Published in final edited form as:

J Clin Child Adolesc Psychol. 2023 September 03; 52(5): 659–674.

doi:10.1080/15374416.2021.2019048.

Subgenual Cingulate Cortex Reactivity to Rejection vs. Acceptance Predicts Depressive Symptoms Among Adolescents with an Anxiety History

Jennifer S. Silk[1], **Stefanie S. Sequeira**[1], **Neil P. Jones**[2], **Kyung Hwa Lee**[3], **Ronald E. Dahl**[4], **Erika. E. Forbes**[2], **Neal D. Ryan**[2], **Cecile D. Ladouceur**[2]

[1]University of Pittsburgh, Department of Psychology, Pittsburgh, PA

[2]University of Pittsburgh, Department of Psychiatry, Pittsburgh, PA

[3]Seoul National University College of Medicine, Department of Psychiatry, Seoul, Korea

[4]University of California at Berkeley, School of Public Health, Berkeley, CA

Abstract

Objective: The goal of this study was to examine whether neural sensitivity to negative peer evaluation conveys risk for depression among youth with a history of anxiety. We hypothesized that brain activation in regions that process affective salience in response to rejection, relative to acceptance, from virtual peers would predict depressive symptoms one year later and would be associated with ecological momentary assessment (EMA) reports of peer connectedness.

Method: Participants were 38 adolescents ages 11-16 (50% female) with a history of anxiety, recruited from a previous clinical trial. The study was a prospective naturalistic follow-up of depressive symptoms assessed 2 years (Wave 2) and 3 years (Wave 3) following treatment. At Wave 2, participants completed the Chatroom Interact Task during neuroimaging and 16 days of EMA.

Results: Controlling for depressive and anxiety symptoms at Wave 2, subgenual anterior cingulate (sgACC; β=.39, p=.010) activation to peer rejection (vs. acceptance) predicted depressive symptoms at Wave 3. SgACC activation to rejection (vs. acceptance) was highly negatively correlated with EMA reports of connectedness with peers in daily life (r= −.71, p<.001).

Conclusion: Findings suggest that elevated sgACC activation to negative, relative to positive, peer evaluation may serve as a risk factor for depressive symptoms among youth with a history of anxiety, perhaps by promoting vigilance or reactivity to social evaluative threats. SgACC activation to simulated peer evaluation appears to have implications for understanding how adolescents experience their daily social environments in ways that could contribute to depressive symptoms.

jss4@pitt.edu .

Keywords

depression; anxiety; neuroimaging; peer rejection; social threat

Rates of depression are alarmingly high among adolescents, with a dramatic spike in recent decades (Mojtabai, Olfson, & Han, 2016). Youth with a history of anxiety are at especially high risk of developing symptoms of depression during adolescence (Pine, Cohen, Gurley, Brook, & Ma, 1998; Rice, Sellers, Hammerton, & et al., 2017). Although not all children with anxiety disorders go on to develop depression, about 75% of youth who do develop depression have a history of at least one anxiety disorder (Kessler, Avenevoli, & Merikangas, 2001). Genetic studies reveal that symptoms of depression in adolescents are correlated with symptoms of anxiety earlier in childhood (Silberg, Rutter, Neale, & Eaves, 2001), suggesting that shared neurobehavioral mechanisms could place anxious children on a trajectory toward depression.

Silk et al. (2012) proposed that neural sensitivity to social evaluative threat, especially threat that occurs in the peer context, such as rejection, may be a key mechanism in the pathway to depression among anxious youth. Social-evaluative threat occurs when an aspect of self-identity that is valued by the individual, such as social status, is perceived to be negatively judged by others, or could be negatively judged in the future (Dickerson & Kemeny, 2004). Sensitivity to social evaluative threat increases in adolescence (Silk, Davis, et al., 2012), a time when the salience of feedback from peers increases (Nelson, Leibenluft, McClure, & Pine, 2005). Major theories of depression highlight a key role for sensitivity to interpersonal threats such as exclusion from a group or rejection by valued others (Coyne, 1976; Gilbert, 1992), and behavioral research has consistently shown that interpersonal stressors that threaten social status and social relationships, such as romantic breakups or conflicts with friends, often precipitate the first episode of depression or predict growth in symptoms (Earnshaw et al., 2017; Lewinsohn, Allen, Seeley, & Gotlib, 1999). In the present study we test the hypothesis that sensitivity to social evaluative threat, in the form of negative compared to positive evaluation from peers, is a risk factor for depressive symptoms among youth with a history of anxiety.

Recent developmental affective neuroscience research utilizing virtual peer feedback tasks, such as Cyberball (Eisenberger, Lieberman, & Williams, 2003), the Chatroom Task (Guyer et al., 2008), and the Chatroom Interact Task (Silk et al., 2014; Silk, Stroud, et al., 2012) has highlighted an affective salience network (ASN) of brain regions involved in monitoring and processing affective salience that are consistently activated by simulated social evaluative threats, such as peer rejection or exclusion (Guyer et al., 2008; Lau et al., 2012; Masten et al., 2009; Silk et al., 2014; Will, van Lier, Crone, & Güroğlu, 2016). Regions within the ASN include the subgenual anterior cingulate cortex (sgACC) (Gunther Moor, van Leijenhorst, Rombouts, Crone, & Van der Molen, 2010; Masten et al., 2009), amygdala (Lau et al., 2012; Whittle et al., 2008), anterior insula (AI) (Masten et al., 2009; Silk et al., 2014), and ventral striatum (VS) (Guyer, Caouette, Lee, & Ruiz, 2014; Telzer, Fuligni, Lieberman, & Galvan, 2013). While studies in adults often implicate the dorsal ACC in responding to exclusion (Eisenberger et al., 2003), studies with adolescents have more often

implicated subgenual or ventral portions of the ACC (Bolling et al., 2011; Masten et al., 2009; Sebastian et al., 2011). A meta-analysis of 46 studies of simulated rejection/exclusion, in fact, revealed that adolescents exhibited sgACC response to a greater extent than adult participants (Rotge et al., 2014). The sgACC plays an important role in monitoring, modulating, and generating emotions (Mayberg, 2003; Siegle et al., 2012), including responses to social feedback (Masten et al., 2009; Rudolph, Miernicki, Troop-Gordon, Davis, & Telzer, 2016; Sebastian et al., 2011; Somerville, Heatherton, & Kelley, 2006). The sgACC may also be critical for sustaining autonomic arousal over time (Rudebeck et al., 2014) and may support predictions about changes in physiological arousal that are needed to navigate current or future environmental conditions (Barrett & Simmons, 2015; Dixon, Thiruchselvam, Todd, & Christoff, 2017). These predictions can be used by other nearby regions with anatomical connections to the sgACC, including the hypothalamus, to trigger physiological changes.

Within the ASN, the amygdala plays a key role in orienting attention toward emotionally salient information, such as potential threat or reward, and facilitating learning (Budygin et al., 2012; Cardinal, Parkinson, Hall, & Everitt, 2002). The AI is involved in representing current internal physical and emotional states and plays a role in interoceptive awareness, potentially supporting the overlap between the perception of physical and emotional states (Zaki, Davis, & Ochsner, 2012). The AI is also involved in generating the subjective experience of “feelings” (Singer, Critchley, & Preuschoff, 2009), including distress associated with exclusion/rejection (Eisenberger et al., 2003; Masten et al., 2009). Although the VS has received more attention for its key role in the brain’s reward circuit, it also plays a role in encoding aversive events and learning from punishment (McCutcheon, Ebner, Loriaux, & Roitman, 2012), including social rejection (Gunther Moor et al., 2010; Guyer et al., 2014; Silk et al., 2014). Collectively, these regions are involved in integrating information about emotional salience and relative risks and rewards in ways that shape learning and future approach-avoidance behaviors.

Recent research reveals that regions of the ASN show hyper-activation in response to simulated rejection or social exclusion among adolescents with depression or depressive symptoms (Masten et al., 2011; Rudolph et al., 2016; Silk et al., 2014). For example, Silk et al. (2014) found that adolescents with major depressive disorder (MDD), compared to healthy controls, showed heightened activation to rejection by a virtual peer in the amygdala, AI, sgACC, and NAcc. Others have shown that increased reactivity to social exclusion vs inclusion on the Cyberball task in regions such as the sgACC, dACC, and AI are associated with diagnoses of depression in adolescence (Jankowski et al., 2018), as well as depressive and broader internalizing symptoms in community samples of teens (Masten et al., 2011; Rudolph et al., 2016). There is consistent behavioral evidence from reaction time and eyetracking studies demonstrating that youth with anxiety symptoms or disorders show a pattern of hypervigilance to socially threatening information, such as angry faces (Abend et al., 2018; Rosen, Price, & Silk, 2019). Evidence over the past decade has also shown that anxious youth have a heightened neural response to the anticipation and receipt of negative social evaluation from virtual peers in regions of the ASN similar to those identified in studies of depression, such as the amygdala, insula, and anterior cingulate cortex (Guyer

et al., 2008; Lau et al., 2012; Spielberg et al., 2014). However, it is not clear whether this neural profile increases risk for a progression toward depression among anxious youth.

