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Increased neural response to peer rejection associated with adolescent depression and pubertal development

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Sensitivity to social evaluation has been proposed as a potential marker or risk factor for depression, and has also been theorized to increase with pubertal maturation. This study utilized an ecologically valid paradigm to test the hypothesis that adolescents with major depressive disorder (MDD) would show altered reactivity to peer rejection and acceptance relative to healthy controls in a network of ventral brain regions implicated in affective processing of social information. A total of 48 adolescents (ages 11–17), including 21 with a current diagnosis of MDD and 27 age- and gender-matched controls, received rigged acceptance and rejection feedback from fictitious peers during a simulated online peer interaction during functional neuroimaging. MDD youth showed increased activation to rejection relative to controls in the bilateral amygdala, subgenual anterior cingulate, left anterior insula and left nucleus accumbens. MDD and healthy youth did not differ in response to acceptance. Youth more advanced in pubertal maturation also showed increased reactivity to rejection in the bilateral amygdala/parahippocampal gyrus and the caudate/subgenual anterior cingulate, and these effects remained significant when controlling for chronological age. Findings suggest that increased reactivity to peer rejection is a normative developmental process associated with pubertal development, but is particularly enhanced among youth with depression.

Keywords: depression; neuroimaging; social exclusion; rejection; adolescence

INTRODUCTION

Rates of depression increase dramatically during adolescence, with one in seven adolescents experiencing an episode of depression prior to adulthood (Kessler, 1994; Beesdo *et al.*, 2009a). This increase begins after mid-puberty and has been linked to the rise in testosterone and estradiol (Angold *et al.*, 1998; Angold *et al.*, 1999; Joinson *et al.*, 2012). Pubertal maturation also appears to encompass a period of neural plasticity, particularly for some kinds of socio-affective learning (Crone and Dahl, 2012), thus, it may be an opportune time to modify neurobehavioral risk factors in ways that could potentially have a positive impact on the life course trajectory. For these reasons, there is a critical need for research that advances mechanistic understanding of normal and abnormal development of social and affective processes (and their neurobehavioral underpinnings) during adolescence, in ways that can inform early prevention and intervention approaches at this vulnerable time in the life course trajectory.

Theorists have proposed that increased sensitivity to social rejection during adolescence may be one factor that can help to explain the increase in depression during the teen years (Prinstein and Aikins, 2004; Davey *et al.*, 2008; Stroud *et al.*, 2009; Silk *et al.*, 2012a). During adolescence, normative changes in the social context along with maturational changes in neural and endocrine systems that influence processing of motivational and socio-affective information could contribute to increased sensitivity to social evaluation, creating a potential window of vulnerability for depression during adolescence.

Adolescents begin to spend more time with their peers and these peer relationships take on increased affective and motivational salience (Larson and Asmussen, 1991; Steinberg and Morris, 2001). It is not known to what extent neural and endocrine changes contribute to the increased salience of peer social status during adolescence, but it is likely that changes such as remodeling of the fronto-striatal dopaminergic systems and a puberty-linked rise in sex hormones could contribute to an increase in motivations to obtain and defend social status among peers (Nelson *et al.*, 2005; Blakemore, 2008; Steinberg, 2008; Crone and Dahl, 2012). Although these changes are normative, they also may lead to increased risk for depression among youth who are particularly reactive to social evaluation, and/or experience high levels of peer rejection and low levels of peer acceptance.

Recently, researchers have begun to examine the neural response to peer acceptance and rejection using virtual peer paradigms such as the Cyberball virtual ball tossing task (Eisenberger *et al.*, 2003) and the Chatroom Task (Guyer *et al.*, 2008). Findings indicate that exclusion/rejection in adolescents activates a ventral affective salience network including the amygdala, medial prefrontal cortex, ventral and dorsal anterior cingulate cortex (ACC), and anterior insula, as well as ventrolateral areas of the prefrontal cortex (VLPFC) involved in the regulation of social distress (Eisenberger *et al.*, 2003; Guyer *et al.*, 2008; Masten *et al.*, 2009; Bolling *et al.*, 2011a; Sebastian *et al.*, 2011). In particular, several studies of adolescents have implicated the subgenual ACC (sgACC), as well as a larger ventral portion of the ACC, in responding to social exclusion and rejection (Masten *et al.*, 2009; Bolling *et al.*, 2011a; Sebastian *et al.*, 2011). Peer feedback tasks have also indicated that social acceptance activates regions involved in reward processing, particularly the nucleus accumbens (NAcc) (Davey *et al.*, 2010; Gunther Moor *et al.*, 2010).

Emerging data from these studies is consistent with the idea that neural response to social evaluation may increase during adolescence. For example, several studies have shown age-related increases across childhood and adolescence in neural response to peer evaluation in regions of this affective processing network, including the NAcc and

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insula, striatum, medial PFC and ventral ACC (Guyer *et al.*, 2009; Gunther Moor *et al.*, 2010; Bolling *et al.*, 2011a). One study that compared response to social exclusion on the Cyberball task among early and middle adolescents and young adults found that activity in the sgACC in response to exclusion was strongest among early adolescents compared with mid adolescents and adults, possibly suggesting a period of peak sgACC reactivity to social rejection during early adolescence (Gunther Moor *et al.*, 2012). There is also evidence that VLPFC activity to social evaluation increases across childhood and adolescence (Gunther Moor *et al.*, 2010; Bolling *et al.*, 2011a), but is decreased in adolescents compared with adults (Sebastian *et al.*, 2011), potentially suggesting that adolescents are less effective at recruiting regulatory resources in response to social threat.

These apparent increases in sensitivity to social evaluation during adolescence may be linked to neurodevelopment of fronto-striatal-limbic systems that respond to social and emotional stimuli (see Paus *et al.*, 2008; Pfeifer and Blakemore, 2012). Gaining a better understanding of how, specifically, pubertal development influences neural responses to social feedback may be helpful in understanding mechanisms associated with the pubertal increased risk for depression, as well as other emotional and behavioral health problems that increase in this maturational period, such as substance abuse and risky behaviors (Steinberg, 2005). Current theoretical models (Nelson *et al.*, 2005; Steinberg, 2008) suggest that changes in socio-emotional behavior during adolescence may be mediated by the influence of sex hormones on neural circuits that support the processing of social and emotional stimuli. Sex hormones are known to play a role in remodeling and activating fronto-limbic-striatal circuits during adolescent brain development (Sisk and Foster, 2004). Consistent with this model, a small body of emerging data has linked self-reported pubertal maturation to increases in sensation-seeking (Martin *et al.*, 2002), physiological and subjective reactivity to emotional words (Silk *et al.*, 2009), and neural response to affective faces (Forbes *et al.*, 2011; Moore *et al.*, 2012). In this study, we examined whether self-reported pubertal maturation is related to neural response to social evaluation.

