Feeling left out: depressed adolescents may atypically recruit emotional salience and regulation networks during social exclusion

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Abstract

Depression is associated with negative attention and attribution biases and maladaptive emotion responsivity and regulation, which adversely impact self-evaluations and interpersonal relationships. Using functional magnetic resonance imaging, we investigated the neural substrates of these impairments. We compared neural activity recruited by 126 clinically depressed and healthy adolescents (ages 11–17 years) during social exclusion (Exclusion > Inclusion) using Cyberball. Results revealed significant interaction effects within left anterior insula (AI)/inferior frontal gyrus and left middle temporal gyrus. Insula hyperresponsivity was associated with peer exclusion for depressed adolescents but peer inclusion for healthy adolescents. In addition, healthy adolescents recruited greater lateral temporal activity during peer exclusion. Complementary effect size analyses within independent parcellations offered converging evidence, as well as highlighted medium-to-large effects within subgenual/ventral anterior cingulate cortex and lateral prefrontal, lateral temporal and lateral parietal regions implicated in emotion regulation. Depressogenic neural patterns were associated with negative self-perceptions and negative information processing biases. These findings suggest a neural mechanism underlying cognitive biases in depression, as reflected by emotional hyperresponsivity and maladaptive regulation/reappraisal of negative social evaluative information. This study lends further support for salience and central executive network dysfunction underlying social threat processing, and in particular, highlights the anterior insula as a key region of disturbance in adolescent depression.

Key words: social exclusion; fMRI; depression; adolescence; emotion regulation; salience

Introduction

Depression is a common, yet serious, disorder associated with severe consequences across social, cognitive and health domains (Rao & Chen, 2009). Adolescent and adult depression are characterized by poor social function and enhanced attention to negative social signals, e.g. facial expressions of anger, fear and sadness or ambiguous expressions (Youngren & Lewinsohn, 1980; Joiner et al., 2002; Joormann et al., 2007; Leyman et al., 2007). Both social and cognitive factors have been posited to contribute to depression. The social risk hypothesis proposes that clinical depression represents a pathological divergence from an adaptive behavioral response to minimize social risk (e.g. social exclusion) (Allen & Badcock, 2003). According to this model, depression reflects negative self-evaluations of perceived social value and burden to others, which impact social perceptual processing.
(including sensitivity to social threat) and influences social behavior. Cognitive vulnerability–stress models propose that negative life events interact with cognitive vulnerability (i.e., negative cognitions and cognitive style) to predict depression (Hankin et al., 2004). Specifically, negative self-representations and negative inferential style act as psychological filters to distort depressed individuals’ responsibility to and interpretations of negative or ambiguous social interactions (Beck, 1987, 2008; Abramson et al., 1989, 2002; Mathews & McLeod, 2005; Alloy et al., 2006). Negative self-representations may influence behavior through several ancillary processes. For example, it is unknown whether negative attributions, exacerbated attention to and/or elevated emotional saliency of ambiguous social signals (all of which have been linked to risk and recurrence of depression) underlie poor social function (Teasdale & Dent, 1987; Abramson et al., 1998; Abramson & Alloy, 2006; Takano & Tanno, 2009). Updated models now emphasize biological contributions, particularly limbic and prefrontal network dysfunction, which may represent neural correlates of cognitive vulnerability, cognitive reactivity and cognitive bias (Alloy & Abramson, 2007; Beck, 2008; Beck & Bredekemeier, 2016). Neuroscience can begin to shed light onto core processes underlying depression development and maintenance. The overarching goal of this study was to illuminate psychological and neural processes that underpin poor social function in depressed youths.

Developmental epidemiological research suggests that adolescents are at an elevated risk for developing depression (Avenevoli et al., 2015). Adolescence may represent a unique ‘widow of vulnerability’, driven by normative social, cognitive and neural changes associated with puberty (Andersen & Teicher, 2008). During adolescence, self-processing, social cognition, and executive functioning abilities undergo dramatic changes (Harter, 1999; Davey et al., 2008), and peer social evaluations become more salient (O’Brien & Bierman, 1998; Brown, 1990). Cognitive vulnerability–stress models posit that increased social stressors interact with cognitive and information processing biases to predict youth depression (Alloy & Abramson, 2007; Hankin, 2008; Jacobs et al., 2008). Adolescent depression is related to heightened interpersonal stress (Shih et al., 2006) and peer victimization (Stapinski et al., 2015), and high levels of peer rejection combined with maladaptive schemas and negative self-referential attributions predict adolescent depression (Prinstein et al., 2005; Braet et al., 2013). Furthermore, brain regions involved in self-concept refinement, sensitivity to peer influence and emotion regulation undergo significant maturation during adolescence (Pfeifer & Blakemore, 2012). Thus, adolescent vulnerability to depression may reflect increased sensitivity to negative peer feedback, coupled with dysfunction of neural regions (or networks) supporting self-processing, emotion responsivity and cognitive regulation (Prinstein & Aikins, 2004; Alloy & Abramson, 2007; Davey et al., 2008; Stroud et al., 2009; Silk et al., 2014; Hankin, 2015; Guyer et al., 2016). This study adopted a biocognitive vulnerability–stress framework to investigate the relationship between increased social stressors and cognitive and information processing biases in adolescent depression. By manipulating peer exclusion, we investigated potential psychological and neural mechanisms underlying maladaptive responsivity to negative or ambiguous social interactions.