Depression is a multifaceted construct and sensitivity to social evaluative threat may contribute to multiple aspects of the disorder. One way in which heightened activation of brain regions within the ASN could contribute to the development of depression is through its influence on risk/reward decision-making in social interactions. Adolescents with a stronger response to social evaluative threat may be less likely to choose to engage in potentially threatening or risky social experiences, therefore losing out on social rewards during a developmental window in which reward-seeking is normative (Galvan, 2010). For example, theorists have proposed that increased neurobiological sensitivity toward threat among anxious youth, in particular, could promote avoidance of potentially risky but also rewarding social activities, such as going to a party, playing a sport, or making a new friend (Caouette & Guyer, 2014; Richey et al., 2019; Silk, Davis, et al., 2012). This is consistent with evidence that attention toward threat competes with and has the potential to interfere with reward processing (Frewen, Dozois, Joanisse, & Neufeld, 2008). Therefore, in these approach-avoidance situations with risk/reward tradeoff, attentional bias to potential threat and associated affective arousal may contribute to avoidance rather than adolescent-typical reward-seeking behaviors. This process may be even more prevalent among anxious youth, who often interpret ambiguous social cues as threatening (Creswell, Schniering, & Rapee, 2005), and may also fail to distinguish safety and threat cues (Lau & Waters, 2017). Thus, anxious youth may avoid engaging in adolescent-normative reward-seeking behaviors, potentially contributing to features of depression such as anhedonia, social isolation, and withdrawal. This pattern is postulated to become especially problematic during adolescence (Silk, Davis, et al., 2012), a time when sensitivity to reward and the salience of peer status are heightened (Galvan, 2013; Nelson et al., 2005). Attending and reacting to the potentially threatening aspects of peer interactions may also contribute to or maintain affective features of depression, such as sad mood and cognitive features such as negative attributions and negatively biased cognitions. Heightened physiological arousal associated with reactivity to social threat (Silk et al. 2012) could also contribute to physical symptoms of depression such as pain and fatigue.

Altered sgACC function in particular may play a central role in supporting the development of depressive symptoms over time. In addition to its role in monitoring and modulating sadness (Mayberg, 2003; Siegle et al., 2012), the sgACC, together with the hypothalamus and periaqueductal gray, are implicated in modulating physiological arousal to adapt to changing environmental conditions (Dixon et al., 2017). SgACC dysfunction could therefore contribute to sadness dysregulation and poorer control of autonomic arousal in emotionally laden contexts, such as negative peer evaluation, contributing to both affective and physical symptoms of depression. Indeed, research has shown that hyperactivity of the sgACC is associated with changes in vagal tone, heart rate variability, and cortisol dynamics, as well as heightened physiological reactivity to proximal and distal threat (Alexander et al., 2020). As discussed above, sgACC-supported heightened reactivity to threat in youth with anxiety could also contribute to avoidance behaviors, increasing risk for anhedonic symptoms of depression. Consistent with the role of the sgACC as a critical region supporting the development of depressive symptoms, Masten et al. (2011) found that sgACC response

to exclusion on the Cyberball Task was associated with depressive symptoms one year later in a community sample of adolescents, suggesting that sgACC reactivity to negative peer feedback could be a prospective risk factor for depressive symptoms, but this possibility has not yet been evaluated in longitudinal studies with adolescents at high risk for depression, such as youth with a history of anxiety.

Collectively, theory and emerging evidence support the potential role of neural sensitivity to social evaluative threat, such as rejection, as a mechanism that conveys risk for depression among anxious youth, but longitudinal data are needed to test this possibility. For the present study, we leveraged a sample of youth originally recruited to participate in an anxiety treatment study to examine whether, among youth with a history of anxiety, heightened response to simulated peer rejection, relative to acceptance, in regions of the ASN, predicted symptoms of depression one year later. We focused on neural response to rejection on the Chatroom Interact task, in which adolescents are led to believe that another adolescent they are interacting with has selected or not selected them to discuss a topic. We hypothesized that sgACC, NAcc, anterior insula and/or amygdala response to peer rejection, relative to peer acceptance, would predict depressive symptoms one year later, above and beyond concurrent symptoms.

A secondary goal of the study was to use ecological momentary assessment (EMA) to establish ecological validity for the task by examining whether brain response to simulated rejection vs. acceptance in the lab relates to real-world perceptions of social connectedness with peers. EMA is an ecologically-valid method of gathering real-time data on emotion and behavior in natural environments through the use of signaling devices (Hormuth, 1986; Stone, Shiffman, & DeVries, 1999). One study using daily diary methods showed that youth who spent more time with peers exhibited reduced AI and ACC activation in response to exclusion on the Cyberball Task (Masten, Telzer, Fuligni, Lieberman, & Eisenberger, 2012), but little is known about how neural response on simulated peer evaluation tasks relates to adolescents' subjective perceptions of their peer interactions throughout the day. This is an important next step in understanding how brain functioning contributes to day-to-day patterns of social interaction in ways that can contribute to depression. Silk et al. (2012) demonstrated that greater pupillary reactivity to rejection, compared to acceptance, on the Chatroom Interact Task, was associated with reduced feelings of connectedness with peers in everyday life reported via EMA, but it remains unknown whether this pattern extends to neural activation in youth with a history of anxiety. We hypothesized that reactivity to simulated peer rejection (vs. acceptance) on the Chatroom Interact Task in the sgACC, NAcc, anterior insula and/or amygdala would be associated with lower perceptions of connectedness with peers during daily social interactions as assessed via EMA over 16 days.

Method

Participants

Participants were 38 youth (19 females) with a history of anxiety who were previously treated via psychotherapy with cognitive behavioral therapy (N = 23) or child-centered therapy (N = 14) as part of a randomized clinical trial (Wave 1; Silk et al. 2018) and were subsequently enrolled in a follow-up study that included assessments two years (Wave 2)

and three years (Wave 3) following treatment to examine risk for depression among youth with a history of anxiety. Participants were originally recruited for the treatment study from a U.S. mid-Western metropolitan region through radio, television, and newspaper advertisements, as well as referrals from pediatricians, school counselors, and mental health clinics. At Wave 1 (pre-treatment), participants met DSM-IV (American Psychiatric Association, 1994) criteria for a diagnosis of generalized anxiety disorder (GAD; 74%), separation anxiety disorder (SAD; 21%), and/or social anxiety disorder (SocAD; 26%), The present report focuses on the follow-up study conducted at Waves 2 and 3. At Wave 2, participants were 11-16 years old (M = 13.66, SD = 1.43), and 11 participants met criteria for a current anxiety disorder (see Table 1). Other current diagnoses included Depressive disorder not otherwise specified (n=1), Motor/Vocal Tic Disorder (n=1), and attention deficit/hyperactivity disorder (ADHD; n=1). At Wave 3, participants were 12-17 years old (M = 14.19, SD = 1.44), and seven participants met criteria for a current anxiety disorder. Other current diagnoses at Wave 3 included ADHD (n=2) and Motor/Vocal Tic Disorder (n=1). Two participants met full criteria for Major Depressive Disorder between Waves 2 and 3. See Table 1 for additional participant characteristics.

Procedure

Full procedures for the Wave 1 RCT are described in Silk et al. (2018). Briefly, youth were randomized to 16 sessions of psychotherapy, with a 2:1 ratio for assignment to cognitive behavioral therapy (CBT) or child-centered therapy (CCT). CBT was delivered using the *Coping Cat* manual (Kendall & Hedtke, 2006) and CCT was a manualized nondirective, supportive therapy based on humanistic principles that was used as an active comparison treatment for the original study (Cohen, Deblinger, Mannarino, & Steer, 2004; Cohen, Mannarino, & Knudsen, 2005). Previous research on this sample showed that both treatments resulted in a positive response for the majority of youth, with acute treatment response rates at 69% for CBT and 60% for CCT (Silk et al. 2018).

Of 105 participants (out of 133 in the randomized trial at Wave 1) who were enrolled in the follow-up study and invited to return to the lab for Wave 2 and Wave 3, a total of 38 completed neuroimaging with usable data and were included in the current study. A parent or legal guardian provided informed consent and adolescents provided assent (Human Research Protection Office #PRO07110273). The Wave 2 assessment included functional neuroimaging during a virtual peer evaluation task along with a 16-day EMA protocol, and both Waves 2 and 3 included clinical assessment. Fifty-five participants completed at least some of the Wave 2 fMRI scan; 50 participants did not complete the scan because they had gotten dental braces (n=20), refusal (n=17), loss to follow up (n=1), claustrophobia (n=2), and other reasons that were not documented (n=10). Of the 55 participants who were scanned, seven failed to complete the Chatroom Interact Task in the scanner because of illness or anxiety (n=2), technical issues (n=2), running out of time (n=2), and one unknown reason. Complete data were available for a final sample of 38 participants. Ten participants who completed the task were excluded from present analyses due to not having a recorded behavioral response on the task (n=2), problems with co-registration of the fMRI data (n=1), excess movement in the scanner (n=1), or missing depression measures (n=6). There were no differences in age, sex, anxiety severity, or depressive severity between the subset of

participants that composed the final sample (N=38) and those who participated in the larger study that did not have usable fMRI data (all *p*'s>.25).

Diagnoses were determined by an independent evaluator who was not aware of original treatment assignment using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Treatment response was defined as a 35% reduction in IE-rated anxiety severity on the Pediatric Anxiety Rating Scale (PARS; RUPP Study Group, 2002) from pre- to post-treatment (Caporino et al., 2013). The present sample included 20 treatment responders (53%) and 16 non-responders (42%). Depressive symptoms were assessed using youth report on the long version of the Mood and Feelings Questionnaire (MFQ-C; Angold, Costello, Messer, & Pickles, 1995). Anxiety symptoms were assessed using youth report on the Screen for Child Anxiety Related Emotional Disorders (SCARED-C: Birmaher et al., 1997). The PARS, MFQ, and SCARED have been shown to be reliable and valid tools for assessing severity of anxiety and depression in clinical samples of children and adolescents (Angold et al., 1995; Birmaher et al., 1997; Caporino et al., 2013)

Chatroom Interact Task.—The Chatroom Interact Task is a mixed block/event-related fMRI task used to examine neural responses to evaluation (Silk et al., 2012b; 2014). The first component of the task was completed in the laboratory about a month (*M*=38.4 days, *SD*=29.6 days) before the fMRI scan. During this laboratory visit, participants were shown photographs and fictitious biographical profiles for potential virtual peers. Participants were asked to choose the top 5 peers that they would be interested in interacting with online at their next visit. Selections were made from within sets of 30 photographs of age-matched (9-11, 12-14, or 15-17) and sex-matched smiling actors. Participants also provided their own biographical profile and photograph.

