



Regular Article

Children's neural reactivity to maternal praise and criticism: Associations with early depressive symptoms and maternal depression

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Abstract

Caregiving experiences are implicated in children's depression risk; however, children's neural reactivity to positive and negative feedback from mothers, a potential mediator of depression risk, is poorly understood. In a sample of 81 children ($M_{\text{age}} = 11.12$ years, $SD_{\text{age}} = 0.63$), some of whom were recruited based on a maternal history of depression ($n = 29$), we used fMRI to characterize children's neural responses to maternal praise and criticism. Maternal history of depression was unrelated to children's brain activity during both the praise and criticism conditions; however, ROI analyses showed that children's self-reported depressive symptoms were negatively associated with functional activity in the left anterior insula and right putamen while hearing maternal criticism. Whole-brain analyses showed that children's depressive symptoms were positively associated with left inferior frontal gyrus activity while listening to maternal praise. These findings complement past work implicating these brain regions in the processing of emotionally salient stimuli, reward processing, and internal speech. Given associations between early depressive symptoms and later disorder, findings suggest that maladaptive neural processing of maternal feedback may contribute to children's early emerging risk for depression.

Keywords: Maternal feedback; Depression; Risk; Neuroimaging; Children

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Introduction

Major depression is among the most common mental disorders with annual and lifetime prevalence rates of 10.4% and 20.6% (Hasin et al., 2018), respectively. Depression is also a global leading cause of disability (Vos et al., 2012), suicide (Bostwick & Pankrats, 2000), increased mortality due to co-occurring health conditions (Cuijpers & Smit, 2002), and a host of other negative psychosocial outcomes (Kessler, 2012). Identifying early emerging vulnerabilities and mechanisms that lead to depression may ultimately reduce its considerable impact by informing prevention and early intervention efforts.

Although relatively few young children meet criteria for a depressive disorder (Costello et al., 2003), the transition from late childhood to adolescence is characterized by a substantial increase in depressive symptoms and disorders (Merikangas et al., 2010a; 2010b). This period of late childhood, immediately prior to adolescent-associated increases in depression prevalence, has the

potential for identification of critical markers of vulnerability to depression. Although research using neuroimaging techniques to identify putative vulnerability mechanisms in youth exists, the majority relies either on youth participants with a personal history of depression or well-past the adolescence-associated increase in depression. This limits what can be gleaned regarding whether findings reflect true markers of vulnerability (i.e., etiological mechanisms), or are better explained as sequelae of previous depressive episodes. By focusing on participants at an age at which prevalence of depression and depression symptoms are typically low, we are better able to identify neural markers of risk, rather than depressive sequelae. Research examining never-depressed youth this age (i.e., 9–12 years old), prior to the onset of depression, is therefore well suited to identifying associations between putative early vulnerability mechanisms and increases in depressive symptoms. Thus, the goal of our study was to investigate the relationship between never-depressed children's neural response to valenced maternal feedback and known markers of depression risk (e.g., children's depressive symptoms [Wesselhoeft et al., 2013] and maternal depression history [Goodman et al., 2011]).

Although depression is etiologically complex, at least some variance in risk appears to stem from early experience, particular early caregiving. Meta-analytic findings from cross-sectional,

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retrospective, and longitudinal studies show moderate associations between negative parenting styles and subsequent depression (McLeod et al., 2007; Yap & Jorm, 2015; Yap et al., 2014). Specifically, parental withdrawal (i.e., lack of involvement with, or interest in, the child), hostility/criticism, inconsistent discipline, over-involvement (i.e., parental interference with age-appropriate autonomy and independence), and both authoritarian and permissive (i.e., demanding, directive, and punitive caregiving) parenting are associated with childhood and adolescent depression symptoms and diagnoses (McLeod et al., 2007; Yap & Jorm, 2015; Yap et al., 2014). In contrast, parental warmth, monitoring (i.e., parental knowledge of their child's activities and relationships), and autonomy granting (i.e., encouragement, acknowledgment, and solicitation of child's opinions and choices) are associated with lower depression in youth (McLeod et al., 2007; Yap & Jorm, 2015; Yap et al., 2014).

As with other etiological factors, the processes by which parenting influences youth depression are complex and likely involve interactions with a variety of endogenous and exogenous influences (e.g., genetics, exposure to negative parental cognitions, behavior, or affect, and exposure to environmental stress; Goodman & Gotlib, 2002). However, an extant literature supports the notion that parenting behavior may confer depression risk at least in part by contributing to the development of maladaptive neural functioning in childhood. For example, meta-analysis has found that extreme forms of maladaptive parenting (e.g., abuse and neglect) are positively associated with children's amygdala and insula reactivity during processing of negative emotional stimuli (Hein & Monk, 2017). However, studies of how more typical caregiving styles (i.e., parental over-involvement, criticism, etc.) relate to children's neural development are rare, which is problematic given ample evidence that more common, relatively mild negative environmental exposures also influence development across the lifespan (e.g., Rutter, 2005).

The small extant literature on normative variation in caregiving and neural development indicates that, among healthy youth, parenting behavior is associated with youths' neural response to affectively valenced stimuli. Specifically, Romund et al. (2016) found that child-reported maternal warmth was associated with decreased amygdala activity when processing fearful face stimuli relative to neutral face stimuli. Similarly, observational ratings of negative parenting behavior (i.e., aggressive and dysphoric affect, and anger toward the child) during a lab-based parent-child interaction task were associated with increased activity in children's amygdala when processing angry and fearful face stimuli (Pozzi et al., 2020). Small volume corrected (SVC) analysis of a *priori* region of interest (ROI) found that child-reported maternal warmth predicted lower functional activity in children's amygdala, insula, subgenual anterior cingulate cortex ACC (sgACC), ventrolateral prefrontal cortex (vlPFC), and anterior cingulate cortex (ACC) during exposure to audio recordings of maternal criticism (Butterfield et al., 2020). In addition, Tan et al.'s (2020) recent review of the relationship between parenting behavior and the neural substrates of emotional reactivity and regulation in children and adolescents noted that positive and supportive parenting behavior is associated with reduced functional activity in brain regions (e.g., amygdala, insula, ACC, vlPFC) relevant to salience detection during processing of negative emotional information. Similarly, Tan et al. (2020) reported that youth who experienced lower positive and supportive parenting tended to show increased functional activity in salience detection regions during negative emotion processing, relative to their peers who experienced more positive

and supportive parenting. While the extant literature is limited to a handful of studies, it appears that positive parenting behavior is associated with lower functional activity in brain regions relevant to detecting, processing, and regulating emotional stimuli in youths, while negative parenting is associated with increased activity in similar regions. These same brain regions are central to prominent theories of the role of the brain in depression and depression risk (Disner et al., 2011), supporting the notion that early caregiving may shape depression risk through its impact on children's early neural development.

Research examining neural function in the context of tests of interpersonal models of depression (Starr & Davila, 2008) may also be relevant to understanding associations between parenting and children's brain development and depression risk. For example, mother-child attachment is related to the brain's functional response to social interactions (DeWall et al., 2012). Early caregiving experiences are also associated with children's vulnerability to depression (Morley & Moran, 2011). Along similar lines, disruptions to interpersonal relationships are associated with the onset of depressive episodes (Eberhart & Hammen, 2006; Monroe et al., 1999; Slavich et al., 2010). Research on the role of neural processing of interpersonal feedback, as it relates to depression risk, has largely relied on "pseudoparticipant" stimuli (i.e., standardized interpersonal feedback stimuli presented to as though it came from another study participant) to elicit neural responses to social inclusion and exclusion (e.g., Davey et al., 2011; Silk et al., 2012; Williams & Jarvis, 2006). Studies using these paradigms in healthy populations generally show that negative interpersonal feedback is typically associated with activation in the anterior insula (AI), ACC, and the inferior orbitofrontal cortex (Cacioppo et al., 2013).

In studies examining neural responses to interpersonal feedback, Davey et al. (2011) found that, relative to healthy controls, adolescents and young adults with depression had significantly greater amygdala activity in response to peer acceptance (i.e., being rated as "likeable" by a pseudoparticipant peer). While Silk et al. (2014) found no differences in neural activity between depressed and healthy adolescents during peer acceptance trials, negative interpersonal feedback (i.e., peer rejection) elicited increased amygdala, sgACC, and striatal activity among depressed adolescents. Studies using the Cyberball Task have found depressed adolescents show increased activity in the insula during negative interpersonal feedback (i.e., social exclusion; Jankowski et al., 2018; Mellick, 2017). Mellick (2017) also reported that negative interpersonal feedback is associated with increased activity in the ventral striatum (VS) among depressed teens. Similarly, *positive* interpersonal feedback (i.e., social inclusion) is associated with *decreased* activity in the middle temporal gyrus (Jankowski et al., 2018), precuneus and middle cingulate (Mellick, 2017) in adolescents with depression.