In addition, there has been little research examining neural response to social evaluation in adolescents with depression. Behavioral studies indicate that rejection from peers often precedes depressive symptoms (Nolan *et al.*, 2003; Rudolph and Conley, 2005). Rejection via social media and mobile technologies (i.e. facebook, text messaging) is increasingly prevalent, and has been linked to teen suicide and depression (O’Keeffe *et al.*, 2011; Luxton *et al.*, 2012). Yet, little is known about the neural response to social evaluation during adolescence in youth with depression, especially in clinical samples. Existing research with depressed youth suggests that adolescents with major depressive disorder (MDD) show altered amygdala reactivity in response to threatening faces (Roberson-Nay *et al.*, 2006; Beesdo *et al.*, 2009b) and decreased striatal response to monetary reward (Forbes *et al.*, 2006). One recent Cyberball study conducted in a non-clinical sample of adolescents showed that sgACC activity to social exclusion predicted increases in depressive symptoms over 1 year (Masten *et al.*, 2011), but neural response to rejection has not been investigated in clinically depressed adolescents. We also investigated whether adolescents with depression differ in response to peer acceptance. In the only study of which we are aware to address this question, Davey *et al.* (2011) provided positive or neutral feedback to 15- to 24-year olds with MDD about how fictitious peers rated their likability. Contrary to findings from studies using monetary reward (Forbes *et al.*, 2006), Davey *et al.* (2011) found that teens and young adults with depression showed increased amygdala response to acceptance compared with controls, highlighting the potential for important differences in neural response to social vs monetary rewards in depression.

In this study, we utilized a new virtual peer interaction task, the Chatroom Interact Task (Silk *et al.*, 2012b), to probe the neural responses to rejection and acceptance from virtual peers during live simulated interaction in a sample of clinically depressed youth and healthy controls. Unlike an earlier Chatroom Task (Guyer *et al.*, 2008), in which adolescents evaluate and receive feedback from virtual peers about whether they would like to participate in an online chat, in the Chatroom Interact Task, participants engage in a live online interaction with virtual participants during which they are repeatedly selected (accepted) and not selected (rejected) to discuss various topics of interest to teens. The task was designed to increase ecological validity and participant engagement with the virtual peers.

First we hypothesized that, relative to healthy controls, youth with current MDD would show increased reactivity to peer rejection in a network of ventral brain regions implicated in affective processing of social information, including the amygdala, sgACC, anterior insula, ventral ACC and VLPFC. We also explored whether depressed youth would show altered reactivity to peer acceptance or rejection relative to controls in regions typically associated with reward processing, such as the NAcc and mPFC, but were unsure whether to expect blunted or increased reactivity given conflicting initial findings on response to monetary and social reward in depressed youth (Forbes *et al.*, 2006, 2009; Davey *et al.*, 2011). We further hypothesized that youth more advanced in pubertal development would show increased neural response to peer rejection and acceptance (above and beyond the effects of age) in regions involved in social and affective processing. Finally, we explored whether the association between pubertal status and neural response to peer rejection and acceptance would differ for depressed youth and healthy controls.

METHODS

Participants

Participants were 48 adolescents (34 female, ages 11–17, $M[s.d.]age = 15.48 [1.68]$). Twenty-one adolescents had a current primary diagnosis of MDD based on DSM-IV (American Psychiatric Association, 1994) criteria and 27 were low-risk controls (CON) with no psychiatric history. MDD and CON adolescents did not differ in age, pubertal status, gender, race, or maternal education (all P 's > 0.45). Because the groups were matched on gender, and MDD is more common among females than males (Kessler *et al.*, 2001), both groups had a higher proportion of females than males.

Youth were recruited from pediatrician’s offices and community advertisements. MDD youth were also referred from University and community mental health clinics. Adolescents’ lifetime and present DSM-IV (American Psychiatric Association, 1994) diagnoses were assessed using the Schedule for Affective Disorders and Schizophrenia in School-Age Children—Present and Lifetime version (Kaufman *et al.*, 1997). MDD youth were included if they were on a stable dose of SSRI medication but still met criteria for MDD ($N = 2$). Participants were excluded if they were taking psychoactive medications other than SSRI’s or had metal objects in their body. CON youth were excluded if they met current or lifetime DSM-IV diagnosis for any Axis I disorder. MDD youth were excluded if they had a current diagnosis of obsessive-compulsive disorder, post-traumatic stress disorder, conduct disorder, substance abuse or dependence and ADHD combined type or predominantly hyperactive-impulsive type, or a lifetime diagnosis of bipolar disorder, psychotic depression, schizophrenia, schizoaffective disorder, or a pervasive developmental disorder. Nine MDD youth had a current or past diagnosis of one or more comorbid anxiety disorders (N 's for each anxiety diagnosis were: panic disorder = 1; specific phobia = 4; generalized anxiety disorder = 6; social phobia = 1; separation anxiety disorder = 3; agoraphobia = 1). One MDD youth had a

comorbid diagnosis of ADHD inattentive only subtype and one MDD youth had a diagnosis of oppositional defiant disorder. Informed consent/assent was obtained from participants and their parents at the initial assessment, and all research procedures were approved by the University of Pittsburgh Institutional Review Board.

Chatroom Interact Task

The Chatroom Interact Task was designed to investigate reactions to social acceptance and rejection from virtual peers in an on-line setting (Silk *et al.*, 2012b). On Day 1, participants were shown photographs and fictitious biographical profiles for potential virtual peers. Participants were asked to choose the top five males and top five females that they would be interested in interacting with online at their next visit. Selections were made from within sets of 30 photographs for each age (9–11, 12–14 or 15–17) and gender grouping. Participants also provided their own biographical profile and photograph.

On Day 2 (approximately 2 weeks later), participants returned to the laboratory and were told that they had been matched with four other youth (two males and two females) selected from the first visit and that these youth were ready to participate in a ‘chat game’ online. They reviewed biographical profiles for selected peers prior to the task. The task takes the form of a structured online interaction, rather than a free-form ‘chat’, in order to give the impression that subjects and virtual peers are interacting in real time while maintaining sufficient standardization across subjects and sufficient repetition across trials to conduct analyses. During neuroimaging, pictures of the peers and participant were projected on the screen 2 at a time, as the subject and virtual peers took turns selecting who they would rather talk to about a series of teen interests (e.g. music, friends; Figure 1). The task proceeded in five blocks, each containing 15 trials in which a person was chosen or not chosen to discuss each topic (total run time 16.7 min). Stimuli were presented using E-prime 1.0 software (Psychology Software Tools, Pittsburgh, PA). Each block began with an instruction about who would be making choices for that block (agent). The photograph of the agent was shown at the bottom left corner of the screen and the photographs of the other two players were shown next to each other in the middle of the screen, as in Figure 1. At the beginning of

each trial, the question ‘Who would you rather talk to about . . .’ with the selected topic for that trial (i.e. . . . ‘music?’) appeared on the screen for 3.34 s (task component durations were chosen to be multiples of our TR, 1.67 s). Feedback was then provided about which person was chosen (the subject or the virtual peer) for 10.02 s. The photograph of the person who was not chosen was superimposed with an ‘X’ and the photograph of the person who was chosen was highlighted around the border. To maintain engagement in the task, in all trials in which the participant was not the agent, he/she was asked to press a button to indicate whether the person on the left or the right was chosen.

