Differential Susceptibility to Parenting in Adolescent Girls: Moderation by Neural Sensitivity to Social Cues

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Abstract

This research examined whether heightened neural activation to social cues confers adjustment advantages in supportive social contexts but adjustment disadvantages in stressful social contexts. Forty-five adolescent girls were exposed to social exclusion during an fMRI scan and reported on parent-child relationship quality and depressive symptoms. Stressful parent-child relationships predicted subsequent depressive symptoms in girls with high and moderate but not low dorsal anterior cingulate cortex, subgenual anterior cingulate cortex, and anterior insula activation during exclusion. In the context of supportive parent-child relationships, however, neural activation to exclusion predicted particularly low levels of depressive symptoms. This support for a biological sensitivity to context model suggests the possibility of redirecting adolescent girls' neural sensitivity to social cues toward more positive adaptation.

Keywords

neural sensitivity to context; parent-child relationships; depressive symptoms

During adolescence, youth begin to show an increasing neural sensitivity to social cues (Davey, Yucel, & Allen, 2008; Morris, Squeglia, Jacobus, & Silk, 2018; Nelson, Jarcho, & Guyer, 2016; Nelson, Leibenluft, McClure, & Pine, 2005; Somerville, 2013). This normative shift has been implicated as creating a developmental context of risk for the emergence of emotional difficulties such as depressive symptoms, particularly in girls (Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009; Schriber & Guyer, 2016). Yet, there are individual differences in the development of neural sensitivity. Moreover, biological sensitivity to context (BSC; Boyce & Ellis, 2005; Ellis & Boyce, 2008) and differential susceptibility (DS; Belsky, Bakermans-Kranburg, & van IJzendoorn, 2007) theories propose such individual differences in neurobiological susceptibility may confer both health advantages and disadvantages—that is, sensitive youth may be more susceptible to the environment “for

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Conflict of interest statement.

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better and for worse” (Belsky et al., 2007). Adjustment in sensitive youth may therefore be contingent on the social context in which they live.¹

Although a small but growing body of evidence supports this perspective (for a review, see Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), minimal research has examined such trade-offs in the context of brain structure or function (Schriber & Guyer, 2016; for exceptions see Whittle et al., 2011; Yap et al., 2008). Given extensive reorganization in brain structure and function during adolescence (Ladouceur, 2012; Nelson et al., 2016), considering how neural networks may serve as moderators of social experience can greatly inform theories of adolescent development (Schriber & Guyer, 2016). The present research used functional magnetic resonance imaging (fMRI) to examine the hypothesis that neural sensitivity to social cues—reflected in heightened activation in the social pain network during social exclusion—would moderate the effect of parent-child relationship quality (PCRQ) on depressive symptoms such that stressful parent-child relationships would predict emotional difficulties (i.e., particularly high levels of depressive symptoms) but supportive parent-child relationships would predict emotional health (i.e., particularly low levels of depressive symptoms) in sensitive girls, whereas insensitive girls would show similar levels of depressive symptoms regardless of PCRQ.

Potential Trade-offs of Biological Sensitivity

BSC (Boyce & Ellis, 2005) and DS (Belsky et al., 2007) theories (Ellis et al., 2011) propose bivalent effects of high neurobiological reactivity to the environment (e.g., vigorous or sustained autonomic, adrenocortical, or other biological responses to stressors), such that more sensitive youth thrive in the face of support but suffer in the face of adversity whereas less sensitive youth show similar adjustment regardless of the social context in which they live (see Figure 1). Some evidence supports this pattern using indices of genetic (DRD4 allele, Bakermans-Kranenburg & van IJzendoorn, 2006; 5-HTTLPR allele; Eley et al., 2004), temperamental (Pluess & Belsky, 2010), hormonal (Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010; Obradovic, Portilla, & Ballard, 2016; Rudolph, Troop-Gordon, & Granger, 2010, 2011), cardiovascular (Boyce et al., 1995), immunological (Boyce et al., 1995), and psychophysiological (Obradovic et al., 2010) sensitivity (for reviews, see Bush & Boyce, 2014; Ellis et al., 2011). Across these studies, various types of social contexts (e.g., parenting, child care quality, peer group experiences, family context, and family income) and types of adjustment (e.g., externalizing behavior problems, prosocial behavior, school engagement, academic competence, cognitive/executive function, and physical illness) have been examined. These studies provide varying levels of rigor in their testing of BSC/DS theories as criteria have evolved over time to determine how closely patterns of data conform to theoretical predictions.

In one of the few studies to examine the prediction of depression, Eley and colleagues (2004) found a significant interaction between the 5-HTTLPR genotype and a composite

¹Although the BSC and DS theories were developed independently, the two theories share evolutionary origins and overlap in their conceptualizations regarding the interactive influence of individual differences and social context on development. Consequently, they have been integrated by the authors into a comprehensive theory (Ellis et al., 2011). We refer to neural sensitivity as a form of BSC given that it represents a biological marker of differential susceptibility.

measure of family adversity predicting the likelihood of adolescent girls' membership in a high (vs. low) depressive symptom group. Specifically, sensitive girls (i.e., those with two short alleles) were more likely to be in the high-depression group than insensitive girls (i.e. those with two long alleles) if they were exposed to high family adversity, but less likely to be in the high-depression group than insensitive girls if they were exposed to low family adversity. More sensitive girls with high family adversity had almost twice the risk (an almost 40% difference) of being in the high-depression group than those with low family adversity whereas less sensitive girls showed less differentiation (about a 10% difference) at high and low levels of family adversity. Overall, the pattern of effects was consistent with BSC/DS although statistical analyses were not conducted to specifically compare the various groups.

