, Savage CR, Alpert NM, Fischman AJ, Jenike MA. The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. *Biol Psychiatry.* Sep 15 1997;42(6):446-452.

50. Blair KS, Smith BW, Mitchell DG, et al. Modulation of emotion by cognition and cognition by emotion. *Neuroimage.* Mar 2007;35(1):430-440.

51. Ochsner KN, Ray RD, Cooper JC, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage.* Oct 2004;23(2):483-499.

52. Davidson RJ, Jackson DC, Kalin NH. Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychological Bulletin.* 2000;126(6):890-909.

53. Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation: A possible prelude to violence. *Science.* 28 July 2000;289:591-594.

54. Beauregard M, Levesque J, Bourgouin P. Neural correlates of conscious self-regulation of emotion. *J Neurosci.* Sep 15 2001;21(18):RC165.

Figure Legends

Figure 1. The Chatroom paradigm consisted of two visits to the laboratory. (a) During the first visit, approximately 2 weeks before the scan, participants viewed photographs of peers and rated how interested they were in chatting online with each peer. A median split divided these ratings into low and high peer desirability categories. Participants were also photographed and told that the same peers would rate them in a similar fashion and learn how they had been rated. (b) During the second visit, while in the scanner, participants reviewed the photographs they had judged previously and rated how interested they thought each peer would be in chatting online with them.

Figure 2. (a) A significant group difference in right amygdala activity is illustrated on high resolution images from a representative subject. Bilateral amygdala activation was greater in patients vs. controls when appraising expected peer evaluation from low vs. high desirability peers ($p<.005$). After correcting for multiple comparisons in the amygdala regions ($p<.05$), the maximum intensity value for the cluster encompassing the left amygdala was $t=3.62$ (x=-23, y=3, z=-20) and for the right amygdala was $t=3.53$ (x=27, y=-3, z=-21) (see *t*-map). (b) Group (patient, control) x peer desirability (low, high) interaction effects on event-elicited percentage signal change in the left ($F[1,26]=13.26$, $p=.001$) and right amygdala ($F[1,26]=12.91$, $p=.001$). Data were extracted at fMRI acquisition during appraisal of expected peer evaluation. Each subject's data were converted to percentage signal change using each subject's voxelwise time series mean as a baseline. Data were then averaged within each functionally defined amygdala region of interest.

Figure 3. Significant group differences in functional connectivity between the right amygdala and left ventrolateral prefrontal cortex (vlPFC) during task performance. Correlation data were averaged within each region that survived a spatial clustering procedure using a corrected $p<0.05$ and extracted to illustrate coactivation patterns within each group. (a) Cross-hairs centered on activation indicating significant group difference in coactivation between the right amygdala seed (x=27, y=-3, z=-21) and left vlPFC, x=-32, y=44, z=-5, $t(26)=3.79$, $p < .01$ (activation survives $p<.001$). (b) Extracted correlation data indicated that patients had significantly greater positive connectivity than controls between activation in the amygdala and vlPFC, specifically during the low peer desirability events. (c) Association between amygdala-vlPFC connectivity and total SCARED score, Spearman $r=.60$, p=.001, $N=27$.

Table 1. Demographic and Clinical Characteristics of Sample and Task Ratings by Group.

	Patients (*n*=14)	Controls (*n*=14)	Statistic	*p*-value
Age, yrs.	12.30±2.76	12.58±2.54	$t(26)=0.27$	0.79
IQ	113.36±14.69	117.86±8.06	$t(26)=1.01$	0.32
Female sex, No. (%)	10 (71.4)	10 (71.4)	$\chi^2=0.0$	1.00
Parent education level[a]	6.27±0.90	6.00±1.00	$t(22)=-0.70$	0.49
Current DSM-IV diagnosis, No. (%)[b]				
Generalized anxiety disorder (GAD)	9 (64.3)	0		
Social phobia (SP)	8 (57.1)	0		
Separation anxiety disorder (SAD)	4 (28.6)	0		
Pediatric Anxiety Rating Scale score[c]	15.21±2.69	NA		
Interest in peers[d]	37.57±19.73	40.29±14.97	$t(26)=0.41$	0.68
Expected peer evaluation[d]	42.14±12.25	53.55±15.30	$t(26)=2.17$	0.04
Low desirable peers	36.06±17.42	43.79±21.57	$t(26)=1.04$	0.31
High desirable peers	48.43±14.27	63.44±15.04	$t(26)=2.71$	0.01

Data are given as mean ± standard deviation except where indicated otherwise. NA, not applicable. [a]Level ranges from 1 (<7 years education) to 7 (graduate/ professional degree). [b]One SP patient had comorbid attention-deficit/hyperactivity disorder. Five GAD, SP, and/or SAD patients had comorbid specific phobia. [c]Items range from 0 (none) to 5 (extreme) anxiety symptoms, total score range is 0 to 25. [d]Scale ranges from 0 (not interested) to 100 (very interested) for participants' interest in chatting with peers and participants' expectation of peers' interest in them.