As in Silk *et al.* (2012b), trials were arranged in blocks so that participants experienced two ‘accept’ blocks in which they were chosen two-third of the time (one same-gender and one opposite-gender) and two ‘reject’ blocks in which they were rejected two-third of the time (one same-gender and one opposite-gender). Topics were presented randomly and repeated in each block, but with a different ‘agent’ for each block. The first three blocks were played with the two same gender virtual peers and the last two blocks were played with the two opposite gender virtual peers. In block 1, the subject was the ‘agent’ and made choices among the two same gender virtual peers. Analyses focus on blocks 2–5, in which the subject was chosen/not chosen by the virtual peers (first same gender, then opposite-gender). Due to time constraints, we did not include a sixth block in which the subject could make choices among the two opposite gender peers. Blocks 2–5 included 60 trials (30 accept and 30 reject), with half of all accept and reject trials from a same gender peer and half from an opposite gender peer. The order of accept and reject blocks and trials were randomized within gender grouping. Participants were not led to believe that they would have additional interaction with the virtual peers beyond the structured ‘chat game’ (i.e. although they chose which participants they would be more interested in discussing topics with, they were not led to expect to engage in an open discussion on these topics with the virtual peers).

Debriefing questionnaire

Participants rated how they felt along six dimensions (happy, sad, angry, nervous, included and excluded) on a 1–5 point scale following

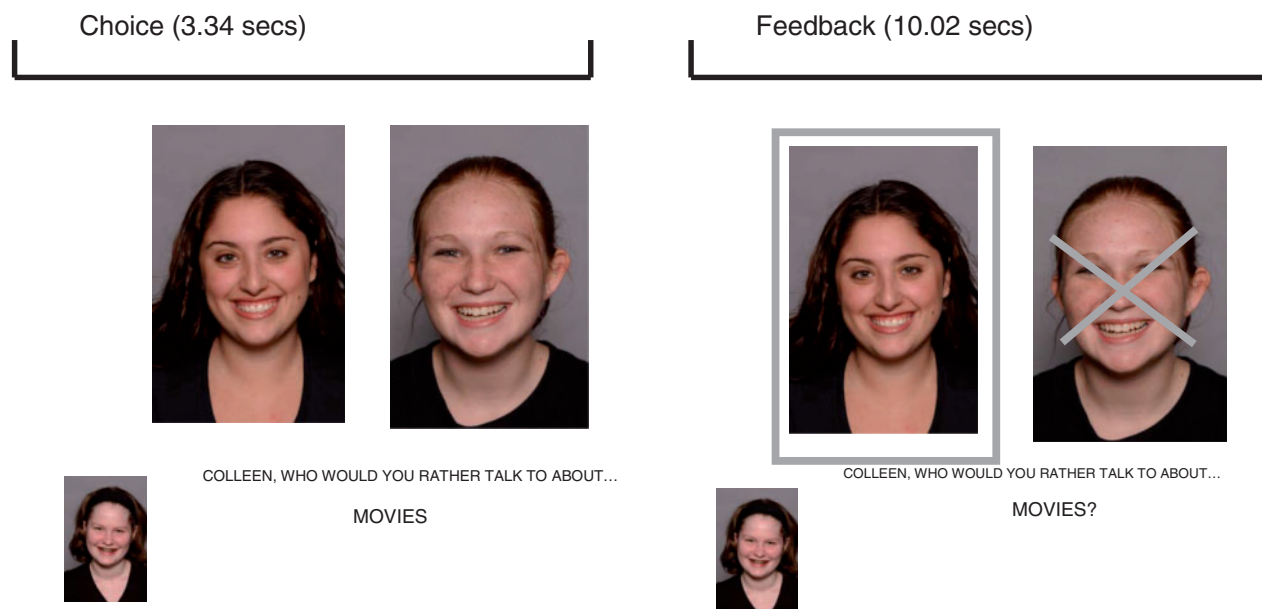


Fig. 1 Depiction of an example trial on the Chatroom Interact Task.

completion of the Chatroom Interact task. Ratings were made after completing the task to determine whether depressed and control subjects differed in mood following completion of the task; therefore, mood ratings were not specific to accept or reject trials. Subjects were debriefed at the conclusion of the task and informed that they had been playing with a preset computer program. Upon questioning, two participants (one MDD and one CON) reported suspicion that the other participants were not real. Analyses were re-run excluding these two participants, and the pattern and significance of findings reported below remained unchanged.

Pubertal status

Self-reported pubertal status was assessed using the Pubertal Development Scale (PDS; Petersen *et al.*, 1988), scored to provide two 5-point scales that differentially capture gonadal and adrenal hormonal signs of pubertal development (Shirtcliff *et al.*, 2009). Physical maturation in humans is marked by independent maturation of the adrenal glands (adrenarche) and the gonads (gonadarche). It is not yet clearly understood how adrenal and gonadal aspects of pubertal maturation may differentially influence neural and behavioral changes during adolescence; therefore, we explored the potential influence of adrenal and gonadal signs of pubertal maturation separately. Signs associated with adrenarche include pubic hair, skin changes and body odor, whereas signs associated with gonadarche include the growth spurt and breast development and menarche (in girls). Scoring takes into account different signs of pubertal development in boys and girls. Scores ranged from 2 to 5 in the present sample.

BOLD functional MRI acquisition, preprocessing and analysis

Imaging acquisition

Images were acquired on a 3T Trio scanner. Thirty-two 3.2 mm slices were acquired parallel to the AC–PC line using a posterior-to-anterior echo planar (EPI) pulse sequence (T2*-weighted imaged depicting BOLD signal; TR = 1670 ms, TE = 29 ms, FOV = 205 mm, flip angle = 75). Thus, there were eight scans per 13.36 s trial. High-resolution T1-weighted MPRAGE images (1 mm, axial) were also collected for use in cross-registration.

Functional MRI data preprocessing

Functional MRI (fMRI) analyses were conducted using NeuroImaging software (NIS) (Fissell *et al.*, 2003), Analysis of Functional Neuroimaging (AFNI) (Cox, 1996) and custom Matlab routines. Functional imaging data were corrected for motion using 3dVolReg implemented in AFNI using the first image as a reference. Quadratic trends within runs were removed and outliers over 1.5 interquartile range from the 25th or 75th percentiles were Winsorized using nis-correct from NIS. Data were temporally smoothed using a 4-point Gaussian filter and converted to %-change based on the median of all imaging data. Data were co-registered to the Colin-27 Montreal Neurological Institute (MNI) template using AIR's 32-parameter non-linear automated warping algorithm (Woods *et al.*, 1998) and spatially smoothed using a 6 mm FWHM filter.