Cognitive and affective impairments in depression
Depression is characterized by cognitive and affective dysfunction, including negative attention and attribution biases and atypical emotion responsivity and regulation (Garber et al., 1995; Garnefski & Kraaij, 2006; Beck, 2008; Joormann & Gotlib, 2010; Braet et al., 2013; Ahmed et al., 2015). Depressed individuals allocate greater attention to negative or depressogenic stimuli (Leung et al., 2009; Ahmed et al., 2015; Ai et al., 2015) and are more likely to perceive neutral stimuli as negative (Arce et al., 2009). Depressed individuals also experience negative emotions more intensely (Sheeber et al., 2009) and have difficulty down-regulating negative affect (Beauregard et al., 2006; Joormann & Gotlib, 2010), which suggests that negative stimuli are more salient. Depressed individuals adopt maladaptive regulation strategies (e.g., self-blame, rumination) more frequently, and they adopt adaptive strategies (e.g., positive reappraisal) less frequently (Garber et al., 1995; Garnefski & Kraaij, 2006; Joormann & Gotlib, 2010; Kerestes et al., 2014). These negative processing biases and maladaptive regulatory skills adversely impact self-perceptions and interpersonal relationships, and they may reflect (or be reflected by) neural dysfunction (Mayberg et al., 1999; Brody et al., 2001; Dsiner et al., 2011; Sliz & Hayley, 2012; Kerestes et al., 2014). Adopting a neuroscience approach is a key to understanding which neural structures and psychological processes underlie depressed adolescents’ atypical reactions to and/or interpretations of negative or ambiguous social interactions.

Neural bases of depression
The neural foundations of depression have been explored extensively. Meta-analyses and systematic reviews link depression pathology to disrupted prefrontal–subcortical–limbic and lateral temporal–limbic networks underlying emotion processing and regulation (Drevets, 2001; Fitzgerald et al., 2008; Dsiner et al., 2011; Fu et al., 2013; Kerestes et al., 2014; Palmer et al., 2014). Key regions include dorsolateral, ventrolateral and medial prefrontal cortex (dIPFC, vIPFC and mPFC); anterior cingulate cortex (ACC); anterior insula (AI) and amygdala. Adopting a neural network framework, depression is linked to dysfunction within the default mode network (supporting self-referential processing), central executive network (supporting cognitive control) and salience network (supporting relevance detection) (Dunlop & Mayberg, 2014). AI, a central node in the salience network and major switching hub between the default mode network and central executive network (Menon & Uddin, 2008; Sridharan et al., 2008; Hamilton et al., 2012), may play a critical role in depression (Sliz & Hayley, 2012, Dunlop & Mayberg, 2014). The following sections review the neural correlates of atypical emotion processing in depression, which may underlie maladaptive responsivity to negative or ambiguous social exchanges.

Neural correlates of atypical emotion responsivity and regulation
Depressed individuals recruit atypical limbic and prefrontal activity during emotion processing, which may reflect maladaptive salience processing or reappraisal (Menon & Uddin, 2010). Consequently, depressed individuals may misinterpret brief social misunderstandings or unintentional exclusions as reflecting negative social evaluations. Negative attentional focus and emotion encoding in depression are associated with limbic dysfunction, particularly AI (Sliz & Hayley, 2012). Depressed adults recruit greater AI activity during negative word encoding, suggesting that AI hyperactivity may represent greater attention to, heightened sensitivity to or impaired disengagement from negative stimuli (Ai et al., 2015). Relatively, depressed adults recruit increased limbic (dorsal ACC, insula and amygdala) activity and reduced prefrontal (dIPFC) activity during negative emotion processing (Hamilton et al., 2012), possibly
reflecting heightened salience processing and attenuated contextualization and/or reappraisal of negative information. Depressed adults show limbic hyperresponsivity to negative facial expressions and limbic hyporesponsivity to positive ones, suggesting that negative social evaluations may be particularly salient (Stuhrmann et al., 2011). Similarly, depressed adolescents recruit atypical AI activity and show aberrant limbic network connectivity during negative emotional facial encoding (Ho et al., 2014; Blom et al., 2015). These neural patterns may reflect atypical AI development in adolescent depression, resulting in hypervigilance to negative cues and impaired regulation of negative affect (Blom et al., 2015). Thus, it is reasonable to expect that such negative biases in emotion perception and attention would be reflected in salience network dysfunction (particularly AI) during negative social interactions, such as peer exclusion.

Prefrontal and limbic dysfunction are also related to maladaptive emotion regulation, particularly for negative affect (Beauregard et al., 2006; Johnstone et al., 2007). Depressed adults show hyperactivity within mPFC, insula, amygdala, and lateral temporal cortex during explicit down regulation of negative emotion, which may reflect greater emotion regulation difficulties (Beauregard et al., 2006). Interestingly, depressed adolescents recruit atypical inferior frontal gyrus (IFG) and amygdala activity during negative emotion appraisal, although developmental differences may exist (Perlman et al., 2012). These findings suggest that inefficient or maladaptive emotion regulation in depression may represent underlying prefrontal-limbic dysfunction, including poor amygdala regulation by mPFC and poor integration of affective responses into interoceptive awareness by AI (Perlman et al., 2012). Broadly, research suggests that depressed adolescents may respond to and/or interpret social challenges (such as social exclusion) maladaptively, due to negative attention or attribution biases, impaired emotion regulation or exacerbated saliency of negative social cues, as reflected on the neural level.

Neural correlates of atypical responsivity to negative social interactions. To date, only two studies (Silk et al., 2014; Platt et al., 2015) have investigated neural responsivity to social rejection in depressed adolescents. Both studies used the Chatroom Interact Task, where participants received social evaluative feedback from peers. Depressed adolescents (ages 11–17 years) recruited greater limbic (subgenual ACC, AI, amygdala and striatum) activity than healthy adolescents upon receiving negative peer evaluative feedback (Silk et al., 2014). This suggests that negative social evaluations are more emotionally or motivationally salient and/or more aversive for depressed adolescents. Limbic hyperactivity also suggests that depressed youth allocate greater attentional resources toward monitoring socially threatening cues. During reappraisal of negative peer evaluative feedback, depressed adolescents (ages 11–15 years) showed enhanced functional coupling between the frontal pole and a lateral prefrontal, subcortical, limbic, inferior parietal and lateral temporal network, possibly representing enhanced integration of emotional reactivity and cognitive control (Platt et al., 2015). Thus, limbic network dysfunction may underlie maladaptive emotional responsivity to social rejection in adolescent depression. However, given the paucity of studies investigating negative social interactions in depressed youth, there is a clear need for additional research.

