OXFORD

Social Cognitive and Affective Neuroscience, 2018, 863–876

doi: 10.1093/scan/nsy055
Advance Access Publication Date: 22 August 2018
Original article

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

Kathryn F. Jankowski[1], Jonathan Batres[2], Hannah Scott[2], Garry Smyda[3], Jennifer H. Pfeifer[1], and Karina Quevedo[2]

[1]Department of Psychology, University of Oregon, [2]Department of Psychiatry, University of Minnesota, [3]School of Public Health, University of Pittsburgh

Correspondence should be addressed to Karina Quevedo, F260/2A West B, 2450 Riverside Avenue South, Site 1 Minneapolis, MN 55454, USA. E-mail: queve001@umn.edu.

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 additional, 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

Received: 9 January 2017; **Revised:** 4 July 2018; **Accepted:** 11 July 2018

(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' responsivity 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 & Bredemeier, 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; Disner *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; Disner *et al.*, 2011; Fu *et al.*, 2013; Kerestes *et al.*, 2014; Palmer *et al.*, 2014). Key regions include dorsolateral, ventrolateral and medial prefrontal cortex (dlPFC, vlPFC 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). Relatedly, depressed adults recruit increased limbic (dorsal ACC, insula and amygdala) activity and reduced prefrontal (dlPFC) 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 hyperreactivity 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, vlPFC 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 inattention (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 11.3–17.8 years; M_{age} (s.d.) = 14.75 (1.63)] recruited from the University of Minnesota [$n = 39$; 16 males; M_{age} (s.d.) = 14.31 (1.60)] and the University of Pittsburgh [$n = 87$; 40 males; M_{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			$\chi^2(1) = 0.52$
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			$\chi^2(6) = 11.74$
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			$\chi^2(4) = 15.64^{**}$
< $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			$\chi^2(1) = 6.48^{*}$
Single	30 (34.9%)	5 (12.8%)	
Cohabitating	56 (65.1%)	34 (87.2%)	
Medication usage	44 (50.6%)		
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 an 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 interaction 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 Craddock *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 depressogenic social cognitive variables underlying our conceptual model: global self-worth, susceptibility to social stress, negative attribution style and negative emotional temperament.

1 There were no statistically significant differences in movement between scanning sites.

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 gyri (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)		−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 antianxiolytic 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

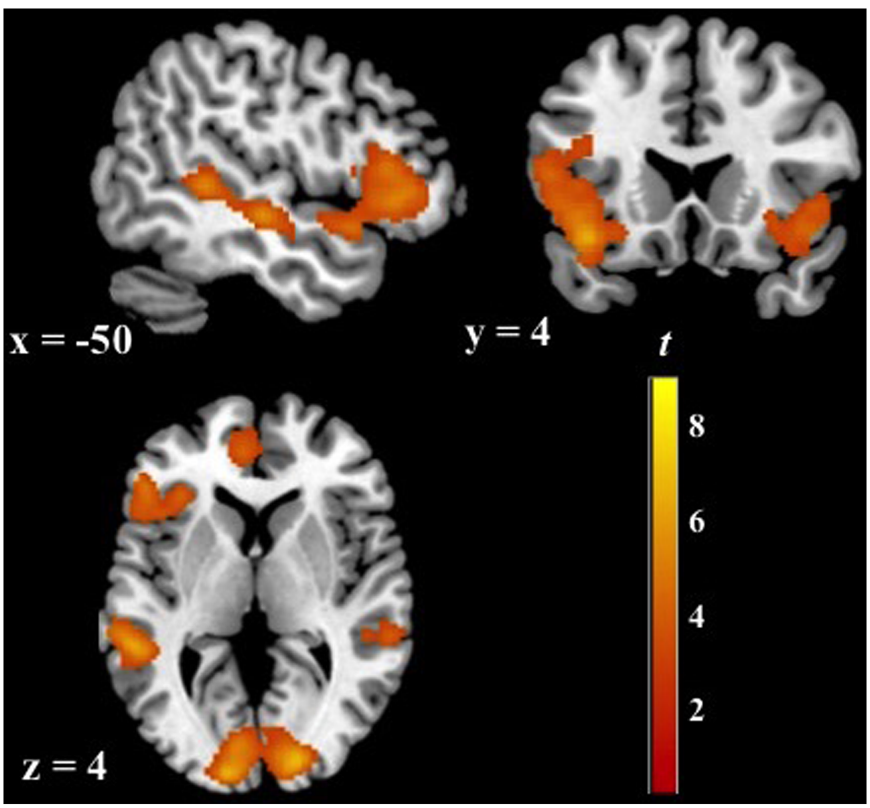

Fig. 1. Activity across groups during social exclusion (Exclusion > Inclusion).