Plan of analyses

We conducted Region of Interest (ROI) analyses on a priori regions specified using AFNI's Talairach atlas including the sgACC, bilateral anterior insula, bilateral NAcc, bilateral ventrolateral prefrontal cortex (VLPFC), ventral ACC (vACC) and medial prefrontal cortex (mPFC). Because AFNI's Talairach atlas ROI incorporates a smaller volume than the anatomical boundaries of the amygdala, the amygdala ROI was anatomically defined by hand tracing on the MNI Colin 27 brain

(as in Siegle *et al.*, 2007). The long duration of each trial enabled slow event related model-free analysis (i.e. examining the empirical shape of the hemodynamic response using scan-within-trial as a repeated measure) and thus eliminated the need for event deconvolution. BOLD activity in ROIs was extracted and effects were tested using mixed-effect analyses with participants as a random factor, valence (acceptance vs rejection) and scan-within-trial (eight scans within each 13.36 s trial) as repeated measures, and group as a fixed factor, assuming an AR1 covariance structure using restricted maximum likelihood estimation. As is standard for slow-event-related analyses, trial-related responses were 'baseline-corrected', i.e. considered with activity at the first scan subtracted from the rest of the scan yielding activity uniquely associated with the trial rather than activity lingering from previous trials. Type I error was controlled using a Bonferroni correction ($P < 0.005$) for mixed effects analyses. None of the a priori regions showed group \times valence \times scan interaction effects, indicating that group differences were primarily a function of mean differences in BOLD amplitude across the timecourse. Therefore, results presented below highlight group \times valence interactions, with BOLD activity averaged across scans for each valence (but see Supplementary Figure S1 for waveforms depicting BOLD activity across scans). We also examined whether any of the group \times valence effects were additionally moderated by gender of the virtual peers (same vs opposite gender) by testing for group \times valence \times gender interactions in the mixed effects models. To identify additional brain areas that differed between MDD and healthy youth in response to rejection or acceptance, a supplemental whole-brain voxelwise ANOVA (analysis of variance) was conducted with participant as a random factor, and group, valence and scan-within-trial as fixed factors. To control type 1 error at $P < 0.05$ across the whole brain for each family of tests (i.e. $< 5\%$ chance that even one voxel was identified in error), voxelwise whole-brain tests at a given statistical threshold ($P < 0.001$) were subjected to empirically determined contiguity thresholds based on the spatial autocorrelation of statistical maps using AFNI's AlphaSim program.

Given the lack of existing data on how pubertal development might influence neural response to peer acceptance and rejection, puberty effects were examined using a whole-brain analysis rather than an ROI approach. A whole-brain regression using AFNI's 3dRegana was conducted to identify areas showing a main effect of pubertal status on response to rejection and/or acceptance controlling for the effects of chronological age. To examine whether the relationship between pubertal status and neural response to social evaluation differed for healthy youth and controls, similar whole brain regression analyses were conducted to identify areas showing group \times pubertal status interaction effects. Analyses were conducted separately using adrenal and gonadal PDS subscales.

RESULTS

Subjective ratings

As shown in Table 1, MDD youth rated themselves as feeling more 'sad', 'nervous' and 'excluded', and less 'happy' immediately following the Chatroom Interact Task compared with CON youth. The two groups did not differ on ratings of feeling 'included'.

fMRI: ROI analyses of group \times valence effects

As shown in Table 2, there were significant group \times valence interaction effects in our a priori regions including bilateral amygdala, sgACC, left anterior insula, left NAcc, bilateral VLPFC and vACC, but not the mPFC. Pairwise comparisons also shown in Table 2 revealed that MDD youth showed increased brain activity to rejection trials compared with CON youth in the bilateral amygdala, sgACC, left anterior insula and left NAcc, but did not differ in response to acceptance trials.

As shown in Figure 2, relative to CON, MDD youth showed increased activation to rejection in the sgACC and left anterior insula. Activations in the left NAcc were also higher during rejection trials in MDD youth relative to CON youth, but this was driven by a deactivation (i.e. decreased activation from a pre-trial baseline) of the NAcc in response to rejection among the CON but not MDD youth. There was also deactivation of the bilateral amygdala in response to rejection compared with baseline among healthy controls that was attenuated in MDD youth. Pairwise *t*-tests comparing MDD youth to controls were not significant in the bilateral VLPFC or vACC, thus these results were not further considered (Supplementary Figure S2). There was also a significant group \times valence \times gender (same vs opposite) interaction effect in the bilateral amygdala, shown in Supplementary Figure S3.

Although not a primary focus of the study, we also found valence main effects in several of the ROIs, including the bilateral insula, bilateral VLPFC, mPFC and vACC (all corrected *P*'s < 0.005). As shown in Supplementary Figure S4, there was greater activation to acceptance compared with rejection in each of these areas across the entire sample.

fMRI: supplemental whole-brain analyses

Supplemental whole-brain analyses revealed no additional group \times valence effects, but several group \times valence \times scan interactions shown in Supplementary Table S1. Notably, MDD youth showed sustained activation in the dorsal ACC (dACC) relative to controls during the later 3 s of the feedback phase during rejection trials (Figure 3). There were

Table 1 Group differences in pubertal status and post-task subjective ratings

	CON <i>M</i> (s.d.)	MDD <i>M</i> (s.d.)	<i>t</i>	df	Cohen's <i>d</i>
Pubertal status					
Adrenal	4.35 (0.97)	4.55 (0.83)	-0.77	44	-0.22
Gonadal	3.96 (0.66)	3.80 (0.75)	0.77	44	0.23
Post-task ratings					
Happy	3.24 (1.08)	2.43 (0.76)	2.93**	46	0.87
Sad	1.35 (0.43)	1.93 (0.78)	-3.26**	46	-0.92
Nervous	1.44 (0.68)	2.29 (1.19)	-3.08**	46	-0.88
Included	3.17 (1.00)	2.86 (0.78)	1.17	46	0.35
Excluded	1.52 (0.63)	2.17 (0.78)	-3.19**	46	-0.92