As previously noted, while investigations of brain activity in youth with depression are essential to understanding the neurobiology of depression, they are limited in their ability to speak to whether identified patterns of brain activity contribute to children's risk for depression or are a consequence of the disorder. Studies of high-risk children prior to onset of disorder are well situated to identify neurobiological risk for depression as it relates to interpersonal feedback. Of the relatively few extant studies, never-depressed children with a family history of depression showed diminished activity in reward-processing regions (e.g., ACC and VS) during positive interpersonal feedback (i.e., peer acceptance; Olino et al., 2015); however, relative to their low-risk peers,

high-risk children showed increased BOLD activity in regions important for self-referential thought (e.g., superior and middle temporal gyri, middle frontal gyri, and precuneus) during positive feedback trials. As with patterns seen in adolescents with depression (Silk et al., 2014), Masten et al. (2011) found that greater activation in never-depressed 13-year-olds' sgACC, dorsomedial PFC (dmPFC), and middle temporal gyrus response to peer rejection during the Cyberball Task prospectively predicted increases in depressive symptoms one year later. Unfortunately, Olino et al. (2015) did not report the relationship between negative social feedback trials (i.e., social rejection) and neural function.

Considering studies of adults, Yttredahl et al. (2018) found that adult women with depression had greater activity in the right AI and dorsal ACC during interpersonal rejection, compared to non-depressed controls. Kumar et al. (2017) reported that, relative to healthy controls, negative interpersonal feedback was associated with increased activity in the amygdala and vLPFC among depressed adults. Overall, while the literature investigating the relationship between interpersonal feedback, depression, and brain activity is somewhat inconsistent, it appears that depression is associated with greater insula, ACC, and striatal activity during negative interpersonal feedback; additionally, increased amygdalar activity is associated with both positive and negative feedback during interpersonal feedback tasks among people with depression. Importantly, evidence of depression-associated differences in neural response to interpersonal feedback can be seen both in youth (e.g., Davey et al., 2011; Jankowski et al., 2018; Mellick, 2017; Silk et al., 2014) and adults (e.g., Kumar et al., 2017; Yttredahl et al., 2018). Additionally, there is some evidence that similar increases in sgACC activity during negative interpersonal feedback is seen in both adolescents with current depression (Silk et al., 2014) and never-depressed children at high risk for depression (Masten et al., 2011).

While this literature provides initial clues concerning brain regions that are important to understanding the relationship between interpersonal feedback and depression risk, much of it has relied on interpersonal feedback from standardized pseudoparticipant peers. Given the stimuli used, this research is limited in its ecological validity for understanding neural processes involved in social or interpersonal feedback. While rigorously controlled experimental paradigms (e.g., the Cyberball task) allow for convenient manipulation of interpersonal feedback and maximize internal validity, the relatively simple stimuli used in these paradigms (i.e., pseudoparticipant "rejection" or "acceptance") may lack external validity in terms of tapping brain activity during "real-world" interactions. Investigation of neural responses to valenced interpersonal feedback would likely benefit from more ecologically valid stimuli from real people known to the participant. Further, with few exceptions (Masten et al., 2011), the studies described above have been conducted in older adolescents or adults with a personal history of depression. As previously mentioned, focusing on neural response to interpersonal feedback in high-risk never-depressed children, prior to increases in depression prevalence typical of adolescence, is well suited to furthering our understanding depression risk. Although peer relationships have increasing importance during adolescence and into adulthood, during childhood the parent-child relationship is thought to be among the most important (Hadiwijaya et al., 2017). Consequently, investigations of children's neural response to interpersonal feedback may be better served by tasks relying on real interpersonal feedback from a developmentally important relationship (e.g., mothers).

Hooley et al. (2005) Maternal Feedback Challenge (MFC) is one such task.

The MFC (Hooley et al., 2005) has previously been used to study interpersonal feedback/caregiving processes in the context of depression and depression risk. During the MFC task, participants listen to audio recordings of their own mother providing neutral, critical, and positive feedback with content directed specifically toward them and drawn from actual topics of discussion between the dyads (Hooley et al., 2005). By using maternal stimuli specific to the participant tasks such as the MFC may have increased ecological validity, potentially capturing how the affective tone of early, naturalistic, day-to-day interactions with mothers (one of children's most important early relationships) is related to brain function and depression risk. Although the MFC does not measure characteristic patterns of parenting per se (i.e., it does not assess the extent to which mothers provide positive and negative feedback to their children), presumably all children are exposed to both positively and negatively valenced feedback from their mothers with regularity. Hence, the MFC can be viewed as an index of individual differences in brain activity in response to valenced interpersonal feedback from their mothers.

In the earliest use of the MFC (Hooley et al., 2005), young adult women with a history of depression had decreased dlPFC activity while listening to maternal criticism stimuli, while never-depressed women had substantial increases in dlPFC activity. In a replication and extension of this study, Hooley et al. (2009) reported the same pattern of significantly lower dlPFC activity, as well as diminished ACC activity, in response to maternal criticism among formerly depressed young women. Additional analyses found that maternal criticism was associated with greater amygdalar activity in formerly depressed women, relative to never-depressed controls (Hooley et al., 2009). In a follow-up study (Hooley et al., 2012), currently depressed young adult women were added to the sample from Hooley et al. (2009) paper. Both current depression and a history of depression were unrelated to BOLD response to maternal criticism or praise in either the dlPFC or amygdala; however, participants' self-reported *perceptions* of maternal criticism were associated with diminished dlPFC and enhanced amygdala response to maternal criticism. That distinct patterns of activity in the ACC, dlPFC, and amygdala are found even once depression has remitted suggests that activation in these regions may be associated with a trait vulnerability to depression, rather than simply being associated with current depression (Hooley et al., 2009; 2012); however, it is also possible that the experience of depression causes lasting changes to brain activity (i.e., a scar effect), such that neural activity remains altered following remission.

The MFC developed by Hooley et al., (2005; 2009; 2012) has only been used in studies of young adult women. While this work is important, the nature of the child-parent relationship undergoes significant changes across development. Specifically, adolescence is marked by increasing conflict in this relationship, generally resolving in a return to harmony in late adolescence/early adulthood (Hadiwijaya et al., 2017). Due to developmental changes in this important relationship, neural activity during tasks like the MFC (and its relationship to depression/depression risk) should be examined prior to and during adolescence. With respect to the small extant literature on this topic, Aupperle et al. (2016) reported that adolescent ($M_{age} = 14.39$ years) internalizing symptoms were positively associated with right amygdala activity during maternal criticism and negatively related to activity during maternal praise; left amygdala activity was also negatively related to both

types of maternal feedback (Aupperle et al., 2016). Unfortunately, Aupperle et al.'s (2016) study was limited by a small sample ($N = 18$) composed solely of adolescent girls. In a study of 9 to 17-year-olds ($M_{\text{age}} = 14.58$ years), Silk et al. (2017) found that adolescents with depression showed greater activity in limbic regions (i.e., parahippocampal gyrus) when listening to maternal criticism (versus neutral feedback), as well as diminished activity in the thalamus, caudate, vmPFC, and precuneus during maternal praise (versus neutral feedback), relative to healthy controls. While both Aupperle et al. (2016) and Silk et al. (2017) provide insight into youths' neural response to maternal feedback, both studies were largely composed of adolescent participants. Given the developmental importance of the mother-child relationship preadolescence, further investigation of neural response to maternal praise and criticism, as it relates to depression risk, is especially relevant in late childhood.

Current study

In summary, maladaptive reactivity to both early caregiving and interpersonal relationships are implicated in depression; however, the neural underpinnings of responsivity to positive and negative feedback from parents in never-depressed children is poorly understood. Further, our understanding of the directionality of the relationship between brain function and depression is limited by the fact that most relevant studies have been done with adults and adolescents with either a history of, or current, depression. In the current study, we therefore focused on 81 never-depressed 9- to 12-year-old children ($M_{\text{age}} = 11.12$, $SD_{\text{age}} = 0.63$), contrasting the functional brain response to ecologically valid positive and negative maternal feedback (i.e., the MFC) among those with and without a maternal history of depression; Connell & Goodman, 2002; Klein et al., 2005). In addition, given the predictive validity of sub-threshold symptoms for later disorder (Cuijpers & Smit, 2004; Shankman et al., 2009), we also examined associations between never-depressed children's early emerging depressive symptoms, which show predictive validity for later depressive episodes (Pickles et al., 2001; Pine et al., 1999), and their brain activity during both positive and negative maternal feedback in the MFC. By focusing analyses on children with no personal history of depression, we aimed to characterize the brain-based correlates of sensitivity to caregiving, a potential mediator of depression risk, in youth. Notably, to our knowledge this is the first study to examine the relationship between children's depression risk and brain response to maternal feedback using the MFC in a sample of never-depressed children.