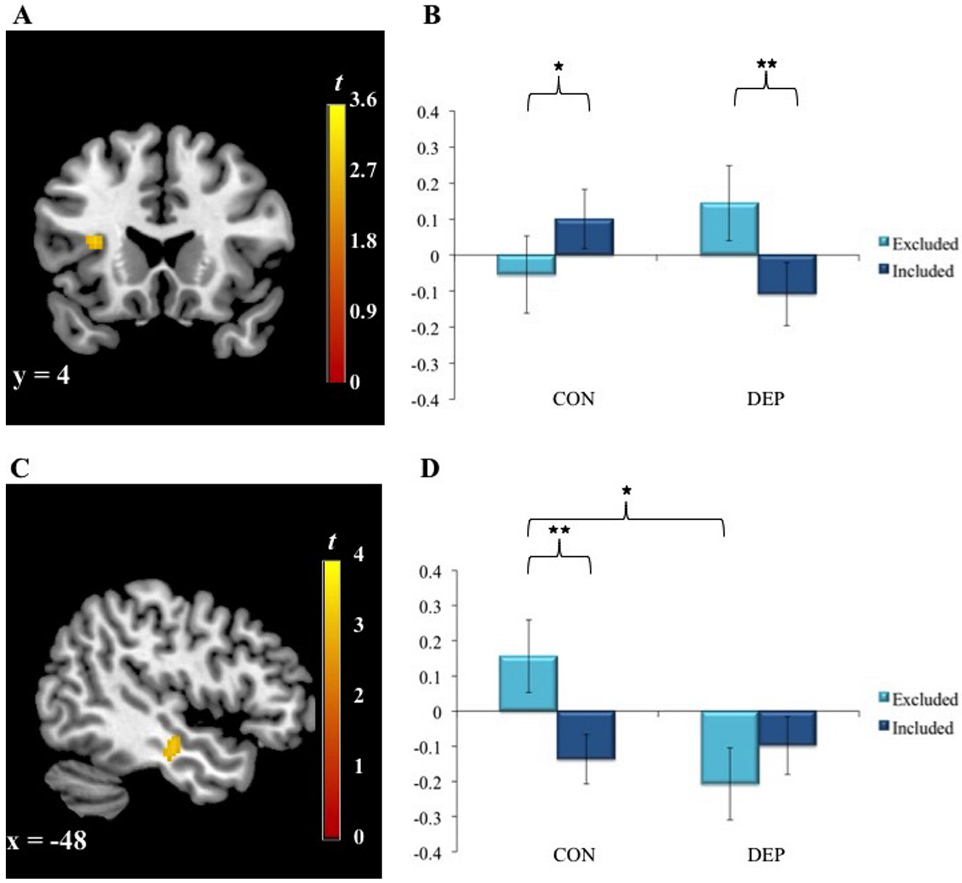

Fig. 2. Regions of group differences between depressed and healthy adolescents during social exclusion (Exclusion > Inclusion) Panels A & B: depressed adolescents recruited greater activity than healthy adolescents within the left anterior insula (AI)/inferior frontal gyrus/ (BA 45/47/13). Panels C & 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

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*
DEP > CON			
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*
CON > DEP			
50		Subgenual anterior cingulate cortex/ventral anterior cingulate cortex/medial orbitofrontal cortex (BA 32/24)	2.13*
99		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 gyus/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		Posterior middle cingulate cortex/paracentral lobule (BA 5/31)	1.48
37		Middle cingulate cortex (BA 24)	1.43
86	L	Fusiform gyrus (BA 19/37)	1.42
122		Dorsomedial prefrontal cortex (BA 8)	1.40
125		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		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		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.