***P* < 0.01.

Table 2 ROI analyses: group \times valence interaction effects

A priori regions	Mixed-effects analysis group \times valence interaction	Pairwise comparisons: MDD > CON	
		Accept	Reject
R amygdala	$F_{(1, 305)} = 17.91^{***}$, $\eta^2 = 0.06$	$t_{(46)} = 0.35$, <i>P</i> = 0.73	$t_{(46)} = 2.13$, <i>P</i> = 0.04*, <i>d</i> = 0.62
L amygdala	$F_{(1, 274)} = 28.91^{***}$, $\eta^2 = 0.10$	$t_{(46)} = 1.26$, <i>P</i> = 0.22	$t_{(46)} = 2.21$, <i>P</i> = 0.03*, <i>d</i> = 0.64
sgACC	$F_{(1, 298)} = 28.01^{***}$, $\eta^2 = 0.09$	$t_{(46)} = 0.32$, <i>P</i> = 0.75	$t_{(46)} = 3.06$, <i>P</i> = 0.00**, <i>d</i> = 0.89
R anterior insula	$F_{(1, 422)} = 3.24$, $\eta^2 = 0.01$	$t_{(46)} = 0.04$, <i>P</i> = 0.97	$t_{(46)} = 0.94$, <i>P</i> = 0.35, <i>d</i> = 0.27
L anterior insula	$F_{(1, 393)} = 19.40^{***}$, $\eta^2 = 0.05$	$t_{(46)} = 0.13$, <i>P</i> = 0.90	$t_{(46)} = 2.03$, <i>P</i> = 0.05*, <i>d</i> = 0.59
R NAcc	$F_{(1, 326)} = 3.94$, $\eta^2 = 0.01$	$t_{(46)} = 0.55$, <i>P</i> = 0.59	$t_{(46)} = 2.04$, <i>P</i> = 0.05*, <i>d</i> = 0.59
L NAcc	$F_{(1, 320)} = 16.15^{***}$, $\eta^2 = 0.05$	$t_{(46)} = 0.10$, <i>P</i> = 0.92	$t_{(46)} = 2.47$, <i>P</i> = 0.02*, <i>d</i> = 0.72
R VLPFC	$F_{(1, 375)} = 13.29^{***}$, $\eta^2 = 0.03$	$t_{(46)} = 0.32$, <i>P</i> = 0.75	$t_{(46)} = 1.68$, <i>P</i> = 0.10, <i>d</i> = 0.50
L VLPFC	$F_{(1, 408)} = 11.29^{***}$, $\eta^2 = 0.03$	$t_{(46)} = 0.14$, <i>P</i> = 0.89	$t_{(46)} = 1.59$, <i>P</i> = 0.12, <i>d</i> = 0.46
mPFC	$F_{(1, 368)} = 2.05$, $\eta^2 = 0.01$	$t_{(46)} = 0.87$, <i>P</i> = 0.39	$t_{(46)} = 1.86$, <i>P</i> = 0.07, <i>d</i> = 0.54
vACC	$F_{(1, 314)} = 8.36^{***}$, $\eta^2 = 0.03$	$t_{(46)} = 0.10$, <i>P</i> = 0.92	$t_{(46)} = 1.68$, <i>P</i> = 0.10, <i>d</i> = 0.50

****P* < 0.005 (Bonferroni corrected *P*-value for mixed effects *F*-tests), ***P* < 0.01, **P* < 0.05; *d*, Cohen's *d* effect size (0.20 = small, 0.50 = medium, 0.8 = large); η^2 , eta-squared effect size (0.01 = small, 0.06 = medium, 0.14 = large). ROI analyses were repeated excluding the two participants taking SSRI medications and all results were replicated, with the exception of the group \times valence interaction effect in the vACC, which was no longer significant [$F_{(1, 302)} = 5.98$, *P* = 0.02, $\eta^2 = 0.02$].

also several valence main and valence \times scan interaction effects, shown in Supplementary Table S2.

fMRI: Whole-brain analysis of pubertal development

Whole-brain regression analyses revealed that more advanced pubertal status, specifically signs associated with adrenarche (i.e. pubic hair and body odor), were associated with increased activity (i.e. less deactivation) to rejection above and beyond the effects of age in the right amygdala/parahippocampal gyrus (Figure 4a) and the left amygdala/parahippocampal gyrus, as well as the caudate extending into the sgACC (*P* < 0.001, 22 voxels contiguity). There were no other areas that showed a main effect for pubertal status. These effects were qualified by group \times pubertal status interaction effects (*P* < 0.001, 30 voxels contiguity) indicating that, contrary to hypotheses, the relationship between pubertal maturation and response to rejection in the left amygdala and caudate/sgACC was stronger among healthy controls than MDD youth. As shown in Figure 4b and c, pubertal maturation was associated with increased sgACC and amygdala activity in controls, but not among depressed youth, who showed greater sgACC and amygdala response to rejection earlier in puberty. There were no significant main or interaction effects for gonadal signs of pubertal maturation on response to rejection, and no effects for either measure of pubertal maturation on response to acceptance.

DISCUSSION

There is little developmental affective neuroscience research to guide strategies for early intervention or prevention of depression during adolescence. The results of this study suggest that although increased neural response to rejection appears to be normative across adolescence, this response is particularly heightened among youth with depression. Relative to healthy controls, MDD youth displayed a potentiated response to peer rejection in a ventral network of brain regions involved in the identification of emotional and social stimuli and the generation of affective states (Phillips et al., 2003), including the sgACC, anterior insula, amygdala and NAcc. These findings highlight potential neural mechanisms that may contribute to the relationship between peer rejection and MDD.

The finding of heightened sgACC activity to social rejection in adolescents with MDD is consistent with a recent Cyberball study conducted in a non-clinical sample of adolescents that showed that sgACC activity to social exclusion predicted increases in depressive symptoms over 1 year (Masten et al., 2011). The sgACC has been suggested to play

