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Associations between childhood irritability and neural reactivity to maternal feedback in adolescence

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ABSTRACT

Early irritability, a transdiagnostic vulnerability for psychopathology, is associated with alterations in neural reactivity to emotional stimuli and reward; however, associations between childhood irritability and neural markers of risk may be mitigated by the quality of caregiving youth receive. We examined longitudinal relationships between irritability in childhood and young adolescents' neural activity of regions typically associated with emotion regulation and reward processing during processing of maternal feedback and tested whether these associations were moderated by youth's perceptions of the parent-child relationship quality. Eighty-one adolescents ($M_{age} = 11.1$ years) listened to maternal critical and praising feedback while undergoing functional magnetic resonance imaging. Age 3 irritability, assessed observationally, was negatively associated with age 11 neural reactivity to maternal criticism in a cluster in the right dorsolateral prefrontal cortex (dlPFC), particularly for youths who reported more positive maternal parenting. Given the role of the dlPFC activation in the effortful processing of emotional stimuli, decreased activation may reflect disengagement from negatively valenced interpersonal feedback in the context of a positive caregiving environment, thereby mitigating psychopathology risk associated with irritability.

1. Introduction

Irritability reflects a proneness to anger and frustration, and is characterized by behaviors such as chronic ill-tempered mood, frequent temper outbursts, and context-inappropriate anger (Brotman, Kircanski, & Leibenluft, 2017; Copeland, Brotman, & Costello, 2015; Dougherty et al., 2013; Mohamed Ali et al., 2021). Persistent and severe irritability is a core symptom of several psychiatric disorders, including oppositional-defiant disorder and major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; *DSM-5*). Emerging work further suggests that normative variations in early irritability are linearly associated with later outcomes, with greater irritability predicting increasing impairment and greater risk for psychopathology (Beauchaine & Tackett, 2019; Copeland et al., 2015; Wakschlag et al., 2015). Although heritable neurobiological mechanisms have been implicated in the pathophysiology of irritability

(Brotman, Kircanski, & Leibenluft, 2017; Riglin et al., 2017; Stoddard et al., 2014; Wiggins et al., 2016), environmental factors such as parenting also influence the trajectory of children's irritability and its associations with outcomes across development (Ezpeleta, Penelo, de la Osa, Navarro, & Trepal, 2019; Ravi et al., 2022). Thus, both endogenous (i.e., within-child) and exogenous factors play a role in the development of irritability and associated maladjustment.

Past work examining irritability has focused almost exclusively on its association with psychopathology, overlooking more proximal indicators of dysfunction (i.e., endophenotypes) that could shed light on the mechanisms that contribute to the continuity of irritability across development. For example, irritability is linked to abnormalities in the functional activity of brain regions involved in processing reward and threat, as well as those implicated in top-down emotion regulation (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013; Leibenluft, 2017; Nielsen, Wakschlag, & Norton, 2021; Perlman et al.,

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2015; Wiggins et al., 2016). Relevant research shows that, relative to typically developing children, clinically irritable youths display increased activation of the anterior cingulate cortex (ACC) during reward processing, but reduced activation in response to blocked goal attainment (Brotman et al., 2017). Clinically irritable children also show reduced activation of the amygdala, striatum, and cortical regions during frustrative non-reward tasks (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013). As such, a heightened neural sensitivity to reward and deficits in top-down regulation of emotion that manifest as pronounced negative responses to non-reward may underlie the frequent temper outbursts and context-inappropriate expressions of anger that characterize clinically significant irritability (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013; Perlman et al., 2015). In addition, irritable youth exhibit atypical patterns of amygdala activation in response to ambiguous faces compared to healthy controls, a finding suggestive of a tendency to interpret ambiguous social stimuli as hostile (Leibenluft, 2017; Wiggins et al., 2016). Similarly, irritable youth show decreased functional connectivity between prefrontal and limbic regions in response to angry faces, consistent with deficits in emotion regulation during threat processing (Stoddard et al., 2017), which may underlie manifestations of irritability in social contexts (Deveney, Stoddard, et al., 2019). Together, these findings implicate abnormalities in neural reactivity to reward and deficits in cognitive control of emotion in clinically significant irritability.

Consistent with a dimensional perspective of trait-symptom associations, a small body of work finds alterations in neural function in healthy, typically developing children with elevated early irritability (Beauchaine & Tackett, 2019; Copeland et al., 2015; Wakschlag et al., 2015). Indeed, these studies find atypical patterns of activation in fronto-striatal regions during cognitive control and reward tasks associated with irritability. For example, parent-reported irritability in otherwise healthy preschool children was associated with greater functional activity of the dorsolateral prefrontal cortex (dlPFC) during inhibitory control tasks (Fishburn et al., 2019; Grabbell et al., 2019; Li, Grabbell, Wakschlag, Huppert, & Perlman, 2017). In addition, Dougherty and colleagues (2018) found that irritability in typically developing children was associated with aberrant patterns of functional connectivity (FC) between the amygdala and frontal regions during a reward processing task. That is, relative to low irritability children who did not show FC differences when they missed or hit rewarding and non-rewarding targets, children with elevated irritability showed decreased amygdala-frontal connectivity in response to missing a rewarding target and increased connectivity when they missed a non-rewarding target. These findings suggest that early emerging irritability, even in otherwise typically developing children, is associated with abnormalities in response modulation during reward processing (Dougherty et al., 2018). As such, neural functioning during emotion and reward processing may serve as an endophenotype linking sub-clinical irritability to later psychopathology.