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

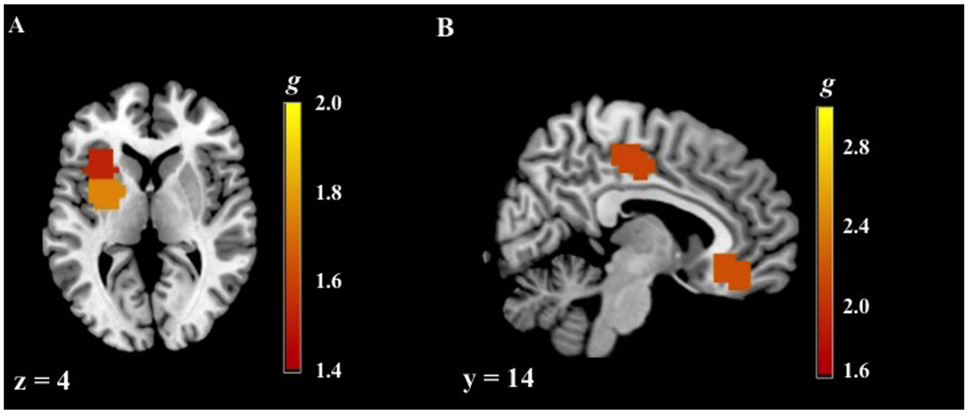

Fig. 3. Group differences in activity between depressed and healthy adolescents during social exclusion (Exclusion > Inclusion) across Craddock's 200 parcels. Panel A: depressed adolescents recruited greater activity than healthy adolescents within parcels representing insula. Panel B: healthy adolescents recruited greater activity than depressed adolescents within parcels representing subgenual anterior cingulate cortex and posterior middle cingulate (not shown: lateral prefrontal cortices). *Note:* Displayed regions represent parcels with moderate effect sizes, $g >= 1.15$, as well as two standard deviations above the mean ($g >= 1.33$ for DEP > CON and $g >= 1.58$ CON > DEP).

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 responsivity 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, Bolling *et al.*, 2011; Vijayakumar *et al.*, 2017), contrary to our hypotheses, there were no significant group differences in ACC activity. Interestingly, findings from the parcellation 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 (Burklund *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 (Burklund *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.*, 2014), 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.

Acknowledgements

The authors would like to sincerely thank the children and families who participated in this study and made this research possible. They would also like to thank Kathryn L. Mills, Danielle Cosme and John C. Flournoy for feedback on and assistance with R programming for the parcellation analyses.

Funding

This research was supported by K01MH092601 from National Institute of Mental Health and a National Alliance for Research on Schizophrenia and Depression (NARSAD) to K.Q. K.F.J. was supported by a National Science Foundation Graduate Research Fellowship (2011122786) and an Autism Speaks Weatherstone Predoctoral Fellowship.

Conflict of interest. None declared.

References

Abramson, L.Y., Alloy, L.B. (2006). Cognitive vulnerability to depression: current status and developmental origins. In: Joiner, T.E., Brown, J.S., Kistner, J., editors. *The Interpersonal, Cognitive, and Social Nature of Depression*, Mahwah, NJ: Lawrence Erlbaum Associates Publishers, 83–100.

Abramson, L.Y., Alloy, L.B., Hankin, B.L., Haeffel, G.J., MacCoon, D.G., Gibb, B.E. (2002). Cognitive vulnerability-stress models of depression in a self-regulatory and psychobiological context. In: Gotlib, I.H., Hammen C.L., editors. *Handbook of Depression*, New York: Guilford.

Abramson, L.Y., Alloy, L.B., Hogan, M.E., *et al.* (1998). Suicidality and cognitive vulnerability to depression among college students: a prospective study. *Journal of Adolescence*, **21**(4), 473–87.

Abramson, L.Y., Metalsky, G.I., Alloy, L.B. (1989). Hopelessness depression: a theory-based subtype of depression. *Psychological Review*, **96**, 358–72.

Ahmed, S.P., Bittencourt-Hewitt, A., Sebastian, C.L. (2015). Neurocognitive bases of emotion regulation development in adolescence. *Developmental Cognitive Neuroscience*, **15**, 11–25.

Ai, H., Opmeer, E.M., Veltman, D., *et al*. (2015). Brain activation during emotional memory processing associated with subsequent course of depression. *Neuropsychopharmacology*, **40**(10), 2454–63.

Allen, N.B., Badcock, P.B. (2003). The social risk hypothesis of depressed mood: evolutionary, psychosocial, and neurobiological perspectives. *Psychological Bulletin*, **129**(6), 887.