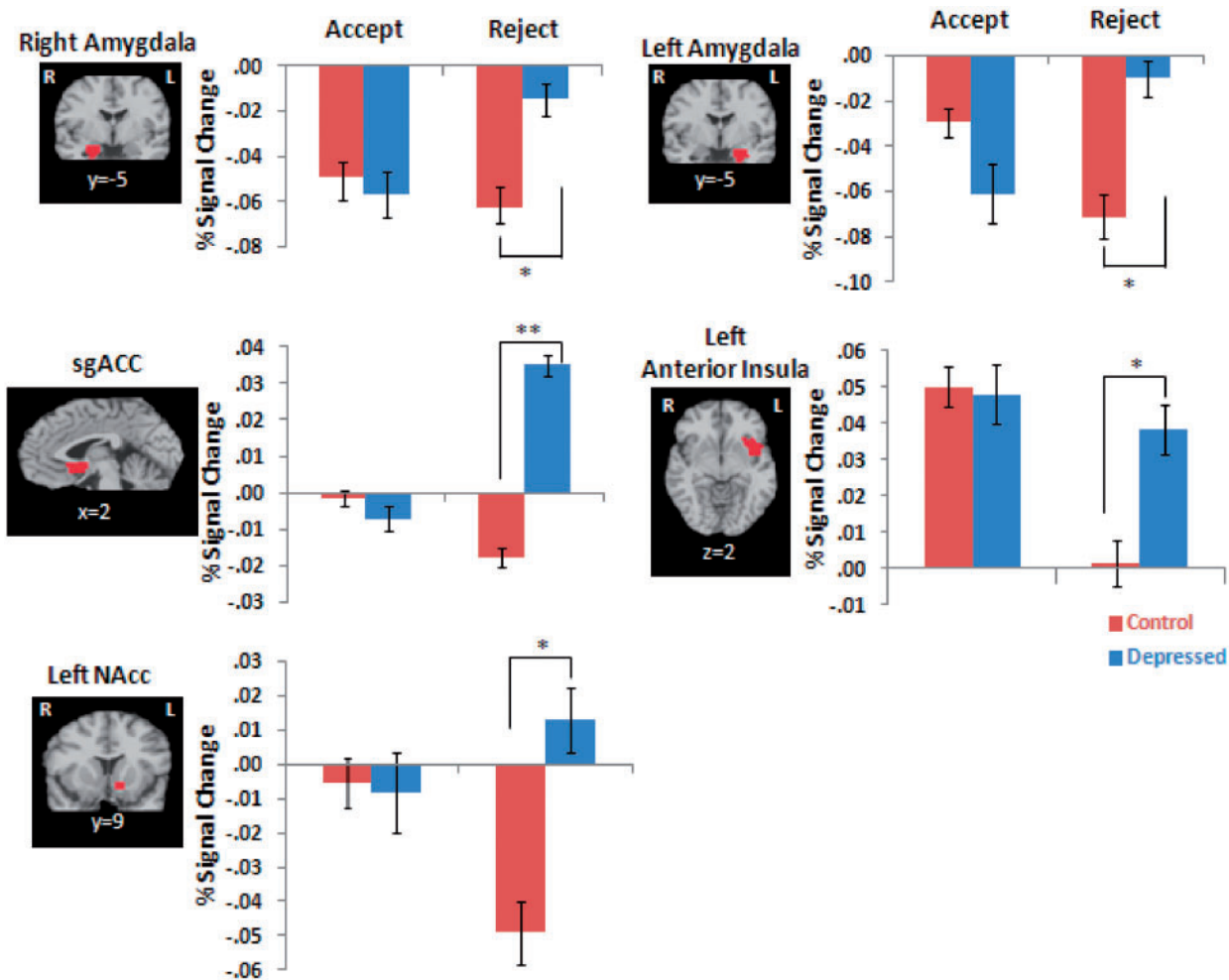


Fig. 2 ROI analyses revealing significant group \times valence (acceptance vs rejection) interaction effects in the bilateral amygdala, sgACC, left anterior insula and bilateral NAcc (corrected $P < 0.005$). Pairwise comparisons show that MDD youth had significantly greater brain activity to rejection trials compared with CON youth ($*P < 0.05$, $**P < 0.01$). No significant group differences were found in acceptance trials.

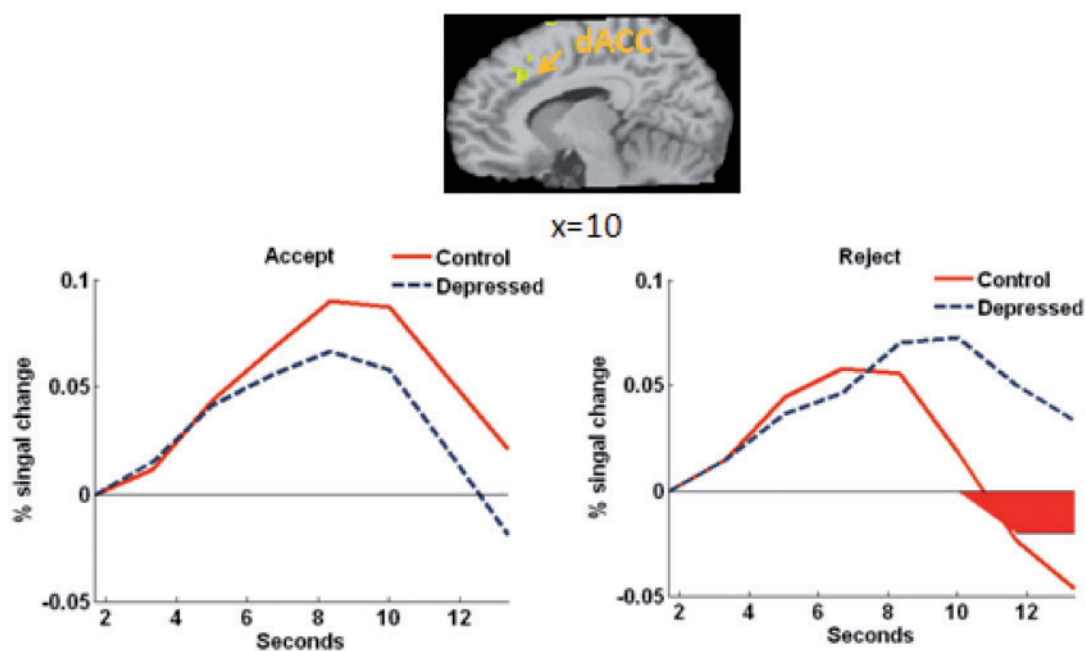


Fig. 3 Time-course in the dACC showing group \times valence \times scan interaction effect in whole-brain analysis ($P < 0.001$, 18 voxels contiguity). MDD youth showed increased dACC activation to rejection compared with controls from 11.69 to 13.36 s [$t_{(46)} = 3.23$, $P < 0.01$; significant scans shown in red].

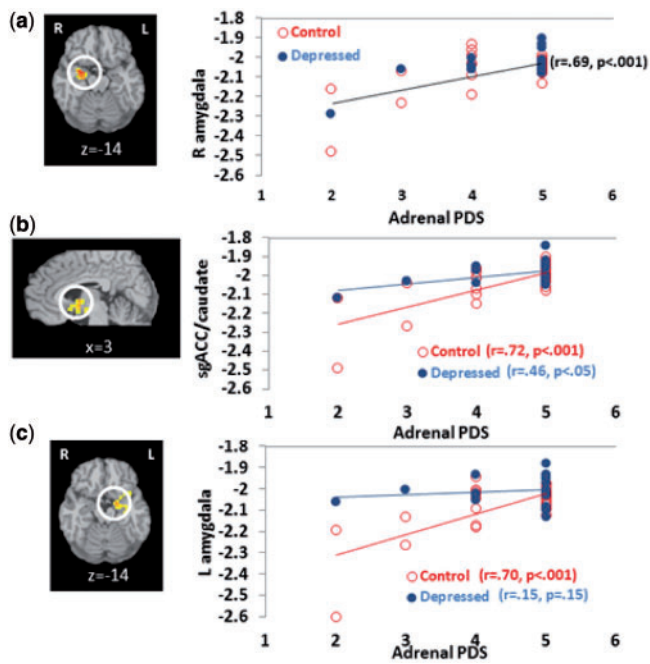


Fig. 4 Relationships between pubertal maturation and response to rejection (negative numbers reflect deactivation from a pre-trial baseline). (a) Significant main effects of adrenal PDS on brain response to rejection were found in the right amygdala, controlling for age; (b, c) significant interaction effects between group and adrenal PDS on brain response to rejection were found in the sgACC/caudate and left amygdala/parahippocampal gyrus, respectively.

a role in monitoring, modulating and/or generating negative emotions (Mayberg, 2003; Siegle *et al.*, 2012) and increases in adults during sadness inductions (Mayberg *et al.*, 1999). Adults with MDD show a reduction in gray matter volume and elevated metabolic activity of the sgACC (Drevets *et al.*, 1997; Mayberg *et al.*, 1999), and sgACC activity is predictive of response to cognitive therapy and medication in adult depression (Mayberg *et al.*, 1997; Keedwell *et al.*, 2010; Siegle *et al.*, 2012). It is interesting that although Masten *et al.* (2009) and Sebastian *et al.* (2011) found increased sgACC response to exclusion (relative to inclusion) in healthy youth, we found increased sgACC response to rejection in depressed compared with healthy adolescents. Although the studies are not directly comparable given the use of different tasks and different analytic models (i.e. exclusion compared with inclusion *vs* bold activation under the curve from baseline to rejection), findings suggest that studies of sgACC response to exclusion in healthy youth may benefit from consideration of levels of depressive symptomatology in the sample. Findings also suggest that investigation of sgACC response to social stimuli in adolescence is an important avenue for future research on adolescent depression.