During the fMRI scan, participants were told that they had been matched with 2 of the previously selected peers and that these youth were ready to participate in a "chat game" online. They reviewed biographical profiles for selected peers prior to the task. During neuroimaging, pictures of the peers and participant were projected on the screen two at a time, as the subject and virtual peers took turns selecting who they would rather talk to about a series of teen interests (e.g., music, friends; see Figure 1). Stimuli were presented using E-prime 1.0 software (Psychology Software Tools, Pittsburgh, PA). The fMRI task was made up of 4 blocks with 15 trials in each block, for a total run time of 15.1 minutes. These included 3 feedback blocks, each containing 15 trials in which a person is chosen or not chosen to discuss each topic. Each block began with an instruction about who would be making choices for that block (agent). The photograph of the agent was shown at the bottom left corner of the screen and the photographs of the other two players were shown next to each other in the middle of the screen, as in Figure 1. In Block 2, the participant made selections among the virtual peers. Analyses focus on Blocks 3-4, in which the participant experienced a rejection block in which they were not chosen for 2/3 of the trials, and an acceptance block in which they were chosen during 2/3 of the trials, with the order of acceptance and rejection blocks randomized. Topics were presented randomly and repeated in each block. Although acceptance and rejection trials were presented within blocks, event-related analyses focus on individual trials. The task also includes an initial

control block that can be used as a perceptual control, which was not utilized in the present study given the focus on social processing (see S1).

At the beginning of each trial, the question "Who would you rather talk to about….." with the selected topic for that trial (e.g.,. … "music?") appeared on the screen for 3.34 seconds. Feedback was then provided about which person was chosen (the subject or the virtual peer) for 10.02 seconds. The photograph of the person who was not chosen was superimposed with an "X" and the photograph of the person who was chosen was highlighted around the border. To maintain engagement in the task, in all trials in which the participant was not the agent, he/she was asked to press a button to indicate whether the person on the left or the right was chosen. Participants were debriefed at the conclusion of the scan using a funnel debriefing procedure (Boynton, Portnoy, & Johnson, 2013) and informed that the other participant responses were computer-generated. Two participants reported suspicion that the other players may not have been real; the pattern of findings was replicated excluding these participants.

MRI Data Acquisition and Preprocessing.—MRI data were collected using a 3.0-T Siemens Trio scanner (Erlangen, Germany). Each functional volume contained 32 oblique axial slices (repetition time (TR): 1670 ms; echo time (TE): 29 ms; flip angle: 75°; FOV: 205 × 205 mm; acquisition matrix: 64 × 64; slice thickness: 3.2 x 3.2 mm in-plane resolution) that were acquired parallel to the AC/PC plane using a posterior-to-anterior echo planar (EPI) pulse sequence. There were 484 volumes in total. Axial anatomical images were acquired using standard T1-weighted spin-echo pulse sequence using a finer in-plane resolution (slice thickness-1 mm, voxel size = 1 × 1 × 1 mm^3, 176 slices, TR = 2100 ms, TE = 3.31 ms, flip angle = 8°, acquisition matrix = 256 × 208, FOV = 256 x 208 mm). Image preprocessing was performed with Statistical Parametric Mapping software (SPM; Wellcome Trust Centre for Neuroimaging). Volumes were manually re-oriented to the AC-PC line, and slice-time corrected. Images were then realigned to correct for head motion, segmented, and coregistered to the participant's mean functional image. Realigned images were spatially normalized to a standard MNI template (Montreal Neurological Institute template) using a 12-parameter affine model and voxels were resampled to be 2 mm^3. Normalized images were spatially smoothed using a 6 mm full-width at half-maximum Gaussian filter. High-pass temporal filtering (0.008 Hz/128 s in SPM) was applied to remove low-frequency drift in the time series.

We used the ArtRepair toolbox for SPM (Mazaika, Hoeft, & Glover, 2009) to determine which subjects to include in analyses using two motion thresholds – a liberal threshold (> 25% of volumes with motion greater than 5 mm, > 3 SD shifts in global intensities, and > 0.5 mm of incremental) and a stringent threshold (> 25% of volumes with motion greater than 3 mm, > 3 SD shifts in global intensities, and > 0.5 mm of incremental). Volumes detected as outliers using the more stringent (3mm) threshold were repaired with interpolation methods and were used for first-level analyses. Given high data loss in this clinical sample associated with the more stringent threshold, we report primary analyses on the less stringent threshold. Secondary analyses using the 3mm threshold to determine the sample size can be found in the online Supplement 1.

fMRI Analyses.—First level analyses were conducted by modeling the fMRI response based on hemodynamic response function (HRF) convolved with the vectors of two feedback conditions (rejection and acceptance) and one control condition. Three regressors were modeled for rejection, acceptance, and control conditions. We also entered six movement parameters into our model as regressors of no interest to control for movement-related signal change. Following standard procedures for conducting neuroimaging analyses using SPM, statistical images (e.g., each voxel with beta weight) were then created for the rejection > acceptance contrast. The formation of this contrast implies that changes in neural activity during the acceptance condition are subtracted from changes in neural activity during the rejection condition. Importantly, both the rejection and acceptance conditions elicit changes in brain activity during social feedback. We focused on the rejection > acceptance contrast ($r_{\text{rejection.acceptance}}$ = 0.85, Spearman-Brown split-half reliability = 0.51) because we are interested in isolating changes in neural activity during negative social feedback relative to more positive social feedback. The control condition does not include a social feedback component, therefore the the rejection > control contrast indexes more general changes in neural activity during social vs. non-social feedback and was therefore of less interest for the present study.

Four ROIs (bilateral amygdala, bilateral NAcc, bilateral AI, and bilateral sgACC) were chosen a priori given prior research linking individual differences in activity in these regions during peer rejection or exclusion to depressive symptoms (Masten et al., 2011; Silk et al., 2014). The bilateral amygdala, bilateral NAcc, and bilateral AI anatomical ROIs were created using the AAL, Talairach Daemon, and IBASPM 71 atlases in the WFU PickAtlas toolbox for SPM12. The sgACC ROI was created using Neurosynth (http://neurosynth.org) and FSL v6.0.3. One anatomical mask of regions encompassing the bilateral subgenual, medial, and/or inferior portions of Brodmann areas 34, 24, and 25 was created by downloading separate masks for each region defined by the Talairach Daemon Labels in FSLeyes (v0.31.2) and adding these masks together using the fslmaths function. This mask was then multiplied by the Neurosynth activation map for the term “subgenual” to ensure the specificity of the ROI. The activation map was thresholded at FDR-corrected p<.001 by default. The resulting ROI mask of the bilateral sgACC, and anatomical masks of the amygdala, NAcc, and AI, are displayed in the online supplement (Figure 1S). Parameter estimates for the rejection > acceptance contrast were extracted for each ROI for each participant using the MarsBar toolbox for SPM12 and used in correlational and regression analyses in SPSS version 26. Supplementary whole-brain analyses are reported in S4.

Ecological Momentary Assessment (EMA).—EMA data were collected within 4 months of the MRI scan (range = 2-97 days, M=35.5 days, SD=23.3 days). Participants were provided answer-only cell phones on which they received calls from a research assistant 28 times between 4 p.m. Thursday and 10 p.m. Monday for two consecutive weekends (10 total days). Participants were called at random times within predetermined blocks two times per day after school on Thursdays, Fridays, and Mondays, and four times per day on Saturdays and Sundays. At each call, participants were asked whom they were interacting with (in person, on telephone, or on computer) when the phone rang. Research assistants then asked participants to rate: “How close or connected do you feel to [this person] right

now?" (Kaurin et al., in press; Silk, Stroud, et al., 2012). Participants provided closeness/connectedness ratings using a Likert-type scale from 1 (not at all) to 5 (extremely). For this study, we only examined how close/connected participants felt to their peers. Close/connected ratings for each peer were summed and averaged across the total number of peers that the participants were with over the EMA period to provide a measure of average close/connectedness to peers in daily life. One participant did not complete the EMA protocol and 10 participants were excluded because they were not with peers during any of the calls, resulting in a final EMA sample of 27. These participants were with peers an average of 5.4 (SD=4.5) times during the EMA collection period, with a range from 1 to 21. Number of calls in the presence of peers was included as a covariate in sensitivity analyses to control for frequency of social interaction.

Analytic Plan

Linear regressions were used to examine how neural activity in each ROI at Wave 2 predicted depressive symptoms at Wave 3, controlling for Wave 2 depressive symptoms and anxiety symptoms. An FDR correction with a false discovery rate of $\alpha = .05$ was used to control for multiple comparisons. Supplemental sensitivity analyses were run adding treatment response (yes/no), diagnostic status (presence of an anxiety or depression diagnosis at or between Waves 2 and 3, dummy coded), age, and sex as predictor variables to the regression models. Given the small sample of participants with complete EMA and imaging data, exploratory bivariate correlations between neural activation to rejection > acceptance and the EMA measure of close/connectedness to peers were run to test potential real-world correlates of high neural reactivity to rejection.