Previous reports have found that depression (Kumar et al., 2017; Silk et al., 2014; 2017; Yttredahl et al., 2018), depression history (Hooley et al., 2009), and depression risk (Aupperle et al., 2016; Masten et al., 2011) are associated with increased BOLD reactivity to negative interpersonal feedback in brain regions responsible for affective salience (e.g., insula, amygdala, sgACC) and reward/punishment processing (e.g., striatal regions including caudate, putamen, and nucleus accumbens). Based on these findings we hypothesized that depression risk, indexed by maternal history of depression, would be associated with children's functional responses to negative maternal feedback in these same regions. Specifically, we predicted that children with a maternal history of depression would have significantly greater BOLD response in affective salience and striatal regions during maternal criticism, relative to children with no maternal history of depression. Furthermore, we predicted that children's subclinical

depressive symptoms (self- and maternal-reported) would be positively associated with BOLD response in these same brain regions during negative maternal feedback. Consistent with literature suggesting that depression is associated with diminished functional activity in regions relevant to emotion regulation (e.g., dlPFC, vlPFC, ACC) during exposure to criticism (e.g., Hooley et al., 2009; 2005), we further predicted that a maternal history of depression and children's own depressive symptoms would be associated with diminished BOLD response in these same brain regions.

To the best of our knowledge, this is the first study to use the MFC to understand the relationship between depression risk and neural response to valenced interpersonal feedback among never-depressed children. As noted earlier, previous work has focused on children and adults with a history of depression, limiting our understanding of whether neural functioning during this task marks preexisting risk for disorder. In contrast, research examining never-depressed youth is well suited to identifying potential neural mechanisms of risk. Thus, based upon previous research on children's neural responses during the MFC (Butterfield et al., 2020; Lee et al., 2014), we first examined the relationship between children's depression risk and neural response to maternal feedback using SVC within three *a priori* ROI. Brain regions implicated by prior research on interpersonal feedback (Butterfield et al., 2020; Lee et al., 2014) were combined into three *a priori* ROIs: (a) the bilateral amygdala, bilateral insula, and the sgACC were included in an affective salience ROI, (b) the bilateral dlPFC, bilateral vlPFC, and bilateral ACC were combined into an emotion regulation ROI, and (c) the bilateral caudate, bilateral putamen, and bilateral nucleus accumbens were merged into a reward-processing ROI. Additionally, exploratory whole-brain analyses were conducted following SVC analyses within the three ROI.

Materials and methods

Participants

Children and their mothers were recruited from a larger ongoing longitudinal study of children's depression risk and temperament development ($N = 409$) that began when children were 3-year-olds. Children with major medical or psychological problems were excluded from participation and all child participants were of typical cognitive development based on the Peabody Picture Vocabulary Test-Fourth Edition ($M = 113.21$, $SD = 14.31$; Dunn & Dunn, 2007). A subset of families from the larger sample was recruited an average of 7.52 years ($SD = 0.58$) later to participate in the current study. Child participants were oversampled for depression risk according to maternal depression history (MH+; Goodman et al., 2011), determined by Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-patient Edition (SCID-I/NP; First et al., 2002) data collected during previous waves of the study. Specifically, children were considered high- or low-risk for depression based on whether their mothers had a history of recurrent major depression ($n = 26$) or a single major depressive episode and an anxiety disorder ($n = 3$)¹. The latter group of children was included to increase our sample size and in light of the high heterotypic continuity and shared etiology between depression and anxiety (Cummings et al., 2014; Kendler et al., 2003), and the preponderance of familial anxiety among those with depression (and vice versa; Lawrence et al., 2019; Micco et al.,

¹We excluded specific phobia and social anxiety limited to public speaking in our definition given that these are less heritable, generally less impairing, and are likely weaker markers of children's risk for internalizing disorder (Kendler et al., 1992).

Table 1. Participant demographic variables

	MH–			MH+			Full Sample		
	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>
Child Sex (M/F)	–	–	31/24	–	–	14/12	–	–	46/36
Child Age (years)	11.16	0.51	55	11.02	0.84	26	11.12	0.63	81
PPVT Standard Score	114.11	14.84	54	111.35	13.24	26	113.21	14.31	80
CBCL-WD	0.89	1.31	53	2.19	2.35	26	1.32	1.81	79
YSR-WD	3.11	2.61	55	3.76	3.06	26	3.32	2.76	81
CDI	5.74	4.4	54	8.35	6.35	26	6.59	5.22	80
SR Response – Neutral MFC	3.59	0.74	54	3.76	0.88	25	3.65	0.79	79
SR Response – Critical MFC	2.64	1.01	55	2.81	1.02	26	2.69	1.01	81
SR Response – Praise MFC	4.62	0.71	55	4.42	0.86	26	4.56	0.76	81
Mean FD – Neutral MFC	0.20	0.08	55	0.19	0.07	26	0.19	0.08	81
Mean FD – Critical MFC	0.21	0.09	55	0.21	0.07	26	0.21	0.08	81
Mean FD – Praise MFC	0.22	0.09	55	0.23	0.07	26	0.22	0.14	81

Note. MH– = No maternal history of depression; MH+ = Maternal history of depression; PPVT = Peabody Picture Vocabulary Test; CBCL-WD = Child Behavior Checklist withdrawn-depressed subscale; YSR-WD = Youth Self-Report withdrawn-depressed subscale; CDI = Children's Depression Inventory 2nd Edition; SR Response = children's self-reported emotional response to MFC stimuli; FD = children's frame-wise displacement (mm).

2009). Of the 29 MH+ families, only two mothers met criteria for a current major depressive episode².

Two hundred and thirty-seven families were contacted (58 MH+) for participation in the current study. Six children were excluded due to contraindications to the MRI environment (e.g., metallic orthodontic work, metallic objects implanted in the body, or self-reported claustrophobia). Of the remaining 231 families, 102 agreed to participate, of which 82 participated in the MFC task in the scanner. There were no significant differences (p 's > 0.09) in demographic variables (e.g., sex, age of child, age of mother, or PPVT score) between those who participated in the study and those who were invited but did not participate. Of the 20 families who agreed to participate but did not contribute MFC data, four participants were unable to finish the MRI visit due to discomfort in the scanner, nine families declined to participate in the MRI portion of the study, and seven families discontinued participation in the current study before the MRI visit. Ultimately, 81 children contributed MRI data of sufficient quality to be analyzed. All children were screened for a personal history of mood disorder (see Procedures and Measures for details).³ The majority of child participants identified their race as White (96%), with one participant each identifying as Black, Hispanic/Latino, and Mixed Race. Modal family income was >\$100,000 CAD (5.1% <\$20,000 CAD; 10.1% \$20,000–\$40,000 CAD; 20.3% \$40,001–\$70,000 CAD; 27.8% \$70,000–\$100,000 CAD; 36.7% >\$100,000 CAD). The demographic data for this sample closely resembles the census data of the community from which it was drawn (i.e., London, Ontario; Statistics Canada, 2006). See Table 1 for an overview of additional demographic statistics of the final sample of 81 participants.

Procedures and measures

Data for this study were collected from children and their mothers across four separate assessment visits (for more details see Vandermeer et al., 2020). Briefly, this included: 1) a phone interview to complete the parent-report portion of the Kiddie Schedule

²Analyses did not change when excluding the two MH+ families with currently depressed mothers, nor when excluding the three MH+ children of mothers with a history of a single depressive episode and anxiety disorder.

³No children were excluded based on current or lifetime history of mood disorder.

for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997); 2) a home visit to complete the child self-report portion of the K-SADS-PL, gather MFC audio stimuli, and complete questionnaire measures; 3) a lab visit to complete the SCID-I/NP with moms and the Trier Social Stress Task for Children (Buske-Kirschbaum et al., 1997) with child participants (not discussed in this paper); 4) a MRI visit.