Neural Sensitivity to Social Exclusion as a Form of Biological Susceptibility to Context

Social pain theory proposes that threats to one's sense of social connectedness, such as exposure to social exclusion, induce neural activation in regions of the brain involved in affective responses to physical pain (Dewall et al., 2010; Eisenberger, 2012; Lieberman & Eisenberger, 2006). Research in adults and adolescents has identified several regions involved in this social pain network, including the dorsal anterior cingulate cortex (dACC), the subgenual anterior cingulate cortex (sgACC), and the anterior insula (Eisenberger, 2015; Masten et al., 2009; Masten, Morelli, & Eisenberger, 2011; Sebastian, et al., 2011; for a review, see Rotge et al., 2014). Individuals who show heightened activation in these regions during exclusion report more distress (e.g., Eisenberger, 2012) and stronger threats to their psychological needs (e.g., Eisenberger, Lieberman, & Williams, 2003), suggesting they are more emotionally responsive to social cues than those without heightened activation. Moreover, this pattern of neural activation predicts persistent emotional distress in the form of concurrent (Rudolph, Miernicki, Troop- Gordon, Davis, & Telzer, 2016; Silk et al., 2014) and subsequent (Masten et al., 2011) depressive and anxiety symptoms in adolescents. Thus, we operationalized neural sensitivity in the form of heightened activation in these three regions in the face of social exclusion.

Consistent with BSC/DS theories, it is plausible that neural sensitivity to social cues reflects a general susceptibility to environmental influences that not only promotes risk in the context of adverse social conditions, but also serves as a protective factor in the context of favorable social conditions (Schriber & Guyer, 2016). Supporting the vulnerability aspect of this theory, one study of adolescent girls revealed that heightened activation in the dACC, sgACC, and anterior insula during exposure to social exclusion predicted higher levels of emotional distress in girls with a history of chronic peer victimization but not in non-victimized girls (Rudolph et al., 2016). A remaining question concerns whether the same neural sensitivity to social cues also may allow adolescent girls to benefit from being embedded in highly nurturing social contexts.

The Role of Parent-Child Relationships

To address this question, the present study examined whether heightened neural sensitivity to social cues helps shape adolescent girls' emotional adjustment in the face of stressful versus supportive parent-child relationships. Although the peer group assumes increasing salience in youths' lives across adolescence, the quality of parent-child relationships (e.g., parental support, trust, respect, and closeness) continues to make a significant contribution to adolescent emotional well-being (Helsen, Vollebergh, & Meeus, 2000; Morris, Silk, Steinberg, Myers, & Robinson, 2007). Whereas adolescent perceptions of parents as unsupportive or untrustworthy predict higher levels of subsequent depressive symptoms, perceptions of parents as warm and supportive predict lower levels of subsequent depressive symptoms (Allen et al., 2006; Branje, Hale, Frijns, & Meeus, 2010; Stice, Ragan, & Randall, 2004). High-quality parent-child relationships also buffer adolescents against depressive/internalizing symptoms in the face of stress (Bowes, Maughan, Caspi, Moffitt, & Arseneault, 2010; Ge, Natsuaki, Neiderhiser, & Reiss, 2009; Yeung Thompson & Leadbeater, 2013), particularly for girls (Davidson & Demaray, 2007; Telzer & Fuligni, 2013).

Adolescent girls with heightened neural sensitivity to social cues may be particularly susceptible to these effects of stressful versus supportive parent-child relationships. Because these adolescents are highly attuned to social feedback, they may suffer in the face of relationship adversity (reflecting sensitivity to social threats) but flourish in the face of relationship support (reflecting sensitivity to social resources) (Boyce & Ellis, 2005). More specifically, emphasizing the importance of the parent-child relationship in susceptibility to the environment, Belsky (2005) speculates that high sensitivity may have risk-augmenting effects when not regulated by caregivers but risk-protective effects when co-regulation by caregivers occurs. In contrast, adolescents with low neural sensitivity to social cues may be impervious to feedback from their environment, showing similar levels of depressive symptoms in stressful and supportive parent-child relationships.