Results

Associations between Neural Activation to Rejection and Depressive Symptoms

Inter-correlations among study variables are shown in Table 2 and preliminary analyses showing relationships between brain activation and treatment response and diagnostic status are shown in S2. Full regression results controlling for depressive symptoms and anxiety symptoms are shown in Table 3 and sensitivity analyses with additional covariates are shown in S3. Controlling for depressive symptoms and anxiety symptoms at Wave 2, sgACC activation to peer rejection vs. acceptance was associated with depressive symptoms at Wave 3 (β=.39, p=.010, p_{fdr}=.040). Depressive symptoms at Wave 2 were associated with depressive symptoms at Wave 3 (β=.36, p=.048), though anxiety symptoms were not (p=.41). The entire model accounted for 47% of the variance in Wave 3 depressive symptoms (Model R^2=.47, $F(3,34)=10.01$, $p<.001$). Results were replicated when excluding the 2 participants who reported suspicion about the task (β=.35, p=.035) and using more stringent movement parameters (see S1). As shown in S3, the finding remains significant in sensitivity analyses controlling for treatment response (yes/no), diagnostic status (presence of an anxiety or depression diagnosis at or between Waves 2 and 3, dummy coded), age, and sex.

Controlling for depressive symptoms and anxiety symptoms at Wave 2, bilateral NAcc activation to rejection vs. acceptance was also significantly associated with depressive

symptoms at Wave 3 (β=.30, p=.041, p_{fdr}=.082; Model R^2=.43, $F(4,34)$=8.46, p<.001), but the results did not survive FDR correction. Neither bilateral AI activation (β=.20, p=.200, p_{fdr}=.270) nor bilateral amygdala activation (β=.16, p=.283, p_{fdr}=.280) to peer rejection vs. acceptance were significantly associated with Wave 3 depressive symptoms after controlling for Wave 2 depressive and anxiety symptoms.

Exploratory Findings: Associations with Real-World Social Experiences

A strong negative correlation was found between sgACC activation to peer rejection vs. acceptance and average close/connectedness to peers in daily life (r=−.71, p<.001; see Figure 2) in the subsample with complete EMA data (N=27). Peer connectedness was not correlated with the number of times each participant was with a peer (r = .016, p = .936), and the association between sgACC activity and connectedness remained significant controlling for the number of calls with peers present and treatment response (r=−.71, p<.001). A modest but nonsignificant correlation also emerged between NAcc activation to peer rejection vs. acceptance and average close/connectedness to peers in daily life (r=−.37, p=.056). No significant brain-EMA associations emerged for the AI or amygdala ROIs. Close/connectedness at Wave 2 was not significantly associated with depressive symptoms at Wave 2 (r=−.38, p=.051) but was significantly associated with lower depressive symptoms at Wave 3 (r= −.44, p=.022).

Discussion

Results from the present study support the hypothesis that heightened sgACC activation to rejection--above and beyond activation to positive feedback in the peer context--may play a role in the pathway to depression among youth with a history of anxiety. Specifically, we found that heightened sgACC activation to simulated rejection, relative to acceptance, from peers predicted depressive symptoms one year later among adolescents with a history of anxiety disorder, above and beyond baseline symptoms and regardless of their current diagnostic status or previous anxiety severity. These findings are consistent with previous research demonstrating altered sgACC activity to social evaluation among clinically depressed youth (Jankowski et al., 2018; Silk et al., 2014). Together, these findings suggest that sgACC activation in response to negative peer evaluation could serve as an underlying risk factor for depression, reflecting the NIMH Research Domain Criteria (RDoC) project's construct of "potential threat" (Insel et al., 2010). Furthermore, heightened activation in response to rejection, compared to acceptance, in the sgACC was highly correlated with momentary reports of connectedness with peers, suggesting that sgACC function has real-world implications for understanding how adolescents experience their social environments in ways that could contribute to depression.

In line with our findings, the sgACC has been the most consistently reported brain region associated with depressive or internalizing symptoms in previous research using simulated peer evaluation tasks in adolescent samples. For example, in adolescents diagnosed with depression, studies have revealed heightened sgACC response to peer rejection vs. acceptance on the Chatroom Interact task (Silk et al., 2014) and in response to peer exclusion vs. inclusion on the Cyberball Task (Jankowski et al., 2018). Similarly, Rudolph

et al. (2016) found that heightened sgACC response to peer exclusion vs. inclusion was associated with concurrent internalizing symptoms, especially in girls with history of peer victimization. In a previous longitudinal study examining the link between neural response to peer feedback and adolescent depression, Masten et al. (2011) found that sgACC activity to social exclusion on the Cyberball Task predicted increases in depressive symptoms over one year among typically developing youth. The present study replicates Masten et al.'s (2011) finding and extends it to a clinical high-risk population, further supporting the potential role of the sgACC response to peer rejection as a risk factor for the development of adolescent depression.

The sgACC, also sometimes referred to as the ventral ACC, appears to play a role in monitoring and/or modulating negative emotions (Mayberg, 2003; Siegle et al., 2012), and has been associated with adolescents' self-reported distress following social exclusion (Masten et al., 2009). It has anatomical connections with both subcortical and cortical regions and is thought to function as a hub or interface between cognitive and affective processing (Ho et al., 2014). Alterations in sgACC structure and function have been strongly implicated in adult depression, including reductions in gray matter volume and elevated metabolic activity (Drevets et al., 1997; Mayberg et al., 1999). Activity within the sgACC has been shown to increase during sadness induction (Mayberg et al., 1999), highlighting its role in processing and/or regulating sadness. Although both the subgenual and dorsal ACC have been implicated in the processing of social rejection/exclusion, a meta-analysis of social interaction paradigms revealed that the sgACC response is more strongly associated with participants' self-report of distress (Rotge et al., 2014) compared to dorsal portions of the ACC. Importantly, in adults, sgACC activity has been shown to predict response to both cognitive therapy and medication (Fonseka, MacQueen, & Kennedy, 2018; Keedwell et al., 2010; Mayberg et al., 1997; Siegle et al., 2012), and deep brain stimulation of the sgACC improves treatment-resistant depression (Kennedy et al., 2011). In adolescents, studies have shown that hyperactivation of the sgACC normalizes following SSRI treatment (Tao et al., 2012), and reductions in sgACC activation to emotional stimuli correlate with symptom improvement in both CBT (Straub et al., 2015) and SSRI treatments (Cullen et al., 2009). Thus, sgACC function may be a key target for intervention or may inform personalization of treatment in depressed youth.

There is also evidence that the sgACC may play a particularly significant role in processing negative social evaluation during adolescence (Bolling et al., 2011; Masten et al., 2009; Sebastian et al., 2011). For example, Rotge et al.'s (2014) meta-analysis showed that adolescents exhibit greater sgACC response to exclusion vs. inclusion than adult participants (Rotge et al., 2014). Gunther Moor et al. (2012) compared response to social exclusion on the Cyberball task among early and middle adolescents and young adults and found that activity in the sgACC in response to exclusion was strongest among early adolescents compared to mid adolescents and adults, possibly suggesting a period of peak sgACC reactivity to social rejection during early adolescence. Silk et al. (2014) also found that sgACC activation to peer rejection, compared to acceptance, was greatest among adolescents more advanced in self-reported pubertal status, potentially implicating the role of pubertal hormones. Developmental changes in the sensitivity of the sgACC to negative social feedback during pubertal development could help account for increased rates of depression

emerging during adolescence, around mid-puberty. The present findings suggest that this is an important avenue for future research.

The results of this study also provide evidence that sgACC response to simulated negative peer evaluation in the laboratory on the Chatroom Interact task tracks closely with real-world peer experience. Specifically, sgACC activation to rejection vs. acceptance was highly correlated (r=.71) with feeling less connected with peers in day-to-day life across the 16 days of EMA. One possible interpretation is that heightened sgACC reactivity to evaluative threat (above and beyond reward) tips the risk/reward balance toward risk avoidance in social situations. This could lead to social withdrawal and a reduced sense of connectedness with peers, although future research is needed to directly measure social avoidance and clarify the mechanisms linking neural responses to threat and patterns of social behavior. There may also be other mechanisms, such as heightened physiological arousal or sadness during peer interaction, through which sgACC reactivity to threat contributes to a diminished sense of peer connectedness. It is also important to note that the EMA reports did not include information about contextual factors contributing to peer connectedness ratings, therefore we cannot rule out other contributors to perceived peer connectedness beyond social threat perceptions, such as overt peer conflict. Nevertheless, this is the first fMRI study to link neural response to rejection with momentary perceptions of peer connectedness among adolescents, although findings are consistent with previous research linking increased pupillary response to rejection with lower momentary perceptions of peer connectedness (Silk et al. 2012) and linking dorsal ACC response to exclusion with reduced amount of time spent with peers (Masten et al., 2012). Findings are also consistent with Eisenberger et al.'s (2007) research in adults linking dorsal ACC response to exclusion with greater EMA reports of social distress, but again suggest that the sgACC may play a more of a role in the processing of social distress among adolescents compared to the dorsal ACC, which appears to play a prominent role in adults. The present finding lends ecological validity to the Chatroom Interact Task and also suggests that the sgACC may play an important role in monitoring emotionally salient social interactions.

It is important to note that the brain-behavior relationships observed in this study are likely bidirectional. Feelings of disconnectedness with peers could play a causal role in amplifying sgACC sensitivity to future peer feedback. Consistent with this idea, Will et al. found that chronically peer-victimized children showed heightened dACC reactivity to exclusion on the Cyberball Task compared to adolescents without a history of victimization (Will et al., 2016). At the same time, neural sensitivity to peer evaluation could lead youth to behave in ways that decrease their connectedness with peers in day-to-day life. For example, Rudolph et al. (2016) found that adolescents with heightened sgACC reactivity to exclusion reported higher avoidance motivation and Masten et al. (2012) found that youth with heightened sgACC response to exclusion spent less time with their friends in daily life. There is also recent evidence that sgACC reactivity to negative social evaluation may index heightened susceptibility to input from the social context. Specifically, Rudolph et al. (2020) found that the link between stressful parent-child relationships and depressive symptoms was stronger among adolescents with average-to-high sgACC reactivity to exclusion vs. inclusion. Future longitudinal research is needed to better understand the temporal sequence through which brain and behavioral responses to negative social experiences shape each other.