No study has used Cyberball, a well-established social exclusion task, in clinically depressed adolescents. Instead, this task has only been explored in healthy adolescents (ages 12–13 years), where depression symptom severity correlated with mPFC, vIPFC and medial parietal activity; and subgenual ACC activity predicted symptom severity 1 year later (Masten et al., 2011). In chronically peer-victimized adolescent girls (ages 14–16 years), depression symptom severity correlated with dorsal and subgenual ACC and AI activity (Rudolph et al., 2016). These findings offer preliminary evidence that atypical limbic and prefrontal activity during Cyberball may underlie maladaptive responsivity to negative social interactions in adolescent depression.

Together, social rejection/exclusion research suggests that adolescent depression may be associated with salience and central executive network dysfunction, which may reflect maladaptive attention allocation, enhanced emotional saliency processing and impaired emotion regulation during negative social interactions. Consequently, these atypicalities may contribute to the development of (or reflect existing) negative processing biases in adolescent depression.

Current study

Informed by biocognitive vulnerability–stress models, the current study investigated the interplay between salient social stressors and biased cognitive processing in adolescent depression. Adopting a developmental neuroscience approach, this study aimed to elucidate the neural underpinnings of maladaptive responsivity to negative social interactions, given that adolescent neural maturation may contribute to elevated depression risk (Alloy & Abramson, 2007). This study expanded upon two prior studies investigating social rejection in clinically depressed adolescents and several studies that used Cyberball to study social exclusion in healthy adolescents with depressogenic profiles. Using Cyberball, we compared neural activity patterns recruited by a large sample of clinically depressed and healthy adolescents during social exclusion. Given previous findings of salience and central executive network dysfunction, we predicted group differences within prefrontal, limbic and possibly lateral temporal regions, specifically hypothesizing that depressed adolescents would show subgenual ACC, AI and/or amygdala hyperactivity during exclusion relative to inclusion. We conducted correlational analyses with depression-relevant social cognitive variables to investigate potential ancillary processes underlying maladaptive responsivity to social exclusion. Our goal was to corroborate and clarify past neuroimaging research and to begin to determine whether attentional, attributional and/or associative processes underlie poor social function in depressed adolescents during negative/ambiguous social interactions.

Materials and methods

Participants

One hundred thirty-four right-handed adolescents were initially recruited for a large, multi-site project investigating neural function in depressed adolescents; eight were excluded from the final analyses because of inattentiveness (i.e. fell asleep during scan; n = 2), slice prescription errors (n = 4) or anatomical abnormalities (n = 2). The final sample consisted of 126 adolescents [56 males; ages 11.5–17.8 years; M\text{age} (s.d.) = 14.75 (1.63)] recruited from the University of Minnesota [n = 39; 16 males; M\text{age} (s.d.) = 14.31 (1.60)] and the University of Pittsburgh [n = 87; 40 males; M\text{age} (s.d.) = 14.94 (1.61)]. Participants represented two groups: clinically depressed adolescents (DEP; n = 87) and healthy community controls (CON; n = 39). Depressed adolescents included short-term in-patients, outpatients evaluated for significant depressive symptoms, and depressed youth treated
Table 1. Differences in demographic variables across depressed and healthy adolescents

|                  | DEP (n = 87) | CON (n = 39) | Comparison statistic |
|------------------|--------------|--------------|----------------------|
| **Gender**       |              |              | χ²(1) = 0.52         |
| Male             | 37 (42.5.0%) | 19 (48.7%)   |                      |
| Female           | 50 (57.5%)   | 20 (51.3%)   |                      |
| **Age, M (s.d.)**| 14.89 (1.67) | 14.43 (1.51) | t(124) = −1.46       |
| **Pubertal status, M (s.d.)** | 3.13 (0.50)   | 2.90 (0.60)   | t(124) = −2.24**     |
| **FSIQ, M (s.d.)** | 107.89 (16.26) | 117.15 (12.24) | t(124) = 3.18**     |
| **Ethnicity**    |              |              | χ²(6) = 11.74        |
| Caucasian        | 48 (55.2%)   | 30 (76.9%)   |                      |
| African American | 10 (7.6%)    | 1 (2.6%)     |                      |
| Hispanic         | 11 (12.6%)   | 1 (2.6%)     |                      |
| East Asian       | 2 (2.3%)     | 3 (7.7%)     |                      |
| American Indian  | 1 (1.1%)     |              |                      |
| Multiethnic      | 11 (12.6%)   | 4 (10.3%)    |                      |
| Other            | 4 (2.8%)     |              |                      |
| **Family income**|              |              | χ²(4) = 15.64**      |
| <$35 000         | 32 (37.6%)   | 4 (10.3%)    |                      |
| $35 000-$75,000  | 25 (29.4%)   | 8 (20.5%)    |                      |
| >$75 000         | 28 (32.9%)   | 26 (69.2%)   |                      |
| **Family structure** |          |              | χ²(1) = 6.48*        |
| Single           | 30 (34.9%)   | 5 (12.8%)    |                      |
| Cohabitating     | 56 (65.1%)   | 34 (87.2%)   |                      |
| **Medication usage** |        |              |                      |
| Anti-depressants | 38 (43.7%)   |              |                      |
| Anti-psychotics  | 5 (5.7%)     |              |                      |
| Mood stabilizers |              |              |                      |
| Stimulants       | 11 (12.6%)   |              |                      |
| Anxiolytics      | 7 (8.0%)     |              |                      |