Whole-brain analyses also revealed greater activity in the dACC in MDD compared with healthy youth to social exclusion, but only from 7 to 9 s after receiving rejection feedback. Although social exclusion in adults typically activates the dACC (Eisenberger *et al.*, 2003, 2007), most studies with adolescents have not shown dACC activation to social exclusion or rejection (Masten *et al.*, 2009; Bolling *et al.*, 2011a; Sebastian *et al.*, 2011; Guyer *et al.*, 2012). This study suggests that dACC activation may be more evident during sustained processing of exclusion/rejection and/or among adolescents higher in depressive symptoms.

We found an interesting pattern of differential activation of the anterior insula to acceptance and rejection for depressed and healthy youth. Although the insula was activated in response to acceptance in both depressed and healthy youth, it was only activated in response to

rejection for depressed youth. There is evidence that the insula is involved in the experience of all emotions, including happy and positive emotions (Damasio *et al.*, 2000; Phan *et al.*, 2002) as well as negative affective states, such as anger (Denson *et al.*, 2008), disgust (Phillips *et al.*, 1997; Jabbi *et al.*, 2008), physical pain (Aziz *et al.*, 2000) and 'social pain' (Eisenberger *et al.*, 2003; Masten *et al.*, 2009). This is consistent with theoretical models suggesting that the insula is responsible for representing current internal physical and emotional states and generating the experience of 'feelings' (Damasio *et al.*, 2000; Craig, 2009; Singer *et al.*, 2009). Singer *et al.* (2009) propose that the anterior insula integrates external and internal physiological signals to generate a dominant feeling state that modulates social and motivational behavior. It appears that acceptance feedback was particularly salient to both depressed and healthy youth in this study. In contrast, our finding that the insula activated in response to rejection in depressed youth but not controls may suggest that the depressed youth experienced rejection trials as more affectively and motivationally salient and/or painful than healthy youth. This finding is also consistent with recent evidence of increased insula activity to rejection among anxious youth (Lau *et al.*, 2012), suggesting that insula response to rejection could be a shared risk factor for anxiety and depression.

The salience of acceptance feedback in both groups is consistent with general evidence for a valence effect across most of our ROIs, in which acceptance more strongly activated ventral areas including not only the insula but also the VLPFC, mPFC and vACC compared with rejection. Although we previously found greater pupil dilation to rejection compared with acceptance in healthy adolescents on this task (Silk *et al.*, 2012b), other adolescent neuroimaging studies have found greater neural responses to acceptance, compared with rejection, in response to virtual peer feedback (Gunther Moor *et al.*, 2010; Guyer *et al.*, 2012). This pattern of results differs from studies that have employed social inclusion/exclusion tasks, such as the Cyberball task, which have typically found greater neural response to exclusion compared with inclusion in adolescents (Masten *et al.*, 2009; Bolling *et al.*, 2011b; Sebastian *et al.*, 2011). The reasons for these differences are unclear and warrant further investigation.

Also consistent with data from a similar virtual peer feedback task (Guyer *et al.*, 2008; Lau *et al.*, 2012), we found bilateral deactivation of the amygdala relative to baseline in response to rejection in healthy controls. This deactivation was attenuated in MDD youth, suggesting that amygdala activity in response to rejection was higher in depressed compared with healthy youth. The pattern of amygdala deactivation could be explained by (i) relatively high levels of baseline amygdala activity in the scanning environment and/or in anticipation of peer responses and (ii) rejection feedback delivered in the context of smiling faces. Social proximity and interaction are known to attenuate threat reactivity in humans (Beckes and Coan, 2011), thus smiling faces of purported interaction partners may be sufficient to reduce threat and deactivate the amygdala in healthy controls, even when conveying rejection feedback. In contrast, the rejection feedback may be more salient than smiling faces for MDD youth. Again, this finding converges with evidence of increased amygdala reactivity to rejection in anxious youth (Guyer *et al.*, 2008; Lau *et al.*, 2012), supporting amygdala reactivity to social rejection as a potential shared biomarker that could help to explain high levels of comorbidity between anxiety and depression in youth (Silk *et al.*, 2012a).

Surprisingly, we found that depressed youth did not differ from controls in neural response to peer acceptance in reward-processing regions, such as the mPFC and NAcc. This differs from several studies that have shown decreased striatal response to monetary reward in adolescent MDD (Forbes *et al.*, 2006, 2009), suggesting that social reward may be more salient than monetary reward for depressed youth. In fact, Davey *et al.* (2011) found increased amygdala response

to social acceptance in an older sample of adolescents and young adults with MDD compared with healthy controls. These discrepant findings highlight the need for additional research on neural response to social vs monetary rewards in adolescents with depression.

Although we did not find group differences in reward-related brain activity in response to peer acceptance, we did find differences in bilateral NAcc response to peer rejection. Specifically, the NAcc displayed a pattern of decreased activation in response to peer rejection among healthy controls that was not present in MDD youth. Although the NAcc has received more attention for its role in the brain's reward circuit (Knutson and Cooper, 2005), it also plays a role in encoding aversive events and punishment (McCutcheon *et al.*, 2012). Other forms of social loss, such as complicated grief, have been shown to activate the NAcc (O'Connor *et al.*, 2008). NAcc activation to peer rejection in MDD youth may suggest that MDD youth experience peer rejection as a form of loss, punishment, or as more strongly aversive than healthy controls.