Semi-structured diagnostic interviews

All children and their mothers were administered structured clinical interviews by graduate students in clinical psychology trained by the senior author (EPH). To assess children's lifetime history of mental disorder, children and their mothers were interviewed using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). Based upon a randomly selected subsample ($N = 11$), all child diagnoses⁴ had 100% inter-rater agreement, including major depression.⁵ In previous studies using the larger sample from which our sample was drawn and other work from our group (Johnson et al., 2016; Mackrell et al., 2014; Sheikh et al., 2014), inter-rater reliability for clinical interviews has been excellent.

Mothers' lifetime history of mental disorder was assessed using the SCID-I/NP (First et al., 2002). All participating mothers had completed the same version of the SCID-I/NP several years prior in a previous wave of data collection; thus, the current SCID-I/NP interviews focused solely on the period of time since participants' previous SCID-I/NP. Similar to the K-SADS-PL, we assessed inter-rater reliability on a random subsample of our participants ($N = 10$). We had excellent inter-rater reliability for all specific diagnoses covered by the SCID-I/NP,⁵ including lifetime history of depressive episodes (Kappa = 1.00).

⁴In total, seven children had a lifetime history of a DSM-IV-TR diagnosis (primarily one of the anxiety disorders; $n = 7$; $n_{ADHD} = 3$; $n_{oppositional\ defiant\ disorder} = 2$). Only four children currently met criteria for a diagnosis.

⁵In the case of some K-SADS and SCID-I/NP diagnoses (e.g., K-SADS depression), no participant had a history of the disorder, precluding the calculation of Cohen's Kappa; however, interviewer agreement on the absence of the diagnosis was 100%.

Table 2. Maternal feedback challenge stimuli

Stimuli Valence	Sentence Stem
Neutral	"(Child's name), one thing I want to talk about is ..."
Praising	"(Child's name), one thing I really like about you is ..."
Critical	"(Child's name), one thing that really bothers me about you is ..."

Note. Sentence stems for each stimuli valence were standardized and mothers were instructed that they were to choose how to complete the sentences, drawing upon topics frequently discussed with their child. Recorded clips were edited to be exactly 30s in length.

Children's depressive symptoms

Children completed self-reported symptom measures, including the Children's Depression Inventory 2nd Edition (CDI; Kovacs, 2011; $\alpha = 0.83$) and the Youth Self-Report (YSR; Achenbach & Rescorla, 2001). Mothers were also asked to report on their child's symptoms by completing the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001). The withdrawn-depressed subscales of the YSR (YSR-WD; $\alpha = 0.72$) and the CBCL (CBCL-WD; $\alpha = 0.72$) were used as indices of child self- and mother-reported children's depressive symptoms, respectively.

Maternal feedback challenge

Maternal feedback challenge stimuli. During fMRI scanning, all children participated in a MFC task adapted from procedures outlined in Hooley et al. (2005). All MFC stimuli were created and collected during the home visit with the family in a quiet room in each participant's home, separate from the child participant. Mothers wrote two feedback stimuli for each of three affective valences for a total of six stimuli (i.e., two neutral, two critical, and two praising comments) for subsequent audio recording. Each of the three affective valence conditions started with a standardized sentence stem specific to that condition (Table 2). To enhance the validity of the task, mothers were told that they could give feedback on any topic they chose, as long as it was an issue frequently discussed with the child. For neutral stimuli, mothers were encouraged to select a topic that they believed their child "would be unlikely to feel strongly about, one way or another"; common topics chosen included the weather, grocery shopping, and other chores or errands for which the mother was responsible. The researcher collecting these stimuli ensured that there was sufficient material in each written statement for a 30s audio recording.

Mothers were then audio recorded using a NESSIE adaptive USB condenser microphone (Blue Microphones, Westlake Village, CA, USA) and Audacity (Version 2.1.2) while reading their valenced feedback statements. Raw audio tracks were then edited by trained graduate students to ensure all audio stimuli were exactly 30s in length (i.e., by cropping extended periods of silence from audio clips), had a maximum amplitude of -1.0 dB (using Audacity's "Amplify" effect), and a consistent dynamic range (using Audacity's "Compressor" effect with default settings). All audio stimuli were reviewed during the editing process to ensure that no essential content was lost and no audio artifacts were introduced during editing.

To ensure that the affective intensity of MFC stimuli was not systematically related to maternal history of disorder, two undergraduate research assistants blind to other study data rated all MFC audio stimuli for their "positivity" and "negativity" on a 10-point scale (1 = "Not at all" and 10 = "Very" positive or negative). Inter-

rater reliability between the two blinded raters was excellent (mean ICC = 0.934, SD = 0.065).

Maternal feedback challenge administration. Children were presented with their individualized MFC audio stimuli over MRI-safe in-ear headphones using E-prime 2.0 (Version 2.0.10.242) during whole-brain fMRI scanning. MFC stimuli were presented in a blocked design such that each of the three scanner runs consisted of two blocks of MFC stimuli of the same valence (i.e., one run each of: two Neutral, two Criticism, two Praise) interspersed with periods of rest (Figure 1). Children were instructed to listen to MFC stimuli while fixating their gaze on a black cross against a white background. Neutral MFC stimuli were always presented first, followed by praise and criticism trials, with the order of praise/criticism presentation counterbalanced across participants. Following each run, children were presented with a 5-point Likert-type rating scale of emotionally valenced cartoon faces (with "1" depicting a frowning "sad" face, "3" depicting an emotionally neutral face, and "5" depicting a smiling "happy" face) and asked to rate their emotional response to the previous run of MFC stimuli.

MRI acquisition

Consistent with best practices for scanning children (de Bie et al., 2010), children completed a "mock scan" session in a replica MRI system prior to participating in the MRI portion of the study. During the mock scan, the upcoming MRI session procedures were explained, and children were given the opportunity to ask questions.

Children's MRIs were obtained using a 3T Siemens Magnetom Prisma scanner with a 32-channel head RF coil (Siemens, Erlangen, Germany). Each of the three runs of the MFC task (i.e., one neutral run with two blocks of feedback, one praise run with two blocks of feedback, and one critical feedback run with two blocks of feedback) consisted of 89 T_2^* -weighted volumes collected using an echo-planar imaging (EPI) sequence ($3 \times 3 \times 3$ mm voxel size, repetition time [TR] = 1000 ms, echo time [TE] = 30 ms, field of view [FOV] = 210 mm) yielding 48 axial slices. T_1 -weighted anatomical scans were also acquired, for co-registration with the EPI series, using a 3D magnetization prepared rapid gradient echo sequence ($1 \times 1 \times 1$ mm voxel size, TR = 2300 ms, TE = 2.98 ms, FOV = 256 mm) yielding 192 sagittal slices per participant.

fMRI quality assurance and preprocessing

All raw DICOM scans were reviewed and converted into NIFTI format using MRICRON software (Rorden et al., 2007). Quality assurance and preprocessing were conducted using SPM12 (Version 7487; <http://www.fil.ion.ucl.ac.uk/spm>) and MATLAB 9.7 (Version 9.7.0.1247435; Mathworks, Inc., Natick, MA, USA). All quality assurance and preprocessing steps were performed separately according to functional run condition (i.e., neutral, critical, and praising feedback runs were preprocessed separately from one another). T_1 -weighted anatomical scans were manually reoriented to set the anterior commissure as the point of origin for all participants. The ArtRepair toolbox (Mazaika et al., 2005, 2009, 2007) was used as a quality assurance protocol. We used a modified batch script (i.e., MemoLab fMRI QA; Kurkela & Ritchie, 2017) in order to automate ArtRepair across multiple subjects. Specifically, ArtRepair was used to flag and interpolate (linear interpolation using the nearest unrepaired scans before and after a flagged scan) individual scans with frame-wise displacement (Power et al., 2012)

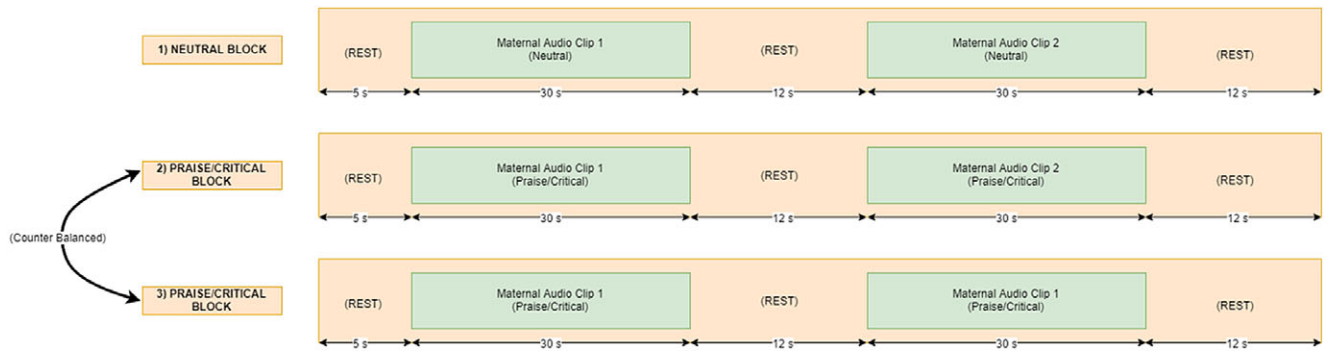


Figure 1. Maternal feedback challenge fMRI design.