Alloy, L.B., Abramson, L.Y. (2007). The adolescent surge in depressio and emergence of gender differences: A biocognitive vulnerability-stress model in developmental context. In: Romer, D., Walker, E.F., editors. *Adolescent Psychopathology and the Developing Brain*, New York: Oxford University Press, 284–312.

Alloy, L.B., Abramson, L.Y., Safford, S.M., Gibb, B.E. (2006). The cognitive vulnerability to depression (CVD) project: current findings and future directions. In: Alloy, L.B., Riskind, J.H., editors. *Cognitive Vulnerability to Emotional Disorders*, New York: Routledge, 43–72.

Andersen, S.L., Teicher, M.H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neuroscience*, **31**(4), 183–91.

Arce, E., Simmons, A.N., Stein, M.B., Winkielman, P., Hitchcock, C., Paulus, M.P. (2009). Association between individual differences in self-reported emotional resilience and the affective perception of neutral faces. *Journal of Affective Disorders*, **114** (1–3), 286–93.

Aron, A.R., Robbins, T.W., Poldrack, R.A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, **8**(4), 170–7.

Avenevoli, S., Swendsen, J., He, J.P., Burstein, M., Merikangas, K.R. (2015). Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. *Journal of the American Academy of Child and Adolescent Psychiatry*, **54**(1), 37–44 e32.

Beauregard, M., Paquette, V., Levesque, J. (2006). Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *NeuroReport*, **17**(8), 843–6.

Beck, A.T. (1987). Cognitive models of depression. *Journal of Cognitive Psychotherapy: An International Quarterly*, **1**, 5–37.

Beck, A.T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry*, **165**(8), 969–77.

Beck, A.T., Bredemeier, K. (2016). A unified model of depression: Integrating clinical, cognitive, biological, and evolutionary perspectives. *Clinical Psychological Science*, **4**(4), 596–619.

Belleau, E.L., Taubitz, L.E., Larson, C.L. (2014). Imbalance of default mode and regulatory networks during externally focused processing in depression. *Social Cognitive and Affective Neuroscience*, **10**(5), 744–751.

Blom, E.H., Connolly, C.G., Ho, T.C., *et al*. (2015). Altered insular activation and increased insular functional connectivity during sad and happy face processing in adolescent major depressive disorder. *Journal of Affective Disorders*, **178**, 215–23.

Bolling, D.Z., Pitskel, N.B., Deen, B., Crowley, M.J., Mayes, L.C., Pelphrey, K.A. (2011). Development of neural systems for processing social exclusion from childhood to adolescence. *Developmental Science*, **14**(6), 1431–44.

Braet, C., Van Vlierberghe, L., Vandevivere, E., Theuwis, L., Bosmans, G. (2013). Depression in early, middle and late adolescence: differential evidence for the cognitive diathesis-stress model. *Clinical Psychology and Psychotherapy*, **20**(5), 369–83.

Brody, A.L., Barsom, M.W., Saxena, S. (2001). Prefrontal-subcortical and limbic circuit mediation of major depressive disorder. *Seminars in Clinical Neuropsychiatry*, **6**(2), 102–12.

Brown, B.B. (1990). Peer groups and peer cultures. In: Feldman, S.S., Elliot, G.R., editors. *At The Threshold: The Developing Adolescent*, Cambridge, MA: Harvard Press, 171–96.

Buhle, J.T., Silvers, J.A., Wager, T.D., *et al*. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex*, **24**(11), 2981–90.

Burklund, L.J., Eisenberger, N.I., Lieberman, M.D. (2007). The face of rejection: rejection sensitivity moderates dorsal anterior cingulate activity to disapproving facial expressions. *Social Neuroscience*, **2**(3–4), 238–53.

Cacioppo, S., Frum, C., Asp, E., Weiss, R.M., Lewis, J.W., Cacioppo, J.T. (2013). A quantitative meta-analysis of functional imaging studies of social rejection. *Scientific Reports*, **3**, 2027.

Conley, C.S., Haines, B.A., Hilt, L.M., Metalsky, G.I. (2001). The children's attributional style interview: developmental tests of cognitive diathesis-stress theories of depression. *Journal of Abnormal Child Psychology*, **29**, 445–63.

Cox, R.W., Reynolds, R.C., Taylor, P.A. (2016). AFNI and clustering: false positive rates redux. *bioRxiv*, 065862.

