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Maternal Depression Is Related to Reduced Error-Related Brain Activity in Child and Adolescent Offspring

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Chronic parental depression is associated with an increased likelihood of depression in offspring. One mechanism by which parental depression may increase risk is through physiological or cognitive tendencies in offspring. Error processing has been studied using the error-related negativity (ERN), an event-related potential that occurs around the time someone commits an error, and has previously been shown to be heritable and blunted in depressed individuals. The current study examined the ERN as a potential biomarker of risk in a sample of never-depressed children whose mothers had a history of recurrent major depressive disorder (MDD), a single episode of MDD, or no lifetime history of any mood disorder. Seventy-eight mother–child dyads participated. The average age for children was 13.13 years ($SD = 2.07$) and 50% were female. Diagnostic interviews and self-report questionnaires were used to assess depression in both mothers and children. A flankers task was used to elicit the ERN and the correct response negativity (CRN) in children. Children of mothers with a history of recurrent MDD exhibited a reduced difference between the ERN and CRN compared to children of mothers with no depression history, even after controlling for children's current depression symptoms. Furthermore, current maternal depression symptoms related to a smaller difference between ERN and CRN in children. This pattern of findings suggests that blunted neural activity differentiating error from correct responses may be one mechanism by which recurrent maternal depression increases risk for depression in offspring and may be useful biomarker of risk.

Major depressive disorder (MDD) is one of the most common mental illnesses, with a lifetime prevalence rate of 16% (Kessler et al., 2003) and an estimated annual economic burden of \$83.1 billion in the United States alone (Greenberg et al., 2003). In addition to the subjective experience of anhedonia and depressed mood that characterize MDD, it is associated with a host of negative outcomes including poor academic performance (Heiligenstein, Guenther, Hsu, & Herman, 1996), higher likelihood of unemployment (Fergusson & Woodward, 2002), difficulty with interpersonal relationships (La Greca & Harrison,

2005), and greater risk of suicide (Fergusson & Woodward, 2002; Harrington et al., 1994). Negative outcomes are even more likely when the depression is chronic or recurrent, and the risk of experiencing a recurrence of MDD in the future increases by 16% with each additional prior episode (Solomon, 2000). Those who have experienced multiple episodes of depression are more likely than those with single episodes to have made a suicide attempt at an early age (Wilhelm, Parker, Dewhurst-Savellis, & Asghari, 1999), are more likely to have experienced chronic medical illness (Wilhelm et al., 1999), tend to report a higher levels of depressive symptoms (Wilhelm et al., 1999), and are less protected from future depression by taking antidepressant medications during periods of remission (Kaymaz, van Os, Loonen, & Nolen, 2008).

Depression is also highly heritable, with genetic factors accounting for approximately 37% of variance in risk

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(Sullivan, 2000). Indeed, a parental history of depression is one of the strongest predictors of depression in offspring (Beardslee, Versage, & Gladstone, 1998) and, by age 15, adolescents with depressed mothers are twice as likely as those with never-depressed mothers to be diagnosed with depression (Hammen & Brennan, 2003). Although risk is conferred by depression in either parent, the association is even stronger for maternal depression (Connell & Goodman, 2002; Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005). A number of reasons for this have been proposed, including depression-related abnormalities in the fetal environment during pregnancy (e.g., low blood flow and abnormal neuroendocrine levels) and a greater effect of depression on maternal parenting style (Connell & Goodman, 2002; Field, Hossain, & Malphurs, 1999; Goodman & Gotlib, 1999). Furthermore, just as greater chronicity of depression in an individual is associated with more negative outcomes, more chronic or recurrent parental depression is associated with an increased likelihood of depression in offspring (Hammen & Brennan, 2003; Keller, 1986; Klein, Clark, Dansky, & Margolis, 1988; Warner, Mufson, & Weissman, 1995). More chronic maternal depression is also associated with an increased risk of other negative outcomes in offspring, including early interpersonal difficulties (Campbell, Cohn, & Meyers, 1994; Teti, Gelfand, Messinger, & Isabella, 1995), behavioral problems (Brennan et al., 2000), and poorer vocabulary (Brennan et al., 2000).

One mechanism by which maternal depression may increase risk in offspring is through altered action monitoring, that is, cognitive processing related to tracking one's own performance. The anterior cingulate cortex (ACC), a brain area associated with action monitoring (Carter & van Veen, 2007), is thought to receive reinforcement learning signals from the mesolimbic dopamine system (Holroyd & Coles, 2002), which shows abnormal activity in association with depression (Drevets, 2001; Nestler & Carlezon, 2006; Pizzagalli et al., 2009). Furthermore, previous findings have found altered action monitoring in currently depressed adults and children (Ladouceur et al., 2012; Olvet, Klein, & Hajcak, 2010; Weinberg, Klein, & Hajcak, 2012). One strategy for identifying neural mechanisms of risk is to examine neural measures in healthy offspring as a function of maternal depression history. In the current study, we focus on action monitoring in healthy youth in relation to maternal depression.

An event-related potential that occurs approximately 50 ms after the commission of an error has been utilized to study action-monitoring and is thought to be generated in the ACC (Miltner et al., 2003). The error-related negativity (ERN) has primarily been studied in relation to anxiety, finding an increased neural response to errors in *anxious* adults and children across a variety of contexts. Adults with obsessive-compulsive disorder (Fitzgerald et al., 2005; Gehring, Himle, & Nisenson, 2000; Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Ursu, Stenger, Shear, Jones, & Carter, 2003; Xiao et al., 2011), as well as healthy adults with elevated levels of trait anxiety (Paulus, Feinstein,

Simmons, & Stein, 2004; Weinberg et al., 2012; Weinberg, Kotov, & Proudfit, 2014), show an enhancement of error-related activity. The ERN is also highly heritable, with an estimated 47% of variance in the ERN due to genetic factors in 12-year-olds (Anokhin, Golosheykin, & Heath, 2008), thereby making it a plausible biomarker of risk.

Comparably fewer studies have investigated the relation of the ERN to depression—and in these studies, findings have been mixed. Although some studies have found that the ERN is enhanced in individuals with depression (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008, 2010), others have found either no difference or a smaller ERN among depressed individuals (Olvet et al., 2010; Ruchow et al., 2006; Ruchow et al., 2004; Schrijvers et al., 2008; Schrijvers et al., 2009). These discrepancies have been attributed by some to task differences such as the use of trial-by-trial feedback versus feedback only at the end of blocks (Weinberg et al., 2012); however, such differences do not fully explain the discrepant results across studies. It is possible that the mixed findings in relation to the ERN and depression may arise from variation in the composition of study samples, such as differences in medication status (Ladouceur et al., 2012) or in the balance of anxious and depressive symptoms (Holmes & Pizzagalli, 2010; Olvet et al., 2010). For example, some studies that have found an enhanced ERN in relation to depression have not controlled for anxiety (Holmes & Pizzagalli, 2008), and another study did not find a relation between anxiety and the ERN in patients with MDD (Schrijvers, De Bruijn, Destoop, Hulstijn, & Sabbe, 2010), making it unclear whether the effects are due to the presence of depression or anxiety.

In studies of unmedicated individuals that do not use trial-by-trial feedback, an attenuating effect of depression on the ERN has consistently been found when anxiety is taken into account (Ladouceur et al., 2012; Olvet et al., 2010; Weinberg et al., 2012, Weinberg et al., *in press.*). For instance, in a recent study comparing adults with generalized anxiety disorder (GAD) only, comorbid MDD and GAD, and healthy controls, the elevated ERN seen in the GAD group was absent in the comorbid MDD/GAD group (Weinberg et al., 2012), suggesting that the presence of a comorbid current diagnosis of MDD may have suppressed the relationship between GAD and an increased ERN. This effect was recently replicated in a larger independent sample; moreover, across diagnostic groups, higher levels of depression symptoms—specifically, psychomotor retardation—were associated with a smaller ERN (Weinberg et al., 2014). The only study to date examining the ERN in the context of childhood depression found a similar result: Among unmedicated 7- to 17-year-olds, those with MDD had a blunted ERN compared to low-risk healthy controls, and this effect was not impacted by the presence of comorbid anxiety disorders (Ladouceur et al., 2012). In line with the possibility that the ERN is reduced in

depression, the ERN is also reduced when levels of available dopamine are decreased pharmacologically (Zirnheld et al., 2006). Together, these studies suggest that MDD—and specific symptoms of depression—are associated with a blunted ERN.

Given the high heritability of maternal depression and the potential association between depression and the ERN, the goal of the current study was to examine the ERN in a sample of never-depressed children whose mothers had a history of recurrent MDD during the children's lives, a single episode of MDD during the children's lives, or no lifetime history of any mood disorder. As no study has yet examined whether a blunted ERN precedes the onset of depression, we wished to examine the ERN as a potential biomarker of *risk* for depression. Consistent with previous studies that have found an attenuated ERN associated with depression in children, a flankers task without trial-by-trial feedback was used. Based on prior research, it was hypothesized that the children of mothers with a history of MDD would show a smaller ERN relative to those without a maternal history of depression and that children of mothers with recurrent MDD would show a smaller ERN than children of mothers with a single MDD episode. Finally, given the previous mixed results regarding the potential impact of anxiety, we examined whether the effects would be maintained after taking into account mothers' and children's anxiety.

METHOD

Participants

Participants in the final study sample were 78 mother-child dyads participating in a larger study of the intergenerational transmission of depression. To qualify for the study, mothers were required to either meet criteria for MDD during the child's lifetime according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., [DSM-IV]; American Psychiatric Association, 1994) or have no lifetime diagnosis of any DSM-IV mood disorder and no other current Axis I diagnosis. Exclusion criteria for both groups included symptoms of schizophrenia, organic mental disorder, alcohol or substance dependence within the last 6 months, or history of bipolar disorder. If more than one child in this age range was eligible within a family, one child was chosen at random to participate. Data from four participants were excluded due to experimenter error during data collection, from two participants due to having an ERN that was more than 3 *SD* above or below the mean, and from 20 children who met criteria for lifetime major or minor MDD. The final sample was 78 children, whose average age was 13.11 years (*SD* = 1.89), with a range of 9 to 17 years old, 50% were female, 87% were Caucasian, 5% were African American, 5% were Biracial, 1% were Hispanic, and 1% identified as Other. Written informed consent was obtained and all

procedures were approved by the university Institutional Review Board.