Researchers have proposed that increased risk for behavioral and emotional health problems in adolescence may be a function of increased reactivity to social and emotional stimuli as a function of pubertal maturation (Nelson *et al.*, 2005; Steinberg, 2005), but little empirical data exist in human adolescents to support this model. This study provides evidence that adolescents more advanced in self-reported pubertal status show more activation to simulated peer rejection in the sgACC and bilateral amygdala, key areas involved in the processing of social affective stimuli and social threat. These findings were driven by a pattern of deactivation in these areas earlier in puberty that was attenuated with pubertal maturation. This is consistent with earlier evidence of increased physiological reactivity to peer rejection on the Chatroom Interact Task among older compared with younger adolescents (Silk *et al.*, 2012b), as well as data showing increased neural response to threatening faces in more pubertally advanced adolescents (Forbes *et al.*, 2011; Moore *et al.*, 2012). These associations remained significant controlling for chronological age, suggesting that the effects may be specific to pubertal maturation. Given high densities of steroid hormone receptors in the amygdala and cerebral cortex (Simerly *et al.*, 1990; Sarkey *et al.*, 2008), changes in reactivity to peer rejection in these regions with puberty could be mediated by the rise of basal levels of sex hormones during pubertal development. These influences could result from direct effects of sex hormones on limbic circuitry, or changes in socio-affective behavior in response to changes in physical appearance. It was interesting, in this study, that adrenal, but not gonadal hormonal signs of pubertal development were associated with neural response to peer rejection. There are several possible explanations for this finding. First, it may be that self rating of the questions assessing adrenarche (i.e. acne and axillary hair) is more accurate at capturing pubertal changes than questions assessing gonadarche (i.e. growth spurt), which can be difficult to self-rate. It is also possible that higher scores on the adrenarche scale may be a marker for early puberty, as adrenarche is the earliest event in the pubertal maturation process. Early pubertal maturation, particularly in girls, is known to be associated with increased psychosocial stress and adversity (Ge *et al.*, 1996), which could help to explain the link between higher adrenarche scores and greater amygdala/ACC hyperactivity to rejection. These findings could also suggest a specific role for dihydroepiandrosterone/dihydroepiandrosterone sulfate DHEA/DHEA(S), which are the primary sex hormones associated with adrenarche. Little is known about the function of DHEA during adolescence. DHEA has been shown to have anxiolytic and antidepressant effects (Schmidt *et al.*, 2005; Malkesman and Weller, 2009; Sripada *et al.*, 2013); however, other studies have shown elevated DHEA in populations exposed to stress, such as individuals exposed to childhood trauma (Kellner *et al.*, 2010), suggesting a potential

compensatory role for elevated levels of DHEA. Furthermore, DHEA is precursor to both testosterone and estradiol; thus, the effects of increased DHEA could be mediated through effects on gonadal hormones. The collection of data on basal and task-related sex hormone responses in adolescents in future peer evaluation studies will be important in order to delineate specific mechanisms through which pubertal maturation influences sensitivity to peer rejection.

Interestingly, contrary to our hypotheses, the relationship between left amygdala and caudate/sgACC activity with pubertal maturation was stronger among healthy youth than depressed youth. Controls showed greater deactivation of the left amygdala and caudate/sgACC compared with depressed youth in the earlier stages of puberty, but by late puberty responses to rejection were similar in both healthy youth and controls. This suggests that greater response to rejection "earlier" in pubertal development may be an important risk factor, or marker for depression. Alternatively, it may be that pubertal steroids have less of an influence on reactivity to rejection in depressed youth because the salience of peer rejection is already maximized in this group.

This study has several limitations. First, because the study is cross-sectional, it is unclear whether increased neural response to peer rejection is a risk factor or correlate of adolescent depression. It may be that adolescents vulnerable to depression enter adolescence with greater sensitivity to social evaluation, or it may be that the experience of frequent peer rejection serves to sensitize or heighten activity in these regions. Future prospective longitudinal research with children and adolescents at high risk for depression may help to address this question. In particular, additional research that incorporates EMA, observational and/or sociometric data on real-world peer relationships with neuroimaging data (as in Eisenberger *et al.*, 2007; Masten *et al.*, 2012) would be valuable in addressing the interplay between social experience and neural response to social rejection during adolescence.

Second, because we did not include an adult comparison group, we do not know whether the present findings are unique to adolescents or may generalize to adults with depression. Third, there is evidence of gender differences in rates of depression (Kessler *et al.*, 2001) as well as interpersonal sensitivity (Rudolph, 2002); however, given our relatively small sample size (particularly for boys), we were not able to investigate gender differences in reactivity to peer acceptance and rejection. Relatedly, there are limitations in combining boys and girls in analyses of the effects of pubertal development, as self-reported pubertal status is based on different criteria for boys and girl, pubertal changes occur along a different timeline for boys and girls, and the effects of pubertal hormones on brain activity may differ for boys and girls. Thus, it is possible that the effects of pubertal development on brain response could differ for males and females based on differences in both the timing of puberty and the levels of different pubertal hormones (Sisk and Foster, 2004). Future research is needed to investigate puberty-specific effects on neural response to social evaluation within larger samples of girls and boys. Furthermore, as gender differences in depression rates appear to emerge during puberty (Angold *et al.*, 1999), further investigation of the interrelationships between puberty, gender and response to social evaluation may contribute to a better understanding of the mechanisms behind gender differences in depression. Finally, although the majority of participants (92%) did not show a clear preference for one virtual peer over the other in the first block, it remains possible that participants' own ratings of the virtual peers during the first block might have influenced their expectations of acceptance and rejection from these peers during later blocks.

Despite these limitations, the study also has several strengths. First, the study is based on a well-characterized clinical sample of youth in a current episode of MDD. The study also utilized a newly developed virtual peer interaction paradigm that included live interaction with age-matched virtual peers. This allowed us to probe responses to

ecologically valid social evaluative stimuli likely to be emotionally salient for adolescents. Additionally, data were obtained on pubertal status, allowing us to address potential puberty-driven developmental effects. Findings highlight neural sensitivity to peer rejection as an important feature of adolescent depression that could be better targeted in intervention and prevention approaches for this prevalent disorder. This need is particularly pressing in the current adolescent 'cyber-culture' which includes increased rates of rejection via social media and mobile technologies, which have been linked to suicide and depression (O'Keeffe et al., 2011; Luxton et al., 2012). Although some current psychosocial interventions for adolescent depression include social skills training (Kennard et al., 2009) or discussion of problematic interpersonal relationships (Mufson et al., 1999), treatments may benefit from an increased focus on augmenting skills for dealing with the ubiquitous experience of peer social evaluation. For example, virtual reality technologies have been used to improve exposure treatments for posttraumatic stress disorder and social phobia (Rothbaum et al., 2001; Anderson et al., 2003), and could potentially be incorporated into adolescent depression interventions as a way to enhance exposure and coping responses to negative peer evaluation. Furthermore, although, once thought to be detrimental for adolescents, recent data suggest that more frequent Internet-based social interaction actually has a positive effect on social connectedness and well-being among youth (Valkenburg and Peter, 2009). It may be possible to harness the effects of positive online social interactions to improve depression interventions. In support of this notion, a recent study showed that a brief period of online interaction with an unknown peer improved reports of self-esteem and perceived relational value and decreased negative affect in adolescents who had just experienced social exclusion via the Cyberball task (Gross, 2009). Targeting skills for coping with negative social interactions among prepubertal youth with neurobiological vulnerabilities for depression may also help to prevent the onset of depression during the transition through adolescence.

FINANCIAL DISCLOSURES

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SUPPLEMENTARY DATA

Supplementary data are available at SCAN online.

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