Study Overview

The goal of this research was to examine the hypothesis that neural sensitivity to social cues may serve as a form of BSC, conferring emotional risks in the context of stressful parent-child relationships but emotional benefits in the context of supportive parent-child relationships. Given our *a priori* focus on the social pain network, we investigated three neural regions of interest (ROIs) that have been implicated as reactive to social feedback in the form of exclusion, including the dACC, sgACC, and anterior insula (Eisenberger, 2015; Falk et al., 2014; Masten et al., 2009; Masten et al., 2011; Sebastian, et al., 2011; for a review, see Rotge et al., 2014). Adolescent girls were the focus of study given evidence for their heightened sensitivity to social cues (Guyer et al., 2009), greater emotional reactivity to social stressors (Rudolph, Flynn, Abaied, Groot, & Thompson, 2009; Rudolph, Lansford, & Rodkin, 2016; Shih, Eberhart, Hammen, & Brennan, 2006), including family disturbances (Davies & Windle, 1997; Rudolph & Flynn, 2007), and elevated risk for depressive symptoms (Rudolph, 2009). We predicted that stressful parent-child relationships would be associated with particularly high levels of subsequent depressive symptoms whereas supportive parent-child relationships would be associated with particularly low levels of

subsequent depressive symptoms in girls who showed heightened neural sensitivity to social cues. In contrast, we expected that girls with dampened neural sensitivity to social cues would show similar levels of depressive symptoms regardless of the quality of their parent-child relationships. To examine whether these effects replicated with a measure of behavioral sensitivity, we conducted a parallel set of analyses using girls' self-report of how much their psychological needs (e.g., need to belong) were threatened during social exclusion (Williams, Cheung, & Choi, 2000).

Method

Participants and Procedures

Participants included 45 adolescent girls ($M_{\text{age}} = 15.41$ years, $SD = .37$, range = 14.88 to 16.34 years) from diverse ethnic groups (68.9% White, 22.2% African American, 4.4% Asian American, and 4.4% other) and socioeconomic backgrounds (51.1% under \$60,000, 22.2% \$60,000 – 89,999, and 26.7% over \$90,000). Five additional girls were scanned but not included due to either a programming malfunction ($n = 2$) or missing data ($n = 2$ missing baseline depressive symptoms; $n = 1$ missing follow-up depressive symptoms). Participants were recruited from a prior longitudinal study (for details on the longitudinal study and recruitment process, see *authors omitted for masked review* and Supplemental Materials). Exclusion criteria included conditions that would prevent participation in the brain scan (e.g., claustrophobia, metal implants, braces). Parents provided written consent and adolescents provided written assent in accordance with the university Institutional Review Board. Participants completed a functional brain scan while playing Cyberball, a laboratory manipulation of social exclusion (Williams et al., 2000). At the time of the scan, girls completed measures of PCRQ and depressive symptoms. Depressive symptoms also were assessed at three-, six-, and nine-month follow-ups. Participants received a monetary incentive for their participation (\$50 for the initial session and \$5 for each follow-up session).

Behavioral Measures

Table 1 presents descriptive and psychometric data for the behavioral measures.

Parent-child relationship quality.—At the time of the scan, youth completed the parent subscale of the Inventory of Parent and Peer Attachment (Armsden & Greenberg, 1987). This 28-item measure assesses three dimensions of PCRQ: communication (e.g., “I tell my parents about my problems and troubles.”), mutual trust and respect (e.g., “My parents accept me as I am.”), and alienation (reverse scored; e.g., “I get upset a lot more than my parents know about.”). Youth rated each item on a 5-point scale (1 = *Almost Never or Never* to 5 = *Almost Always or Always*). Scores were computed as the mean of the items, with higher scores reflecting positive PCRQ (more supportive and less stressful) and lower scores reflecting negative PCRQ (more stressful and less supportive). The reliability and validity of this measure have been established (Armsden & Greenberg, 1987).

Depressive symptoms.—At the time of the scan and at the three follow-up assessments, youth completed the Short Mood and Feelings Questionnaire (SMFQ; Angold, Costello,

Messer, & Pickles, 1995) to assess depressive symptoms (e.g., “I felt unhappy or miserable.”). Youth indicated how much they experienced each symptom on a 4-point scale (1 = *Not at All* to 4 = *Very Much*). Scores were computed as the mean of the 13 items at each wave. Depressive symptom scores were highly intercorrelated across the follow-up waves ($r_s = .72 - .82$, $p_s < .001$). To capture these stable depressive symptoms across the nine-month follow-up period, a composite depressive symptom score was calculated by standardizing scores within wave and averaging across the three-month, six-month, and nine-month follow-ups. Composite scores can increase reliability and validity (De Los Reyes et al., 2015; McCrae, Kurtz, Yamagata, & Terracciano, 2011). Reliability and validity of the SMFQ have been documented (Angold et al., 1995), and this measure differentiates depression from other psychiatric diagnoses (Thapar & McGuffin, 1998).

fMRI Task

While completing the scan, participants were exposed to social rejection using Cyberball (Williams et al., 2000), which creates a subjective experience of being excluded. Participants were told they would be playing an on-line ball-throwing game with two peers (ostensibly in another room) also completing the same study and connected via the Internet. Participants could see the photographs of the other two players on a computer screen as well as their own ‘hand’ that they controlled using a button-box. Throughout the game, the ball was thrown back and forth among the three players. When the participant received the ball, she returned it to either player by pushing one of two buttons. The throws of the other two ‘players’ were determined by the pre-set program. Each participant completed two rounds. In the inclusion round, she was equally included in the tosses. In the exclusion round, she was excluded after ten tosses. Each round of the task included 58 total tosses.