threshold of > 0.9 mm (Siegle *et al.*, 2014) or frame-wise global signal intensity threshold $> 1.3\%$ deviation from the mean (default setting from Kurkela & Ritchie, 2017). Scanner runs with excessive repair (i.e., $\geq 20\%$ [18 TR]) or where mean frame-wise displacement was > 0.9 mm were dropped from further analyses.⁶ Preprocessing included realignment to a mean image, co-registering functional data to T_1 -weighted anatomical scans in a standardized MNI space with $2 \times 2 \times 2$ mm voxels, and spatial smoothing using a three-dimensional 6 mm full width at half maximum (FWHM) Gaussian smoothing kernel. Registration was manually checked by comparing participants' mean functional images with T_1 -weighted anatomical scans.

Data analyses

fMRI data analyses

SPM12 was used to analyze all fMRI data. All fMRI analyses included children's age and sex as covariates. All analyses of the MFC fMRI data were modeled using mixed effects models in which individual children's data were first modeled using a fixed effects model (i.e., Level 1) before modeling group differences and regressions using a random effects model (i.e., Level 2).

Level 1: intra-individual analyses

A first-level, fixed effects multiple regression was used to model functional responses of individuals. Neutral, Praise, and Critical MFC conditions were modeled separately at this stage using a canonical hemodynamic response function (Poldrack *et al.*, 2011). Motion parameters (three translational and three rotational, per scanner run) were treated as covariates in these analyses (Jahn, 2019; Poldrack *et al.*, 2011). Main effects of each of the three MFC conditions were modeled by contrasting activity during MFC stimuli presentation with functional activity during the resting portion of the MFC task (e.g., Neutral vs. Rest, Praise vs. Rest, and Criticism vs. Rest).

Level 2: group and regression analyses

At Level 2, a 2×3 factorial ANOVA was conducted to examine differences in functional response to the MFC (as modeled at Level 1) according to maternal depression history, modeled as a between-subjects factor; MFC stimuli condition was modeled as a within-subjects factor. Similarly, random effects regression analyses were modeled to test associations between children's self- (i.e., CDI and YSR-WD) and mother-reported (i.e., CBCL-WD) depressive

⁶Only two participants' scan runs were dropped. One participant's neutral stimuli scans were dropped due to excessive repair and another participant's praise scans were dropped due to high mean frame-wise displacement.

symptoms, and BOLD activity modeled at level one (Jahn, 2019). Children's sex and age were included as covariates in all level-two analyses. Participant counterbalancing of MFC stimuli presentation order were also entered as covariates; however, given that counterbalancing did not meaningfully alter results, this variable was dropped in final analyses to retain statistical power.

Results of Level 2 analyses were first interpreted using SVC to constrain analyses within three *a priori* regions of interest (ROI; Nieto-Castanon *et al.*, 2003), chosen based on previous research on interpersonal feedback (Butterfield *et al.*, 2020; Lee *et al.*, 2014). Although SVC requires less stringent corrections for multiple comparisons relative to whole-brain analyses, this is only problematic in scenarios where SVC analyses are conducted based upon *posteriori* hypotheses (i.e., an effect identified at the whole-brain level does not survive corrections and is then used to guide selection of ROI for SVC analyses). Given our *a priori* approach, the less stringent multiple comparison correction is appropriate in the current study; Nieto-Castanon *et al.*, 2003). The three ROI were composed of brain regions relevant to cognitive processes related to interpersonal feedback. Anatomical regions were combined into three ROI based on their putative functional role and to reduce the total number of comparisons being conducted. These included: (a) an affective salience ROI (bilateral amygdala, bilateral insula, and the sgACC); (b) an emotion regulation ROI (bilateral dlPFC, bilateral vlPFC, and bilateral ACC); and (c) a reward-processing ROI (bilateral caudate, putamen, and nucleus accumbens). All ROIs were anatomically defined using the WFU PickAtlas (Maldjian *et al.*, 2004; 2003), and the Automated Anatomical Labeling atlas 3 (AAL; Rolls *et al.*, 2020) and Talairach Daemon (TD; Lancaster *et al.*, 1997, 2000) atlases (see Supplemental table for definitions of ROI in which SVC analyses were conducted). Finally, exploratory whole-brain analyses were conducted. Based on recommendations by Woo *et al.* (2014) all analyses were conducted using cluster-extend thresholding with a voxel-wise threshold of $p < 0.0001$ and a cluster-level significance threshold of $p < 0.05$ (family-wise error corrected) both during SVC analyses and whole-brain level of analysis.

Results⁷

MFC stimuli

Indicating that children responded to the MFC stimuli as intended, there was a significant effect of MFC condition on children's

⁷Although no child participant had a lifetime depression history based on the K-SADS-PL (lifetime or current), three ($N_{MH+} = 2$) had CDI scores above the suggested cutoff (> 19) for clinically significant symptoms in a community sample (Kovacs, 2011); excluding these participants from analyses did not change the pattern of results.

self-reported emotional response for the three conditions, $F(1.77, 138.23) = 120.18, p < 0.001$. Post hoc analyses by pairwise t tests found that children experienced neutral stimuli ($M = 3.65, SD = 0.78$) as more positive than critical stimuli ($M = 2.69, SD = 1.01; t(78) = 7.73, p < 0.001$), praise stimuli were experienced as more positive than neutral stimuli ($M = 4.56, SD = 0.76; t(78) = -9.29, p < 0.001$), and praise stimuli as more positive than critical stimuli ($t(80) = 13.19, p < 0.001$). Independent t -test analyses of MFC “positivity” and “negativity” rated by two blinded undergraduate research assistants found that feedback stimuli did not differ according to maternal history of depression (all $p > 0.21$; see Supplemental Table 2 for details). Additionally, blinded research assistants also rated praise stimuli as significantly more positive than critical stimuli ($t(77) = 71.69, p < 0.001$) and critical stimuli were rated as significantly more negative than praise stimuli ($t(77) = -34.80, p < 0.001$).

Correlations among major study variables

See Table 3 for bivariate correlations among all major study variables. All continuous measures of depressive symptoms (i.e., CDI, CBCL-WD, and YSR-WD) were positively associated with one another. Children with a maternal history of depression had higher CDI and CBCL-WD scores than children without a maternal depression history, although they did not differ in YSR-WD scores. CDI and CBCL-WD scales were negatively associated with children’s self-reported emotional response to MFC praise stimuli (i.e., as children’s self- and parent-reported depressive symptoms increased, maternal praise stimuli were rated less positively); however, children’s self-reported emotional responses to MFC neutral and critical stimuli were unrelated to either measure of children’s depressive symptoms. Children’s self-reported emotional responses to MFC stimuli did not differ based on maternal depression history for any of the three conditions (all $p > 0.05$). Movement in the scanner (operationalized as mean frame-wise displacement, in mm) was strongly associated within individuals across MFC trials and was negatively correlated with age. Importantly, average scanner movement did not differ across maternal risk group nor was it associated with any of the symptom measures (i.e., CDI, CBCL-WD, or YSR-WD) for any of the MFC conditions.

MFC fMRI results

Small volume correction analyses

Factorial ANOVA found no main effects of maternal depression history, MFC stimuli condition, nor interactive effects between the two factors during SVC analyses.

SVC analyses identified a number of voxel clusters that were significantly related to children’s self-reported depressive symptoms (CDI scores). Specifically, during maternal criticism trials (i.e., negative interpersonal feedback), children’s self-reported CDI scores were negatively related to BOLD activity in the affective salience ROI (i.e., left AI; Table 4; Figure 2A) and the reward-processing ROI (i.e., right putamen; Table 4; Figure 2B); both the AI and putamen have been previously linked to depressogenic processes (e.g., Dedovic et al., 2014; Gotlib et al., 2010; He et al., 2019; Thomas et al., 2011). No other voxel clusters were related to any of the other independent variables (i.e., CBCL-WD, or YSR-WD) based on SVC analyses of a *priori* ROI.