Additional research is needed to delineate the precise mechanisms through which sgACC reactivity to threat contributes to the development of depressive symptoms. Several theorists have proposed that one pathway through which neural sensitivity to threat may increase risk for depression is by increasing avoidance of potentially risky but rewarding social experiences (Richey et al., 2019; Rudolph et al., 2016; Silk, Davis, et al., 2012). Consistent with this possibility, Rudolph et al. (2016) found that self-reported avoidance motivation accounted for the link between sgACC and insula reactivity to exclusion and internalizing symptoms in peer-victimized adolescent girls. Our study was not powered or designed to test a formal mediational model since the EMA assessment of social behavior (i.e. the mediator) was obtained several weeks prior to the fMRI scan (i.e. the predictor); therefore, future larger-scale studies are needed evaluating pathways through which neural response to social threat influences social approach and avoidance behaviors in daily life and subsequent depressive symptoms.

Additionally, in recognition that depression is unlikely to be a unitary construct, initiatives such as the NIMH RDoC project (Insel et al., 2010) encourage a focus on dimensions underlying depression such as alterations in positive (i.e. approach) and negative valence systems (i.e. sad mood). Future research is needed to explore the link between sgACC reactivity to social evaluation and specific subdimensions of depression, such as anhedonia, sad mood, and cognitive and physiological features. This will help to clarify the mechanisms through which brain response to social evaluation contributes to depression risk in adolescents and could highlight more precise intervention and prevention targets.

Surprisingly, we did not find that NAcc, amygdala or anterior insula activity in response to simulated peer rejection significantly predicted the subsequent development of depressive symptoms in anxious youth. Increased activation in these regions in response to rejection has been shown in previous studies of youth with MDD (Jankowski et al., 2018; Silk et al., 2014). It is possible that these discrepancies could be accounted for by the fact that youth in the present sample were at high-risk for depression but none met full criteria for MDD at the time of assessment. Furthermore, samples in these previous studies were not selected for anxiety. Anxious youth are known to show amygdala hyperactivation to socially threatening stimuli (Guyer et al., 2008; Lau et al., 2009; Monk et al., 2008). Thus, it is possible that amygdala reactivity to rejection was heightened as a function of anxiety history in the present sample and could not differentiate anxious youth who developed symptoms of depression from those who did not. It is also important to note that the NAcc response to rejection vs. acceptance was significantly associated with depressive symptoms prior to correcting for multiple comparisons, therefore a smaller effect for this region may be found in larger more fully-powered studies.

The present findings should be considered in light of several limitations. The longitudinal clinical sample was small, limiting our power to detect small and medium effects, to test mediational models, or to detect age- or sex-specific effects that might emerge in a larger sample. We also used relatively liberal movement parameters in order to preserve power, although we were able to replicate the sgACC finding in a smaller subsample with more conservative movement parameters. The primary sgACC showed some signs of robustness, as it remained significant when correcting for multiple comparisons, more conservative

motion parameters, and also survived sensitivity analyses with additional exploratory covariates. However, we did not correct for multiple comparisons in the sensitivity analyses with additional covariates or more conservative motion parameters because of sample size considerations. Therefore, caution is warranted in generalizing conclusions until our primary finding can be replicated in a larger sample, which would provide more power to include corrections for multiple comparisons while retaining a larger number of covariates and more stringent motion parameters. Interpretations are also based on a single fMRI scan at one point in time, therefore we cannot speak to developmental change in neural sensitivity to social threat. Additionally, because the fMRI BOLD signal does not represent an absolute value and is affected by technical (e.g., scanning parameters) and patient-specific factors, it is typically expressed as a contrast of percent change from baseline in neural activity between two conditions (Moutsatsos & Pantelis, 2020). Concerns have been raised regarding the validity of using contrasts as individual difference measures (Infantolino, Luking, Sauder, Curtin, & Hajcak, 2018; Meyer, Lerner, De Los Reyes, Laird, & Hajcak, 2017). However, contrasts can isolate theoretically relevant variance as long as they capture the relevant individual differences variance (Luking, Nelson, Infantolino, Sauder, & Hajcak, 2017; Moriarity & Alloy, 2021). This is likely the case for the current study, given the strong conceptual rationale for comparing brain activity during rejection and acceptance, which allowed us to isolate the negative effects of rejection above and beyond social feedback more generally. Nevertheless, findings must be interpreted as reflecting the difference in brain response to rejection versus acceptance rather than absolute response to rejection. It is also important to recognize that the sgACC functions within a network of neural regions; future studies are needed to examine the role of sgACC functional connectivity during social rejection and risk for depression.

Although the use of a clinical sample is a strength of the study, results may not generalize to anxious youth who have never sought or received treatment. All results were replicated controlling for treatment response, but it is still possible that the previous treatment for anxiety received two years before the present study may have altered participants' neural response to social threat or the association between that response and either depressive symptoms or peer connectedness. Future research examining change in neural sensitivity to peer rejection throughout treatment would be valuable for addressing this issue. There was also significant variability in severity of anxiety and anxiety diagnoses at two-year follow-up, adding significant heterogeneity to the sample that could influence generalizability. However, all results were maintained controlling for current or recent diagnosis of anxiety disorder. Additionally, although the sample is at high risk for depression and there was significant variability in depressive symptoms, only two participants met full criteria for a major depressive disorder during the follow-up phase of the study, perhaps reflecting attenuated risk for depression among anxious youth who have received treatment (Silk et al., 2019). Finally, the sample was comprised primarily of White participants from urban or suburban middle-to-upper class backgrounds, therefore findings may not generalize to more diverse populations.

Despite these limitations, the study benefits from a well-characterized clinical sample and a prospective longitudinal design, which allowed us to provide some of the first data supporting the potential role of the sgACC in conveying risk for future depressive

symptoms in adolescents. Additionally, we utilized an ecologically valid laboratory task, with ecological validity further strengthened by our inclusion of EMA measures of real-world peer connectedness. Results of the study have potential clinical implications, supporting the development of experimental therapeutics, targeted brain stimulation, or psychopharmacological approaches to targeting sgACC function in adolescents with and at-risk for depression. Findings also point to the potential value of using behavioral approaches, such as CBT, to target cognitive/affective responses to social threat in anxious youth as a cost-effective mechanism to prevent the development of depression later in adolescence (Silk et al., 2019).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Abend R, de Voogd L, Salemink E, Wiers RW, Pérez-Edgar K, Fitzgerald A, … Bar-Haim Y (2018). Association between attention bias to threat and anxiety symptoms in children and adolescents. Depress Anxiety, 35(3), 229–238. doi:10.1002/da.22706 [PubMed: 29212134]

Alexander L, Wood CM, Gaskin PLR, Sawiak SJ, Fryer TD, Hong YT, … Roberts AC (2020). Over-activation of primate subgenual cingulate cortex enhances the cardiovascular, behavioral and neural responses to threat. Nature Communications, 11(1), 5386. doi:10.1038/s41467-020-19167-0

Angold A, Costello EJ, Messer SC, & Pickles A (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. International journal of methods in psychiatric research, 5, 1–12.

American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, D.C.: Author.

Barrett LF, & Simmons WK (2015). Interoceptive predictions in the brain. Nature Reviews Neuroscience, 16(7), 419–429. doi:10.1038/nrn3950 [PubMed: 26016744]

Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, & Neer SM (1997). The screen for child anxiety related emotional disorders (scared): Scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry, 36(4), 545–553. [PubMed: 9100430]

Bolling DZ, Pitskel NB, Deen B, Crowley MJ, Mayes LC, & Pelphrey KA (2011). Development of neural systems for processing social exclusion from childhood to adolescence. Dev Sci, 14(6), 1431–1444. doi:10.1111/j.1467-7687.2011.01087.x [PubMed: 22010901]

Boynton MH, Portnoy DB, & Johnson BT (2013). Exploring the ethics and psychological impact of deception in psychological research. IRB, 35(2), 7–13. [PubMed: 23672145]

Budygin EA, Park J, Bass CE, Grinevich VP, Bonin KD, & Wightman RM (2012). Aversive stimulus differentially triggers subsecond dopamine release in reward regions. Neuroscience, 201, 331–337. doi:10.1016/j.neuroscience.2011.10.056 [PubMed: 22108611]

Caouette JD, & Guyer AE (2014). Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. Dev Cogn Neurosci, 8, 65–76. doi:10.1016/j.dcn.2013.10.003 [PubMed: 24239049]

Caporino NE, Brodman DM, Kendall PC, Albano AM, Sherrill J, Piacentini J, … Walkup JT (2013). Defining treatment response and remission in child anxiety: Signal detection analysis using the pediatric anxiety rating scale. Journal of the American Academy of Child & Adolescent Psychiatry, 52(1), 57–67. doi:10.1016/j.jaac.2012.10.006 [PubMed: 23265634]

Cardinal RN, Parkinson JA, Hall J, & Everitt BJ (2002). Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. Neurosci Biobehav Rev, 26(3), 321–352. doi:10.1016/s0149-7634(02)00007-6 [PubMed: 12034134]

Cohen JA, Deblinger E, Mannarino AP, & Steer RA (2004). A multisite, randomized controlled trial for children with sexual abuse-related ptsd symptoms. Journal of the American Academy of Child & Adolescent Psychiatry, 43(4), 393–402. [PubMed: 15187799]

Cohen JA, Mannarino AP, & Knudsen K (2005). Treating sexually abused children: 1 year follow-up of a randomized controlled trial. Child Abuse & Neglect, 29(2), 135–145. [PubMed: 15734179]