Following the scan, girls completed the Need-Threat Scale (Williams et al., 2000), a 12-item self-report measure (higher scores reflect more threat to one’s needs) assessing feelings of belongingness (e.g., “I felt ‘disconnected’.”), rejection (e.g., “I felt rejected.”), self-esteem (e.g., “I felt good about myself.”), and social control (e.g., “I felt powerful.”) associated with the ball-throwing game. Youth indicated how much they experienced each feeling on a 5-point scale (1 = *Not at All* to 5 = *Very Much So*). Scores were computed as the mean of the 12 items.

fMRI Data Acquisition and Analysis

fMRI data acquisition.—Imaging data were collected using a 3 Tesla Siemens Trio MRI scanner. The Cyberball task included T2*-weighted echoplanar images (EPI) [slice thickness=3 mm; 38 slices; TR=2sec; TE=25msec; matrix=92×92; FOV=230 mm; voxel size 2.5×2.5×3mm³]. Structural scans consisted of a T2*-weighted, matched-bandwidth (MBW), high-resolution, anatomical scan (TR=4sec; TE=64msec; FOV=230; matrix=192×192; slice thickness=3mm; 38 slices) and a T1* magnetization-prepared rapid-acquisition gradient echo (MPRAGE; TR=1.9sec; TE=2.3msec; FOV=230; matrix=256×256; sagittal plane; slice thickness=1mm; 192 slices). The orientation for the MBW and EPI scans was oblique axial to maximize brain coverage.

fMRI data preprocessing and analysis.—Neuroimaging data were preprocessed and analyzed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Preprocessing for each participant's images included spatial realignment to correct for head motion (no participant exceeded 2mm of maximum image-to-image motion in any direction). The realigned functional data were coregistered to the high resolution MPAGE, which was then segmented into cerebrospinal fluid, grey matter, and white matter. The normalization transformation matrix from the segmentation step was then applied to the functional and T2 structural images, thus transforming them into standard stereotactic space as defined by the Montreal Neurological Institute and the International Consortium for Brain Mapping. The normalized functional data were smoothed using an 8mm Gaussian kernel, full-width-at-half maximum, to increase the signal-to-noise ratio.

Statistical analyses were performed using the general linear model (GLM) in SPM8. The task was modeled as a block design, with two blocks: inclusion and exclusion. The 10 initial throws in the exclusion round were modeled as a separate regressor and not included in the contrast of interest. High-pass temporal filtering with a cutoff of 128 seconds was applied to remove low-frequency drift in the time series. Serial autocorrelations were estimated with a restricted maximum likelihood algorithm with an autoregressive model order of 1. The parameter estimates resulting from the GLM were used to create linear contrast images comparing exclusion to inclusion. Random effects, group-level analyses were performed on all individual subject contrasts. ROI analyses included the identical ROIs as previous work (Falk et al., 2014), including the dACC, sgACC, and anterior insula (see Figure 2).

Anatomical ROIs were constructed using the Wake Forest University PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003), using a combination of Brodmann areas, the AAL atlas, and structural masks, all provided within the PickAtlas. The dACC ROI was defined as the union of Brodmann areas 24 and 32 (dilated to 2mm), as well as the anterior, middle, and posterior cingulate masks from the AAL atlas. Brodmann areas 8 and 9 were subtracted from the mask and further restricted to voxels bounded by ($x=-16$ to 16 , $y=0$ to 33 , and $z=6$ to 52). The sgACC ROI included regions of the cingulate and paracingulate cortices ventral to the corpus callosum and posterior to the genu. The anterior insula ROI was defined by all voxels within the left and right insula masks provided by the PickAtlas that were anterior to the $y=0$ plane. Parameter estimates of signal intensity were extracted from the ROIs using MarsBar for the contrast exclusion-inclusion.

We selected the specific ROIs based on several studies identifying individual differences within these regions, suggesting that they may be susceptibility biomarkers, consistent with the BSC/DS theories. Rather than selecting regions that robustly activate during Cyberball, and that may therefore not show individual differences, our aim was to focus on regions that may differentiate sensitive and insensitive individuals. For instance, these regions consistently show activation during Cyberball that correlates with individual differences such as time spent with peers (Masten et al., 2013), chronic peer rejection (Will, van Lier, Crone, & Güro lu, 2016), and depression (Jankowski et al., in press; Masten et al., 2009).

Overview of Analyses

SPSS version 24 was used to conduct the central analyses. First, we conducted correlation analyses to examine the pattern of associations among the variables. Next, we conducted two sets of analyses to examine whether findings were consistent with a BSC model. To support this model, several criteria need to be met: (a) there should be a significant interaction between social context (PCRQ) and sensitivity (neural activation) predicting adjustment (depressive symptoms); (b) the association between PCRQ and depressive symptoms should be significant in girls with high but not low sensitivity; (c) within adverse social contexts (stressful parent-child relationships), levels of depressive symptoms should be significantly higher in girls with high than low sensitivity; and (d) within favorable social contexts (supportive parent-child relationships), levels of depressive symptoms should be significantly lower in girls with high than low sensitivity (Ellis et al., 2011; Roisman et al., 2012).

To test criterion (a), three separate hierarchical multiple regression analyses were conducted to examine the interactive contribution of PCRQ and neural sensitivity in each ROI (dACC, subgenual ACC, and anterior insula) to follow-up depressive symptoms, adjusting for initial levels of depression. Prior to analysis and calculation of the interaction terms, each variable was standardized. Initial depressive symptoms were entered at the first step, the main effects of parent-child relationship quality and neural sensitivity were entered at the second step, and two-way PCRQ $\times$ Neural Sensitivity interaction terms were entered at the third step. To test criterion (b), we conducted simple slope analyses predicting depressive symptoms from PCRQ at low (-1 *SD*), moderate (mean), and high ($+1$ *SD*) levels of neural sensitivity (Aiken & West, 1991) and we depicted the results graphically.