Whole-brain analyses

Similar to results during SVC analyses, ANOVA showed no main effect of maternal depression history during whole-brain analysis. Although there was a significant within-subjects effect⁸ (i.e., MFC stimuli condition), we found no evidence of an interaction between the two factors (i.e., maternal depression history and MFC stimuli condition).

Exploratory whole-brain analyses showed that BOLD activity in a cluster of voxels largely comprised of the left inferior frontal gyrus (Table 4; Figure 2C) was related to children’s CDI scores during the maternal praise condition. Specifically, while listening to maternal praise, children with higher self-reported depressive symptoms had greater BOLD activity within a portion of the left inferior frontal gyrus, a region previously implicated in language comprehension (Liakakis et al., 2011) and inner dialog (Morin & Hamper, 2012; Morin & Michaud, 2007). No other significant voxel clusters were identified using whole-brain analyses.

Discussion

Past work has explored the relationship between depression and neural responses to parental and other interpersonal feedback in both adults and adolescents with a history of, or current, depression. To better understand children’s neural reactivity to maternal feedback prior to the development of depression, we examined never-depressed children’s functional brain response during positive (i.e., praise) and negative (i.e., criticism) feedback from their mother. To our knowledge, this is the first study to investigate indices of children’s risk for depression using an ecologically valid maternal feedback task in youth with no personal history of depression. Children’s BOLD response to maternal feedback stimuli did not differ according to maternal depression status using either SVC within a *priori* ROI or whole-brain analyses. However, children’s depressive symptoms were related to neural responses to maternal criticism following SVC analyses of brain regions involved in emotional and reward/punishment processing. In addition, exploratory whole-brain analyses identified a relationship between children’s depressive symptoms and functional activity in the left inferior frontal gyrus during maternal praise stimuli.

Contrary to our hypotheses, children’s functional activity did not differ during either the maternal praise or criticism trials based on a maternal history of depression. This contrasts with previous reports of significant differences in BOLD activity of limbic and prefrontal regions during maternal feedback for both adults and adolescents with personal histories of depression (Hooley et al., 2009; 2005; Silk et al., 2017). Specifically, Hooley et al., (2009; 2005) found that, relative to healthy controls, adults who had recovered from depression showed increased BOLD response in the amygdala and diminished BOLD activity in the dlPFC and ACC in response to maternal criticism. This suggests that maladaptive brain activity during maternal criticism that persists *after* recovery from depression (Hooley et al., 2009; 2005; Silk et al., 2017) may be a lasting consequence of depression itself (i.e., a scarring effect) rather than a preexisting risk factor. Importantly, given the focus of our study, none of our child participants had current or previous diagnoses of depression and children’s depressive symptoms were generally relatively low, as one would expect in a community-based sample of never-depressed children. If past work showing increased Amygdala, and diminished dlPFC and ACC activity in response to maternal criticism (Hooley et al., 2009;

⁸As the main effect of the within-subjects factor was not relevant to our study aims, it is not discussed further here.

Table 3. Correlations among study variables

Variable	1	2	3	4	5	6	7	8	9	10
1. Maternal Depression History	–									
2. Sex	.02	–								
3. Age	–.11	.13	–							
4. CDI	.24*	.04	–.20	–						
5. CBCL-WD	.34**	.17	–.17	.49**	–					
6. YSR-WD	.11	–.09	–.21	.66**	.47**	–				
7. SR Response – Neutral MFC	.10	.06	.07	–.05	–.06	–.08	–			
8. SR Response – Critical MFC	.08	.00	–.29**	–.01	–.10	–.03	.24*	–		
9. SR Response – Praise MFC	–.12	.07	.05	–.27*	–.28*	–.14	.28*	–.02	–	
10. Mean FD	–.01	–.06	–.36**	.03	–.04	.06	–.01	.01	.02	–

Note. * = $p < 0.05$. ** = $p < 0.01$. Maternal Depression History was dummy coded such that 0 = no and 1 = yes; CDI = Children's Depression Inventory, 2nd Edition; CBCL-WD = Child Behavior Checklist withdrawn-depressed subscale; YSR-WD = Youth Self-Report withdrawn-depressed subscale; SR Response = children's self-reported emotional response to MFC stimuli; mean FD = children's mean frame-wise displacement across all three runs (mm).

2005; Silk *et al.*, 2017) is a *consequence* of depression, our nonsignificant findings may be driven by the fact that depressive symptoms are low in our sample, which is notably younger than those in previous studies of adolescent and adult participants. Thus, it is also possible that the pattern of brain activity reported by Hooley *et al.*, (2009; 2005) and Silk *et al.* (2017) does not emerge until later in development. Continued longitudinal study of this sample will allow us to determine whether similar BOLD patterns (i.e., Hooley *et al.*, 2009; 2005; Silk *et al.*, 2017) emerge later in development and presage depression (i.e., a marker of risk) or only emerge following onset of depression (i.e., scarring). In addition, it is possible that publication bias has led to artificially inflated effect sizes in the literature, contributing to difficulty in replication.

It is important to note that children's neural activity in the current study was associated solely with their self-reported symptoms of subclinical depression. Previous research has found that, even when well below the threshold needed for diagnosis, depressive symptoms are longitudinal predictors of risk for depressive disorder (e.g., Bertha & Balázs, 2013; Brennan *et al.*, 2002; Cuijper & Smit, 2004; Fergusson *et al.*, 2005; Goodman *et al.*, 2011; Klein *et al.*, 2005; Wesselhoeft *et al.*, 2013). In contrast, we did not find associations between maternal depression history and youths' brain function. Importantly, children in our study were extensively assessed to ensure none had ever experienced depression, suggesting that the patterns of neural reactivity reported are detectable outside of the context of clinically significant depression. While replication of our findings is needed, they may inform continued efforts toward identifying neural markers of emerging depressive

symptoms, which could potentially prove useful in the development of early identification, prevention, and intervention efforts.

Children's self-reported subclinical depressive symptoms were negatively associated with brain activity in the left AI and right dorsal striatum (DS) (i.e., right putamen) during maternal criticism, suggesting this pattern of BOLD activity marks subclinical depression. The insula has an array of functional roles, including (but not limited to) attention, decision-making, music and time perception, and awareness of bodily movement and sensations (Chang *et al.*, 2013; Craig, 2009; Gasquoin, 2014); however, a convergence of contemporary research suggests the AI also has a primary role in the cognitive representation and processing of subjective feelings and emotions (Chang *et al.*, 2013; Craig, 2009). This is consistent with fMRI literature on interpersonal feedback showing that the AI tends to be more active during processing of negative interpersonal feedback (e.g., social rejection) in healthy participants (Cacioppo *et al.*, 2013) and has greater activity in groups with depression during negative interpersonal feedback (Jankowski *et al.*, 2018; Kumar *et al.*, 2017; Mellick, 2017; Yttredahl *et al.*, 2018). In contrast, others have found that subclinical depressive symptoms are associated with *diminished* AI activity in response to negative interpersonal feedback (e.g., social rejection and social-evaluative threat; Dedovic *et al.*, 2014; He *et al.*, 2019). Taken together with the current findings, these studies suggest that, while depression is associated with increased AI BOLD response to negative social information, healthy individuals at risk for depression (i.e., never-disorder individuals with subclinical depressive symptoms) demonstrate a diminished AI BOLD

Table 4. fMRI regression analysis results based on relationship to CDI scores

Contrasts			Peak Voxel MNI Coordinates					Anatomical Region	<i>k</i>	<i>p</i> _{FWE}
Level 1	Level 2	ROI	<i>F</i>	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>			
Main Effect of Praise	CDI +	Whole-Brain	21.65	4.19	-34	12	26	Left inferior frontal gyrus	38	.046
Main Effect of Criticism	CDI -	ASN	24.86	4.48	-36	10	4	Left AIC	21	.008
		RN	22.69	4.29	32	2	-8	Right putamen	6	.029

Note. All values refer to two-tailed regression analyses. All analyses included six motion parameter time courses (three translational and three rotational, per scanner run), children's age, and children's sex as covariates. CDI = Children's Depression Inventory; + = positive relationship; - = negative relationship; ASN = affective salience network ROI; RN = reward network ROI; *p*_{FWE} = family-wise error corrected *p* value.