Measures

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1997) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) were used to assess for current DSM-IV Axis I disorders in mothers and their children, respectively. The SCID-I and K-SADS-PL were administered by separate interviewers. For the K-SADS-PL, mothers and children were interviewed separately. Of those participants included in the current study, 19 mothers met criteria for a single lifetime MDD episode, 36 met criteria for recurrent MDD, and 43 did not meet criteria for lifetime MDD. Twenty children met criteria for a lifetime MDD or minor depression and were excluded from all analyses. In a follow-up analysis, mothers and children with a lifetime anxiety disorder were excluded from the analysis: Thirteen mothers and six children met criteria for a lifetime anxiety disorder. To assess interrater reliability, a subset of 20 SCID and K-SADS interviews from this project were coded by a second interviewer, and kappa coefficients for MDD diagnoses in mothers and children were excellent (all κ s = 1.00).

Mothers' and children's current symptoms of depression were evaluated with Beck Depressive Inventory–II (BDI-II Beck, Steer, & Brown, 1993) and the Children's Depression Inventory (CDI Kovacs, 1985), respectively. Both measures have demonstrated excellent reliability and validity in previous research (Beck et al., 1993; Kovacs, 1981, 1985; Smucker, Craighead, Craighead, & Green, 1986). In addition, both exhibited excellent internal consistency in this study (BDI-II: α = .94; CDI: α = .86).

Mothers' and children's current symptoms of anxiety were evaluated with the Multidimensional Anxiety Scale for Children (Baldwin & Dadds, 2007), as well as the Beck Anxiety Inventory (Fydrich, Dowdall, & Chambless, 1992). Both measures have demonstrated excellent reliability and validity in previous research (Baldwin & Dadds, 2007; Fydrich et al., 1992). In addition, both exhibited excellent internal consistency in this study (Multidimensional Anxiety Scale for Children: α = .85; Beck Anxiety Inventory: α = .88).

Procedure

Potential participants were recruited from the community through a variety of means (e.g., television, newspaper and bus ads, flyers). Mothers responding to the recruitment advertisements were initially screened over the phone to determine potential eligibility. Upon arrival at the laboratory, mothers provided informed consent and children provided assent to participate in the study. As

part of the broader assessment battery, children completed EEG tasks including the flankers task. During this time, the mother was administered the K-SADS-PL by a trained interviewer. After completing the K-SADS-PL with the mother, the same interviewer then administered the K-SADS-PL to the child. While children were being administered the K-SADS-PL, the mother was then administered the SCID-I by a separate interviewer. Families were compensated \$50 for their participation in this part of the study.

EEG Task and Materials

An arrow version of the flankers task was administered to measure neural activity time-locked to error and correct responses (i.e., the ERN and correct response negativity [CRN], respectively). On each trial, horizontally aligned arrowheads were presented for 200 ms, followed by an ITI that varied randomly between 2,300 to 2,800 ms. Half of the trials were compatible (“<<<<<<” or “>>>>>>”) and half were incompatible (“<<>><<” or “>><<>>”); the order of trials was randomly determined. Participants were instructed to press the right button on a game controller if the center arrow was facing to the right and to press the left button if the center arrow was facing to the left. After a practice block of 30 trials, participants completed 11 blocks of 30 trials (330 trials total) with each block initiated by the participant. Participants received feedback based on their performance at the end of each block. If performance was 75% correct or lower, the message “Please try to be more accurate” was displayed; if performance was above 90% correct, the message “Please try to respond faster” was displayed; otherwise the message “You’re doing a great job” was displayed.

Psychophysiological Recording, Data Reduction, and Analysis

Continuous EEG recordings were collected using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, the Netherlands). Thirty-four electrode sites were used, based on the 10/20 system, in addition to two electrodes on the right and left mastoids. Eye movements and eye blinks (electrooculogram) were recorded using four facial electrodes: vertical eye movements and blinks were measured via two electrodes placed approximately 1 cm above and below the right eye and horizontal eye movements were measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio by a BioSemi ActiveTwo system. The data were digitized at a sampling rate of 1024 Hz with a 24-bit resolution, using a low-pass fifth-order sinc filter with a half-power cutoff of 204.8 Hz. Each active electrode was measured online with respect to a

common mode sense active electrode producing a monopolar (nondifferential) channel.

Data processing was performed offline with Brain Vision Analyzer, Brain Products, Gilching, Germany. Offline, the data were referenced to the average of the left and right mastoids, and band-pass filtered from 0.1 to 30 Hz. The continuous EEG was segmented for each trial beginning 500 ms before the response and continuing for 800 ms after the response. We used a semiautomatic procedure for all segmented data to detect and reject artifacts that included the following criteria: a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than .50 μV within any 100 ms interval. These intervals were rejected from individual channels within each trial. After this, visual inspection of the data was conducted to detect and reject any remaining artifacts. Eye-blink and ocular corrections were conducted per Gratton, Coles, and Donchin (1983).