To test criteria (c) and (d), we examined (1) the *SD* differences in depressive symptoms between high versus low levels of neural sensitivity at low (stressful) and high (supportive) levels of PCRQ (to quantify the size of the differences); (2) the Regions of Significance (RoS) with respect to PCRQ (i.e., the values of PCRQ at which the differences between high versus low levels of neural sensitivity are significant; when the lower-bound and upper-bound RoS fall within -2 *SD* and $+2$ *SD*, there is support for a plasticity model; Roisman et al., 2012); (3) the Proportion of Interaction (PoI) with respect to PCRQ, which is the proportion of the total area represented on either side of the crossover of regression lines in an interaction plot; and (4) the Proportion Affected (PA) with respect to PCRQ, which represents the proportion of youth who experience the benefits of supportive PCRQ.

Results

Intercorrelations among the Variables

Table 2 presents intercorrelations among the variables. PCRQ showed a marginal negative correlation with dACC activation but nonsignificant correlations with sgACC and insula activation. dACC activation was significantly positively correlated with insula but not sgACC activation; sgACC and insula activation also were not significantly associated. Higher levels of PCRQ (i.e. supportive parent-child relationships) were negatively correlated with initial and follow-up depressive symptoms. dACC activation and sgACC activation

were significantly positively correlated with initial depressive symptoms and marginally positively correlated with follow-up depressive symptoms; insula activation was not significantly associated with depressive symptoms.

Parent-Child Relationship Quality × Neural Sensitivity Contributions to Depressive Symptoms

Three separate hierarchical multiple regression analyses examined the interactive contribution of PCRQ and neural sensitivity in each ROI (dACC, sgACC, and anterior insula) to follow-up depressive symptoms, adjusting for initial depressive symptoms. In each regression, initial depressive symptoms significantly predicted follow-up depressive symptoms (Table 3). We used a Bonferroni correction of $p < .0167$ (.05/3) given that we conducted three regression analyses.

dACC activation.—The regression including dACC activation revealed a significant main effect of PCRQ, a nonsignificant main effect of dACC activation, and a significant PCRQ × dACC Activation interaction (Table 3). As shown in Figure 3a, decomposition of this interaction revealed that stronger PCRQ significantly predicted lower levels of depressive symptoms in girls with high, $\beta = -0.56$, $t(43) = -4.29$, $p < .001$, and moderate, $\beta = -0.32$, $t(43) = -3.09$, $p = .004$, but not low, $\beta = 0.06$, $t(43) = 0.41$, $p = .686$, levels of dACC activation. At low (stressful) levels of PCRQ, girls with high dACC activation had depressive symptom scores *.61 SD higher* than those with low dACC activation. At high (supportive) levels of PCRQ, girls with high dACC activation had depressive symptom scores *.50 SD lower* than those with low dACC activation. The lower-bound and upper-bound RoS were at $-.49 SD$ and $.88 SD$, respectively. The PoI was 41% to the right of the crossover and 59% to the left of the crossover, and the PA was 58%. Collectively, these indexes provide support for a plasticity model (Del Giudice, 2017; Roisman et al., 2012).

sgACC activation.—The regression including sgACC activation revealed a significant main effect of PCRQ, a nonsignificant main effect of sgACC activation, and a significant PCRQ × sgACC Activation interaction (Table 3). As shown in Figure 3b, decomposition of this interaction revealed that stronger PCRQ significantly predicted lower levels of depressive symptoms in girls with high, $\beta = -0.59$, $t(43) = -4.02$, $p < .001$, and moderate, $\beta = -0.31$, $t(43) = -2.91$, $p = .006$, but not low, $\beta = -0.03$, $t(43) = -0.21$, $p = .835$, levels of sgACC activation. At low (stressful) levels of PCRQ, girls with high sgACC activation had depressive symptoms scores *.58 SD higher* than those with low sgACC activation. At high (supportive) levels of PCRQ, girls with high sgACC activation had depressive symptom scores *.41 SD lower* than those with low sgACC activation. The lower-bound and upper-bound RoS were at $-.51 SD$ and $1.27 SD$, respectively. The PoI was 36% to the right of the crossover and 64% to the left of the crossover, and the PA was 53%. Collectively, these indexes provide support for a plasticity model (Del Giudice, 2017; Roisman et al., 2012).