Although parenting is a well-established and robust predictor of child outcomes, limited work has explored how it relates to the neural markers of risk that underlie irritability. A well-developed literature links parenting to offspring emotional competence, particularly self-regulation (Eisenberg et al., 2001; Eisenberg, Cumberland, & Spinrad, 1998; Thompson & Meyer, 2007; Zahn-Waxler, 2010), which is impaired in youths high in irritability (Brotman, Kircanski, & Leibenluft, 2017). This work finds that parents' self-expression and reactions to their children's emotions shape youths' own emotion regulation skills (Dallaire et al., 2006; McKee, Colletti, Rakow, Jones, & Forehand, 2008), in part via neurobiological mechanisms (Belsky & De Haan, 2011; Whittle et al., 2014, 2016; Yap et al., 2008). For instance, Romund et al. (2016) found that adolescent-reported maternal warmth and support, but not control, were associated with decreased activity in the amygdala in response to fearful faces, suggesting that youth-perceived maternal care may attenuate reactivity to negatively valenced emotional stimuli. In contrast, Cosgrove and colleagues (2022) did not

find associations between youth-reported parenting quality and their neural activation during passive viewing of emotional pictures; rather, parenting was related to neural reactivity only during dyadic tasks that involved the parent. Specifically, youths who reported low parental support of their emotion expression exhibited decreased neural reactivity in the amygdala and increased activation in the anterior insula and dlPFC in response to parental errors that were associated with loss to both parent and youth during a dyadic monetary reward task (Cosgrove et al., 2022). Given the involvement of the amygdala, insula, ACC, and dlPFC in emotional reactivity and regulation, these findings point to the role of the parent-child relationship in shaping children's neural reactivity. Moreover, these associations appear particularly salient when indexed in the context of parent-child interactions, relative to more general tasks of emotional processing.

Irritable children, for whom emotion regulation is particularly challenging, may be especially sensitive to parental influences relative to children without this temperamental vulnerability (Slagt, Dubas, Dekovic, & van Aken, 2016). For instance, Ravi and colleagues (2022) demonstrated that offspring with elevated irritability in childhood showed elevated irritability in adolescence, particularly in the context of critical or minimizing parental responses to child expressed negative emotion. Similarly, Lengua (2006) demonstrated that low parental warmth and rejection predicted the growth of irritable temperament as children transitioned into adolescence (Lengua, 2006). However, whether interactions between parenting and irritability influence irritable children's subsequent development via neural functioning in regions relevant to self-regulation has not, to our knowledge, been investigated.

Adolescents' experience of parental influences may be partly determined by the overall caregiving environment that unfolds over development. That is, parents' behaviors may differentially impact children's outcomes depending on the emotional climate in which they are expressed, thus distinguishing between the overall parenting style and specific parenting behaviors that are circumscribed to a particular context (Darling & Steinberg, 1993; Lee, Daniels, & Kissinger, 2006). For instance, Van Petegem et al. (2017) demonstrate that in the context of perceived supportive parenting, adolescents appraise parental demands positively, relative to youth who perceive the parenting context as controlling. Thus, exploring how youth-reported parenting moderates their processing of parental feedback may inform our understanding of the individual differences in youths' responsivity to parental influences, particularly irritable youths who may be more sensitive to parental feedback.

Our review of the current literature points to the involvement of neurobiological mechanisms that underlie reward, threat, and emotion processing in irritability. However, tasks of general emotion processing may fail to elicit neural processes relevant to processing interpersonal feedback. Moreover, while parenting interacts with children's irritability to predict youth outcomes, investigations that measure parenting broadly fall short of informing our understanding of how youth with elevated irritability process parental feedback specifically. These are critical gaps in the literature as, particularly during adolescence, youth in general exhibit a heightened sensitivity to interpersonal feedback, evidenced by findings of elevated emotional responsivity during processing of social cues and internal states of others at the neural and behavioral levels (Blakemore & Mills, 2014; Somerville, 2013).

Maternal feedback challenge tasks (MFC; Hooley et al., 2009; Hooley, Gruber, Scott, Hiller, & Yurgeh-Todd, 2005) may be especially useful in understanding neural development in the context of irritability and caregiving. The MFC is an ecologically valid task that has been shown to evoke neural responses in regions involved in processing interpersonally relevant stimuli, emotional reactivity, and emotion regulation that have been implicated in the pathophysiology of irritability. While undergoing a functional magnetic resonance imaging (MRI) scan, youth listen to audio recordings of praising, neutral, and critical feedback from their own mothers, allowing researchers to

examine the neural correlates of valenced parental feedback. Lee and colleagues (2014) used the MFC in a sample of healthy adolescents finding that maternal criticism, relative to neutral maternal comments, was associated with increased activation in brain regions implicated in processing of affective stimuli (i.e., putamen, insula), and decreased activation in regions involved in the cognitive control of emotion (i.e., dlPFC, ACC). These patterns of activation in healthy adolescents are reflective of increased emotional reactivity and decreased executive control of emotion that are typical during this developmental stage (Casey, Heller, Gee, & Cohen, 2019; Lee et al., 2015). Moreover, in a sample of high-risk youth (i.e., with a history of anxiety disorder), adolescents who perceived their mothers to be warm and supportive showed less activation in the amygdala as well as regions of the emotion regulation circuitry (i.e., insula, subgenual anterior cingulate [sgACC], right ventrolateral prefrontal cortex [vlPFC], and the ACC) in response to maternal criticism (Butterfield et al., 2021). This lower activation of the sgACC in response to maternal criticism further mediated the association between maternal warmth and reduction of adolescent internalizing symptoms two years later, suggesting that youth perceptions of positive parenting may support healthy development via influences on offspring neural development (Butterfield et al., 2021). The aforementioned studies support the ecological validity of the MFC task in evoking neural networks involved in processing interpersonally relevant feedback from parents, yet limited work has explored how youths' individual differences relate to their neural processing of parental feedback.