Note: CON = healthy control group; Cohabitating = married parents, cohabitating; DEP = depressed group; Single = single parent, separated/divorced, widowed. *P < 0.05, **P < 0.01. Missing data: family income (n = 2) and family structure (n = 1).

in clinical school-based settings. Diagnosis was based on a psychological evaluation using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (Kaufman et al., 1997), according to Diagnostic Statistical Manual-IV (DSM-IV) criteria. Healthy adolescents were free of present and past psychiatric diagnoses and recruited via flyers and radio ads. Groups were matched on age and sex ratio. All participants had a Full Scale IQ (FSIQ) > 70 (Wechsler, 1999). (See Table 1 and Supplementary Materials for additional information.)

Procedures

Participants completed a clinical interview and questionnaires assessing depressogenic variables. One to two weeks later, they completed a scanning appointment (magnetic resonance imaging [MRI] scan, post-scan interview and debriefing). Both universities’ institutional review boards approved the study.

Cyberball. Cyberball simulates real-time social exclusion (Williams et al., 2000, 2002). Participants believed they were playing an online, interactive ball-toss game with two peers during MRI scanning. Participants were told that players could request the ball via button press, which controlled for potential motor confounds across exclusion and inclusion blocks and increased ecological validity.

Participants first practiced tossing the ball on an empty screen (‘practice block’), which familiarized them with the task and served as a control for social ball passing. Next, participants played Cyberball with virtual players. During an ‘inclusion block’, all players had an equal chance of receiving the ball. During an ‘exclusion block’, participants were excluded, and virtual players only passed the ball to each other. During an ‘inclusion-short block’, all players once again had an equal chance of receiving the ball.

Depression-relevant variables. This study adopted a biocognitive vulnerability-stress model, which suggests that social stressors, combined with cognitive vulnerability, contribute to depression and, consequently, poor social function. Our model proposes that negative self-representations may influence social behavior through several ancillary processes, including negative attribution style and exacerbated attention to or/and elevated emotional saliency of ambiguous social signals. To investigate the relationship between atypical neural responsivity to social exclusion and depressogenic profiles, participants completed several questionnaires. We assessed global self-worth (representing negative self-representations)
using the Self-Perception Profile for Children (Harter, 1982), social stress (representing feelings of stress during social interactions, in particular, being excluded from social activities) using the Behavior Assessment System for Children—Second Edition (Reynolds & Kamphaus, 2004), negative attribution style using the Children’s Attributional Style Questionnaire (Conley et al., 2001) and negative emotional temperament (representing proneness to anxiety and emotional/behavioral negative engagement, in particular, stress reaction) using the Multidimensional Personality Questionnaire-Bf (Patrick et al., 2002).

Data acquisition and analysis

Data were acquired using 3T Siemens Trio MRI scanners. Localizers were acquired to allow slice prescription. Blood oxygen level-dependent echo-planar images were acquired across the whole brain with a T2-weighted gradient echo sequence (TR/TE = 3340/30 ms, flip angle = 90°, field of view = 200 × 200 mm; matrix = 80 × 80; sixty 2 mm slices, descending acquisition) along the anterior commissure–posterior commissure transverse oblique plane. A high-resolution T2-weighted structural scan was acquired coplanar to the functional sequence (TR/TE = 2100/3.31 ms, flip angle = 8 degrees, field of view = 256 × 200 mm, matrix = 200 × 256, one hundred seventy-six 1 mm slices).

Data were preprocessed and analyzed using SPM8 at the single-subject level and SPM12 at the group level, which permitted saving individual subjects’ residuals. Functional images were realigned to the mean functional image, slice-time corrected, coregistered to the structural image, motion-corrected, segmented, normalized to a standard MNI template and smoothed using a 7 mm full-width-half-maximum Gaussian kernel.

For each subject, condition effects were estimated via the Generalized Linear Model using a canonical hemodynamic response function. A 128 s high-pass filter removed low-frequency noise, and an autoregressive model, AR(1), estimated temporal autocorrelation. Subject-level models included four conditions: practice, inclusion, exclusion and inclusion-short blocks. Nuisance regressors included six rigid-body motion parameters and volumes representing excessive motion.1 (See Supplementary Materials for motion information.) Planned contrasts (Exclusion > Inclusion, not including Inclusion-Short) were entered at the group level to estimate population effects. No explicit masks were used.

To investigate neural patterns representing social exclusion across all subjects, we conducted a one-sample t-test for Exclusion > Inclusion. To investigate the influence of clinical depression, we conducted a two-sample t-test for DEP > CON (Exclusion > Inclusion). To determine if certain conditions drove group differences, we conducted a 2 (group: DEP, CON) × 2 (condition: Exclusion > Practice, Inclusion > Practice) full factorial analysis of variance (ANOVA). Parameter estimates were extracted from significant clusters using MarsBar to tease apart inter-association effects and to conduct correlations. A combined voxel-height and cluster-extent threshold was calculated to control for Type 1 error using Monte Carlo simulations via AFNI’s 3dClustSim (AFNI_16.1.13; 4 March 2016); an \( \alpha = 0.05 \) was achieved via \( P < 0.001 \), \( k > 117 \) for both one- and two-sample t-tests. (In previous versions of 3dClustSim, an \( \alpha = 0.05 \) was achieved via \( P < 0.005 \), \( k > 86 \) and 87 for one- and two-sample t-tests, respectively.) Smoothness estimates entered into 3dClustSim represented an average of subject-level spatial autocorrelation function (acf) parameters based on individual subjects’ residuals from each group-level model, as calculated by 3dFWHMx using the -acf flag.