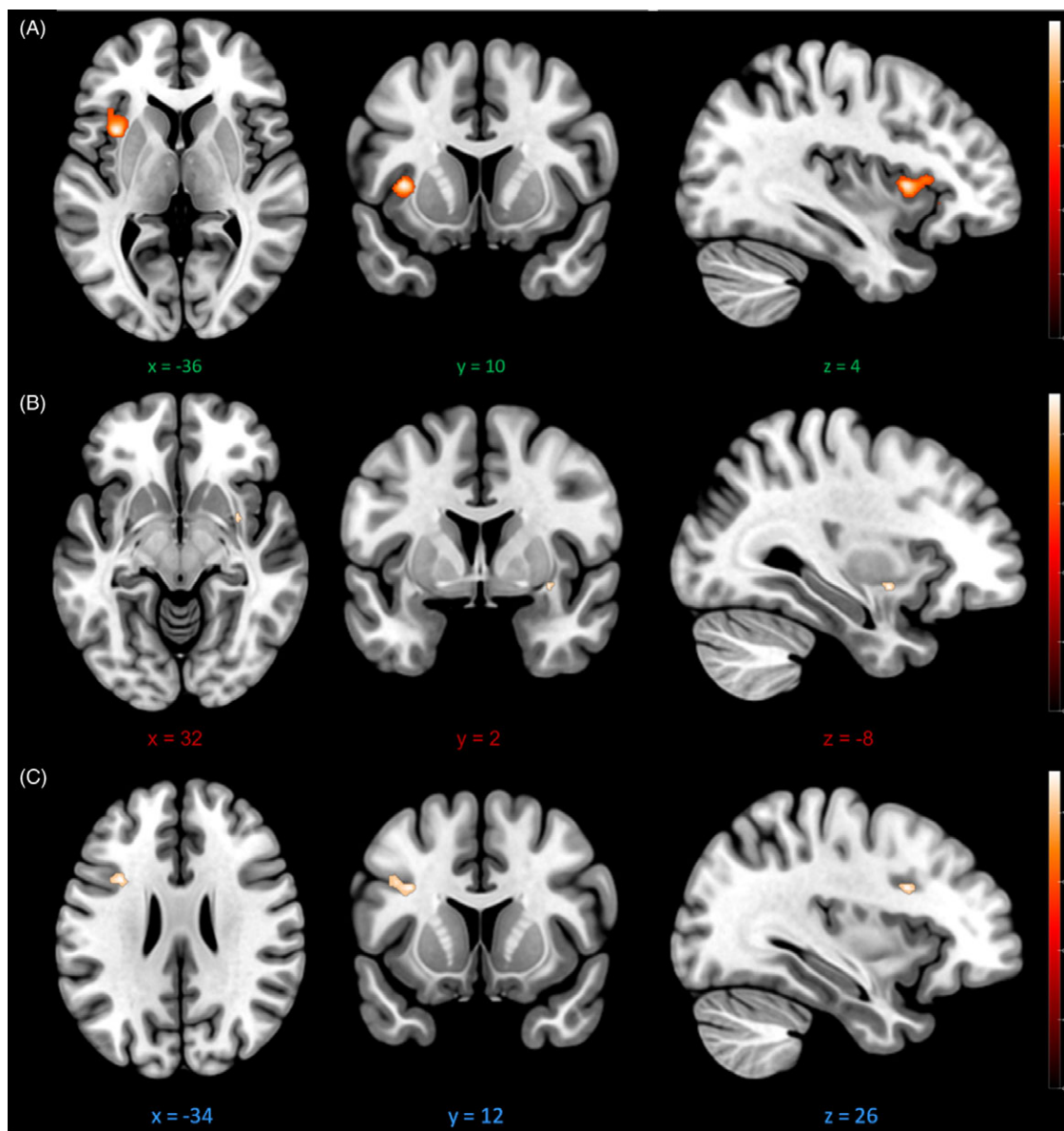


Figure 2. (A) a priori ROI analysis (affective salience ROI) shows that children's subclinical depressive symptoms (Children's Depression Inventory scores) are negatively associated with BOLD activity in the left anterior insula during maternal criticism. Significant cluster ($k = 21$, $p_{FWE} = 0.008$) highlighted in green. (B) a priori ROI analysis (reward network ROI) shows that children's subclinical depressive symptoms (Children's Depression Inventory scores) are negatively associated with BOLD activity in the right putamen during maternal criticism. Significant cluster ($k = 6$, $p_{FWE} = 0.029$) highlighted in red. (C) Exploratory whole-brain analysis shows that children's subclinical depressive symptoms (Children's Depression Inventory scores) are positively associated with BOLD activity in the left inferior frontal gyrus during maternal praise. Significant cluster ($k = 38$, $p_{FWE} = 0.046$) highlighted in blue.

response to negative social information. As noted above, subclinical depressive symptoms are known predictors of risk for depressive disorder. Ongoing research with this sample has the potential to determine whether identified patterns of neural activity while processing maternal criticism are true prospective markers of depressive risk (i.e., indicative of vulnerability to depression).

Our results are consistent with previous findings that, even in the absence of disorder, depressive symptoms are associated with neural processing of negative social information by the AI (Dedovic *et al.*, 2014; He *et al.*, 2019). This could reflect the early emergence of neurobiological risk for depression characterized by maladaptive processing of interpersonal feedback, ultimately contributing to dysfunction in interpersonal relations. We speculate that this may be related to well-established findings that interpersonal and social skills deficits both predict, and are predicted by, depression (e.g., Eberhart & Hammen, 2006; Monroe *et al.*, 1999; Segrin, 2000). Although our results bolster existing evidence for aberrant patterns of AI activity in both subthreshold and clinical depression, the reasons for the inconsistent directionality of this relationship is unclear. While speculative, risk associated with hypoactivation of the AI, a core structure in salience detection (Uddin, 2015), may limit the capacity to attend to and process negative social information. This may, in turn, contribute to subsequent challenges in interpersonal functioning and an increased risk for depression (Eberhart & Hammen, 2006; Monroe *et al.*, 1999; Segrin, 2000). Continued deficits in interpersonal functioning, in the context of the dysphoria associated with the onset of clinically significant depression, may then potentiate salience of negative social information, accounting for the inconsistency in patterns between at-risk and depressed populations.

Future research aimed at explaining this inconsistency should directly compare AI response in samples at risk for and with current depression. It is important to note that, in contrast to our young sample, most studies reporting on AI activity during social feedback (e.g., Dedovic *et al.*, 2014; He *et al.*, 2019; Jankowski *et al.*, 2018; Kumar *et al.*, 2017; Mellick, 2017; Yttredahl *et al.*, 2018) have studied older adolescents or adults. Ongoing longitudinal study of our sample is well positioned to examine whether onset of depression during adolescence/early adulthood is associated with a subsequent shift to patterns of increased AI response to negative interpersonal feedback. Similarly, focusing on AI activity and salience detection of negative social information, as it relates to changes in depression status longitudinally, is necessary to help explain inconsistent patterns in AI activity between at-risk and depressed samples. Regardless, our findings suggest that neural mechanisms for depressive risk may be present in the years preceding onset of depression, possibly contributing to deficits in interpersonal functioning and social skills deficits.

In addition to the negative relationship between depression risk and AI BOLD activity during maternal criticism, we also found a negative association between children's subclinical depressive symptoms and BOLD activity in the right striatum. The striatum is a set of subcortical structures with a central role in the processing of affective stimuli (including rewarding and punishing stimuli; Delgado, 2007) and motor activity (Grillner *et al.*, 2005). Although not entirely distinct, these functional roles are typically thought to be separated along structural subdivisions, with the VS more heavily involved in processing affective stimuli (e.g., rewarding and punishing stimuli) and the DS responsible for motor activity (O'Doherty *et al.*, 2004). The bulk of extant literature has focused on the relationship between reward-related striatal activity, mainly in the VS, finding that depression is associated with

diminished striatal response to reward (e.g., Keren *et al.*, 2018); however, our analyses identified a cluster of voxels in the right DS (i.e., the putamen) where the BOLD response was negatively associated with children's subclinical depressive symptoms during critical maternal feedback. Although not specific to critical maternal feedback, a number of studies have identified depression and depression risk-associated decreases in putamen activity in response to negative stimuli (including negative social information). Thomas *et al.* (2011) found that remitted depression was associated with diminished putamen activity during exposure to negative social cues (e.g., sad faces). Similarly, Gotlib *et al.* (2010) found that loss of monetary reward was associated with a diminished putamen response among those at high familial risk for depression. Finally, during negative social interactions, trait neuroticism (a well-established risk factor for depression; Goldstein & Klein, 2014) was negatively associated with putamen response (Servaas *et al.*, 2015). These studies suggest that negative and aversive stimuli are associated with diminished putamen activity among those at risk for depression, in the context of depressive disorder, and even following recovery from depression. These findings, combined with our own, suggest that diminished putamen response to negative stimuli (including social information) may mark depression risk.