We therefore examined whether childhood irritability predicted adolescent processing of maternal feedback, and, toward further characterizing this association, whether adolescent-reports of parent-child relationship quality moderated neural responsivity to their mothers' affectively valenced feedback. We used youth-reported caregiving given that parents and youth show low agreement on measures of caregiving (Korelitz & Garber, 2016) and some work suggests that adolescents' perception of the parent-child relationship is associated more strongly with later outcomes relative to parent-report (Bolkan, Sano, de Costa, Acock, & Day, 2010; Guion, Mrug, & Windle, 2009). We capitalized on observational measures of irritability, which predict outcomes above and beyond parent-report (Mohamed Ali et al., 2021), allowing a multi-method approach for examining interrelations between children's early emerging temperament and parenting during adolescence. We expected that early irritability would be associated with atypical patterns of neural reactivity to maternal criticism and praise, particularly in the dlPFC based on past work linking functional activity in this region to irritability (Cosgrove et al., 2022; Fishburn et al., 2019; Grabell et al., 2019; Li et al., 2017). We expected that perceived positive parenting would moderate these associations for irritable youth, such that adolescent-reported positive parenting would be associated with greater activity of regions that underlie self-regulation in irritable youths, who may be especially sensitive to parental influences (Kiff, Lengua, & Bush, 2011; Oldehinkel, Veenstra, Ormel, de Winter, & Verhulst, 2006). However, given the lack of studies linking irritability to neural reactivity to parental feedback, we also conducted exploratory whole-brain analyses following ROI analyses.

2. Methods

2.1. Participants

A sample of 81 community-dwelling youths (44% girls) and their mothers were drawn from a larger sample of 409 families (50.1% girls) who were part of a larger, ongoing, multi-wave study of child development. At baseline, families were recruited from the community using advertisements in local daycares, recreational facilities, and the University of Western Ontario's developmental participant pool. Children included in the larger longitudinal study had at least one biological parent who could participate in the study, were free of significant medical and psychological problems, and were of average cognitive

ability ($M = 112.00$; $SD = 14.05$) as assessed by the Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn, 1997) at baseline. The larger sample was predominantly White (93.2%), well educated (> 70% of parents had attained college or university level education), middle-class families (53.3% reported an annual household income between CAD \$40,000 and CAD \$100,000), consistent with the demographic characteristics of the region from which they were drawn (Statistics Canada, 2017). Most children came from two-parent homes (87.6%). Participants in the current study did not differ from the larger sample on any demographic variables (i.e., age, sex, ethnicity, family income, PPVT scores; all $p > .05$). Study procedures for all waves of data collection were approved by the University of Western Ontario's Research Ethics Board. The primary caregiver provided consent for themselves and their child's participation, and assent was obtained from youths.

Participants in the current study were originally invited for a follow-up study that examined associations between maternal depression and youth risk for psychopathology (Liu et al., 2020, 2022; Vandermeer et al., 2020, 2022). Given the expense of imaging data, for the current study (T2), we recruited families drawn from the larger sample based on a maternal depression history, assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Nonpatient Edition (First, Spitzer, Gibbon, & Williams, 1996), to increase power. Of these 102 families, 82 youth participated in the MRI portion of the study, and the remaining youth either declined ($n = 9$), were unable to finish the MRI visit due to discomfort in the scanner ($n = 4$) or dropped out of the follow-up prior to the MRI visit ($n = 7$). Imaging data from one youth was dropped due to excessive motion in the scanner. As such, the current sample consists of 81 youth: Twenty-six high-risk children whose mothers had a lifetime history of recurrent major depression, or a single major depressive episode and an anxiety disorder, and 55 low-risk children with no maternal history of major depressive or anxiety disorder. This sample size is comparable to that reported in past fMRI studies that tested adolescents' neural activity during the MFC (i.e., range of $Ns = 23-63$; Butterfield et al., 2021; Hooley et al., 2009, 2005; K. H. Lee et al., 2015; Silk et al., 2017). Children were screened for both past and current depressive disorder using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (KSADS-PL; Kaufman et al., 1997) conducted with both the primary caregiver and the child; no child was excluded based on as history of depression (detailed recruitment procedures are described in Vandermeer et al., 2020).

2.2. Procedure

Data used here were collected at two time points, approximately 8 years apart. At T1, children ($M_{age} = 3.43$, $SD = 0.28$) completed observational measures in the laboratory to assess child temperament. In the current study, referred to here as T2, youths ($M_{age} = 11.1$, $SD = 0.63$) completed questionnaire measures assessing perceived mother-child relationship quality during a visit conducted in the child's home. Audio recordings of maternal feedback was also collected during this visit (described below). Approximately 4 weeks later youths attended an MRI visit during which functional neural reactivity to maternal feedback was recorded.

2.3. Measures

2.3.1. Observed child irritability

At age 3, children participated in the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995), which consists of 12 emotionally evocative tasks, each two to six minutes long, designed to elicit behavior relevant to child temperament. Children's behavior is video-recorded and later coded for expressions of emotion by trained undergraduate and graduate student raters. Coders were trained by a "master" coder and had to reach 80% agreement before coding independently. Intermittent reliability checks

were conducted to maintain an interclass correlation (ICC) of .80 and prevent coder drift. Typically, children's facial, vocal, and bodily expressions of positive affect, sadness/anger, or fear are aggregated across all 12 tasks, although different tasks are designed to elicit a particular emotion (e.g., in one task designed to elicit positive affect, the child and experimenter race with two remote-controlled cars). There is no single agreed-upon operationalization of irritability (Beauchaine & Tackett, 2019; Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017; Copeland et al., 2015; Craig, Hietanen, Markova, & Berrios, 2008; Leibenluft & Stoddard, 2013); in the current study, we conceptualized irritability as a low-threshold, context-inappropriate anger by aggregating children's expressions of anger across Lab-TAB tasks that were not typically anger-eliciting ($\alpha = 0.78$). Previous work from our group (see Mohamed Ali et al., 2021, for additional details) supports the construct validity of this approach to indexing childhood irritability.