Craddock, R.C., James, G.A., Holtzheimer, P.E., 3rd, Hu, X.P., Mayberg, H.S. (2012). A whole brain fMRI atlas generated via spatially constrained spectral clustering. *Human Brain Mapping*, **33**(8), 1914–1928.

Davey, C.G., Yücel, M., Allen, N.B. (2008). The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neuroscience & Biobehavioral Reviews*, **32**(1), 1–19.

Deen, B., Pitskel, N.B., Pelphrey, K.A. (2011). Three systems of insular functional connectivity identified with cluster analysis. *Cerebral Cortex*, **21**(7), 1498–506.

Disner, S.G., Beevers, C.G., Haigh, E.A., Beck, A.T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, **12**(8), 467–77.

Drevets, W.C. (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current Opinion in Neurobiology*, **11**(2), 240–9.

Dunlop, B.W., Mayberg, H.S. (2014). Neuroimaging-based biomarkers for treatment selection in major depressive disorder. *Dialogues in Clinical Neuroscience*, **16**(4), 479.

Eklund, A., Nichols, T.E., Knutsson, H. (2016). Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences*, **113**(28), 7900–5.

Ferguson, C.F. (2009). An effect size primer: a guide for clinicians and researchers. *Professional Psychology: Research and Practice*, **40**(5), 532–8.

Fitzgerald, P.B., Laird, A.R., Maller, J., Daskalakis, Z.J. (2008). A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping*, **29**(6), 683–95.

Fu, C.H., Steiner, H., Costafreda, S.G. (2013). Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiology of Disease*, **52**, 75–83.

Fu, C.H., Williams, S.C., Cleare, A.J., *et al*. (2004). Attenuation of the neural response to sad faces in major depressionby antidepressant treatment: a prospective, event-related functional magnetic resonance imagingstudy. *Archives of General Psychiatry*, **61**(9), 877–89.

Garber, J., Braafladt, N., Weiss, B. (1995). Affect regulation in depressed and nondepressed children and young adolescents. *Developmental Psychopathology*, **7**(01), 93–115.

Garnefski, N., Kraaij, V. (2006). Relationships between cognitive emotion regulation strategies and depressive symptoms: a comparative study of five specific samples. *Personality and Individual Differences*, **40**(8), 1659–69.

Gerber, J.P., Chang, S.H., Reimel, H. (2017). Construct validity of Williams' ostracism needs threat scale. *Personality and Individual Differences*, **115**, 50–3.

Guyer, A.E., Silk, J.S., Nelson, E.E. (2016). The neurobiology of the emotional adolescent: from the inside out. *Neuroscience & Biobehavioral Reviews*, **70**, 74–85.

Hamilton, J.H., Furman, D.J., Chang, C., Thomason, M.E., Dennis, E., Gotlib, I.H. (2011). Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biological Psychiatry*, **70**(4), 327–33.

Hamilton, J.P., Etkin, A., Furman, D.J., Lemus, M.G., Johnson, R.F., Gotlib, I.H. (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. *The American Journal of Psychiatry*, **169**(7), 693–703.

Hankin, B.L. (2008). Cognitive vulnerability-stress model of depression during adolescence: Investigating depressive symptom specificity in a multi-wave prospective study. *Journal of Abnormal Child Psychology*, **36**, 999–1014.

Hankin, B.L. (2015). Depression from childhood through adolescence: risk mechanisms across multiple systems and levels of analysis. *Current Opinion in Psychology*, **4**, 13–20.

Hankin, B.L., Abramson, L.Y., Miller, N., Haeffel, G.J. (2004). Cognitive vulnerability-stress theories of depression: examining affective specificity in the prediction of depression versus anxiety in three prospective studies. *Cognitive Therapy and Research*, **28**(3), 309–45.

Harter, S. (1982). The perceived competence scale for children. *Child Development*, **53**, 87–97.

Harter, S. (1999). The Construction of the Self: A Developmental Perspective. Guilford Press, New York, NY, US.

Ho, T.C., Yang, G., Wu, J., *et al.* (2014). Functional connectivity of negative emotional processing in adolescent depression. *Journal of Affective Disorders*, **155**, 65–74.

Immordino-Yang, M.H., Yang, X.F., Damasio, H. (2014). Correlations between social-emotional feelings and anterior insula activity are independent from visceral states but influenced by culture. *Frontiers in Human Neuroscience*, **8**, 728.