As described above, the DS (including the putamen) is implicated in numerous cognitive functions; however, previous research and theory has focused on its role in goal-directed behavior, decision-making processes (including selection and initiation of behavioral actions), and stimulus-response learning (Balleine *et al.*, 2007; Haruno & Kawato, 2006). Whereas a healthy response to critical social feedback may include engaging in constructive behaviors with an aim of reducing future criticism (e.g., changing behavior that is viewed negatively by others), our findings show that, as depressive symptoms increase, functional activity in brain regions responsible for recruiting such behaviors (i.e., the DS/putamen) *decreases* during exposure to negative social stimuli. A diminished ability to respond adaptively to negative feedback may reflect children's emerging depression risk. Morgan *et al.* (2019) study of never-depressed 6- to 8-year-olds at high familial risk for depression found lower DS activity during rewarding social stimuli was associated with decreased reward-seeking activity. Although we did not measure reward-processing or goal-directed behavior in the current study, our findings complement these studies, suggesting that diminished DS activity in the context of depression risk may be related to decreases in goal-directed behavior.

In addition to the aforementioned SVC results, exploratory whole-brain analysis found CDI scores were positively associated with BOLD activity in a cluster of voxels largely comprised of the opercular and triangular portions of the left inferior frontal gyrus during maternal praise trials. There is little research on the role of the left inferior frontal gyrus during interpersonal feedback; however, the importance of the left inferior frontal gyrus in speech production and comprehension (the left inferior frontal gyrus contains Broca's area) is well established. In addition to its primary role in speech, and like many other regions in the brain, numerous other functional roles have been suggested for the left inferior frontal gyrus (e.g., language processing, working memory, fine motor control, empathy; Liakakis *et al.*, 2011). Some research (Morin & Hamper, 2012; Morin & Michaud, 2007) indicates that the left inferior frontal gyrus is activated during self-reflection tasks due to the private, internal dialog that occurs when processing abstract information related to the self (e.g., emotions, personality, etc.). The valenced MFC stimuli children heard while in the scanner

(i.e., personalized maternal praise and criticism directed toward children) may account for the activation of the left inferior frontal gyrus; however, why this activity was related to children's depressive symptoms is unclear. It may be that children with higher self-reported depressive symptoms find it more challenging to process the relevance of positive self-relevant information, if it is inconsistent with their self-views. Processing what is perceived as incongruent information in turn leads to cognitive interference, generating activation in the left inferior frontal gyrus. Indeed, we previously found that children at high risk for depression had greater activation in similar regions when processing positive self-referential adjectives, in this same sample (Liu et al., 2020).

Although no relationship was found between children's depressive symptoms and their self-reported emotional response to either MFC neutral or critical stimuli, both CDI and CBCL-WD were negatively associated with children's self-reported emotional response to MFC praise stimuli. Specifically, as self- and maternal-reported depressive symptoms increased, children's self-reported emotional response to MFC praise stimuli became less positive. While behavioral responses to the maternal stimuli were not a focus of the current study, these findings are consistent with previous research findings suggest that depression is associated with attenuated emotional response to affectively positive stimuli (Bylsma et al., 2008). Further, at least some of this diminished emotional positivity may be related to the aforementioned pattern of increased functional response to praise in the left inferior frontal gyrus (and potential increased self-talk). Examining how behavioral and neural responses to maternal feedback are related to one another and to depression over time is an important next step for this line of research.

Findings from our fMRI analyses differed depending on which depressive symptom scale was used, with most of our significant results related to children's self-reported symptoms (i.e., the CDI). In contrast, associations between children's brain activity and both YSR-WD and CBCL-WD scales were nonsignificant in all *a priori* SVC analyses, with one small effect found for CBCL-WD during exploratory whole-brain analysis of maternal praise. At least some of the variability in our results may be due to differences in the content of the three scales used. Of the three, the CDI was the only self-report instrument designed to assess children's depressive symptoms specifically. Both the CBCL-WD and YSR-WD are subscales derived from larger instruments designed to capture a broad array of mental health and behavior problems (i.e., the CBCL and YSR) and both emphasize low mood and social withdrawal, rather than the depressive syndrome specifically. Thus, our findings may be most relevant to brain function as it pertains to depression relatively narrowly defined. In addition, maternally reported child depressive symptoms are known to show poor convergence with child self-report (De Los Reyes & Kazdin, 2005) and may be capturing more observable depressive symptoms, which may be less relevant to interpersonal feedback and related neural activity than depressive symptoms as experienced and reported by children.

Our study had a number of strengths including its examination of high-risk youth without a depression history themselves, a strategy that is better equipped to speak to neural risk mechanisms, compared to the bulk of previous work studying adults or older adolescents with a personal history of depression. By relating functional activity to established markers of risk in rigorously screened, healthy, never-depressed children, prior to the typical age of onset for depression, we were able to better identify functional associations with depressive symptoms that may precede disorder.

Additionally, use of a community-based sample of families, rather than recruiting solely from clinical sources, may increase generalizability of our findings to typically developing youth. Instead of relying on artificial feedback from pseudoparticipants, as in the majority of interpersonal feedback investigations, the MFC task (Hooley et al., 2005) allowed us to understand risk-associated differences in brain function using a far more ecologically valid operationalization of interpersonal feedback and mother-child interactions. To the best of our knowledge this is the first study to use such stimuli to understand depression risk processes in never-depressed children. Finally, we used standardized semi-structured clinical interviews (SCID-I/NP and K-SADS-PL) to assess for personal history of mental disorder among mother and child participants, respectively. This allowed us to ensure that children's risk for depression was not confounded by personal history of depressive disorders, and that risk due to maternal depression history was based on the gold standard assessment of mental disorder.

In addition to the aforementioned strengths, our study also had some important limitations. First, the cross-sectional nature of our data precludes conclusions regarding causal relationships between neural reactivity and depressive symptoms. Although we have conceptualized children's depressive symptoms as an index of risk for future depressive disorder, we do not yet know whether the patterns of neural reactivity associated with children's symptoms will ultimately be associated with future diagnoses. While our findings highlight brain regions that may be important to children's depression risk, effects were generally small, and our participants reported relatively low depressive symptoms. Further study of this sample as they enter the age of risk for greater depressive symptoms and disorder is necessary to better establish links between neural reactivity and depression. Similarly, investigation of child participants with greater variability in depressive symptoms would be a useful complement to the current research. Additionally, despite thorough investigation of both children and mothers' mental health history, we did not collect data on other family members' (e.g., siblings, fathers, grandparents, etc.) history of depression. We chose to focus on maternal history of depression as it is especially relevant to children's depression risk (Connell & Goodman, 2002; Klein et al., 2005); however, more extensive characterization of family history should be explored in future study. Furthermore, we did not collect data on children's pubertal development. While we attempted to control for this by including age as a covariate in all imaging analyses, given both the age of our sample and relationships between pubertal status and depression onset (Angold & Costello, 2006), future studies should account for pubertal status when assessing the relationship between depressive risk and fMRI response to maternal feedback. Inter-rater reliability for diagnostic interviews were based on a relatively small subsample (e.g., $N_{SCID} = 10$ and $N_{K-SADS} = 11$) of participant families for whom audio recordings of clinical interviews were acquired. Consistent with previous reports of inter-rater reliability for clinical interview data published by our group on this and other samples (Johnson et al., 2016; Mackrell et al., 2014; Sheikh et al., 2014), we were able to demonstrate excellent inter-rater reliability for children and mothers' diagnoses; however, future studies should aim to use a larger subsample for determining inter-rater reliability, as per Saito et al. (2006). Finally, although the participants in our study are demographically representative of the region from which they were recruited (i.e., London, Ontario; Statistics Canada, 2006), the relative lack of diversity is an important limitation. It is crucial that future efforts focus on testing our findings

in more culturally, ethnically, and socioeconomically diverse samples.

Conclusion

To the best of our knowledge, this is the first fMRI study of depression risk in never-depressed children to use the MFC to explore depression-associated differences in processing maternal praise and criticism. We found that children's risk for depression, characterized by subclinical depressive symptoms, was related to brain activity during processing of personally relevant interpersonal feedback from an important caregiver (e.g., mothers). In particular, depression risk is associated with diminished functional activity in regions responsible for salience detection (i.e., the AI) and goal-directed behavioral responding (i.e., putamen) during negative social feedback (i.e., maternal criticism). Reduced responding in the regions during processing of negative social information may contribute to depression vulnerability by reducing one's ability to effectively attend to and respond to information.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0954579422000840>.

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Conflicts of interest. None.

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