Recent discussions about the merits and limitations of adopting stringent statistical significance thresholds in neuroimaging analyses (Cox et al., 2016; Eklund et al., 2016) prompted us to adopt a complementary approach that explored effect sizes using Cradock et al.’s (2012) 200 independent parcels. This approach drastically reduces the number of multiple comparisons (from over 100 000 to under 200) and examines activity within meaningful subunits, whose boundaries reflect network connectivity patterns. Parameter estimates representing mean activity for Exclusion > Inclusion were extracted from each parcel per group. Effect sizes (Hedges’ g) were calculated for each parcel using R (3.3.1). We reported regions with moderate effect sizes, based on strict threshold guidelines (Ferguson, 2009) (see Supplementary Materials for details.) We also noted when effect sizes were two or more standard deviations above the mean. Anatomical labels were determined via visual inspection and confirmed with automated labeling programs (xjview and Mango software).

When significant interaction effects between task and group were observed, follow-up analyses were conducted in Statistical Package for Social Sciences (SPSS) 22; FSIQ, family income, family structure and pubertal status were included as covariates to control for group differences (see Table 1.) To investigate potential ancillary processes of maladaptive responsivity to social exclusion, we conducted correlations between parameter estimates representing group differences in neural activity and depressive/socia cognitive variables underlying our conceptual model: global self-worth, susceptibility to social stress, negative attribution style and negative emotional temperament.

Results

Effect of task on activity across groups

Results from the one-sample t-test revealed that adolescents recruited activity within medial and lateral frontal and lateral temporal regions during Exclusion > Inclusion, including mPFC/perigenual ACC, left IFG (extending into superior temporal gyrus/middle temporal gyrus (STG/MTG)), right IFG, right precentral gyrus (extending into IFG), right precentral/postcentral gyr (extending into supramarginal gyrus), right STG/MTG and bilateral occipital cortex (see Table 2 and Figure 1.)

Group differences in activity

We compared activity recruited by depressed and healthy adolescents during Exclusion > Inclusion using a two-sample t-test. No group differences survived stringent statistical thresholds based on updated Monte Carlo simulations, although a few clusters were detected when thresholds were relaxed to \( P < 0.005 \) and \( k > 100 \) (which exceeded the threshold calculated using earlier versions of 3dClustSim). Depressed adolescents recruited greater activity within left AI/IFG [Brodmann Area (BA) 45/47/13; peak: −34, 32, 4, \( t(124) = −4.04, P < 0.001 \), while healthy adolescents recruited greater activity within left MTG (BA 21; peak: −46, −16, −16), \( t(124) = 3.98, P < 0.001 \). (See Figure 2.)

To investigate if certain conditions drove group differences, we conducted a 2 (group) × 2 (condition) repeated measures ANOVA in SPSS. There was a significant group-condition
Table 2. Activity across groups during social exclusion (Exclusion > Inclusion)

| Region                                      | Hemisphere | x   | y   | z   | t     | k     |
|---------------------------------------------|------------|-----|-----|-----|-------|-------|
| Lingual gyrus                               | L/R        | -16 | -88 | -8  | 8.93  | 3781* |
| Inferior frontal gyrus (BA 45/47)           | L          | -40 | 18  | -14 | 6.51  | 2792* |
| Medial prefrontal cortex/perigenual anterior cingulate cortex (ACC) (BA 9/10) | L          | -10 | 46  | 14  | 4.70  | 1153* |
| Superior/middle temporal gyrus (BA 22)      | R          | 66  | -32 | 14  | 4.60  | 528*  |
| Inferior frontal gyrus (BA 47)              | R          | 40  | 26  | -12 | 4.40  | 491*  |
| Precentral/postcentral gyrus (BA 6)         | R          | 62  | -12 | 42  | 4.30  | 133   |
| Precentral gyrus (BA 44/45/9)               | R          | 62  | 10  | 22  | 3.63  | 157   |

Note: Voxel-height and cluster-extent thresholds of $P < 0.005$ and $k = 100$. $P < 0.001$ and $k = 117$ for $\alpha = 0.05$, reflecting thresholds calculated via Monte Carlo simulations in AFNI using 3dClustSim (2016), as determined by averaged individual acf estimates. BA = putative Brodmann’s area.

Interaction effect within left AI/IFG, $F(1,124) = 16.29$, $P < 0.001$, which was robust to controlling for group differences in FSIQ, family income, family structure and pubertal status, $F(1,118) = 11.21$, $P = 0.001$. This interaction effect was also robust to controlling for medication usage (binary scores representing total medication usage, as well as only antidepressant or anxiolytic usage). Exploring simple effects, depressed adolescents recruited greater AI/IFG activity during exclusion relative to inclusion, $t(86) = 4.24$, $P < 0.001$, while healthy adolescents recruited greater AI/IFG activity during inclusion relative to exclusion, $t(38) = -2.19$, $P = 0.035$. Depressed adolescents recruited greater AI/IFG activity than healthy adolescents during the exclusion condition, while healthy adolescents recruited greater AI/IFG activity than depressed adolescents during the inclusion condition, although these differences were non-significant, $t(124) = -1.39$, ns and $t(124) = 1.39$, ns, respectively.