Insula activation.—The regression including insula activation revealed a significant main effect of PCRQ, a nonsignificant main effect of insula activation, and a significant PCRQ × Insula Activation interaction (Table 3). As shown in Figure 3c, decomposition of this interaction revealed that stronger PCRQ significantly predicted lower levels of depressive

symptoms in girls with high, $\beta = -0.54$, $t(43) = -3.65$, $p < .001$, and moderate, $\beta = -0.27$, $t(43) = -2.46$, $p = .018$, but not low, $\beta = 0.01$, $t(43) = 0.04$, $p = .965$, levels of insula activation. At low (stressful) levels of PCRQ, girls with high insula activation had depressive symptoms scores .71 *SD higher* than those with low insula activation. At high (supportive) levels of PCRQ, girls with high insula activation had depressive symptom scores .45 *SD lower* than those with low insula activation. The lower-bound and upper-bound RoS were at $-.57$ *SD* and 1.50 *SD*, respectively. The PoI was 28% to the right of the interaction and 72% to the left of the interaction, and the PA was 53%. Collectively, these indexes provide support for a plasticity model, although the PoI index was weaker than that for the dACC and subACC (Del Giudice, 2017; Roisman et al., 2012).

Summary.—For each ROI, results supported criteria (a) and (b). We used multiple indexes to examine criteria (c) and (d). With regard to the *SD* differences in depressive symptoms, there is no clear cut-off in terms of what size difference would support a BSC model; however, across the three models the average *SD* difference was .54, suggesting meaningful differences between more and less sensitive girls. With regard to the RoS, all of our models included lower and upper bounds within -2 *SD* and $+2$ *SD*. With regard to the PoI and PA, again there is no clear cut-off, but it has been suggested that a range of .40 - .60 (Roisman et al., 2012) or even a wider range of .20 - .80 (Del Giudice, 2017) supports a BSC model, with ideal indexes close to 50%. Our average PoI index was 35% to the right of the crossover and 65% to the left of the crossover, with stronger indexes for the dACC and subgenual ACC than the insula. Finally, our average PA was 54%. Thus, across the various indexes there was strong support for the BSC model.

Parent-Child Relationship Quality x Behavioral Sensitivity Contributions to Depressive Symptoms

The regression including self-report scores on the Need-Threat Scale revealed a significant main effect of PCRQ ($\beta = -0.25$, $t(43) = -2.34$, $p < .001$), a nonsignificant main effect of Need-Threat ($\beta = -0.03$, $t(43) = -0.33$, $p = .742$), and a significant PCRQ X Need-Threat interaction ($\beta = -0.26$, $t(43) = -3.00$, $p = .005$). As shown in Figure 3d, decomposition of this interaction revealed that stronger PCRQ significantly predicted lower levels of depressive symptoms in girls with high, $\beta = -0.54$, $t(43) = -4.02$, $p < .001$, and moderate, $\beta = -0.25$, $t(43) = -2.37$, $p = .023$, but not low, $\beta = 0.04$, $t(43) = 0.28$, $p = .784$, levels of Need-Threat. At low (stressful) levels of PCRQ, girls with high levels of Need-Threat had depressive symptoms scores .46 *SD higher* than those with low levels of Need-Threat. At high (supportive) levels of PCRQ, girls with high levels of Need-Threat had depressive symptom scores .57 *SD lower* than those with low levels of Need-Threat. The lower-bound and upper-bound RoS were at $-.95$ *SD* and $.62$ *SD*, respectively. The PoI was 59% to the right of the interaction and 41% to the left of the interaction, and the PA was 58%. Collectively, these indexes provide support for a plasticity model (Del Giudice, 2017; Roisman et al., 2012).

Discussion

The BSC (Boyce & Ellis, 2005; Ellis et al., 2011) and DS (Belsky et al., 2007) theories propose that individual differences in sensitivity to the environment can confer health risks in the context of harmful social conditions but health benefits in the context of favorable social conditions. In an empirical test of this model, the present research examined whether neural sensitivity to social cues may serve as one type of biological susceptibility, predicting either better or worse emotional adjustment in adolescent girls depending on the quality of their parent-child relationships. Results confirmed that neural sensitivity moderates the contribution of PCRQ to depressive symptoms: Whereas more sensitive girls experienced differing levels of depressive symptoms within stressful versus supportive relationships, less sensitive girls were not emotionally responsive to the quality of their parent-child relationships. Several critical indexes (Roisman et al., 2012) supported a differential susceptibility model, with the most robust results emerging for the dACC and the sgACC.

Context-Dependent Consequences of Neural Sensitivity to Social Cues

Stressful parent-child relationships predicted higher levels of subsequent depressive symptoms in girls with high and moderate but not low levels of neural sensitivity in the dACC, sgACC, and anterior insula. This pattern is consistent with prior research linking activation in the social pain network with depressive and internalizing symptoms (Masten et al., 2009; Rudolph et al., 2016; Silk et al., 2014) as well as with evidence showing that a heightened social pain response interacts with youths' social experiences to predict emotional adjustment (Rudolph et al., 2016). Girls who experience parent-child relationships characterized by low levels of trust and communication and high levels of alienation are likely receiving frequent negative social feedback that may threaten their sense of self-worth and compromise their ability to regulate emotions, leading to depressive symptoms (Abaied & Rudolph, 2014; Morris et al., 2007). Those with heightened neural sensitivity to social cues may be particularly attuned to this feedback, thereby increasing their emotional risk, whereas less sensitive girls may be less likely to encode such feedback or to integrate it into their sense of self, thereby reducing their emotional risk.