2.3.2. Perceived mother-child relationship quality

At age 11 (T2), with the assistance of a trained research assistant, youths completed the Parental Bonding Instrument (PBI; Parker, Tupling, & Brown, 1979) during a home visit. The PBI is a 25-item self-report questionnaire that assesses offspring perceptions of their mother's and father's care and overprotection, separately, during the past year. As mothers were the primary caregivers in our sample, and given research pointing to the significance of maternal care to youth outcomes (Bornstein, 2002; Braza et al., 2015; Milevsky, Schlechter, Netter, & Keehn, 2007), we used youths' report of their mothers' parenting styles in this study. As overprotective parenting is less relevant to current study questions,² and because maternal warmth and affection are strongly implicated in youth development (Morris, Criss, Silk, & Houtberg, 2017; Morris, Silk, Steinberg, & Robinson, 2009), we used the 12-item maternal care subscale of the PBI ($\alpha = 0.77$), which taps offspring perceptions of mothers' affection and nurturance (e.g., "spoke to me in a warm and friendly voice").

2.3.3. Functional activity during maternal feedback

2.3.3.1. Maternal feedback challenge. At child age 11, samples of maternal feedback were acquired during a visit to the child's home, prior to the MRI visit. Mothers were instructed to write two brief feedback stimuli for each of three valence conditions: neutral, critical, and praising, for a total of six stimuli. Mothers were given a standardized sentence stem specific to each condition; neutral (i.e., "[Child's name], one thing I want to talk to you about today is ..."), critical (i.e., "[Child's name], one thing that really bothers me about you is ..."), and praising (i.e., "[Child's name], one thing I really like about you is ..."). For the neutral condition, mothers discussed mundane topics they believed their child would not feel strongly about, such as grocery shopping or the weather. As our interest was in exploring youths' neural responses to valenced interpersonal feedback, we do not discuss the neutral condition further. Stimuli were collected by trained graduate students and research assistants who ensured that mothers gave feedback on topics frequently discussed with the child to ensure their relevance and that there was sufficient material for a 30 s audio recording.

Next, mothers read each of their written statements while being audio recorded using NESSIE adaptive USB condenser microphone (Blue Microphones, Westlake Village, CA, USA) and Audacity software

² "Overprotection" assessed by the PBI describes perceived parental enforcement of control that undermines child autonomy. While this parenting style is generally considered to be associated with maladaptive child outcomes, evidence supporting this notion has been modest. That is, association between youth-reported parental involvement and their outcomes appears to depend on culture (Hiramura et al., 2010; Jackson-Newsom, Buchanan, & McDonald, 2008), parent and youth gender (Hiramura et al., 2010), and parental use of discipline (McKinney, Milone, & Renk, 2011).

(Version 2.1.2). Raw audio clips were then edited to ensure consistency across participants in terms of length and volume: extended periods of silence were cropped so that all clips were exactly 30 s in length, amplitude was adjusted using Audacity's "Amplify" effect so that clips had a maximum amplitude of -1.0 dB and compressed to have a consistent dynamic range using Audacity's "Compressor" effect. Two strategies were used as a validation check for these stimuli: First, two undergraduate research assistants blind to other study data rated how positive or negative each stimulus was on a 10-point scale (1 = "Not at all" and 10 = "Very"). Second, while in the scanner, youths provided a mood rating on a 5-point visual Likert-type scale after each condition.

2.3.3.2. MRI acquisition. Prior to undergoing the MRI scan, children completed a "mock scan" session in a replica MRI system to familiarize them with the MRI environment and to determine whether they would be likely to be compliant with the imaging data collection procedures (De Bie et al., 2010). During the mock scan, children were explained the MRI session procedures and invited to ask questions. fMRI data were acquired on a 3 T Siemens Magnetom Prisma scanner with a 32-channel head RF coil (Siemens, Erlangen, Germany). Separate runs were completed for each of the three MFC conditions (i.e., praise, neutral, critical). Each run of the MFC task consisted of 89 T_2^* -weighted volumes collected using an echo-planar imaging (EPI) sequence with the following parameters: voxel size = $3 \times 3 \times 3$ mm, 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 collected for the purpose of co-registration, using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence with the following parameters: voxel size = $1 \times 1 \times 1$ mm, TR = 2300 ms, TE = 2.98 ms, FOV = 256 mm, yielding 192 sagittal slices per participant.

During fMRI scanning, youths listened to their individualized MFC audio stimuli over MRI-safe in-ear headphones. Stimuli were presented in a block design using E-prime 2.0 (Version 2.0.10.242), for a total of three runs. Each run consisted of the two blocks of the 30-second audio clips of that condition (e.g., praise) separated by a 12-second rest period. A run of neutral feedback was always presented first, followed by either praise or criticism runs, counterbalanced between participants. Youths were instructed to listen to the MFC stimuli while fixating their gaze on a black cross against a white background. At the end of each run, youths were asked to rate their emotional response using a 5-point Likert scale depicted as 5 emotionally valenced cartoon faces (i.e., "1" depicting a frowning "sad" face, "3" depicting an emotionally neutral face, and "5" depicting a smiling "happy" face).