Additionally, there was a significant group–condition interaction effect within left MTG, $F(1,124) = 15.86$, $P < 0.001$, which was robust to controlling for group differences in FSIQ, family income, family structure and pubertal status, $F(1,118) = 14.88$, $P < 0.001$. This interaction effect was also robust to controlling for medication usage. Exploring simple effects, healthy adolescents recruited greater MTG activity during exclusion relative to inclusion, $t(38) = 4.45$, $P < 0.001$, while depressed adolescents recruited similar MTG activity during exclusion and inclusion, $t(86) = -1.79$, ns. Healthy adolescents recruited greater MTG activity than depressed adolescents during the exclusion condition, $t(124) = 2.90$, $P = 0.004$, while there were no significant group differences during the inclusion condition, $t(124) = -0.28$, ns.

Complementary effect size analyses using Craddock et al.’s (2012) 200 parcels confirmed and extended these results (see Table 3 and Figure 3). Depressed adolescents recruited greater activity during Exclusion > Inclusion within parcels representing left AI (extending into IFG and claustrum/putamen); healthy adolescents recruited greater activity within parcels...
Fig. 2. Regions of group differences between depressed and healthy adolescents during social exclusion (Exclusion > Inclusion) Panels A & B: depressed adolescents recruited greater activity than healthy adolescents within the left anterior insula (AI)/inferior frontal gyrus (BA 45/47/13). Panels C & D: healthy adolescents recruited greater activity than depressed adolescents within the left middle temporal gyrus (BA 21). BA = putative Brodmann’s area. Note: CON = 39; DEP = 87. Panel B: *$P < 0.005$, **$P < 0.001$. Panel D: *$P < 0.05$, **$P < 0.005$. CON = healthy control group; DEP = depressed group.

representing lateral temporal regions. Healthy adolescents also recruited greater activity within parcels representing subgenual/ventral ACC, as well as medial prefrontal, lateral prefrontal and lateral parietal regions. Group differences reflected medium-to-large effect sizes.

**Correlations with depression-relevant variables.** We correlated parameter estimates from regions reflecting group differences with variables representing depressogenic social cognitive profiles. Across all participants, left AI/IFG activity (reflecting neural patterns recruited by depressed adolescents) correlated positively with negative emotional temperament, $r(122) = 0.30$, $P = 0.001$; and social stress, $r(122) = 0.32$, $P < 0.001$. Across all participants, left MTG activity (reflecting neural patterns recruited by healthy adolescents) correlated positively with global self-worth, $r(124) = 0.23$, $P = 0.009$. Left MTG activity correlated negatively with negative emotional temperament, $r(122) = -0.25$, $P = 0.006$; and social stress, $r(122) = -0.24$, $P = 0.007$. (Separate correlations within each group were non-significant.)

**Discussion**

Influenced by biocognitive vulnerability–stress models, the current study investigated the interplay between salient social stressors and maladaptive cognitive and neural processing in adolescent depression. We compared activity recruited by clinically depressed and healthy adolescents during peer exclusion to better understand how negative/ambiguous social interactions are differentially processed. Depressed adolescents recruited greater left AI/IFG activity than healthy adolescents during exclusion relative to inclusion. Specifically, depressed adolescents recruited greater AI activity when they were excluded by peers, while healthy adolescents recruited greater activity when they were included. Results from the parcellation approach offer converging evidence, as represented by moderately large effect sizes. These findings offer further evidence of salience network dysfunction in depression and highlight AI as a key region of disturbance (Sliz & Hayley, 2012). AI is a central node in the salience network associated with identifying subjective relevance (Menon & Uddin, 2010). Depressed individuals recruit greater AI activity when viewing negative facial expressions (Fu et al., 2004; Keedwell et al., 2005; Zhong et al., 2011), which suggests that negative social stimuli are highly salient. Depressed individuals may be particularly sensitive to signals of social evaluative threat. AI activity is associated with observing and experiencing disgust (Wicker et al., 2003), and depressed individuals show left AI hyperresponsivity to facial expressions of disgust (Surguladze et al., 2010). Surguladze et al. (2010) hypothesized that AI hypersensitivity to social disgust may reflect an emotion processing bias in depression, which reinforces perceptions of interpersonal rejection. Research on social rejection in depression corroborates this interpretation. Depressed adolescents recruit greater left AI activity...
when they receive negative social evaluative feedback, which supports heightened sensitivity to socially threatening cues (Silk et al., 2014). Building off of this interpretation, left AI hyperactivity to exclusion relative to inclusion in the current study may suggest that signals of social threat are more emotionally salient and meaningful to depressed adolescents, who may give greater weight to negative social evaluations, relative to positive ones. Therefore, AI hyperresponsivity to socially threatening cues may serve as a biological mechanism for cognitive biases in depression.

In addition, healthy adolescents recruited greater left MTG activity than depressed adolescents during exclusion relative to inclusion. Specifically, healthy adolescents recruited greater MTG activity when they were excluded by peers, while depressed adolescents recruited similar activity during exclusion and inclusion. Several studies suggest that MTG is involved in emotion regulation via semantic processing (Whitney et al., 2011a, 2011b, 2012). Thus, healthy adolescents may selectively engage in adaptive appraisal of negative social evaluative information, while depressed adolescents do not. Results from the parcellation approach offer converging evidence and highlight potential group differences in subgenual/ventral ACC, as well as medial prefrontal, lateral prefrontal and lateral parietal regions implicated in emotion regulation (Ochsner et al., 2012). These findings lend further support for central executive network dysfunction in depression (Hamilton et al., 2012; Sliz & Hayley, 2012), which may underlie impaired emotion regulation (Silk et al., 2003). Ochsner et al.’s (2012) model of cognitive control of emotion posits that a left-lateralized prefronto-temporal network is responsible for reinterpreting affective information during emotion regulation, and lateral temporal regions play an intermediary role in linking a prefrontal cognitive control system with a subcortical affective reactivity system. A recent meta-analysis supports this model, proposing that cognitive control regions modulate semantic representations of emotional stimuli, which are generated by lateral temporal regions (Buhle et al., 2014). Thus, prefronto-lateral temporal network dysfunction may underlie maladaptive cognitive appraisal of negative social interactions in depression. This interpretation corroborates with reports of lateral prefrontal, lateral temporal and limbic network dysfunction in adolescent depression during reappraisal of negative social evaluative feedback (Platt et al., 2015). Thus, the current findings may reflect depressed adolescents’ failure to engage in adaptive regulation and reappraisal of socially threatening cues.