Jacobs, R.H, Reinecke, M.A., Gollan, J.K., & Kane, P. (2008). Empirical evidence of cognitive vulnerability for depression among children and adolescents: A cognitive science and developmental perspective. *Clinical Psychology Review*, **28**(5), 759–782.

Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *Journal of Neuroscience,* **27**(33), 8877–84.

Joiner, T.E., Jr., Lewinsohn, P.M., Seeley, J.R. (2002). The core of loneliness: lack of pleasurable engagement—more so than painful disconnection—predicts social impairment, depression onset, and recovery from depressive disorders among adolescents. *Journal of Personality Assessment*, **79**(3), 472–91.

Joormann, J., Gotlib, I.H. (2010). Emotion regulation in depression: relation to cognitive inhibition. *Cognition and Emotion*, **24**(2), 281–98.

Joormann, J., Talbot, L., Gotlib, I.H. (2007). Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology*, **116**(1), 135–43.

Kaufman, J., Birmaher, B., Brent, D., *et al.* (1997). Schedule for affective disorders and schizophrenia for school-aged children—present and lifetime (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child Adolescent Psychiatry*, **36**, 980–8.

Keedwell, P.A., Andrew, C., Williams, S.C., Brammer, M.J., Phillips, M.L. (2005). A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biological Psychiatry*, **58**(6), 495–503.

Kerestes, R., Davey, C.G., Stephanou, K., Whittle, S., Harrison, B.J. (2014). Functional brain imaging studies of youth depression: a systematic review. *Neuroimage Clinical*, **4**, 209–231.

Leung, K.K., Lee, T.M., Yip, P., Li, L.S., Wong, M.M. (2009). Selective attention biases of people with depression: positive and negative priming of depression-related information. *Psychiatry Research*, **165**(3), 241–51.

Leyman, L., De Raedt, R., Schacht, R., Koster, E.H. (2007). Attentional biases for angry faces in unipolar depression. *Psychological Medicine,* **37**(3), 393–402.

Mathews, A., McLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*, **1**, 167–95.

Masten, C.L., Eisenberger, N.I., Borofsky, L.A., McNealy, K., Pfeifer, J.H., Dapretto, M. (2011). Subgenual anterior cingulate responses to peer rejection: a marker of adolescents' risk for depression. *Developmental Psychopathology*, **23**(1), 283–92.

Masten, C.L., Eisenberger, N.I., Borofsky, L.A., *et al.* (2009). Neural correlates of social exclusion during adolescence: understanding the distress of peer rejection. *Social Cognitive and Affective Neuroscience*, **4**(2), 143–57.

Mayberg, H.S., Liotti, M., Brannan, S.K., *et al.* (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *American Journal of Psychiatry*, **156**(5), 675–82.

Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Kennedy, S.H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, **45**(5), 651–660.

McRae, K., Gross, J.J., Weber, J., *et al.* (2012). The development of emotion regulation: an fMRI study of cognitive reappraisal in children, adolescents and young adults. *Social Cognitive and Affective Neuroscience*, **7**(1), 11–22.

Menon, V., Uddin, L.Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, **214**(5–6), 655–67.

Moss, H.E., Abdallah, S., Fletcher, P., *et al.* (2005). Selecting among competing alternatives: Selection and retrieval in the left inferior frontal gyrus. *Cerebral Cortex*, **15**, 1723–35.

O'Brien, S.F., Bierman, K.L. (1998). Conceptions and perceived influence of peer groups- Interviews with preadolescents and adolescents. *Child Development*, **59**(5), 1360–5.

Ochsner, K.N., Silvers, J.A., Buhle, J.T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, **1251**, E1–24.

Onoda, K., Okamoto, Y., Nakashima, K., *et al.* (2010). Does low self-esteem enhance social pain? The relationship between trait self-esteem and anterior cingulate cortex activation induced by ostracism. *Social Cognitive and Affective Neuroscience*, **5**(4), 385–91.

Palmer, S.M., Crewther, S.G., Carey, L.M., Team, S.P. (2014). A meta-analysis of changes in brain activity in clinical depression. *Frontiers in Human Neuroscience*, **8**, 1045.

Patrick, C.J., Curtin, J.J., Tellegen, A. (2002). Development and validation of a brief form of the Multidimensional Personality Questionnaire. *Psychological Assessment*, **14**(2), 150.