Providing a novel perspective on neural sensitivity, however, girls with heightened activation in the dACC, sgACC, and anterior insula also experienced particularly low levels of depressive symptoms in the context of supportive parent-child relationships. This pattern suggests a more nuanced perspective on the role of neural sensitivity in adolescent girls' emotional adjustment. When sensitive girls are embedded in a nurturing social context, they may be particularly receptive to enriching experiences, thereby promoting emotional health, whereas less sensitive girls may benefit less from the favorable features of their environment (Boyce & Ellis, 2005; Ellis et al., 2011). These proposed health-promoting consequences of neural sensitivity to social cues are consistent with both psychological (Cooper, Shaver, & Collins, 1998; Helgeson, 1994; Rudolph & Conley, 2005; for a review, see Rose & Rudolph, 2006) and neuroscience (Masten et al., 2009; for a review, see Schriber & Guyer, 2016) research showing that social sensitivity can have beneficial consequences, but extends this line of inquiry to demonstrate the critical role of social context in determining whether social sensitivity makes a protective or harmful contribution to emotional adjustment. The

findings also are consistent with the role of the ACC and anterior insula as core nodes in the salience network, which is activated in response to emotionally salient stimuli (Menon & Uddin, 2010; Seeley et al., 2007) and may therefore be involved in processing of both negative and positive feedback (Schriber & Guyer, 2016). Documenting this pattern of BSC using a neural marker of sensitivity extends prior research using other biological markers by opening up the possibility of monitoring moment-to-moment variability in processing of social cues, which may inform prevention and intervention efforts to redirect attention to, and encoding of, particular aspects of social input from the environment.

Notably, a parallel pattern of effects emerged when examining girls' behavioral sensitivity to social cues, as reflected in their self-report of threats to their psychological needs during social exclusion. Higher scores on the Need-Threat Scale reflect a greater impact of being excluded on girls' sense of belongingness, acceptance, self-esteem, and perceived control. Thus, the emergence of a similar pattern of findings using this measure of behavioral sensitivity bolsters the idea that girls who are more attuned to the psychological impact of social cues or encode them as more self-relevant are at greater risk for depression in the face of stressful environments but are at particularly low risk for depression in the face of supportive environments whereas the emotional health of girls who are less attuned to social cues is not contingent on the quality of their parent-child relationships.

Contributions and Limitations

This study contributes to a small but growing body of research highlighting how individual differences in biological susceptibility can have either beneficial or detrimental consequences for development contingent on the environments in which youth live (e.g., Bakermans-Kranenburg & van IJzendoorn, 2006; Boyce et al., 1995; Obradovic et al., 2010, 2016; Pluess & Belsky, 2010; Rudolph et al., 2010, 2011; Rutter, 2014; for reviews, see Bush & Boyce, 2014; Ellis et al., 2011). Evidence for this pattern of developmental adaptation underscores the importance of considering possible trade-offs of sensitivity rather than classifying individual characteristics as maladaptive or adaptive. Of interest, there is some evidence that neural sensitivity to exclusion as assessed in this study may emerge in the context of exposure to adverse peer environments, such as rejection (Will et al., 2016) or victimization (Rudolph et al., 2016). However, the current research suggests that if youth have an alternative nurturing social environment (e.g., a supportive family), they may be able to overcome the maladaptive outcomes often associated with this neural sensitivity and even transform it into a protective factor. This idea is supported by research showing that certain regions implicated in social-affective processing (including the dACC, sgACC, and insula) are responsive to bivalenced (i.e., both negative and positive) social feedback (Jankowski et al., in press; Schriber & Guyer, 2016), and that heightened activation in these regions can predict both healthy and unhealthy developmental outcomes (for a review, see Schriber & Guyer, 2016).

Despite the advances provided by this research, conceptual elaboration of the BSC/DS framework will require identifying the processes through which neural sensitivity enhances or compromises emotional well-being. We speculated that neural sensitivity may intensify processing (e.g., attention, encoding) of social cues, both favorable and threatening, or

enhance the likelihood of these cues being internalized as self-relevant. More broadly, it has been suggested that sensitivity interacts with protective environments to predict cognitive and social competence but interacts with risky environments to predict lower thresholds for anticipating threat and increase vigilance and wariness (Ellis & Boyce, 2008). It may be that youth acquire strong self-regulatory ability within supportive parent-child relationships, which helps them to leverage their sensitivity in a productive way, whereas poor self-regulatory ability stemming from stressful parent-child relationships may channel their sensitivity toward heightened emotional distress (Eisenberg, 2001; Schrier & Guyer, 2016). Research directly investigating such behavioral pathways through which biological sensitivity unfolds will enrich our understanding of BSC/DS and its implications for development.

Future research also will need to expand in several ways on methodologies used to elucidate neural sensitivity to context. First, we focused on neural sensitivity to social cues in the form of social exclusion. According to a BSC/DS framework, the same biological characteristics that heighten vulnerability to environmental adversity also make youth likely to benefit from environmental resources (Ellis et al., 2011). Future research will therefore need to examine the association between neural sensitivity to threatening and rewarding features of the environment to examine whether girls who are prone to feel more social pain in the context of social threats also experience more social pleasure in the context of social resources.