Adopting a broader network approach, the current findings suggest that salience and central executive network dysfunction may contribute to depression pathology. Salience network

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Table 3. Group differences in activity between depressed and healthy adolescents during social exclusion (Exclusion > Inclusion) across Craddock’s 200 parcels

| Parcel | Hemisphere | Region | g     |
|--------|------------|--------|-------|
| 6      | L          | Insula/putamen/claustrum (BA 13) | 1.75* |
| 191    | L          | Anterior Insula (BA 13)          | 1.53* |
| 63     | L          | Superior frontal gyrus (BA 9)    | 1.43* |
| 50     | R          | Subgenual anterior cingulate cortex/ventral anterior cingulate cortex/medial orbitofrontal cortex (BA 32/24) | 2.13* |
| 99     | L          | Posterior middle cingulate cortex/paracentral lobule (BA 31) | 2.07* |
| 112    | L          | Middle frontal gyrus/superior frontal gyrus (BA 8) | 1.73* |
| 178    | L          | Middle frontal gyrus (BA 6)      | 1.66* |
| 19     | R          | Superior frontal gyrus (BA 8)    | 1.61* |
| 89     | R          | Middle frontal gyrus/superior frontal gyrus (BA 6/8) | 1.53 |
| 154    | R          | Superior frontal sulcus/middle temporal gyrus/superior temporal gyrus/insula (BA 22/13) | 1.52 |
| 54     | R          | Postcentral gyrus/paracentral lobule (BA 7/5) | 1.52 |
| 156    | R          | Subgenual anterior cingulate (BA 25) | 1.52 |
| 194    | L          | Posterior middle cingulate cortex/paracentral lobule (BA 5/31) | 1.48 |
| 37     | L          | Middle cingulate cortex (BA 24)  | 1.43 |
| 86     | L          | Fusiform gyrus (BA 19/37)        | 1.42 |
| 122    | R          | Dorsomedial prefrontal cortex (BA 8) | 1.40 |
| 125    | R          | Dorsomedial prefrontal cortex (BA 8) | 1.34 |
| 151    | L          | Middle temporal gyrus (BA 21)    | 1.33 |
| 167    | L          | Superior parietal lobule/precuneus (BA 7) | 1.32 |
| 116    | L          | Angular gyrus/precuneus (BA 39)  | 1.32 |
| 124    | R          | Superior parietal lobule (BA 7)  | 1.31 |
| 55     | R          | Ventromedial prefrontal cortex (BA 10) | 1.25 |
| 196    | R          | Declive/fusiform gyrus (BA 37/39) | 1.23 |
| 155    | L          | Middle temporal gyrus (BA 21/22/37) | 1.21 |
| 39     | R          | Lingual gyrus (BA 18)            | 1.20 |
| 16     | L          | Fusiform gyrus (BA 37)           | 1.18 |
| 102    | R          | Medial prefrontal cortex (BA 10) | 1.18 |
| 93     | L          | Lingual gyrus (BA 18/19)         | 1.18 |
| 85     | R          | Precentral gyrus (BA 6)          | 1.16 |

Note: Reported regions had moderate effect sizes, g > = 1.15. *g > = two standard deviations above the mean (g > = 1.33 for DEP > CON and g > = 1.58 CON > DEP). BA = putative Brodmann’s area; CON = healthy control group; DEP = depressed group.
hyperresponsivity and central executive network hyporesponsivity to negative stimuli are consistently reported in depression (Hamilton et al., 2012). In particular, AI/IFG, a major switching hub between the default mode network and central executive network (Sridharan et al., 2008; Menon & Uddin, 2010), may play a key role in depressogenic information processing biases. AI/IFG dysfunction may underlie depressogenic rumination by facilitating maladaptive switching between default mode and central executive networks, resulting in impaired attentional control and poor disengagement from negative self-referential processing (Hamilton et al., 2011; Belleau et al., 2014). Framed within the context of normative heightened peer salience during adolescence, disruptions within salience and central executive networks (particularly AI/IFG) in the current study may represent enhanced attention allocation, elevated emotional responsibility and attenuated regulation and/or appraisal of negative social evaluative cues, which may adversely bias depressed adolescents’ sensitivity to and interpretations of brief social challenges.

Neural associations with depression-relevant variables

Across all adolescents, atypical neural patterns during social exclusion tracked with depression-relevant variables. Adolescents who recruited greater left AI/IFG activity (reflecting neural patterns of depressed adolescents) reported greater susceptibility to social stress and negative emotionality. This suggests that depressed adolescents are more vulnerable to feeling anxious and stressed during social exclusion, which may reflect elevated emotional salience of negative social evaluations. Adolescents who recruited greater left MTG activity (reflecting neural patterns of healthy adolescents) reported greater global self-worth, in addition to reduced susceptibility to social stress and attenuated negative emotionality. Together, these findings corroborate and strengthen the above interpretations by suggesting that atypical neural patterns recruited by depressed adolescents reflect cognitive and emotional processing biases. Research suggests that peer rejection and adolescent depression are reciprocally related (Platt et al., 2013), and cognitive biases may moderate this relationship (Prinstein & Aikins, 2004; Hankin, 2015). Thus, the brief experience of being excluded by peers may be particularly salient and distressing for depressed adolescents, may be interpreted as signaling peers’ negative social evaluations and may corroborate feelings of self-worthlessness. This interpretation offers further evidence that maladaptive cognitive reactivity and cognitive biases in depression have neural underpinnings (Beck, 2008; Beck & Bredemeier, 2016). Correlations did not hold within each group separately, which suggests that this relationship may be specific to clinical depression, and not likely generalized to subclinical traits in healthy adolescents.