2.3.3.3. fMRI Preprocessing. Raw DICOM images were converted to NIFTI format using MRICron software (Rorden, Karnath, & Bonilha, 2007). Quality assurance and preprocessing were performed separately for each functional run condition and conducted using SPM12 (Version 7847) and MATLAB R2018a (Version 9.4.0.813654; Mathworks, Inc., Natick, MA, USA). T_1 -weighted images were manually oriented so that the anterior commissure was the point of origin for all participants. Quality assurance procedures were performed using the ArtRepair toolbox (Mazaika, Hoeft, Glover, & Reiss, 2009; Mazaika, Whitfield-Gabrieli, Reiss, & Glover, 2007; Mazaika, Whitfield, & Cooper, 2005). Individual scans with frame-wise displacement > 0.9 mm or frame-wise global signal intensity $> 1.3\%$ deviation from the mean were flagged and interpolated using the nearest unflagged scan before or after the flagged scan (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Siegel et al., 2014). Based on parameters provided by Siegel et al. (2014) for motion censoring to improve the quality of fMRI data, scanner runs with excessive repair, i.e., $\geq 20\%$ (18 TR), or frame-wise displacement > 0.9 mm were dropped from further analyses. This resulted in one subject being dropped due to high mean framewise displacement. Functional images were preprocessed using a standard pipeline that included realignment to a mean image, co-registration to

T_1 -weighted anatomical scans standardized in MNI space with $2 \times 2 \times 2$ mm voxels, and spatial smoothing using a $6 \text{ mm} \times 6 \text{ mm} \times 6 \text{ mm}$ full-width at half-maximum (FWHM) Gaussian kernel. Registration was manually checked by comparing participants' mean functional images with T_1 -weighted anatomical scans.

2.4. Data analyses

Analyses were conducted using SPM12 and SPSS. fMRI data were modelled using mixed effects models, such that single-subject analyses were first conducted on individual children's data using a fixed effects model (i.e., Level One), followed by group-level analyses using a random effects model (i.e., Level Two).

2.4.1. Level one analyses

Individual functional responses to each maternal feedback condition were modeled separately using a 30 s boxcar function convolved with a canonical hemodynamic response function (Poldrack, Mumford, & Nichols, 2011). Motion parameters (i.e., three translational and three rotational per scanner per run) were treated as covariates. Main effects of each MFC condition were modeled by contrasting functional activity during that condition to activity during rest, i.e., Criticism vs. Rest and Praise vs. Rest.

2.4.2. Level two analyses

Second-level analyses were conducted to examine associations between early irritability and functional activity in the Criticism and Praise conditions, testing moderations by youth's perceived parent-child relationship quality. As such, relative neural activation (as modelled in single-subject analyses) was regressed on observed age 3 irritability (scores on Lab-TAB irritability), child-reported perceived parenting (i.e., scores on PBI care), and their interaction (Lab-TAB irritability \times PBI care score). Child age was included as a covariate in all level two analyses.³ Based on the literature on the neural correlates of irritability and parenting (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013; Deveney, Grasso, et al., 2019; Dougherty et al., 2018; Perlman et al., 2015; Stoddard et al., 2017), we used a voxel-wise small volume correction approach (Nieto-Castanon, Ghosh, Tourville, & Guenther, 2003) within a priori anatomical Regions-of-Interest (ROI) to examine neural activation in regions previously implicated in childhood irritability. A priori ROIs were defined using the WFU PickAtlas toolbox (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) and the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), tested separately. ROIs were bilateral amygdala, dlPFC, ACC, and putamen (see Appendix for ROI definitions). We then extracted subject-wise average values of % signal changes from clusters in which the interaction effect was significant using the MAR-Seille Boîte À Région d'Intérêt toolbox for SPM (MarsBaR; Brett, Anton, Valabregue, & Poline, 2002) and imported these into SPSS (v.28) to probe interaction effects. Finally, we conducted exploratory whole-brain analyses examining associations between variables of interest and neural functional activity. We applied a cluster-level significance threshold of $p < .05$, family-wise error corrected during all analyses.

3. Results

3.1. Bivariate correlations

Correlations between all major study variables are presented in Table 1. Perceived maternal care was positively associated with self-

³ As our participants were oversampled for a maternal history of depression (Liu et al., 2020, 2022; Vandermeer et al., 2020, 2022), maternal risk status was also included as a covariate. Given that doing so did not change the pattern of results, maternal risk was dropped from analyses to conserve statistical power.

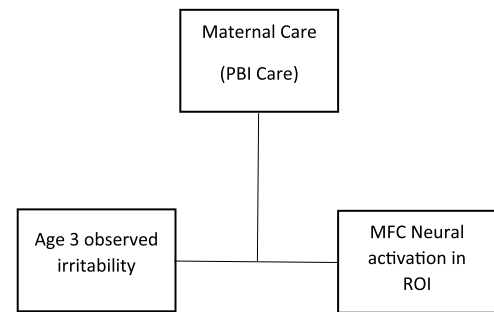


Fig. 1. Moderation model tested predicting neural activation in each ROI in the maternal criticism and praise conditions.

reported emotional response to maternal praise during the fMRI task. Age 3 irritability was positively correlated with youth's self-reported emotional response to maternal criticism, such that youth with higher irritability scores reported more positive mood following critical maternal feedback. Age 3 irritability was unrelated to adolescent-reported maternal care at age 11.

3.2. fMRI Results

3.2.1. Neural activation to maternal criticism

We found a significant main effect of age 3 irritability on neural reactivity to maternal criticism in a cluster in the right dlPFC, a region implicated in top-down emotion regulation (MNI peak coordinates: 48, 30, 38; $T = 3.95$; $k = 31$; $p_{FWE} < 0.05$; SVC applied; Fig. 2). Specifically, irritability was negatively associated with activation in this region. No main effect of maternal care was observed. Further, the interaction between age 3 irritability and perceived maternal care was significant in a right dlPFC cluster that overlapped with the cluster of the significant main effect of age 3 irritability (MNI peak coordinates: 48, 30, 38; $T = 3.87$; $k = 33$; $p < .05$; SVC applied; Fig. 2). Probing interaction patterns in SPSS based on the mean values of % signal changes of the significant cluster for the interaction effect showed that the association between early irritability and neural activation in this region was significant for youth who reported high maternal care only ($\beta = 0.92$; $t(77) = 2.53$; $p = .01$; Fig. 3). That is, for these youth, irritability was associated with smaller % signal change to maternal criticism relative to rest. Association between irritability and neural reactivity in the criticism condition was not significant at mean ($\beta = 0.16$; $t(77) = 0.63$; $p = .53$), or low maternal care ($\beta = -0.59$; $t(77) = -1.63$; $p = .11$). The Johnson-Neyman region of significance analysis further showed that the association between irritability and neural reactivity to maternal criticism became significant at very high perceived maternal care (> 34 ; Fig. 4). Although the slope of irritability was also significant at very low maternal care (< 26.5), we do not interpret this finding further as the test of simple slopes for this group was not significant. No associations between variables of interest and functional activity to maternal criticism were observed in other ROIs, or during whole-brain analyses.