Table 2. Spearman Correlations among Task Ratings, Anxiety Severity, Amygdala Activation, and Amygdala-Ventrolateral-Prefrontal-Cortex Connectivity across Participants (*N*=28).

	Interest in peers[a]	Expected peer evaluation[b]	Total SCARED score[c]	L amygdala activation[d]	R amygdala activation[d]	R amygdala-vlPFC[d]
Interest in peers	--					
Expected peer evaluation	.56**	--				
Total SCARED score	-.13	-.38*	--			
L amygdala activation	.12	-.11	.34	--		
R amygdala activation	.07	-.17	.42*	.69**	--	
R amygdala-vlPFC	-.09	-.39*	.60**	.30	.41*	--

* p < .05, ** p < .01. L=left; R=right; SCARED=Screen for Child Anxiety Related Emotional Disorders; vlPFC=ventrolateral prefrontal cortex. [a]Scale ranges from 0 (not interested) to 100 (very interested) for participants' interest in peers. [b]Scale ranges from 0 (not interested) to 100 (very interested) for participants' expectations of peers' interest in them. [c]Items range from 0 (not true) to 2 (very/often true) anxiety symptoms, total score range is 0 to 82. [d]Activation while viewing undesirable vs. desirable peers.

Table 3. Activation Areas in Patients vs. Controls for the Low vs. High Peer Desirability Contrast while Appraising Expected Peer Evaluation (*df* = 26)

Region	x	y	z	*t*	BA	Volume (vmul)
Left anterior cingulate	-15	30	-8	-3.53	32	358
Left amygdala	-23	3	-20	3.62	NA	174
Right amygdala	27	-3	-21	3.53	NA	164
Left Cerebellum	-5	-70	-29	3.66	NA	153
Left middle/inferior frontal gyrus	-41	43	5	-3.38	46	153

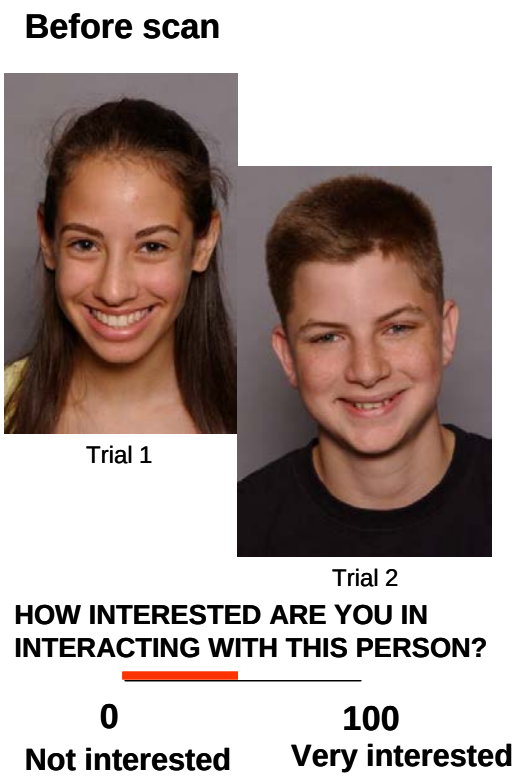
Negative *t*-values indicate greater activation in controls vs. patients; positive *t*-values indicate greater activation in patients vs. controls. Activations survived a small-volume correction at $p < .01$, with a voxel threshold of 92. LPI coordinates are reported.