Perlman, G., Simmons, A.N., Wu, J., *et al.* (2012). Amygdala response and functional connectivity during emotion regulation:

a study of 14 depressed adolescents. *Journal of Affective Disorders*, **139**(1), 75–84.

Petersen, A., Crockett, L., Richards, M., Boxer, A. (1988). A self-report measure of pubertal status: reliability, validity, and initial norms. *Journal of Youth and Adolescence*, **17**(2), 117–33.

Pfeifer, J.H., & Blakemore, S.J. (2012). Adolescent social cognitive and affective neuroscience: past, present, and future. *Social Cognitive and Affective Neuroscience*, **7**(1), 1–10.

Phinney, J.S. (1992). The multigroup ethnic identity measure: a new scale for use with diverse groups. *Journal of Adolescent Research*, **7**(2), 156–76.

Platt, B., Campbell, C.A., James, A.C., Murphy, S.E., Cooper, M.J., Lau, J.Y. (2015). Cognitive reappraisal of peer rejection in depressed versus non-depressed adolescents: functional connectivity differences. *Journal of Psychiatric Research*, **61**, 73–80.

Platt, B., Cohen Kadosh, K., Lau, J.Y. (2013). The role of peer rejection in adolescent depression. *Depression and Anxiety*, **30**(9), 809–21. doi:10.1002/da.22120

Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage*, **10**(1), 15–35.

Poznanski, E.O., Cook, S.C., Carroll, B.J. (1979). A depression rating scale for children. *Pediatrics*, **64**, 442–50.

Poznanski, E.O., Grossman, J.A., Buchsbaum, Y., Banegas, M., Freeman, L., Gibbons, R. (1984). Preliminary studies of the reliability and validity of the children's depression rating scale. *Journal of the American Academy of Child Psychiatry*, **23**(2), 191–7.

Prinstein, M.J., Aikins, J.W. (2004). Cognitive moderators of the longitudinal association between peer rejection and adolescence depressive symptoms. *Journal of Abnormal Child Psychology*, **32**(2), 147–58.

Prinstein, M.J., Cheah, C.S., Guyer, A.E. (2005). Peer victimization, cue interpretation, and internalizing symptoms: preliminary concurrent and longitudinal findings for children and adolescents. *Journal of Clinical Child and Adolescent Psychology*, **34**(1), 11–24.

Puigdemont, D., Pérez-Egea, R., Portella, M.J., *et al.* (2012). Deep brain stimulation of the subcallosal cingulate gyrus: Further evidence in treatment resistant major depression. *International Journal of Neuropsychopharmacology*, **15**, 121–33.

Rao, U., Chen, L. (2009). Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders. *Dialogues in Clinical Neuroscience*, **11**(1), 45–62.

Ray, R.D., Ochsner, K.N., Cooper, J.C., Robertson, E.R., Gabrieli, J.D., Gross, J.J. (2005). Individual differences in trait rumination and the neural systems supporting cognitive reappraisal. *Cognitive Affective and Behavioral Neuroscience*, **5**(2), 156–68.

Reynolds, C.R., Kamphaus, R.W. (2004). *BASC-2: Behavior assessment for children, second edition manual*, Circle Pines, MN: American Guidance Service.

Robin, A.L., Foster, S.L. (1989). *Negotiating parent–adolescent conflict: a behavioral-family systems approach*, New York: Guilford Press.

Rotge, J.-Y., Lemonge, C., Hinfray, S., *et al.* (2014). A meta-analysis of the anterior cingulate contribution to social pain. *Social Cognitive Affective Neuroscience*, **10**(1), 19–27.

Rudolph, K.D., Miernicki, M.E., Troop-Gordon, W., Davis, M.M., Telzer, E.H. (2016). Adding insult to injury: neural sensitivity to social exclusion is associated with internalizing symptoms in chronically peer-victimized girls. *Social Cognitive and Affective Neuroscience*, **11**(5), 829–42.

Sheeber, L.B., Allen, N.B., Leve, C., Davis, B., Shortt, J.W., Katz, L.F. (2009). Dynamics of affective experience and behavior in depressed adolescents. *Journal of Child Psychology and Psychiatry*, **50**(11), 1419–27.

Shih, J.H., Eberhart, N.K., Hammen, C.L., Brennan, P.A. (2006). Differential exposure and reactivity to interpersonal stress predict sex differences in adolescent depression. *Journal of Clinical Child and Adolescent Psychology*, **35**(1), 103–15.