Second, this research involved a test of the neural sensitivity to context theory specifically in the context of social exclusion and parent-child relationships in adolescent girls. This leaves open the question of whether a similar pattern would emerge when study parameters vary. For example, it would be interesting to examine this theory using other types of social cues, such as acceptance or rejection during the Chat Room (Guyer et al., 2008, 2009, 2015) or Virtual School (Jarcho et al., 2013, 2016) tasks as well as assessing other types of environmental contexts (e.g., peer or romantic relationships) not only with self-reports but also other methods and informants. Given the comprehensive nature of the BSC and DS theories and the fact that support for these theories has been found for multiple types of biological susceptibility and multiple social contexts (for a review, see Ellis et al., 2011), one might expect that the findings are not specific to this task or to parent-child relationship quality; however, research aimed at expanding the scope of these findings provides a useful direction for future research. Moreover, it is unclear whether a similar pattern of biological sensitivity to context would generalize to adolescent boys. Although adolescent girls, on average, show higher levels of social sensitivity than boys (Rose & Rudolph, 2006), there are likely individual differences in boys that may shape their emotional development.

Third, health benefits in the present study were reflected in particularly low levels of depressive symptoms but it will be important to also determine whether sensitive girls show particularly elevated levels of enhanced adjustment (e.g., positive emotions, adaptive social behavior) in high-support contexts. Moreover, although this research established the predictive contribution of PCRQ and neural sensitivity to depression across nine months, it is unclear whether neural sensitivity has enduring risks or benefits for girls' well-being. Thus, longer-term studies are needed to track trajectories of depressive symptoms over the course of adolescence using advanced statistical analyses such as growth curve modeling.

Conclusion

Overall, this research suggests that the rise in neural sensitivity among girls across adolescence does not deterministically set the stage for heightened emotional distress. Rather, efforts to improve the social contexts in which girls live (e.g., through family and peer intervention efforts) may alter the meaning of this sensitivity such that it forecasts increasing levels of emotional well-being. More broadly, this research highlights the complex nature of individual differences and their implications for developmental adaptation, calling into question the characterization of personal characteristics as solely adaptive or maladaptive.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Illustration of results predicted by biological sensitivity to context model.

Figure 2.
Anatomical masks for the regions of interest.

Figure 3a.

Prediction of follow-up depressive symptoms from the interactive contribution of parent-child relationship quality and dACC activation, adjusting for initial depressive symptoms.

Figure 3b.

Prediction of follow-up depressive symptoms from the interactive contribution of parent-child relationship quality and subgenual ACC activation, adjusting for initial depressive symptoms.

Figure 3c.

Prediction of follow-up depressive symptoms from the interactive contribution of parent-child relationship quality and insula activation, adjusting for initial depressive symptoms.

Figure 3d.

Prediction of follow-up depressive symptoms from the interactive contribution of parent-child relationship quality and need-threat, adjusting for initial depressive symptoms.

Table 1

Descriptive Statistics and Psychometric Information for the Measures

Variable	<i>M</i>	<i>SD</i>	Cronbach's <i>α</i>
Parent-Child Relationship Quality	3.78	.92	0.97
Wave 1 Depressive symptoms	1.63	.74	0.95
Wave 2 Depressive symptoms	1.69	.83	0.97
Wave 3 Follow-up Depressive symptoms	1.59	.71	0.94
Wave 4 Follow-up Depressive symptoms	1.66	.82	0.96

Note. Wave 1 = time of scan; Wave 2 = three-month follow-up; Wave 3 = six-month follow-up; Wave 4 = nine-month follow-up.

Table 2

Bivariate Correlations Among the Variables

Variable	1	2	3	4	5
1. PCRQ	--	--	--	--	--
2. dACC activation	-.25 ⁺	--	--	--	--
3. sgACC activation	-.08	.16	--	--	--
4. Insula activation	.00	.61 ^{**}	.05	--	--
5. Initial depressive symptoms	-.63 ^{**}	.33 [*]	.31 [*]	.13	--
6. Follow-up depressive symptoms	-.67 ^{**}	.28 ⁺	.27 ⁺	.11	.80 ^{**}

Note. PCRQ = parent-child relationship quality; dACC = dorsal anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex.

⁺
 $p < .10$.

^{*}
 $p < .05$.

^{**}
 $p < .01$.

Table 3

Parent-Child Relationship Quality and Brain Activation Predicting Follow-up Depressive Symptoms

Predictors	<i>dACC</i>		<i>sgACC</i>		<i>Insula</i>	
	β	<i>t</i>	β	<i>t</i>	β	<i>t</i>
Step 1						
Initial Depressive Symptoms	.80	8.64**	.80	8.64**	.80	8.64**
Step 2						
Initial Depressive Symptoms	.62	5.31**	.60	4.95**	.62	5.33**
PCRQ	-.27	-.36	-.28	-2.46	-.28	-2.39
Brain Activation	.00	.04	.06	.68	.03	.33
Step 3						
Initial Depressive Symptoms	.55	5.23**	.56	4.98**	.61	5.63**
PCRQ	-.25	-2.46*	-.31	-2.91*	-.27	-2.46
Brain Activation	.03	.34	.04	.47	.06	.75
PCRQ x Brain Activation	-.29	-3.54*	-.25	-3.01*	-.22	-2.61*

* $p < .0167$ (Bonferroni corrected).** $p < .001$.

Note. PCRQ = parent-child relationship quality; dACC = dorsolateral anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex.