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Neurophysiological Processing of Emotion in Children of Mothers with a History of Depression: the Moderating Role of Preschool Persistent Irritability

Ellen M. Kessel[1] · **Autumn Kujawa**[1] · **Lea R. Dougherty**[2] · **Greg Hajcak**[1] · **Gabrielle A. Carlson**[3] · **Daniel N. Klein**[1,3]

Abstract Research on emotion-processing biases in offspring of depressed parents has produced a variety of findings. Child persistent irritability may be a useful clinical feature that demarcates subgroups of offspring with distinct patterns of emotion processing. The present study examined whether early persistent irritability moderated the relationship between maternal lifetime history of a depressive disorder and appetitive- and aversive-emotion processing in 338 never-depressed preadolescent children (43.8% female). When children were 3, mothers were interviewed about children's persistent irritability. Six years later, EEG was recorded while children completed a task in which the late positive potential (LPP), a neural index of emotional reactivity, was measured in response to appetitive, aversive, and neutral images. At both assessments, mothers were interviewed about their own psychopathology. Among offspring of depressed mothers, children characterized by high levels of early persistent irritability showed an enhanced LPP to appetitive and aversive compared to neutral images (i.e., ΔLPP), whereas children with low levels of early irritability showed attenuated ΔLPPs. In offspring of mothers with no history of depression, there was no association between irritability and emotion processing. Findings suggest that persistent irritability influences the pattern of emotion-processing aberrations in offspring of depressed mothers.

Keywords Offspring · Depression · Irritability · Emotion processing · Event-related potentials

Offspring of depressed parents are at elevated risk for depression, as well as a variety of other adverse outcomes including anxiety and externalizing disorders (Goodman et al. 2011). It is important to identify the processes that mediate this risk. A major focus of research in this area is emotion-processing abnormalities (Gotlib et al. 2014). Compared to their low risk counterparts, children of mothers with a history of depression have been consistently found to show aberrant patterns of emotion processing—a broad term that encompasses both neural and attentional reactivity to and regulation of emotional stimuli. However, the nature and pattern of these abnormalities differ between studies.

Behavioral, physiological, and neuroimaging studies have reported that offspring of depressed parents are more reactive to negative emotional information than offspring of non-depressed parents. For example, high-risk offspring show increased physiological reactivity (Burkhouse et al. 2014), selective attention (Joormann et al. 2007) and enhanced amygdala reactivity (Monk et al. 2008; Swartz et al. 2015) in response to threatening and aversive stimuli. However, other studies report a diametrically opposed pattern of processing for negatively valenced stimuli. These studies have reported that high-risk youth are characterized by emotional disengagement and attentional avoidance in response to negative stimuli (Kujawa et al. 2012; Nelson et al. 2015). For example, Gibb et al. (2009) found that daughters of depressed parents showed an attention bias *away* from sad faces. Still other fMRI studies fail to find any differences in

✉ Ellen M. Kessel
ellen.kessel@stonybrook.edu

[1] Department of Psychology, Stony Brook University, Stony Brook, NY 11794-2500, USA

[2] Department of Psychology, University of Maryland-College Park, College Park, USA

[3] Department of Psychiatry, Stony Brook University School of Medicine, New York, USA

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emotional reactivity, and instead suggest that offspring demonstrate reduced regulatory activity in response to aversive images (Mannie et al. 2011)

In addition to abnormalities in processing aversive stimuli, a smaller body of research indicates that offspring of depressed parents exhibit attenuated reactivity to appetitive stimuli such as happy faces and monetary reward. For example, Monk et al. (2008) found that compared to children of mothers without a lifetime history of depression, at-risk offspring showed reduced striatal activation in response to positive affective expressions. However, other studies find that high-risk offspring show intact processing of positive emotional stimuli (e.g. Burkhouse et al. 2014). This diversity of findings raises the possibility that there may be different subgroups of offspring of depressed parents who are characterized by distinct patterns of emotion processing abnormalities.

Particular symptom dimensions or temperament traits may be useful in demarcating distinct patterns of emotion processing in offspring of depressed parents. One potential candidate feature that is associated with parental history of depression is irritability (Dougherty et al. 2013; Krieger et al. 2013). Irritability is present in one-third to one-half of children and adults with depression, and there are notable differences between depressed youth and adults with and without irritability (Judd et al. 2013; Stringaris et al. 2013). For example, depressions accompanied by irritability are associated with greater comorbidity and a more severe and persistent course (Judd et al. 2013; Stringaris et al. 2013). In addition, irritability can be an early precursor to adolescent and adult depressive disorders (Vidal-Ribas et al. 2016), although many depressed adolescents and adults do not have a history of childhood irritability (Stringaris et al. 2013; Stringaris and Taylor 2015). Moreover, Whelan et al. (2015) recently found that childhood irritability uniquely mediated the relationship between maternal depressive symptoms and the later development of adolescent depression over and above childhood anxiety and depressive symptoms. Taken together, these data raise the possibility that irritability may mark a distinct pathway in the development and intergenerational transmission of depression.

There has been growing interest in the emotion processing correlates of childhood irritability. Most of this research has focused on Severe Mood Dysregulation (SMD), a condition characterized by severe, persistent irritability, in conjunction with hyperarousal symptoms. SMD was initially developed as a possible phenotype for childhood bipolar disorder (Leibenluft et al. 2003). However, subsequent research has shown that, like chronic irritability, SMD predicts later depressive, rather than bipolar, disorder (Brotman et al. 2006). Research on SMD suggests that it is characterized by hyperreactivity to potentially threatening and aversive cues (Thomas et al. 2013). For example, using the dot-probe task, Hommer et al. (2013) demonstrated that SMD symptoms were associated with greater attention bias toward angry facial cues. Consistent with these findings, neuroimaging evidence suggested that youth with SMD exhibited greater blood-oxygen-level-dependent (BOLD) activity in the medial occipital gyrus, posterior cingulate, and superior temporal gyrus—brain regions supporting emotion processing and social cognition—to angry faces (Thomas et al. 2014).

As the literature on SMD and its biological correlates is generally based on older children and adolescents, the extrapolation of these findings to other age groups must be done cautiously. However, given evidence that symptoms of irritability show moderate stability over time (Leibenluft et al. 2006), it is possible that irritability could also be associated with similar biological correlates at other ages. In addition to the literature on SMD, we have recently shown that persistent irritability in 3-year-old children prospectively predicted enhanced reward sensitivity in middle childhood (Kessel et al. 2016). Taken together, these studies suggest that irritability may be related to increased reactivity, regardless of the valence of the precipitating stimuli. As this differs from the patterns of deficits found in some studies of offspring of depressed parents (i.e., hyporeactivity to negative and positive stimuli), it is plausible that the presence of persistent irritability in children could account for some of the inconsistencies in the literature on emotion-processing biases in offspring of depressed mothers.

Event-related potentials (ERPs) derived from electroencephalography (EEG) can assess brain processes related to emotion processing across development (Kujawa et al. 2013). The late positive potential (LPP) is an ERP component that reflects facilitated attention to, and increased perceptual processing of, emotional versus neutral stimuli in both children (Kujawa et al. 2013) and adults (Schupp et al. 2004). Specifically, the amplitude of the LPP is larger for both appetitive and aversive compared to neutral stimuli beginning around 300 ms after a stimulus is presented; this differentiation persists throughout the duration of picture presentation (Hajcak and Olvet 2008). Thus, the emotional modulation of the LPP appears to index relatively early engagement with salient stimulus content.

The LPP is analyzed as the difference between mean amplitudes of emotional and neutral stimuli (i.e. the ΔLPP) in order to isolate neural activity elicited by emotional valence (Luck 2005). The ΔLPP shows good to excellent reliability across trials (Moran et al. 2013), and is also relatively stable throughout development (Kujawa et al. 2013); thus, the ΔLPP may reflect trait-like individual differences in patterns of emotional processing. Previous research has examined the ΔLPP in offspring of mothers with a history of depressive disorder. However, in parallel with the broader literature on maternal depression and child emotional reactivity, findings are also mixed. Several studies have found that maternal risk is associated with a blunted ΔLPP to aversive compared to neutral

faces (e.g. Kujawa et al. 2012), and a blunted LPP across emotional and neutral images (Nelson et al. 2015). However, one study reported that maternal risk is associated with an *enhanced* ΔLPP to aversive emotional stimuli (Speed et al. 2016). Importantly, no study to date has examined individual differences in the ΔLPP in relation to maternal depression in tandem with early persistent irritability in children.