Correct and error trials were averaged separately, using the window from -500 to -300 ms before the response as the baseline. For each subject, the ERN was quantified as the average activity from 0 to 100 ms after errors at a pooling of electrodes (Fz, FCz, Cz, FC1, and FC2), where the ERN was maximal. The CRN was evaluated in the same time window and at the same electrodes, after correct responses. Consistent with prior research (see Moser, Moran, Schroder, Donnellan, & Yeung, 2013, for a meta-analysis), we also focused on the ΔERN , which is the difference between the ERN and CRN (average activity on error trials minus average activity on correct trials). Behavioral measures for the flankers task included the number of error trials for each subject and accuracy expressed as a percentage of correct responses out of all trials. Reaction times (RTs) on error and correct trials were calculated separately, as were RTs on trials that followed correct and error trials to evaluate posterror RT slowing. Posterror slowing is the degree to which individuals slow down after making errors and is thought to reflect recruitment of cognitive control processes (Rabbitt, 1966).

All statistical analyses were conducted using SPSS (Version 17.0) General Linear Model Software, with Greenhouse-Geisser correction applied to p values with multiple- df , repeated-measures comparisons when necessitated by violation of the assumption of sphericity. Mixed-model repeated measures analyses of variance (ANOVAs) were conducted to examine RT and posterror slowing with error and correct RT as within-subject variable and maternal depression (never depressed, single episode, or recurrent depression) as the between-subject variable. One-way ANOVAs were conducted to examine differences in error commission, accuracy, CDI, and BDI scores between the maternal depression groups. For error-related brain activity, a mixed-model repeated measures ANOVA was conducted with response type (i.e., error or correct) as the

within-subject variable and maternal depression (never depressed, single episode, or recurrent depression) as the between-subject variable. Follow-up analyses were conducted to examine the robustness of the effects. We examined the potential impact of maternal depression symptoms (as measured by the BDI), child depression symptoms (as measured by the CDI), and maternal and child anxiety. Age was controlled for in all analyses.

RESULTS

Clinical Variables

CDI and BDI data are presented in Table 1 for the no maternal MDD, single-episode maternal MDD, and recurrent maternal MDD groups. Results of a one-way ANOVA suggested that neither child or mom's age nor children's CDI scores varied by maternal depression group, $F(2, 77) = 1.18, p = .31, \eta_p^2 = .03$; $F(2, 76) = 0.16, p = .85, \eta_p^2 = .00$; and $F(2, 74) = 2.74, p = .07, \eta_p^2 = .07$, respectively. In contrast, the groups did differ significantly in BDI scores, $F(2, 74) = 9.63, p < .001, \eta_p^2 = .21$. Follow-up t tests indicated that mothers in the recurrent maternal MDD group had more depression symptoms relative to the no maternal MDD group, $t(59) = 4.05, p < .001, r_{effect\ size} = .47$, and single maternal MDD group, $t(37) = 2.61, p = .013, r_{effect\ size} = .39$. Maternal depression symptoms did not differ between the no maternal MDD and single maternal MDD group, $t(52) = -.88, p = .39$. Thus, recurrent MDD in mothers was uniquely related to higher current levels of depression.

Behavioral Data

Accuracy and RT data are presented in Table 1. Overall, children's RTs were faster on error trials than on correct trials, $F(1, 67) = 54.67, p < .001, \eta_p^2 = .45$. RTs did not differ as a function of maternal depression, $F(2, 67) = 0.42, p = .66, \eta_p^2 = .01$.¹ In addition, the three groups differed neither in terms of the number of errors committed, $F(3, 74) = 0.16, p = .85, \eta_p^2 = .00$, nor by their accuracy, $F(3, 74) = 0.68, p = .68, \eta_p^2 = .00$.

Posterror and correct RT data are also presented in Table 1. In a mixed-model repeated measures ANOVA wherein RTs on posterror and correct trials were entered as within-subject variables and maternal depression (never depressed, single episode, or recurrent depression) was entered as the between-subject variable, with age entered as a covariate, neither the effect of trial type, $F(1,$

¹ When trial congruency (correct vs. incorrect) was included as a factor in the model, there was a main effect of congruency, $F(1, 54) = 4.18, p = .03, \eta_p^2 = .07$, such that children were faster on congruent trials. However, the Maternal MDD \times Congruency interaction was not significant, $p > .20$.

68) = 0.02, $p = .90, \eta_p^2 = .00$, nor the Maternal Depression \times Trial Type interaction, $F(2, 68) = 2.34, p = .10, \eta_p^2 = .06$, was significant.

Error-Related Brain Activity

Figure 1 presents topographic maps for the children in the no maternal MDD (top, right), single maternal MDD (middle, right), and recurrent maternal MDD (bottom, right) groups, depicting voltage differences (in μV) across the scalp for the ΔERN . Grand average response-locked event-related potentials at pooled sites where the ERN was scored are also presented in Figure 1 for the no maternal MDD (top, left), single maternal MDD (middle, left), and recurrent MDD (bottom, left) groups. Average ERN, CRN, and ΔERN values are presented for all three groups in Table 1.