3.2.2. Neural activation to maternal praise

Neither early irritability, maternal care, nor their interaction were associated with neural responses to maternal praise in any of the ROIs or during whole-brain analyses (see supplementary material).table.

4. Discussion

Childhood irritability, an established marker of risk for psychopathology, has neural correlates (Brotman, Kircanski, & Leibenluft, 2017; Copeland et al., 2015; Leibenluft, 2017; Leibenluft & Stoddard, 2013) that may be shaped by maternal care. However, extant research on irritability has almost exclusively focused on child psychopathology as an outcome, overlooking more proximal indicators of dysfunction, such as

Table 1
Bivariate Correlations between Major Study Variables.

	M (SD)	1	2	3	4	5	6	7	8
1. Age 3 Irritability	0.21 (0.21)								
2. Age 11 PBI Mat Care	31.81 (3.82)	-0.15							
3. Mood Rating Criticism	2.68 (1.02)	0.26*	.15						
4. Mood Rating Praise	4.54 (0.77)	-0.18	0.31**	-.02					
5. Child Sex	-	-0.12	0.16	0.01	0.08				
6. Family Income	-	0.01	-0.09	-0.10	-0.11	-0.01			
7. Ethnicity	-	-0.01	0.03	0.19	0.03	-0.04	-0.19		
8. PPVT score	113.21 (14.31)	-0.18	0.01	-0.18	-0.01	-0.08	0.20	0.05	

Note. ** $p < .01$; * $p < .05$; PBI = Parental Bonding Instrument; Mat = Maternal; Child sex: boys = 1, girls = 2; Family Income: 1 < \$20,000, 2 = \$20,000 - \$40,000, 3 = \$40,001 - \$70,000, 4 = \$70,002 - \$100,000, and 5 > \$100,001; Ethnicity: 1 = White, 0 = Other; PPVT = Peabody Picture Vocabulary Test

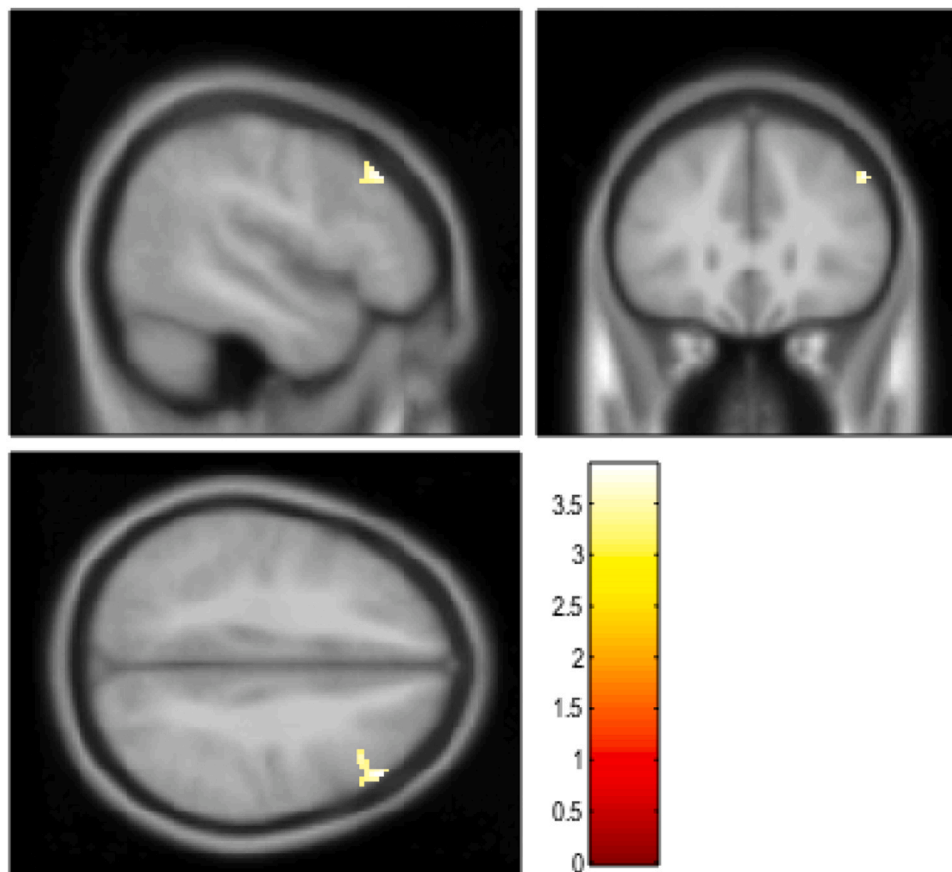


Fig. 2. a priori ROI analysis showing the region in the right dlPFC (48, 30, 38) where activation during the maternal criticism condition was significantly associated with the interaction of irritability and perceived maternal care.

youths' functional brain reactivity in regions relevant to the development of disorder. Despite the importance of parenting to predicting child outcomes, to our knowledge, no work has investigated associations between early irritability and youths' neural reactivity to their parents' feedback. We found that, in response to maternal criticism, early irritability was negatively associated with activation in the right dlPFC, a region implicated in cognitive control of emotion (Ochsner & Gross, 2005). However, youth-reported parenting moderated this association such that early irritability predicted decreased dlPFC reactivity to maternal criticism relative to rest, particularly among youths reporting relatively high maternal care.