The current study aimed to determine whether early childhood persistent irritability moderated the relationship between maternal history of depression and a neural measure of appetitive and aversive emotional-processing biases, the ΔLPP, in a never-depressed sample of 9-year old children. We hypothesized that at-risk children with and without a history of early persistent irritability would exhibit distinct patterns of emotional reactivity. We used a structured interview to assess persistent irritability in a large community sample of three-year old children. Six years later, children completed an emotion-processing task while ERPs were recorded. Given evidence that youth irritability and aberrant patterns of emotion processing are both associated with maternal anxiety and substance use disorders (Dougherty et al. 2013; Heitzeg et al. 2008; Nelson et al. 2015; Wiggins et al. 2014), and with youth depressive, anxiety, and externalizing symptoms (Bar-Haim et al. 2007; Dougherty et al. 2013, 2015; Kilford et al. 2015; Pincham et al. 2014), we controlled for maternal history of anxiety and substance use disorders and for children's concurrent anxiety, depressive and disruptive behavior disorder (DBD) symptoms.

Method

Participants

Participants were part of a larger prospective study of the role of temperament in risk for psychopathology (see Olino et al. 2010). Five hundred and fifty-nine families with 3-year-old children were recruited through a commercial mailing list. Families with children with no significant medical condition or developmental disability living with at least one biological parent were eligible. Only one child per family was included. Of those families, 541 provided diagnostic information about the child. At age nine, 425 families returned for a laboratory visit, at which time the emotion- processing task was administered. Data was not collected from 17 participants due to task refusal and data loss. Data from 65 participants were excluded due to poor EEG quality.[1] Because the aim of the study was to identify early markers of familial risk for depression, we also excluded four children who had already experienced a lifetime depressive episode and one child who was missing data on maternal depressive disorders. Thus, this report's final sample consisted of 338 children (43.8% female): 93.8% White, 3.3% Black/African American, 2.7% Asian and 0.3% Native American. With regards to ethnicity, 7.4% were of Hispanic/Latino origin. In 30.9%, one parent, and in 34.3% of families, two parents had a college degree. At the initial assessment of preschool child psychopathology, the mean child age was 3.55 (*SD* = 0.27), and at the follow up assessment, the mean age was 9.21 (*SD* = 0.41).

Procedure

Parents provided written informed consent and the Institutional Review Board approved all study procedures. Families were compensated for their time. When the children were approximately three-years-old, mothers were assessed for histories of psychopathology, and one parent reported on their child's current psychopathology. Families were invited back to the lab as close as possible to the child's ninth birthday. After verbal assent from children were obtained, children began the EEG portion of the visit, including a 10-min emotion-processing task. Children and one parent (typically mothers) also completed a semi-structured diagnostic interview to assess lifetime child psychopathology, and mothers completed another diagnostic interview assessing their own psychopathology.

Measures

Preschool Persistent Irritability At age three, a parent (typically the mother) was interviewed regarding their child's symptoms using the Preschool Age Psychiatric Assessment (PAPA; Egger et al. 2004). The PAPA uses a three-month primary period in order to maximize the accuracy of parents' reports. PAPA items were rated for intensity, frequency, and duration. The intensity rating indicates whether a symptom was absent or present and the extent to which it was intrusive, interfering, and generalizable across activities. A rating of two or higher indicates that the symptom was present at a threshold level of intensity. Six items from the PAPA were used to assess irritability. Items corresponded to items from the Affective Reactivity Index (ARI), a parent-and child-reported chronic irritability scale for youth (Stringaris et al. 2012). The PAPA items used were: irritable mood, prone to feelings of anger under minor provocation, prone to displays of anger under minor provocation, prone to feelings of frustration under minor provocation, discrete episodes of temper without violence, and discrete episodes of excessive temper with violence or attempts at damage directed against oneself, others, or property. Following Brotman et al. (2006) and Copeland et al. (2013), each item was coded as present if a child was prone to the

[1] The 65 subjects that were removed due to poor EEG data did not differ on preschool persistent irritability, $p = ns$. However, those that were removed due to poor EEG data were more likely to have a mother with a lifetime history of depressive disorder ($p = 0.05$) and anxiety disorder ($p < 0.05$) and have greater depressive ($p < 0.01$) and disruptive behavior ($p < 0.01$) symptoms at age 9.

behavior/feeling at least once every other day (i.e. 45 times in the past three months). In addition, to assess whether the child experienced irritable mood for a long time, this criterion was coded present if the child was rated as having at least a 30-min duration on the irritable mood, prone to frustration, annoyance or anger, or difficulty recovering from temper tantrums items. The total irritability scale consisted of the sum of symptoms coded as present according to the intensity, frequency, and duration criteria listed above (see Dougherty et al. 2013 for further details). The Cronbach alpha coefficient for internal consistency for the persistent irritability scale was 0.74.