Silk, J.S., Siegle, G.J., Lee, K.H., Nelson, E.E., Stroud, L.R., Dahl, R.E. (2014). Increased neural response to peer rejection associated with adolescent depression and pubertal development. *Social Cognitive Affective Neuroscience*, **9**(11), 1798–807.

Silk, J.S., Steinberg, L., Morris, A.S. (2003). Adolescents' emotion regulation in daily life: links to depressive symptoms and problem behavior. *Child Development*, **74**(6), 1869–80.

Sliz, D., Hayley, S. (2012). Major depressive disorder and alterations in insular cortical activity: A review of current functional magnetic imaging research. *Frontiers in Human Neuroscience*, **6**, 323.

Sridharan, D., Levitin, D.J., Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, **105**(34), 12569–74.

Stapinski, L.A., Araya, R., Heron, J., Montgomery, A.A., Stallard, P. (2015). Peer victimization during adolescence: concurrent and prospective impact on symptoms of depression and anxiety. *Anxiety, Stress, & Coping*, **28**(1), 105–20.

Stroud, L.R., Foster, E., Papandonatos, G.D., *et al.* (2009). Stress response and the adolescent transition: performance versus peer rejection stressors. *Development and Psychopathology*, **21**(1), 47–68.

Stuhrmann, A., Suslow, T., Dannlowski, U. (2011). Facial emotion processing in major depression: a systematic review of neuroimaging findings. *Biology of Mood and Anxiety Disorders*, **1**(1), 1–10.

Surguladze, S.A., El-Hage, W., Dalgleish, T., Radua, J., Gohier, B., Phillips, M.L. (2010). Depression is associated with increased sensitivity to signals of disgust: a functional magnetic resonance imaging study. *Journal of Psychiatry Resesarch*, **44**(14), 894–902.

Takano, K., Tanno, Y. (2009). Self-rumination, self-reflection, and depression: self-rumination counteracts the adaptive effect of self-reflection. *Behavior Research and Therapy*, **47**(3), 260–4.

Teasdale, J.D., Dent, J. (1987). Cognitive vulnerability to depression: an investigation of two hypotheses. *British Journal of Clinical Psychology*, **26**(2), 113–26.

Thompson-Schill, S.L., D'Esposito, M., Aguirre, G.K., Farah, M.J. (1997). Role of the left inferior frontal gyrus in retrieval of semantic knowledge. *Proceedings of the National Academy of Sciences*, **94**(26), 14792–7.

Vijayakumar, N., Cheng, T.W., Pfeifer, J.H. (2017). Neural correlates of social exclusion across ages: a coordinate-based meta-analysis of functional MRI studies. *Neuroimage*, **153**, 359–68.

Wechsler, D. (1999). *Wechsler Abbreviated Intelligence Scale*, San Antonio: The Psychological Corporation.

Whitney, C., Jefferies, E., Kircher, T. (2011). Heterogeneity of the left temporal lobe in semantic representation and control: priming multiple versus single meanings of ambiguous words. *Cerebral Cortex*, **21**(4), 831–44.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M.A., Jefferies, E. (2011). The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. *Cerebral Cortex*, **21**(5), 1066–75.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M.A., Jefferies, E. (2012). Executive semantic processing is underpinned by a large-scale neural network: revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. *Journal of Cognitive Neuroscience*, **24**(1), 133–47.

Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., Rizzolatti, G. (2003). Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. *Neuron*, **40**(3), 655–64.

Williams, K.D., Cheung, C.K., Choi, W. (2000). Cyberostracism: effects of being ignored over the internet. *Journal of Personality and Social Psychology*, **79**(5), 748–62.

Williams, K.D., Govan, C.L., Croker, V., Tynan, D., Cruickshank, M., Lam, A. (2002). Investigations into differences between social- and cyberostracism. *Group Dynamics: Theory, Research, and Practice*, **6**(1), 65.

Youngren, M.A., Lewinsohn, P.M. (1980). The functional relation between depression and problematic interpersonal behavior. *Journal of Abnormal Psychology*, **89**(3), 333–41.

Zhong, M., Wang, X., Xiao, J., Yi, J., Zhu, X., Liao, J., … & Yao, S. (2011). Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression. *Biological Psychology*, **88**(2–3), 233–242.