Table 4. Group Differences in Voxels with Significant Associations with the Right and Left Amygdala Seed Voxels for the Low vs. High Peer Desirability Contrast

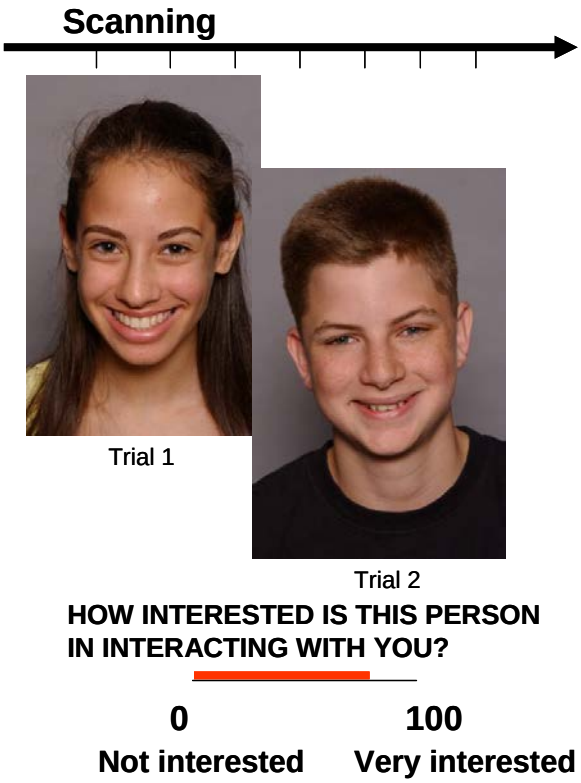
Correlation direction	x	y	z	*t*	Region	BA	k
Connectivity with right amygdala							
P (+) > C (-)	-32	44	-24	3.79	L middle frontal gyrus	47	12
C > P	11	-14	-16	-3.32	R parahippocampal gyrus	34/28	18
C > P	5	-38	-25	-4.39	R cerebellum	NA	37
C > P	-23	-77	33	-3.62	L precuneus	19	46
Connectivity with left amygdala							
C > P	-14	-65	18	-3.03	L precuneus	31	9
C > P	-41	-11	-4	-2.97	L insula	13	12
C > P	-29	-62	3	-3.65	L middle occipital gyrus	19	13
C > P	17	62	24	-3.71	R superior frontal gyrus	10	20
P > C	47	2	-25	3.48	R middle temporal gyrus	21	20
C > P	-29	38	-4	-3.26	L parahippocampal gyrus	36/37	22

Abbreviations: P=patients; C=controls; BA=Brodmann Area; k=number of surviving voxels; NA, Not applicable. (+)=positive correlation, (-)=negative correlation. Each line in the table represents one voxel within the specific neural region. All activations are corrected for multiple comparisons at $p<0.01$ and spatial extent of 216 vmul. LPI coordinates are reported.

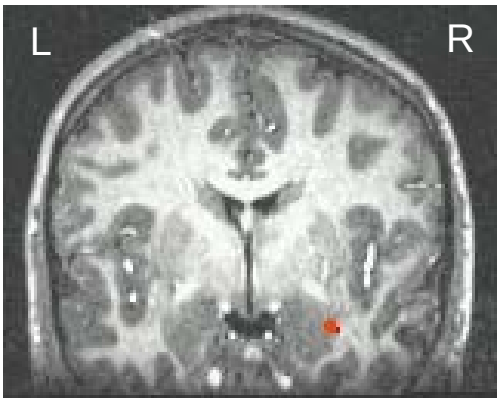
(a)


Before scan
Trial 1
Trial 2
HOW INTERESTED ARE YOU IN INTERACTING WITH THIS PERSON?
0
Not interested
100
Very interested