Maternal Psychopathology At the age three assessment, biological mothers were interviewed using the Structured Clinical Interview for DSM–IV Non-patient Edition (SCID; First et al. 1996). Interrater reliability (kappa) was 93 for lifetime depressive disorder, 0.91 for lifetime anxiety disorder and 1.00 for lifetime substance abuse disorder (n = 30). At the age nine assessment, the SCID was re-administered to biological mothers to assess psychopathology in the years since the initial assessment. Interrater reliabilities (kappa) were 0.91, 0.73, and 0.90 for depressive, anxiety, and substance use disorders, respectively. At both waves, interviews were conducted by advanced clinical psychology graduate students and master's-level clinicians under the supervision of a licensed clinical psychologist. Diagnoses from the age three and nine assessments were combined to yield lifetime diagnoses. 122 (36.1%) of mothers had a lifetime history of major depressive or dysthymic disorders; however only 4 (3.3%) were in a current episode at the time of the age 9 assessment.

Current Child Psychopathology At the age nine assessment, one parent (generally the mother) and the child were interviewed using the Schedule of Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime (K-SADS-PL; Axelson et al. 2009). Advanced doctoral students in clinical psychology and a master's-level clinician, supervised by a child psychiatrist and a clinical psychologist, administered the K-SADS first to the parent and then to the child. Summary ratings for each symptom were derived based on the combination of parent and child reports. Current symptoms of depressive, anxiety, and disruptive behavior disorders were rated on a 3-point scale (0 = *not present*; 1 = *subthreshold*; 2 = *threshold*), and were summed to create dimensional scores that were used as covariates. Inter-rater reliabilities (intraclass correlations) for depressive, anxiety, and DBD scores were 0.83, 0.82 and 0.93, respectively.

Emotion Processing Task The Emotion Interrupt task is a computerized task that requires participants to click either the left or right mouse button in response to a target (a left or right arrow) while viewing developmentally appropriate appetitive, aversive, and neutral images selected from the International Affective Picture System (IAPS; Lang et al. 2008). The task was administered using Presentation software (Neurobehavioral Systems) similar to the version used in previous studies (Kujawa et al. 2013). A total of 60 developmentally appropriate pictures were selected: 20 appetitive scenes (e.g., children playing, cute animals, babies), 20 neutral scenes (e.g., people in neutral situations, neutral outdoor scenes, household objects), and 20 aversive scenes (e.g., sad or angry people, weapons, aggressive animals). Each image was randomly presented once in each of two blocks for a total of 120 trials. Each trial began with an 800 ms fixation (+), then an image was presented for 1000 ms followed by a target (< or >) presented for 150 ms and the same picture presented for an additional 400 ms. The inter-trial interval varied randomly between 1500 and 2000 ms. (see Kujawa et al. 2013 for details).

EEG Recording and Analysis Continuous electroencephalogram (EEG) was recorded using a 34-channel Biosemi system based on the 10/20 system (32 channel cap with the addition of Iz and FCz). Two electrodes were placed on the left and right mastoids, and the electrooculogram (EOG) generated from eye blinks and movements was recorded from two facial electrodes approximately one cm above and below the participant's left eye, one electrode approximately one cm to the left of the left eye, and one approximately one cm to the right of the right eye. The ground electrode during acquisition was formed by the Common Mode Sense active electrode and the Driven Right Leg passive electrode. The data were digitized using ActiView software at 24-bit resolution with a LSB value of 31.25 nV and a sampling rate of 1024 Hz, using a low-pass fifth order sinc filter with a half-power cutoff of 204.8 Hz. Off-line analysis was performed using Brain Vision Analyzer software (Brain Products). All data were converted to a mastoid reference and band-pass filtered with cutoffs of 0.1 and 30 Hz. The EEG was segmented for each trial, beginning 200 ms before each picture onset and continuing for 1000 ms after the initial image presentation. The EEG was corrected for eye blinks (Gratton et al. 1983), and semi-automated artifact rejection was used to remove artifacts with a voltage step of more than 50 μV between sample points, a voltage difference of 300 μV within a trial, or a maximum voltage difference of less than 0.5 μV within 100 ms intervals. Visual inspection was then used to reject trials in which additional artifacts were observed. ERPs were constructed by separately averaging the responses to appetitive, neutral, and aversive images. Only correct trials were included in averages to ensure that participants were paying attention.[3] ERPs were baseline corrected to the 200 ms interval prior to stimulus onset. The LPP was scored as the mean activity 300–1000 ms after the onset of the pre-target image averaged at parietal (P3, P4, and Pz) and occipital sites (O1, O2, and Oz), which is consistent with previous developmental research