The dlPFC is a key region within the affective salience circuitry that is involved in processing emotionally salient stimuli, playing a role in the top-down modulation of amygdala reactivity to negatively valenced

stimuli (Banks, Eddy, Angstadt, Nathan, & Luan Phan, 2007; Golkar et al., 2012; Ochsner & Gross, 2005; Uchida et al., 2014). In particular, the dlPFC is involved in processes such as response inhibition, diverting attention from threatening stimuli, and reappraisal of emotion (Banks et al., 2007; Golkar et al., 2012), and is therefore a critical structure in the development of emotion regulation competence. Decreased dlPFC activation in response to negatively valenced stimuli has been demonstrated among depressed individuals, where a persistent negative mood state is prevalent (Hooley et al., 2009). Similarly, alterations in dlPFC activity have also been implicated in the pathophysiology of irritability (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017; Nielsen et al., 2021). Our finding that irritability was associated with decreased neural activation to maternal criticism is consistent with previous work that implicates reduced dlPFC activation among at risk individuals (Hooley

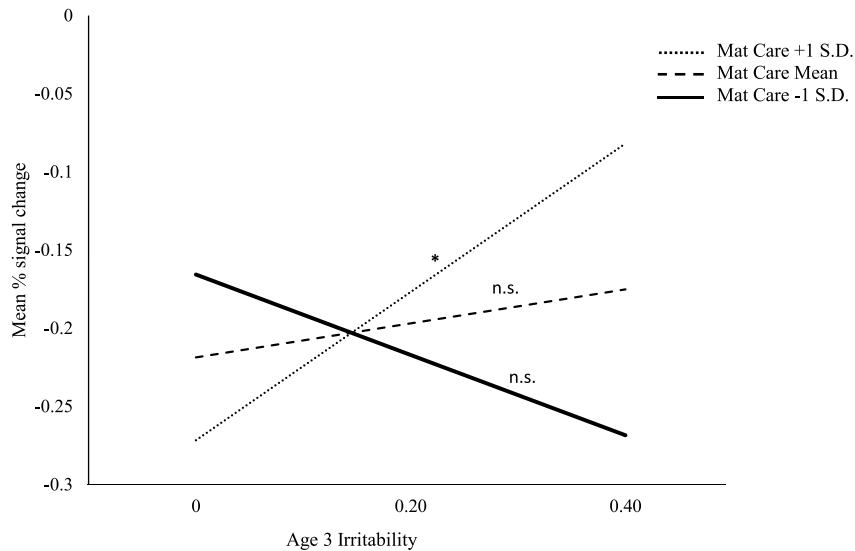


Fig. 3. Early irritability is associated with decreased neural reactivity of the right dlPFC during maternal criticism relative to rest among youth who reported high maternal care (* $p < .05$; n.s. = not significant).

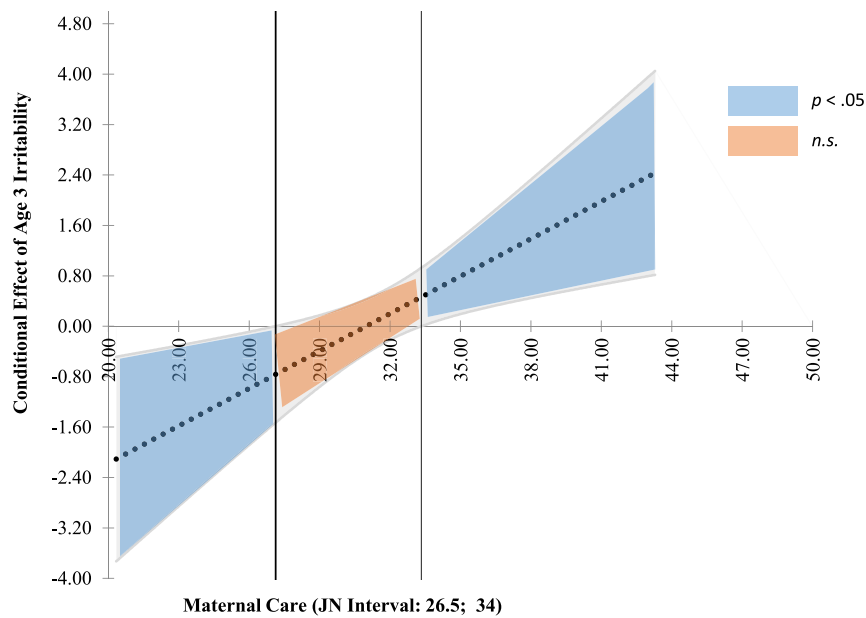


Fig. 4. Johnson-Neyman region of significance analysis shows that the simple slope of age 3 irritability predicting neural reactivity of the dlPFC during maternal criticism is significant at very high and very low maternal care.

et al., 2009, 2005; Koenigs & Grafman, 2009).

We expected that a positive parent-child relationship quality may mitigate against this vulnerability by supporting adaptive recruitment of neural resources implicated in inhibiting emotional reactivity to negative maternal feedback (i.e., greater dlPFC activation to maternal criticism). However, among youth reporting high maternal care, irritability was associated with decreased dlPFC activation during maternal criticism. This might suggest more pronounced deficits in cognitive control of emotion among irritable youth who perceive their mothers to be more caring. Alternatively, it may be that positive parenting supports irritable youths' disengagement from negative maternal feedback, a strategy that has been shown to be effective in managing negative emotions in the short term (Lee et al., 2015; Parsafar, Fontanilla, & Davis, 2019; Rice, Levine, & Pizarro, 2007). Future work should examine how the use of different emotion regulation strategies is associated with neural

activation during interpersonally relevant tasks among irritable youth.