We completed a mixed-model repeated measures ANOVA with response type (i.e., error or correct) as the within-subject variable and maternal depression (never depressed, single episode, or recurrent depression) as the between-subject variable. The effect of response type was significant, $F(1, 74) = 27.35, p < .001, \eta_p^2 = .27$, confirming that the ERN ($M = 1.29, SD = 6.79$) was more negative than the CRN ($M = 4.53, SD = 6.31$). Overall, there was no main effect of maternal group on neural activity (i.e., collapsing across error and correct trials), $F(2, 74) = 0.03, p = .97, \eta_p^2 < .001$. There was, however, a significant interaction between maternal group and response type (error vs. correct), $F(2, 74) = 3.52, p = .04, \eta_p^2 = .09$. Follow-up t tests suggested that neither the CRN nor the ERN alone differed between maternal depression groups, all $ps > .40$. However, the relative difference between error and correct trials (i.e., the ΔERN) was smaller in the recurrent maternal MDD group compared to the no maternal MDD group, $t(60) = 2.82, p = .007, r_{effect\ size} = .34$. The ΔERN did not differ between the recurrent maternal MDD group and the single maternal MDD group, $t(38) = 1.80, p = .08, r_{effect\ size} = .28$. Furthermore, the ΔERN did not differ between the no maternal MDD group and the single maternal MDD group, $t(52) = 0.31, p = .75, r_{effect\ size} = .04$.²

A series of follow-up analyses were then conducted to examine the robustness of these effects (i.e., a smaller

² An alternative approach for isolating error-specific activity is using regression-based residual measures between error and correct trials (Meyer, Lerner, De Los Reyes, Laird, & Hajcak, under review). We calculated the ERN_{res} by saving the unstandardized residuals in a regression wherein the CRN was entered predicting the ERN (and alternatively calculated the CRN_{res} by entering the ERN predicting the CRN). Results suggested that it was error-specific activity that was attenuated in the recurrent maternal MDD group, $F(2, 77) = 3.46, p = .03$ for the ERN_{res} , and there was a trend-level association for activity specific to correct trials (i.e., CRN_{res}), $F(2, 77) = 2.81, p = .07$. These results suggest that the ERN_{res} and CRN_{res} related to MDD in opposing ways—the recurrent MDD group was characterized by a smaller (less negative) ERN_{res} and a larger (more negative) CRN_{res} , which is consistent with the analyses on the ΔERN .

TABLE 1

Means and Standard-Deviations of Clinical Variables, Behavioral Data, and Error-Related Brain Activity for Children With No Maternal MDD, a Single Maternal MDD, and Recurrent Maternal MDD

	No Maternal MDD ^a	Single Maternal MDD ^b	Recurrent Maternal MDD ^c
Clinical Variables			
Child Age	13.01 (1.68) _a	13.74 (1.76) _a	12.84 (2.23) _a
Mom Age	44.87 (6.37) _a	44.13 (7.22) _a	43.97 (6.50) _a
CDI	3.75 (5.52) _a	3.14 (3.48) _a	6.95 (6.95) _a
Maternal BDI	3.79 (5.48) _a	5.13 (4.01) _a	10.70 (7.82) _b
Reaction Time (ms)			
Error Trials	375.35 (46.39) _a	403.23 (100.99) _a	409.87 (53.74) _a
Correct Trials	487.41 (84.19) _a	515.38 (134.82) _a	523.29 (78.96) _a
Posterror Trials	488.68 (92.73) _a	541.98 (149.50) _a	554.43 (83.58) _a
Postcorrect Trials	476.34 (83.78) _a	513.18 (131.13) _a	514.89 (74.60) _a
Accuracy			
No. of Errors	51.13 (20.64) _a	52.00 (34.91) _a	55.37 (31.39) _a
No. of Correct Trials	270.63 (27.48) _a	251.44 (67.43) _a	261.67 (39.98) _a
% Correct	84.10% (6.34) _a	82.14% (13.11) _a	82.41% (10.08) _a
ERPs (μV)			
ERN	0.67 (6.24) _a	0.47 (8.26) _a	2.82 (6.65) _a
CRN	5.06 (6.33) _a	4.39 (5.33) _a	3.78 (7.07) _a
ΔERN	-4.39 (4.71) _a	-3.92 (5.81) _a	-0.97 (4.58) _b

Note: Values with the same subscripts within rows were not statistically different at the $p < .05$ level. MDD = major depressive disorder; CDI = Child Depression Inventory; BDI = Beck Depression Inventory; ERP = event-related potential; ERN = error-related negativity; CRN = correct-related negativity; ΔERN = ERN minus the CRN.

^a $N = 38$. ^b $N = 16$. ^c $N = 24$.