(Kujawa et al. 2013) and where the difference between emotional and neutral images were maximal. The LPP was examined as the difference between the mean amplitude on appetitive and aversive relative to neutral trials (ΔLPP-Appetitive and ΔLPP- Aversive).[2,3]

Data Analysis

We conducted a mixed-model ANOVA to examine the main and interactive effects of maternal depression and preschool persistent irritability on ΔLPP at occipital and parietal sites (Luck 2005). In the models, Emotion (ΔLPP-Aversive, ΔLPP-Appetitive) and Electrode Site (Occipital, Parietal) were entered as a within-subject variable and maternal history of depression and preschool persistent irritability and their interaction were entered as between-subject variables. Child characteristics (sex, age, depressive, anxiety and DBD symptoms) and other maternal psychopathology (maternal lifetime diagnoses of anxiety, and substance disorders) were also entered as covariates. Continuous variables were centered to examine interactions. The preschool persistent irritability and current depression, anxiety, and DBD scores were standardized (z-score). As all interactions involved one continuous and one categorical variable, significant interactions were interpreted by evaluating the model separately for children with and without maternal histories of depression.

Results

Descriptive statistics and bivariate correlations between all study variables are presented in Table 1. Current depressive symptoms were weakly correlated with both anxiety and DBD symptoms. Current anxiety symptoms were significantly associated with both a maternal history of depression and anxiety; current depressive symptoms were associated with a maternal history of anxiety; and DBD symptoms were associated with a maternal history of depression. Persistent irritability symptoms at age three were associated with a maternal history of depressive, anxiety, and substance use disorders, a higher number of both anxiety and DBD symptoms at age nine, and a more enhanced or positive ΔLPP to appetitive images at parietal sites.

A mixed-model ANOVA was computed to examine the effects of maternal depression and early persistent irritability on the ΔLPP at occipital and parietal sites. The overall main effects of emotion, $F(1, 327) = 32.39$, $\eta^2 = 0.09$, $p < 0.001$, electrode site, $F(1, 327) = 8.41$, $\eta^2 = 0.02$, $p < 0.001$, and their interaction, $F(1, 327) = 12.01$, $\eta^2 = 0.03$, $p < 0.001$ were significant. There was no main effect of maternal history of depression, $F(1, 327) = 0.237$, $\eta^2 = 0$, $p = ns$. Additionally, the emotion X maternal depression, emotion X preschool persistent irritability, and emotion X maternal depression X preschool persistent irritability, electrode site X maternal depression, electrode site X preschool persistent irritability, and electrode site X maternal depression X preschool persistent irritability, and emotion X electrode site X maternal depression, emotion X electrode site X preschool persistent irritability, and emotion X electrode site X maternal depression X preschool persistent irritability interactions were not significant.

However, there was there was a marginally significant main effect of persistent irritability $F(1, 327) = 3.78$, $\eta^2 = 0.01$, $p = 0.05$, that was qualified by a significant interaction between maternal depression and age 3 persistent irritability, $F(1, 327) = 6.94$, $\eta^2 = 0.02$, $p < 0.01$. For offspring of mothers with a history of depression, greater irritability at age three was associated with an enhanced ΔLPP to emotional images (both aversive and appetitive) and both occipital and parietal sites, $F(1, 113) = 11.73$, $\eta^2 = 0.09$, $p < 0.001$. For offspring of mothers with no history of depression, the effect of early irritability was not significant, $F(1, 207) = 0.89$, $\eta^2 = 0.01$, $p = ns$. (see Fig. 1).[4]