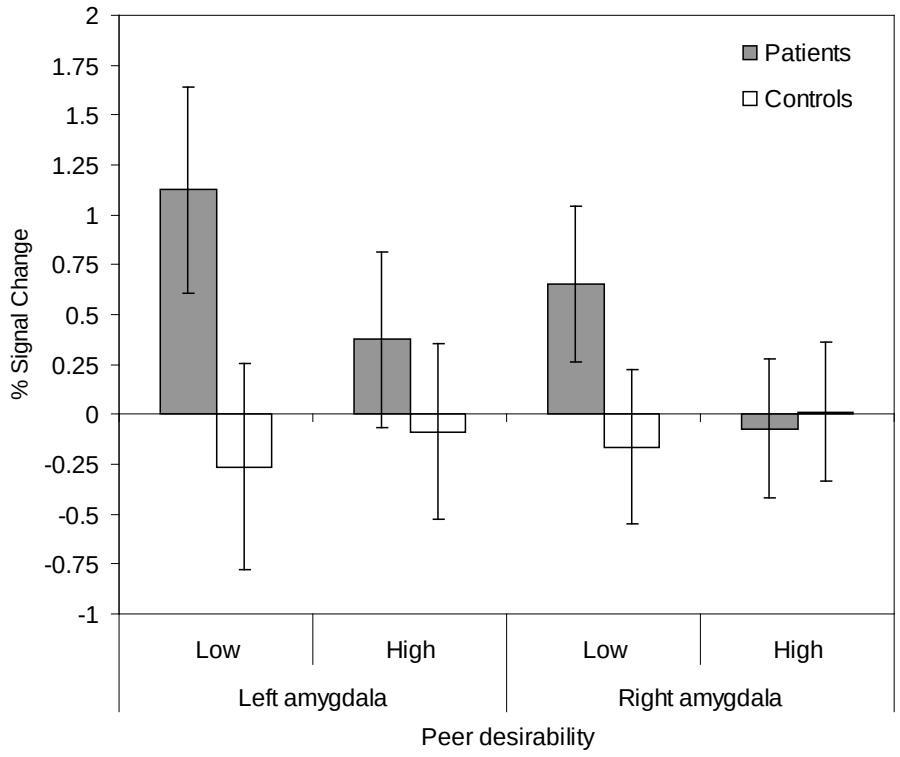
(a)


Scanning
Trial 1
Trial 2
HOW INTERESTED IS THIS PERSON IN INTERACTING WITH YOU?
0
Not interested
100
Very interested

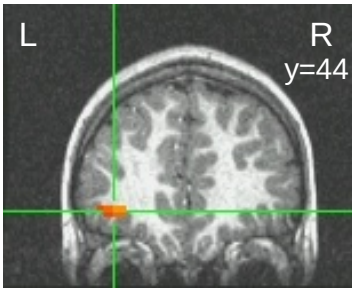
(a)


L
R

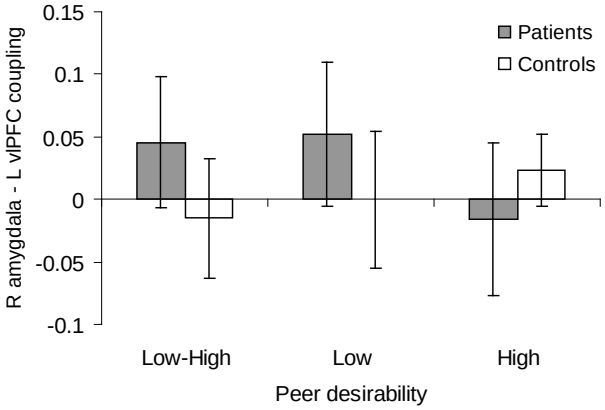
(b)


2
1.75
1.5
1.25
1
0.75
0.5
0.25
0
-0.25
-0.5
-0.75
-1
% Signal Change
Patients
Controls
Low
High
Low
High
Left amygdala
Right amygdala
Peer desirability

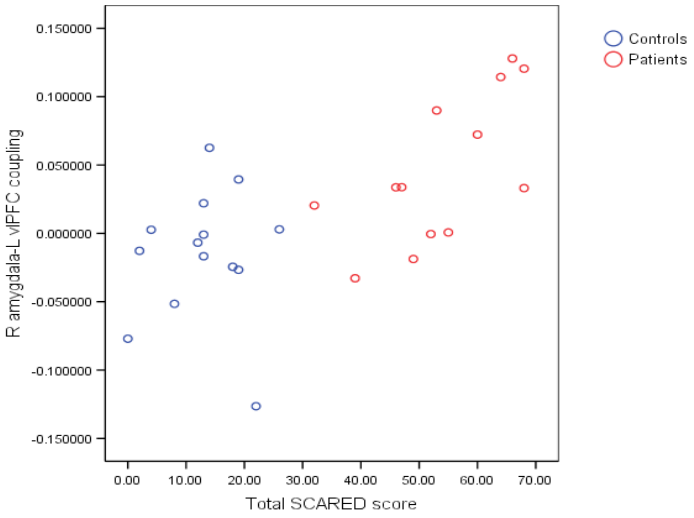
(a)


L
R
y=44

(b)


R amygdala - L vlPFC coupling
0.15
0.1
0.05
0
-0.05
-0.1
Patients
Controls
Low-High
Low
High
Peer desirability

(c)


R amygdala-L vlPFC coupling
0.150000
0.100000
0.050000
0.000000
-0.050000
-0.100000
-0.150000
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
Total SCARED score
Controls
Patients