Our findings are also relevant to previous work examining associations between irritability and activation of prefrontal regions during tasks of cognitive flexibility (Li et al., 2017) and inhibitory control (Fishburn et al., 2019; Liuzzi et al., 2020) in otherwise healthy preschool children. Past studies showed increased frontal activation during tasks of cognitive control among preschoolers with elevated early irritability in the absence of behavioral differences in performance between low and high irritability children (Fishburn et al., 2019; Li et al., 2017; Liuzzi et al., 2020). These findings suggest that currently healthy children with elevated irritability may be able to recruit more neural resources for inhibitory control, potentially reducing risk for negative mental health outcomes. In contrast, our findings suggest that different functional activity patterns characterize the neural correlates of irritability in adolescence. That is, it may be that increased dlPFC activation during

tasks of cognitive control among healthy children with elevated irritability do not persist in adolescence, potentially explaining the increased prevalence of maladaptive outcomes in this developmental window. Alternatively, patterns of dlPFC activation in irritable youth may be task dependent. That is, although the dlPFC is implicated in processing of interpersonal feedback (Butterfield et al., 2021; Lee et al., 2015; Silk et al., 2017; Vandermeer et al., 2022), irritable youth may show increased activation of this region during tasks of executive function but reduced neural reactivity to interpersonally relevant stimuli. We also note that we assessed irritability in childhood rather than concurrently to the assessment of neural reactivity to maternal feedback. Although emerging work points to the relative stability of irritability (Beauchaine & Tackett, 2019; Kessel et al., 2021; Klein et al., 2021; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016; Mohamed Ali et al., In Preparation), longitudinal investigation of the neural correlates of irritability across childhood is needed to further corroborate our findings.

We did not observe main effects of irritability or interactions between irritability and maternal care in predicting adolescents' neural reactivity to maternal praise. Past work found that typically developing youth with elevated irritability exhibited increased activation of the putamen to reward during a monetary incentive delay task, specifically in the context of poor executive function abilities (Kryza-Lacombe, Palumbo, Wakschlag, Dougherty, & Wiggins, 2022). In addition, children with elevated irritability show alterations in functional connectivity between regions of the reward circuitry during frustrative non-reward, such that they exhibit poorer regulation of the reward circuitry when anticipated reward is thwarted (Dougherty et al., 2018; Nielsen et al., 2021). These findings are indicative of hypersensitivity to reward as well as problems coping with frustration in irritable youth. However, despite the relevance of irritability to depressive disorders, wherein blunted neural reactivity to positive parental feedback have been identified (Silk et al., 2017), to our knowledge, past work has not explored mechanisms of processing positive interpersonal feedback in irritability. Our failure to find associations between early irritability and neural reactivity to maternal praise may point to independent pathways underlying responsivity to social (e.g., evoked by parental praise) versus non-social (i.e., evoked by monetary incentive tasks) reward, in the context of irritability. This notion is supported by past work showing differential associations between different types of reward, subject-specific characteristics (e.g., age, gender, personality) and patterns of neural reactivity to reward (Delmonte et al., 2012; Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009; Rademacher et al., 2010). Alternatively, mothers' praising comments may be a common and familiar experience for the youth in this community, low-risk sample, such that there is limited variability in youths' neural reactivity to maternal praise.

Our study has several important strengths. We used a multimethod approach for assessing our variables of interest, incorporating an observational measure of early irritability that is suited to its conceptualization as a temperamental trait. This approach is also useful in light of the significant limitations of parent-reported child behavior (Clark, Durbin, Donnellan, & Neppl, 2017; De Los Reyes & Kazdin, 2005; Goodman et al., 2011). In addition, given past work implicating specific brain regions in both the pathophysiology of irritability and neural

processing of parental feedback, we had strong hypotheses that permitted ROI analysis. Relative to whole-brain voxelwise analyses, this approach limits the number statistical tests, thereby controlling for Type I error (Poldrack, 2007). However, there are several limitations to our current study. Considering our limited power, we did not examine sex differences in the relationship between irritability and neural functioning. In addition, we measured irritability in childhood only; thus, although other work from our group supports the stability of early irritability over several years (Mohamed Ali et al., In Preparation), future longitudinal studies with repeated measures of neural activation, parenting, and youth characteristics at all waves will prove useful for testing causal links between early irritability and later neural development. Our findings implicate regions within the prefrontal cortex that show protracted development across the lifespan, which is thought to underlie improvements in self-regulation capacities that typically emerge over adolescence (Casey et al., 2019; Durston & Casey, 2006). As such, although we captured an important "snapshot" of neural reactivity in early adolescence, additional follow-up is needed to adequately trace adolescent development in these brain regions. Additionally, although the patterns of neural reactivity observed should be related to adolescents' self-regulation (Ochsner & Gross, 2005; Phillips, Drevets, Rauch, & Lane, 2003), we did not include behavioral measures of this construct. Finally, our sample consisted largely of Caucasian, middle-to-upper class families who were highly educated, and youths were of average to above average cognitive ability. The homogeneity of our sample may therefore preclude the generalizability of our findings to more diverse samples.

Our findings show that youth's neural reactivity to parental feedback is dependent on their early irritability and perceived parent-child relationship quality, and particularly points to shared neural pathways between irritability and processing of interpersonal feedback. These findings have important implications for understanding environmental influences on irritable youth, particularly in adolescence.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix

Definition of regions of interest (ROIs).

ROI	Definition by Atlas Label
Bilateral amygdala	Amygdala_L, Amygdala_R
Bilateral dlPFC	Frontal_Mid_L, Frontal_Mid_R
ACC	Cingulum_Ant_L, Cingulum_Ant_R, Cingulum_Mid_L, Cingulum_Mid_R, Cingulum_Post_L, Cingulum_Post_R
Bilateral putamen	Putamen_L, Putamen_R

Note: L= Left, R = Right; dlPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.biopsycho.2023.108645](https://doi.org/10.1016/j.biopsycho.2023.108645).

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