ΔERN among children with recurrent maternal depression compared to no maternal depression). The ΔERN did not vary by child depression symptoms, $r(76) = .00$, $p = .99$, and when children's CDI scores were included as a covariate in the analysis, the difference between error and correct trials (the ΔERN) still differed between children of mothers with recurrent MDD versus no history of depression, $F(2, 72) = 3.05$, $p = .05$, $\eta_p^2 = .09$, suggesting that the results were not due simply to the children's current depression. This group difference was also maintained when we statistically controlled for mothers' BDI-II scores, $F(1, 58) = 5.50$, $p = .02$, $\eta_p^2 = .09$, suggesting that they were not simply a function of group differences in current depressive symptom levels. Finally, the group difference was maintained when excluding mothers and children with current or past anxiety disorders, $F(2, 54) = 3.42$, $p = .04$, $\eta_p^2 = .11$, suggesting that the results were not due to anxiety in the mother or child. In addition, when the children with a major or minor lifetime history of MDD were included in the analysis, the pattern of results remained the same, $F(2, 92) = 3.34$, $p = .02$, $\eta_p^2 = .07$. A follow-up analysis in which maternal BDI score was included in the model as a covariate and maternal depression group was entered as the between-subject factor, suggested that although maternal depression status was still related to the ΔERN, $F(2, 72) = 2.89$, $p = .06$, $\eta_p^2 = .07$, maternal BDI was not related to the

ΔERN, $F(1, 72) = .11$, $p = .74$, $\eta_p^2 = .00$. Again, post hoc analyses suggested that when controlling for maternal BDI scores, the ΔERN was smaller in the recurrent maternal depression group compared to the no maternal MDD group, $F(1, 58) = 5.50$, $p = .02$, $\eta_p^2 = .09$. When child anxiety symptoms (measured by the Multidimensional Anxiety Scale for Children; Baldwin & Dadds, 2007) were entered as a covariate in the analyses, the pattern of results remained consistent, $F(2, 65) = 3.07$, $p = .05$, $\eta_p^2 = .09$, as well as when maternal anxiety symptoms (measured by the Beck Anxiety Inventory; Fydrich et al., 1992) were entered as a covariate, $F(2, 73) = 2.65$, $p = .07$, $\eta_p^2 = .07$. In a follow-up model investigating whether maternal BDI scores related to the ΔERN across maternal depression groups, results suggested that a smaller ΔERN in children was associated with higher current maternal depression symptoms, $r(76) = .25$, $p = .02$ (see Figure 2).

DISCUSSION

The primary goal of this study was to examine reduced error-related brain activity as a potential biomarker of risk among children of depressed mothers. Consistent with hypotheses, we found that children of mothers with a history of recurrent MDD exhibited blunted error-related brain

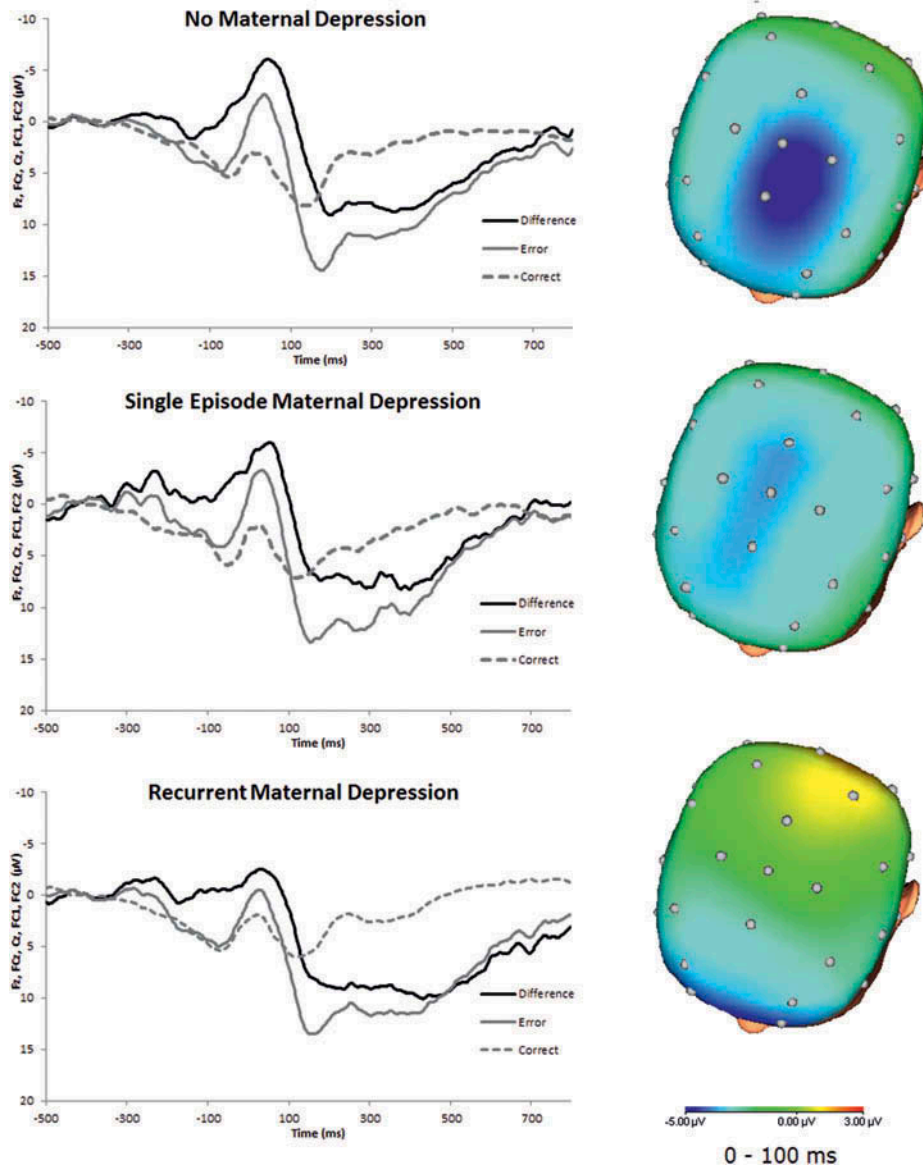


FIGURE 1 On the left, response-locked ERP waveforms for correct and error trials, as well as the difference waves. On the right, topographic maps of activity (error minus correct). Top = children with no maternal depression, middle = children with a single episode of maternal depression, bottom = children with recurrent maternal depression.