Coyne JC (1976). Depression and the response of others. Journal of Abnormal Psychology Vol 85(2) Apr 1976, 186–193. [PubMed: 1254779]

Creswell C, Schniering CA, & Rapee RM (2005). Threat interpretation in anxious children and their mothers: Comparison with nonclinical children and the effects of treatment. Behav Res Ther, 43(10), 1375–1381. [PubMed: 16086987]

Cullen KR, Gee DG, Klimes-Dougan B, Gabbay V, Hulvershorn L, Mueller BA, … Milham MP (2009). A preliminary study of functional connectivity in comorbid adolescent depression. Neurosci Lett, 460(3), 227–231. doi:10.1016/j.neulet.2009.05.022 [PubMed: 19446602]

Dickerson SS, & Kemeny ME (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. Psychological Bulletin, 130, 355–391. [PubMed: 15122924]

Dixon ML, Thiruchselvam R, Todd R, & Christoff K (2017). Emotion and the prefrontal cortex: An integrative review. Psychol Bull, 143(10), 1033–1081. doi:10.1037/bul0000096 [PubMed: 28616997]

Drevets WC, Price JL, Simpson JR Jr., Todd RD, Reich T, Vannier M, & Raichle ME (1997). Subgenual prefrontal cortex abnormalities in mood disorders. Nature, 386(6627), 824–827. [PubMed: 9126739]

Earnshaw VA, Elliott MN, Reisner SL, Mrug S, Windle M, Emery ST, … Schuster MA (2017). Peer victimization, depressive symptoms, and substance use: A longitudinal analysis. Pediatrics, 139(6), e20163426. doi:10.1542/peds.2016-3426 [PubMed: 28562268]

Eisenberger NI, Gable SL, & Lieberman MD (2007). Functional magnetic resonance imaging responses relate to differences in real-world social experience. Emotion Vol 7(4) Nov 2007, 745–754. [PubMed: 18039043]

Eisenberger NI, Lieberman MD, & Williams KD (2003). Does rejection hurt? An fmri study of social exclusion. Science, 302(5643), 290–292. [PubMed: 14551436]

Fonseka TM, MacQueen GM, & Kennedy SH (2018). Neuroimaging biomarkers as predictors of treatment outcome in major depressive disorder. J Affect Disord, 233, 21–35. doi:10.1016/j.jad.2017.10.049 [PubMed: 29150145]

Frewen PA, Dozois DJ, Joanisse MF, & Neufeld RW (2008). Selective attention to threat versus reward: Meta-analysis and neural-network modeling of the dot-probe task. Clin Psychol Rev, 28(2), 307–337. doi:S0272-7358(07)00106-7 [pii] [PubMed: 17618023]

Galvan A (2010). Adolescent development of the reward system. Frontiers in Human Neuroscience, 4, 6. [PubMed: 20179786]

Galvan A (2013). The teenage brain: Sensitivity to rewards. Current Directions in Psychological Science, 22(2), 88–93.

Gilbert P (1992). Depression: The evolution of powerlessness. New York: Guilford.

Gunther Moor B, Güroğlu B, Op de Macks ZA, Rombouts SARB, Van der Molen MW, & Crone EA (2012). Social exclusion and punishment of excluders: Neural correlates and developmental trajectories. Neuroimage, 59(1), 708–717. doi:10.1016/j.neuroimage.2011.07.028 [PubMed: 21791248]

Gunther Moor B, van Leijenhorst L, Rombouts SA, Crone EA, & Van der Molen MW (2010). Do you like me? Neural correlates of social evaluation and developmental trajectories. Soc Neurosci, 5(5-6), 461–482. doi:925873572 [pii] [PubMed: 20721813]

Guyer AE, Caouette JD, Lee CC, & Ruiz SK (2014). Will they like me? Adolescents' emotional responses to peer evaluation. International journal of behavioral development, 38(2), 155–163. doi:10.1177/0165025413515627 [PubMed: 25076803]

Guyer AE, Lau JY, McClure-Tone EB, Parrish J, Shiffrin ND, Reynolds RC, … Nelson EE (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. Archives of General Psychiatry, 65(11), 1303–1312. [PubMed: 18981342]

Ho TC, Yang G, Wu J, Cassey P, Brown SD, Hoang N, … Yang TT (2014). Functional connectivity of negative emotional processing in adolescent depression. J Affect Disord, 155, 65–74. doi:10.1016/j.jad.2013.10.025 [PubMed: 24268546]

Hormuth SE (1986). The sampling of experiences in situ. Journal of Personality, 54(1), 262–293.

Infantolino ZP, Luking KR, Sauder CL, Curtin JJ, & Hajcak G (2018). Robust is not necessarily reliable: From within-subjects fmri contrasts to between-subjects comparisons. Neuroimage, 173, 146–152. [PubMed: 29458188]

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, … Wang P (2010). Research domain criteria (rdoc): Toward a new classification framework for research on mental disorders. Am J Psychiatry, 167(7), 748–751. doi:10.1176/appi.ajp.2010.09091379 [PubMed: 20595427]

Jankowski KF, Batres J, Scott H, Smyda G, Pfeifer JH, & Quevedo K (2018). Feeling left out: Depressed adolescents may atypically recruit emotional salience and regulation networks during social exclusion. Soc Cogn Affect Neurosci, 13(8), 863–876. doi:10.1093/scan/nsy055 [PubMed: 30059994]

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, … Ryan N (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (k-sads-pl): Initial reliability and validity data. Journal of the American Academy of Child & Adolescent Psychiatry, 36(7), 980–988. [PubMed: 9204677]

Kaurin A, Sequeira, S. SL, Ladouceur CD, McKone KMP, Rosen D, Jones N, … Silk JS (in press). Modeling sensitivity to social threat in adolescent girls: A psychoneurometric approach. Journal of Abnormal Psychology.

Keedwell PA, Drapier D, Surguladze S, Giampietro V, Brammer M, & Phillips ML (2010). Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. Journal of Affective Disorders, 120(1-3), 120–125. [PubMed: 19539998]

Kendall PC, & Hedtke KA (2006). Cognitive-behavioral therapy for anxious children: Therapist manual. . Ardmore, PA: Workbook Publishing.

Kennedy SH, Giacobbe Peter, M.D., M.Sc. ,, Rizvi Sakina J., B.Sc. ,, Placenza Franca M., Ph.D. ,, Nishikawa Yasunori, B.Sc. ,, Mayberg Helen S., M.D. , and, & Lozano Andres M., M.D., Ph.D. (2011). Deep brain stimulation for treatment-resistant depression: Follow-up after 3 to 6 years. American Journal of Psychiatry, 168(5), 502–510. doi:10.1176/appi.ajp.2010.10081187 [PubMed: 21285143]

Kessler RC, Avenevoli S, & Merikangas KR (2001). Mood disorders in children and adolescents: An epidemiologic perspective. Biol Psychiatry, 49(12), 1002–1014. [PubMed: 11430842]

Lau JYF, Goldman D, Buzas B, Fromm SJ, Guyer AE, Hodgkinson C, … Ernst M (2009). Amygdala function and 5-htt gene variants in adolescent anxiety and major depressive disorder. Biol Psychiatry, 65(4), 349–355. [PubMed: 18950748]

Lau JYF, Guyer AE, Tone EB, Jenness J, Parrish JM, Pine DS, & Nelson EE (2012). Neural responses to peer rejection in anxious adolescents. International journal of behavioral development, 36(1), 36–44. doi:10.1177/0165025411406854 [PubMed: 35197655]

Lau JYF, & Waters AM (2017). Annual research review: An expanded account of information-processing mechanisms in risk for child and adolescent anxiety and depression. Journal of Child Psychology and Psychiatry, 58(4), 387–407. doi:10.1111/jcpp.12653 [PubMed: 27966780]

Lewinsohn PM, Allen NB, Seeley JR, & Gotlib IH (1999). First onset versus recurrence of depression: Differential processes of psychosocial risk. Journal of Abnormal Psychology, 108(3), 483–489. [PubMed: 10466272]

Luking KR, Nelson BD, Infantolino ZP, Sauder CL, & Hajcak G (2017). Internal consistency of functional magnetic resonance imaging and electroencephalography measures of reward in late childhood and early adolescence. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2(3), 289–297. doi:10.1016/j.bpsc.2016.12.004 [PubMed: 29057369]

Masten CL, Eisenberger NI, Borofsky LA, McNealy K, Pfeifer JH, & Dapretto M (2011). Subgenual anterior cingulate responses to peer rejection: A marker of adolescents' risk for depression. Development and Psychopathology, 23(1), 283–292. doi:10.1017/S0954579410000799 [PubMed: 21262054]

Masten CL, Eisenberger NI, Borofsky LA, Pfeifer JH, McNealy K, Mazziotta JC, & Dapretto M (2009). Neural correlates of social exclusion during adolescence: Understanding the distress of peer rejection. Soc Cogn Affect Neurosci, 4(2), 143–157. doi:nsp007 [pii] 10.1093/scan/nsp007 [PubMed: 19470528]

Masten CL, Telzer EH, Fuligni AJ, Lieberman MD, & Eisenberger NI (2012). Time spent with friends in adolescence relates to less neural sensitivity to later peer rejection. Soc Cogn Affect Neurosci, 7(1), 106–114. doi:nsq098 [pii] [PubMed: 21183457]

Mayberg HS (2003). Modulating dysfunctional limbic-cortical circuits in depression: Towards development of brain-based algorithms for diagnosis and optimised treatment. British Medical Bulletin, 65, 193–207. [PubMed: 12697626]

Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, … Martin et, a. (1997). Cingulate function in depression: A potential predictor of treatment response. Neuroreport, 8(4), 1057. [PubMed: 9141092]

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, … Fox PT (1999). Reciprocal limbic-cortical function and negative mood: Converging pet findings in depression and normal sadness. American Journal of Psychiatry, 156(5), 675–682. [PubMed: 10327898]

Mazaika P, Hoeft F, & Glover G (2009). Methods and software for fmri analysis of clinical subjects. Neuroimage, 47. doi:10.1016/S1053-8119(09)70238-1

McCutcheon JE, Ebner SR, Loriaux AL, & Roitman MF (2012). Encoding of aversion by dopamine and the nucleus accumbens. Frontiers in Neuroscience, 6. doi:10.3389/fnins.2012.00137

Meyer A, Lerner MD, De Los Reyes A, Laird RD, & Hajcak G (2017). Considering erp difference scores as individual difference measures: Issues with subtraction and alternative approaches. Psychophysiology, 54(1), 114–122. doi:10.1111/psyp.12664 [PubMed: 28000251]

Mojtabai R, Olfson M, & Han B (2016). National trends in the prevalence and treatment of depression in adolescents and young adults. Pediatrics, 138(6).

Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HM, … Pine DS (2008). Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry, 65(5), 568–576. doi:65/5/568 [pii] [PubMed: 18458208]

Moriarity DP, & Alloy LB (2021). Back to basics: The importance of measurement properties in biological psychiatry. Neuroscience & Biobehavioral Reviews, 123, 72–82. doi:10.1016/j.neubiorev.2021.01.008 [PubMed: 33497789]

Moutsatsos A, & Pantelis E (2020). Functional imaging. In Conti A, Romanelli P, P. E., S. S., C. Y., & L. M. 10.1007/978-3-030-50668-1_9 (Eds.), Cyberknife neuroradiosurgery. (pp. 129–139). Switzerland: Springer, Cham.

Nelson EE, Leibenluft E, McClure E, & Pine DS (2005). The social re-orientation of adolescence: A neuroscience perspective on the process and its relation to psychopathology. Psychol Med, 35(2), 163–174. [PubMed: 15841674]

Pine DS, Cohen P, Gurley D, Brook J, & Ma Y (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry, 55(1), 56–64. [PubMed: 9435761]

Research Units On Pediatric Psychopharmacology Anxiety Study Group (2002). The Pediatric anxiety rating scale (PARS): Development and psychometric properties. Journal of the American Academy of Child & Adolescent Psychiatry, 41, 1061–1069. [PubMed: 12218427]

Rice F, Sellers R, Hammerton G, & et al. (2017). Antecedents of new-onset major depressive disorder in children and adolescents at high familial risk. JAMA Psychiatry, 74(2), 153–160. doi:10.1001/jamapsychiatry.2016.3140 [PubMed: 27926743]

Richey JA, Brewer JA, Sullivan-Toole H, Strege MV, Kim-Spoon J, White SW, & Ollendick TH (2019). Sensitivity shift theory: A developmental model of positive affect and motivational deficits in social anxiety disorder. Clin Psychol Rev, 72, 101756. doi:10.1016/j.cpr.2019.101756 [PubMed: 31351312]

Rosen D, Price RB, & Silk JS (2019). An integrative review of the vigilance-avoidance model in pediatric anxiety disorders: Are we looking in the wrong place? J Anxiety Disord, 64, 79–89. doi:10.1016/j.janxdis.2019.04.003 [PubMed: 31051420]

Rotge J-Y, Lemogne C, Hinfray S, Huguet P, Grynszpan O, Tartour E, … Fossati P (2014). A meta-analysis of the anterior cingulate contribution to social pain. Social Cognitive and Affective Neuroscience, 10(1), 19–27. doi:10.1093/scan/nsu110 [PubMed: 25140048]

Rudebeck PH, Putnam PT, Daniels TE, Yang T, Mitz AR, Rhodes SE, & Murray EA (2014). A role for primate subgenual cingulate cortex in sustaining autonomic arousal. Proc Natl Acad Sci U S A, 111(14), 5391–5396. doi:10.1073/pnas.1317695111 [PubMed: 24706828]

Rudolph KD, Davis MM, Modi HH, Fowler C, Kim Y, & Telzer EH (2020). Differential susceptibility to parenting in adolescent girls: Moderation by neural sensitivity to social cues. J Res Adolesc, 30 Suppl 1, 177–191. doi:10.1111/jora.12458 [PubMed: 30270464]

Rudolph KD, Miernicki ME, Troop-Gordon W, Davis MM, & Telzer EH (2016). Adding insult to injury: Neural sensitivity to social exclusion is associated with internalizing symptoms in chronically peer-victimized girls. Soc Cogn Affect Neurosci, 11(5), 829–842. doi:10.1093/scan/nsw021 [PubMed: 26892162]

Sebastian CL, Tan GC, Roiser JP, Viding E, Dumontheil I, & Blakemore SJ (2011). Developmental influences on the neural bases of responses to social rejection: Implications of social neuroscience for education. Neuroimage, 57(3), 686–694. doi:S1053-8119(10)01265-6 [pii] [PubMed: 20923708]

Siegle GJ, Thompson WK, Collier A, Berman SR, Feldmiller J, Thase ME, & Friedman ES (2012). Toward clinically useful neuroimaging in depression treatment: Prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. Archives of General Psychiatry, 69(9), 913–924. [PubMed: 22945620]

Silberg J, Rutter M, Neale M, & Eaves L (2001). Genetic moderation of environmental risk for depression and anxiety in adolescent girls. British Journal of Psychiatry 179, 116–121.

Silk JS, Davis S, McMakin DL, Dahl RE, & Forbes EE (2012). Why do anxious children become depressed teenagers?: The role of social evaluative threat and reward processing. Psychol Med, 42(10), 2095–2107. doi:S0033291712000207 [pii] 10.1017/S0033291712000207 [PubMed: 22340187]

Silk JS, Price RB, Rosen DK, Ladouceur CD, Forbes EE, Siegle GJ, … Ryan ND (2019). A longitudinal follow-up study examining adolescent depressive symptoms as a function of prior anxiety treatment. J Am Acad Child Adolesc Psychiatry, 58(3), 359–367. doi: 10.1016/j.jaac.2018.10.012 [PubMed: 30768411]

Silk JS, Siegle GJ, Lee KH, Nelson EE, Stroud LR, & Dahl RE (2014). Increased neural response to peer rejection associated with adolescent depression and pubertal development. Soc Cogn Affect Neurosci, 9(11), 1798–1807. doi:10.1093/scan/nst175 [doi] [PubMed: 24273075]

Silk JS, Stroud LR, Siegle GJ, Dahl RE, Lee KH, & Nelson EE (2012). Peer acceptance and rejection through the eyes of youth: Pupillary, eyetracking and ecological data from the chatroom interact task. Social Cognitive and Affective Neuroscience, 7(1), 93–105. doi:10.1093/scan/nsr044 [PubMed: 21775386]

Singer T, Critchley HD, & Preuschoff K (2009). A common role of insula in feelings, empathy and uncertainty. Trends Cogn Sci, 13(8), 334–340. doi:10.1016/j.tics.2009.05.001 [PubMed: 19643659]

Somerville LH, Heatherton TF, & Kelley WM (2006). Anterior cingulate cortex responds differentially to expectancy violation and social rejection. Nat Neurosci, 9(8), 1007–1008. [PubMed: 16819523]

Spielberg JM, Forbes EE, Ladouceur CD, Worthman CM, Olino TM, Ryan ND, & Dahl RE (2014). Pubertal testosterone influences threat-related amygdala-orbitofrontal coupling. Soc Cogn Affect Neurosci. doi:nsu062 [pii]

Stone AA, Shiffman SS, & DeVries MW (1999). Ecological momentary assessment. Kahneman Daniel (Ed); Diener Ed (Ed); Schwarz Norbert (Ed). (1999). Well-being: The foundations of hedonic psychology.

Straub J, Plener PL, Sproeber N, Sprenger L, Koelch MG, Groen G, & Abler B (2015). Neural correlates of successful psychotherapy of depression in adolescents. J Affect Disord, 183, 239–246. doi:10.1016/j.jad.2015.05.020 [PubMed: 26025370]

Tao R, Calley CS, Hart J, Mayes TL, Nakonezny PA, Lu H, … Emslie GJ (2012). Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. Am J Psychiatry, 169(4), 381–388. doi:10.1176/appi.ajp.2011.11040615 [PubMed: 22267183]

Telzer EH, Fuligni AJ, Lieberman MD, & Galvan A (2013). Ventral striatum activation to prosocial rewards predicts longitudinal declines in adolescent risk taking. Dev Cogn Neurosci, 3(1), 45–52. doi:10.1016/j.dcn.2012.08.004 [PubMed: 23245219]

Whittle S, Yap MB, Yucel M, Fornito A, Simmons JG, Barrett A, … Allen NB (2008). Prefrontal and amygdala volumes are related to adolescents' affective behaviors during parent-adolescent interactions. Proc Natl Acad Sci U S A, 105(9), 3652–3657. [PubMed: 18299581]

Will G-J, van Lier PAC, Crone EA, & Güroğlu B (2016). Chronic childhood peer rejection is associated with heightened neural responses to social exclusion during adolescence. J Abnorm Child Psychol, 44(1), 43–55. doi:10.1007/s10802-015-9983-0 [PubMed: 25758671]

Zaki J, Davis JI, & Ochsner KN (2012). Overlapping activity in anterior insula during interoception and emotional experience. Neuroimage, 62(1), 493–499. doi:10.1016/j.neuroimage.2012.05.012 [PubMed: 22587900]