Absence of significant group differences in ACC and amygdala activity

While both depressed and healthy adolescents recruited perigenual ACC activity during social exclusion (corroborating past findings, Bolting et al., 2011; Vijayakumar et al., 2017), contrary to our hypotheses, there were no significant group differences in ACC activity. Interestingly, findings from the parcelation approach offer preliminary evidence that group differences within these regions may exist, such that depressed adolescents may recruit reduced subgenual/ventral ACC activity during social exclusion compared to healthy adolescents. Thus, ventral regions of the ACC may play a greater role in social exclusion in adolescent depression than dorsal regions.

Research exploring the relationship between ACC activity during social exclusion and depression yields mixed results. Dorsal ACC activity is associated with reduced depressive symptoms (Masten et al., 2011) and greater interpersonal competence (Masten et al., 2009) in healthy adolescents. However, dorsal ACC activity is also associated with greater depressive symptoms in chronically peer-victimized adolescents (Rudolph et al., 2016), lower self-esteem in healthy adults (Onoda et al., 2010) and greater rejection sensitivity in healthy adolescents (Masten et al., 2009) and adults (Burkland et al., 2007). Rostral/perigenual ACC activity is associated with reduced depressive symptoms (Masten et al., 2011) and greater interpersonal competence (Masten et al., 2009) in healthy adolescents. Ventral/subgenual ACC activity is associated with reduced rejection sensitivity in healthy adults (Burkland et al., 2007) but also greater depressive symptoms in chronically peer-victimized adolescents (Rudolph et al., 2016), greater depressive symptoms in healthy adolescents at 1-year follow-up (Masten et al., 2011) and lower self-esteem in healthy adults (Onoda et al., 2010). Depressed adolescents recruit greater subgenual ACC activity during social exclusion (Silk et al.,...
but subgenual ACC stimulation is associated with reduced symptom severity in treatment-resistant clinically depressed adults (Mayberg et al., 2005; Puigdemont et al., 2012). This review, combined with the current findings, suggests that the impact of clinical depression on neural responsivity to social evaluative threat may manifest differently from the impact of subclinical depression or depression-relevant traits in non-depressed individuals, and that developmental differences may exist (Masten et al., 2009). Furthermore, different subregions of the ACC may play distinct roles in social exclusion (Rotge et al., 2014). Contrary to our hypotheses, neither depressed nor healthy adolescents recruited amygdala activity, and there were no group differences within this region. While maladaptive emotion reactivity and regulation are linked with amygdala dysfunction, these patterns are typically observed during emotional facial processing (Kerestes et al., 2014). A recent meta-analysis highlighted AI and IFG, but not amygdala, as key neural substrates of social rejection/exclusion (Cacioppo et al., 2013). Thus, AI/IFG hyperreactivity in the current study may reflect atypical salience processing of socially threatening information inherent in negative social interactions.

Strengths, limitations and future directions
The current study offers several strengths. First, it explored the impact of depression on neural responsivity to social exclusion within clinically depressed adolescents. While previous studies using Cyberball have adopted proxies for depression (including depression symptom severity in healthy individuals), the impact of clinical and subclinical depression may manifest differently on the neural level. Second, this study adopted large sample sizes that allowed us to generalize our findings with greater confidence. Third, this study conducted correlations with social cognitive variables associated with depressogenic profiles to explore potential ancillary processes underlying maladaptive responsivity to social exclusion. Fourth, this study adopted a two-pronged methodological approach for exploring group differences in neural activity, including implementing statistical thresholds across clusters of activation and measuring effect sizes within independently defined parcels. Compared to traditional methods, a parcellation approach significantly reduces the number of multiple comparisons from over 100 000 to under 200, and parcellations represent meaningful subunits based on network activation patterns. The current findings may serve as preliminary evidence for more stringent hypothesis testing, and this analytical method may prove useful in generating hypotheses and reducing statistical error in future research.

Two possible limitations relate to our inclusion criteria. First, medication usage was not exclusionary, although it was controlled for analytically. Second, comorbid diagnoses were not exclusionary. Yet given that depressed adolescents typically have comorbid disorders (Avenevoli et al., 2015) and most inpatients receive medication, our sample more accurately reflects the real-world manifestation of depression. Future research should tease apart the separable influences of clinical depression and related psychological and social contextual factors, including anxiety, suicidality and interpersonal conflict. In addition, research should further investigate the relationship between salience and central executive network connectivity and cognitive biases underlying depression vulnerability. Finally, it warrants repetition that the current findings should be interpreted with caution, given their lack of significance by current conventions. However, we hope the notable effect sizes observed via the parcellation approach will encourage further exploration and serve as preliminary evidence for more stringent hypothesis testing.

Conclusions
This study revealed moderately large group differences within left-lateralized limbic, ventrolateral prefrontal and lateral temporal regions during social exclusion. These atypicalities may reflect maladaptive salience processing, attribution of meaning and/or emotion regulation. The current findings converge with previous reports of atypical AI and ACC recruitment by depressed adolescents during social rejection, which lend support for a shared neural mechanism underlying maladaptive responsivity to negative social evaluations. Neural dysfunction may be responsible for attentional and attributional biases toward signals of social evaluative threat, which may substantiate feelings of social rejection and reduced self-worth, and which may, in turn, adversely influence interpersonal relationships.

Supplementary data
Supplementary data are available at SCAN online.

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Conflict of interest
None declared.

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