activity compared to children of mothers with no depression history. These results were specific to the Δ ERN and were not observed for the ERN or CRN individually, suggesting that the effect is due to the difference between correct and incorrect trials rather than to either trial type considered individually. The current findings are consistent with previous studies that found attenuated error processing in currently depressed adults (Olvet et al., 2010; Weinberg et al., 2012) and children (Ladouceur et al., 2012) and extended these findings by examining the relationship of *maternal* depression to the Δ ERN in never-depressed children. Of importance, maternal depression group difference in Δ ERN

was maintained when we statistically controlled for mothers' and children's current depression symptom levels, suggesting that they are not simply state effects due to current symptoms and may in fact index *risk* for depression in children.

Along with other previously explored mechanisms (e.g., HPA axis reactivity, attributional style, self-image, attentional biases), a blunted Δ ERN may be another mechanism by which maternal depression increases risk for depression in offspring. Given that the ERN is highly heritable (Anokhin et al., 2008), it is possible that chronically depressed mothers confer risk to offspring via genetic disposition toward

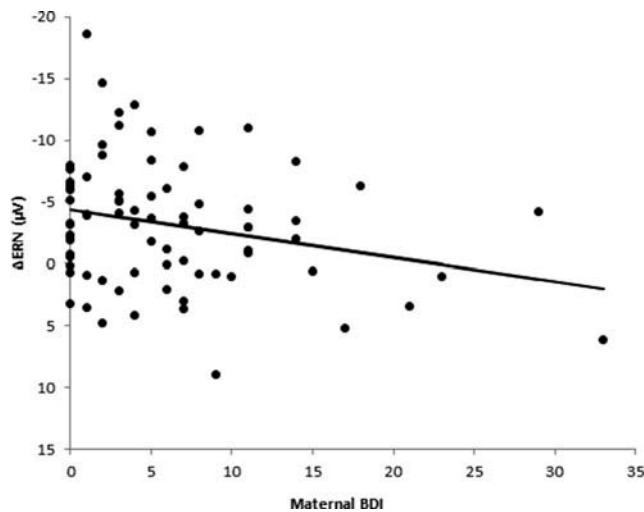


FIGURE 2 Scatter plot depicting the relationship between maternal depression symptoms and child error-related brain activity. ERN = error-related negativity; BDI = Beck Depression Inventory.

reduced neural reactivity during action monitoring. Indeed, recurrent MDD in parents is associated with increased heritability (Bland, Newman, & Orn, 1986) and greater risk for depression in offspring (Brennan et al., 2000; Keller, 1986; Klein et al., 1988) compared to single-episode MDD. Alternatively, it is also possible that chronically depressed mothers impact children's Δ ERNs via environmental pathways (e.g., parenting, life stress, modeling). Supporting this hypothesis, maternal depression has been linked to altered parenting styles (Lovejoy, Graczyk, O'Hare, & Neuman, 2000), and we recently found that harsh parenting styles are related to an larger Δ ERN in offspring (Meyer et al., 2014). Future studies might further examine the route by which recurrent maternal depression impacts the ERN.

There are a number of ways in which a blunted Δ ERN may confer risk for depression. Reduced ACC metabolism and activity during a Stroop task (George et al., 1997; Pizzagalli et al., 2001), as well as reduced ACC activity during reward processing (Forbes et al., 2006) and cognitive tasks (Halari et al., 2009), have been observed in depressed individuals. The Δ ERN is thought to reflect reinforcement learning signals sent from the mesolimbic dopamine system to the ACC (Holroyd & Coles, 2002) and, therefore, a reduction in this neural response may reflect dysfunction with dopaminergic systems that impact risk for depression. A relatively small Δ ERN may reflect differences in motivation, volition, attention, or learning that may also relate to risk for depression. In this way, a reduced Δ ERN may relate to learning or executive functioning impairments, which frequently characterize depressed children (Favre et al., 2009). In the current study, neither accuracy nor reaction times differed between the maternal depression groups. However, posterror

slowing was larger during incongruent trials among children in the recurrent maternal MDD group in the absence of improved accuracy. Posterror slowing is thought to indicate the recruitment of cognitive control (Rabbitt, 1966), and slowing during incongruent trials has been attributed to perceptual interference or competition among competing responses (Eriksen & Eriksen, 1974; Eriksen & Schultz, 1979). This suggests that children in the recurrent maternal MDD group may have had to recruit more cognitive control to deal with error commission and incongruent stimuli to achieve the same outcome as children without a history of maternal recurrent depression, potentially indicating relative processing inefficiency.