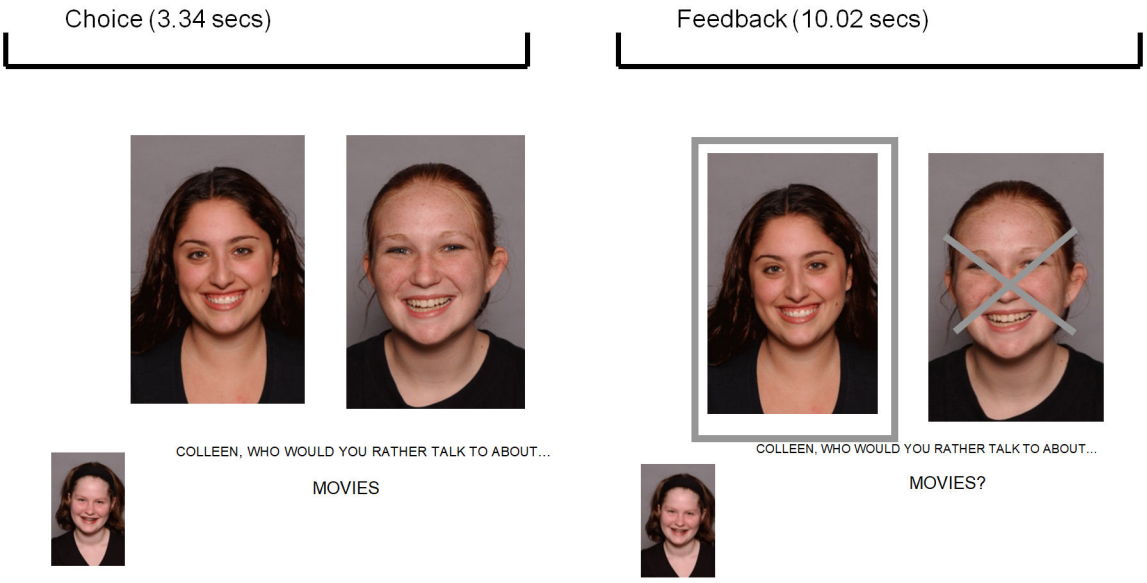

Figure 1.
Chatroom Interact Task

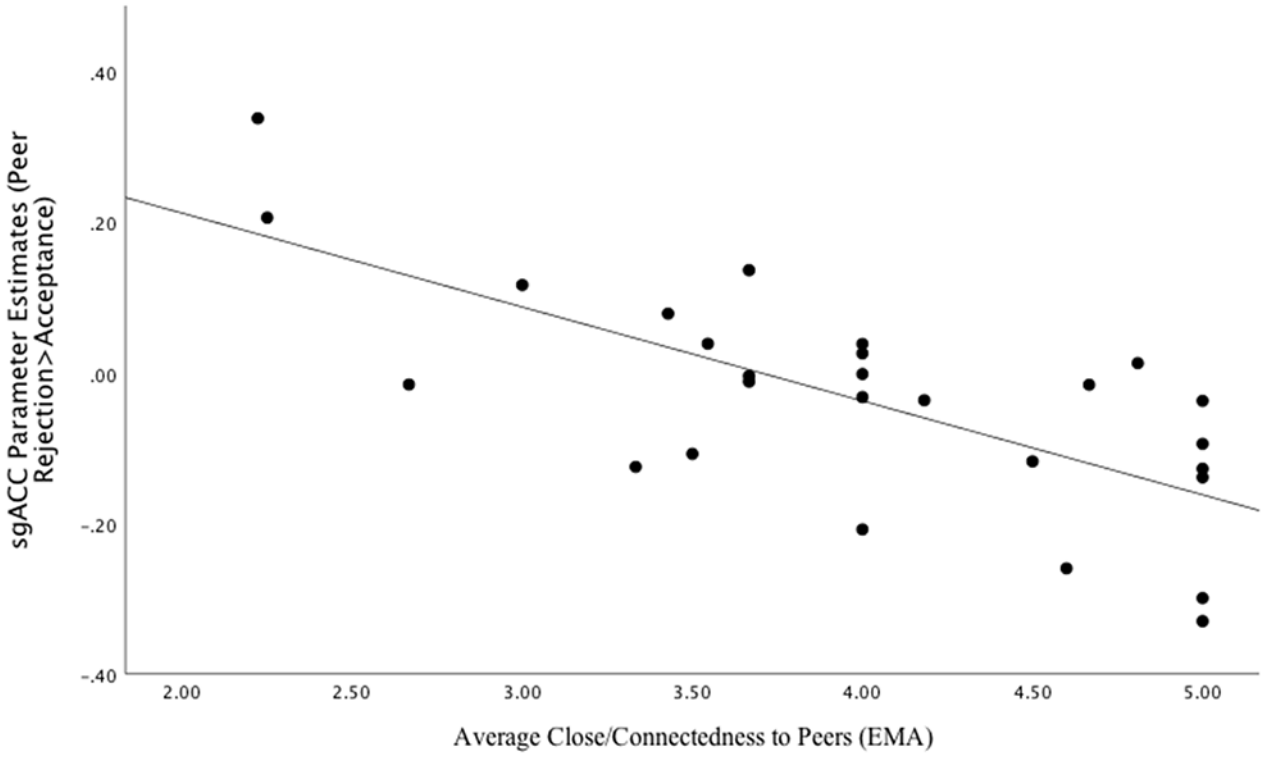

Figure 2.

Associations between Average Close/Connectedness to Peers in Daily Life and sgACC Activation to Peer Rejection vs. Peer Acceptance.

Table 1.

Demographic and Clinical Characteristics

	N	%	Mean	SD	Range
Sex – Female	19	50%			
Race					
White	35	92.1%			
Black or African American	2	5.3%			
Biracial	1	2.6%			
Wave 2					
Age			13.66	1.43	11.52 – 16.39
Anxiety symptoms (SCARED)			17.87	11.45	1 – 43
Depressive symptoms (MFQ)			11.03	10.41	0 – 42
Current Anxiety/Depression Diagnosis					
GAD only	5	13.2%			
SocAD only	1	2.6%			
SP only	2	5.3%			
SEP & SP	1	2.6%			
GAD & SocAD	1	2.6%			
GAD, SocAD, & DepNOS	1	2.6%			
Wave 3					
Age			14.19	1.44	12.60 – 17.10
Anxiety symptoms (SCARED)			15.79	11.89	0 – 45
Depressive symptoms (MFQ)			9.16	10.12	0 – 30
Current Anxiety/Depression Diagnosis					
GAD only	2	5.3%			
SocAD only	1	2.6%			
SP Only	3	7.9%			
GAD, SocAD, & SEP	1	2.6%			
Past year MDD	2	5.3%			

Note.

*SCARED = Screen for Child Anxiety Related Emotional Disorders – child report, MFQ = Mood and Feelings Questionnaire – child report, GAD = generalized anxiety disorder, SocAD = social anxiety disorder, SEP = separation anxiety disorder, SP = specific phobia, DepNOS = depressive disorder not otherwise specified, MDD = major depressive disorder.

Table 2.

Intercorrelations between Primary Variables Included in Analyses

	MFQ Wave 2	MFQ Wave 3	SCARED Wave 2	SCARED Wave 3	Close/ connected (EMA)	sgACC	NAcc	AI	Amygdala
MFQ Wave 2	1								
MFQ Wave 3	.59**	1							
SCARED Wave 2	.59**	.35*	1						
SCARED Wave 3	.55**	.63**	.56**	1					
Close/connected (EMA)	−.38t	−.44*	−.34t	−.39*	1				
sgACC	.38*	.53*	−.01	.46*	−.71**	1			
NAcc	.10	.31t	−.24	.24	−.37t	.59**	1		
AI	−.08	.12	−.39*	−.18	−.08	.25	.57**	1	
Amygdala	−.12	.06	−.38*	−.16	−.07	.16	.58**	.54**	1

Note.

*p<.05

**p<.001

tp<.10; sgACC = subgenual anterior cingulate cortex, NAcc = nucleus accumbens, AI = anterior insula, EMA = ecological momentary assessment, MFQ = Mood and Feelings Questionnaire, SCARED = Screen for Child Anxiety Related Emotional Disorders; Brain regions indicate parameter estimates in that region (all bilateral) for the rejection > acceptance contrast.

Table 3.

Primary Results from Regression Analyses predicting Wave 3 Depressive Symptoms

	ß	*t*	*p*	R^2	*F (df)*	*p*
SgACC				.47	10.01 (3,34)	<.001
Depressive symptoms (Wave 2)	**.36**	**2.05**	**.048**			
Anxiety symptoms (Wave 2)	.14	.84	.406			
sgACC activation	**.39**	**2.74**	**.010***			
Nucleus Accumbens				.43	8.46 (3,34)	<.001
Depressive symptoms (Wave 2)	**.48**	**2.84**	**.008**			
Anxiety symptoms (Wave 2)	.14	.78	.443			
NAcc activation	**.30**	**2.12**	**.041**			
Amygdala				.37	6.76 (3,34)	.001
Depressive symptoms (Wave 2)	**.57**	**3.35**	**.002**			
Anxiety symptoms (Wave 2)	.07	.40	.695			
Amygdala activation	.16	1.09	.283			
Anterior Insula				.38	7.03 (3,34)	.001
Depressive symptoms (Wave 2)	**.55**	**3.20**	**.003**			
Anxiety symptoms (Wave 2)	.10	.54	.596			
Anterior insula activation	.20	1.31	.200			

Note. Anxiety symptoms were measured using the SCARED (child report); depressive symptoms were measured using the MFQ (child report). Neural activation values were calculated for the contrast rejection>acceptance. SgACC = subgenual anterior cingulate cortex; Diagnosis = presence of any anxiety or depression diagnosis at or between Waves 2 and 3; Treatment Responder = response (yes/no) to psychotherapy at Wave 1. Bolded values are statistically significant at $p<.05$ and values with an asterisk remained significant following a Benjamini-Hochberg false discovery rate correction of .05.