It is also possible that a reduced Δ ERN reflects motivational deficits among high-risk offspring. For example, volition has been related to ACC functioning (Nitschke & Mackiewicz, 2005) and is often impaired in depressed individuals. Therefore, it is possible that a diminished Δ ERN may relate to disinterest or low motivation during task performance. According to the emotion context insensitivity model, depression is related to reduced reactivity to both positive and negative stimuli (Bylsma, Morris, & Rottenberg, 2008). It is possible, therefore, that the reduced Δ ERN in children at risk for depression reflects a more general reduction in reactivity to negative compared to more neutral stimuli. To help differentiate among these possibilities, future work is needed to elucidate the specific psychological and biological mechanisms linking reduced Δ ERN to risk for depression.

It is important to note that it was not the ERN that specifically related to recurrent maternal MDD status, but rather the Δ ERN (error minus correct activity). A follow-up regression-based approach suggested that error-specific activity (the ERN_{res}) was decreased in the recurrent maternal MDD group. However, at a trend level, neural activity that was specific to correct trials (the CRN_{res}) was *increased* in the recurrent maternal MDD group. These results suggest that the *blunting* is somewhat specific to error processing but that recurrent maternal MDD may also relate to neural processes on correct trials in the opposing direction. Again, depression is related to motivational and engagement deficits. It is possible that offspring of mothers with recurrent MDD were less engaged in the task and, due to low attention, were less able to determine that they had made a correct response. It is also possible that children in the recurrent maternal MDD group displayed a negative bias wherein they perceived they were making errors on correct trials, thereby displaying a larger CRN_{res} . Future work is needed to clarify this issue.

A previous study investigating the relationship between maternal depression and the Δ ERN in offspring found no differences between children with and without a maternal history of depression (Torpey et al., 2013). However, this is not inconsistent with the current findings insofar as Torpey et al. (2013) did not investigate *recurrent* maternal

depression. It is possible that a large portion of the children included in that study had mothers with a single MDD episode, in which case we might not expect offspring Δ ERN to be altered. Furthermore, it is possible that differences in findings may be due to developmental influences: the relationship between psychopathology and the Δ ERN has been shown to shift across development (Meyer, Weinberg, Klein, & Hajcak, 2012) and the children included in the Torpey et al. (2013) study were relatively young compared to the current study.

Although maternal depression has been consistently associated with depression in offspring (Beardslee et al., 1998; Connell & Goodman, 2002; Hammen & Brennan, 2003; Klein, Clark, et al., 1988; Sullivan, 2000), it has also been associated with a range of other outcomes, including higher levels of anxiety, aggression, conduct problems, oppositional behavior, attention deficit hyperactivity disorder, and general negative affect in children (Goodman et al., 2011). It is possible that the children in the recurrent maternal depression group reflect a heterogeneous group, on different developmental trajectories. A blunted Δ ERN may predict the onset of later depressive episodes but could also be related to subsequent externalizing outcomes. In fact, a blunted ERN has been observed in individuals with externalizing symptoms (Hall, Bernat, & Patrick, 2007; Olvet & Hajcak, 2008). Longitudinal studies are needed to determine whether a blunted Δ ERN is related to specific risk trajectories across development.

One limitation to the current study is that we were unable to examine how paternal depression relates to children's Δ ERN. It is possible that recurrent maternal depression is particularly important or that both maternal and paternal depression would have a unique relationship with error processing in children. Furthermore, the current study included participants between the ages of 9 and 17. Future studies should examine the impact parental depression may have on error processing at earlier and later developmental time points. In addition, the current study included relatively fewer children with mothers with a single MDD episode (16 children). A post hoc power analysis suggested that although the current study was sufficiently powered to detect differences between the single MDD and no MDD groups (power = .84), it was not sufficiently powered to detect differences in the single MDD and recurrent MDD groups (power = .64). Future studies in larger samples should explore whether a single maternal depressive episode may impact children's Δ ERNs differently than recurrent maternal MDD. Finally, as the current study was cross-sectional, prospective studies are required to determine whether a reduced Δ ERN at certain developmental periods may predict the later onset of depression, in addition to or in conjunction with, other risk factors (e.g., HPA axis reactivity, attributional style, self-image, attentional biases). If a blunted Δ ERN does confer risk for the onset of subsequent

depression, it may be fruitful to investigate ways in which the Δ ERN can be modified to reduce risk. For example, recent findings suggest that attention bias modification can alter the ERN (Nelson, Jackson, Amir, & Hajcak, 2015) and thereby may be one method of altering risk trajectories.

In summary, therefore, the current results provide the first evidence that recurrent maternal depression is associated with altered error processing in children of depressed mothers. It is important that this effect was observed in children with no prior history of depression themselves and was maintained when statistically controlling for the influence of mothers' and children's current depressive symptoms, suggesting that the reduced Δ ERN observed in children of mothers with a history of recurrent MDD is not due simply to the presence of current depression in mothers or children. To truly determine whether Δ ERN reflects a mechanism in the intergenerational transmission of risk, longitudinal research will be needed. However, if supported, it would reflect a novel biomarker of risk and target for intervention (Nelson et al., 2015).

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