Discussion

The current study aimed to determine whether early childhood persistent irritability moderated abnormalities in emotional processing of appetitive and aversive stimuli in offspring of mothers with a lifetime history of depression. We found that among offspring of mothers with histories of depression, high levels of early persistent irritability predicted enhanced ΔLPPs (i.e., increased reactivity to emotional vs. neutral stimuli) to both appetitive and aversive emotional images. Importantly, these associations were independent of child demographics,

[2] The mean number of LPP trials to unpleasant stimuli was 31.76 (*SD* = 5.27) at parietal sites, and 32.96 (*SD* = 4.93) at occipital sites. The mean number of LPP trials to pleasant stimuli was 31.95 (*SD* = 5.24) at parietal sites, and 32.12(*SD* = 4.94) at occipital sites. The mean number of LPP trials to neutral stimuli was 33.34 (*SD* = 5.08) at parietal sites, and 33.49 (*SD* = 4.76) at occipital sites.

[3] Consistent with previous studies using the Emotion Interrupt task to elicit the LPP in response to emotional images in children (Kujawa et al. 2012; 2013), we observed weaker effects for the ΔLPP-Appetitive compared to the ΔLPP-Aversive at both occipital, $t(337) = -6.83$, $p < 0.05$, and parietal sites $t(337) = -10.47$, $p < 0.05$. LPPs have previously been observed to be larger in response to aversive compared to appetitive stimuli in children, but this may be because developmentally appropriate subcategories (e.g., cute, furry animals and babies) have weaker effects on the LPP than more salient images such as erotica or other developmentally inappropriate stimuli (Weinberg and Hajcak 2010). This may have contributed to the difference in magnitude between ΔLPP-Appetitive compared to the ΔLPP-Aversive.

[4] Accuracy across all conditions differed between groups $F(1335) = 8.03$, $p < 0.05$, such that offspring of mothers with a history of depressive disorder (*M* = 81.84% *SD* = 12.46) had a lower accuracy rate than offspring of mothers with no history of depressive disorder (*M* = 85.21% *SD* = 9.20). When accuracy was included as a covariate in the current analyses, results were virtually identical.

Table 1 Descriptive statistics and pearson's correlations/phi coefficients between study variables in a sample of (N = 338) preadolescent children

	M(SD) or %	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Gender (% female)	43.8%	__	-0.01	-0.07	-0.07	-0.01	-0.11*	0.06	0.07	0.03	0.06	0.04	-0.06	-0.09
2. Age	9.21(0.41)		__	-0.02	-0.06	0.01	-0.03	0.01	0.04	-0.02	0.01	-0.01	0.04	0.09
3. Age 3 persistent irritability	0.71(1.29)			__	0.03	0.25**	0.33**	0.22**	0.14**	0.13*	0.04	0.10	0.05	0.11*
4. Current depression	0.38(1.33)				__	0.13*	0.21**	0.10	0.16**	0.07	-0.09	0.01	-0.04	0.06
5. Current anxiety	3.60(5.63)					__	0.03	0.25**	0.23**	0.09	-0.06	-0.01	-0.05	0.06
6. Current DBD	0.92(2.38)						__	0.12*	0.07	-0.05	0.04	0.07	0.02	0.06
7. Maternal depression	36.1%							__	0.23***	0.16**	0.01	0.04	-0.09	0.03
8. Maternal anxiety	35.5%								__	0.26***	0.03	0.01	-0.01	0.03
9. Maternal SUD	22.2%									__	0.00	-0.01	-0.01	-0.03
10. Δ LPP aversive occipital	5.26(7.22)										__	0.55**	0.72**	0.34**
11. Δ LPP appetitive occipital	2.79(6.68)											__	0.38**	0.69**
12. Δ LPP aversive parietal	4.84(6.78)												__	0.54**
13. Δ LPP appetitive parietal	1.19(6.54)													__

DBD disruptive behavior disorder, *SUD* Substance Use Disorder, *LPP* late positive potential

* $p \leq .05$, ** $p < 0.01$, *** $p < 0.001$

maternal lifetime history of anxiety and substance use disorders, and children's concurrent symptoms of depression, anxiety, and DBD. In contrast, in offspring of mothers who did not have a lifetime history of depression, there were no associations between early persistent irritability and the ΔLPP to either aversive or appetitive stimuli.

Results of the present study are consistent with previous studies indicating that offspring of mothers with a lifetime

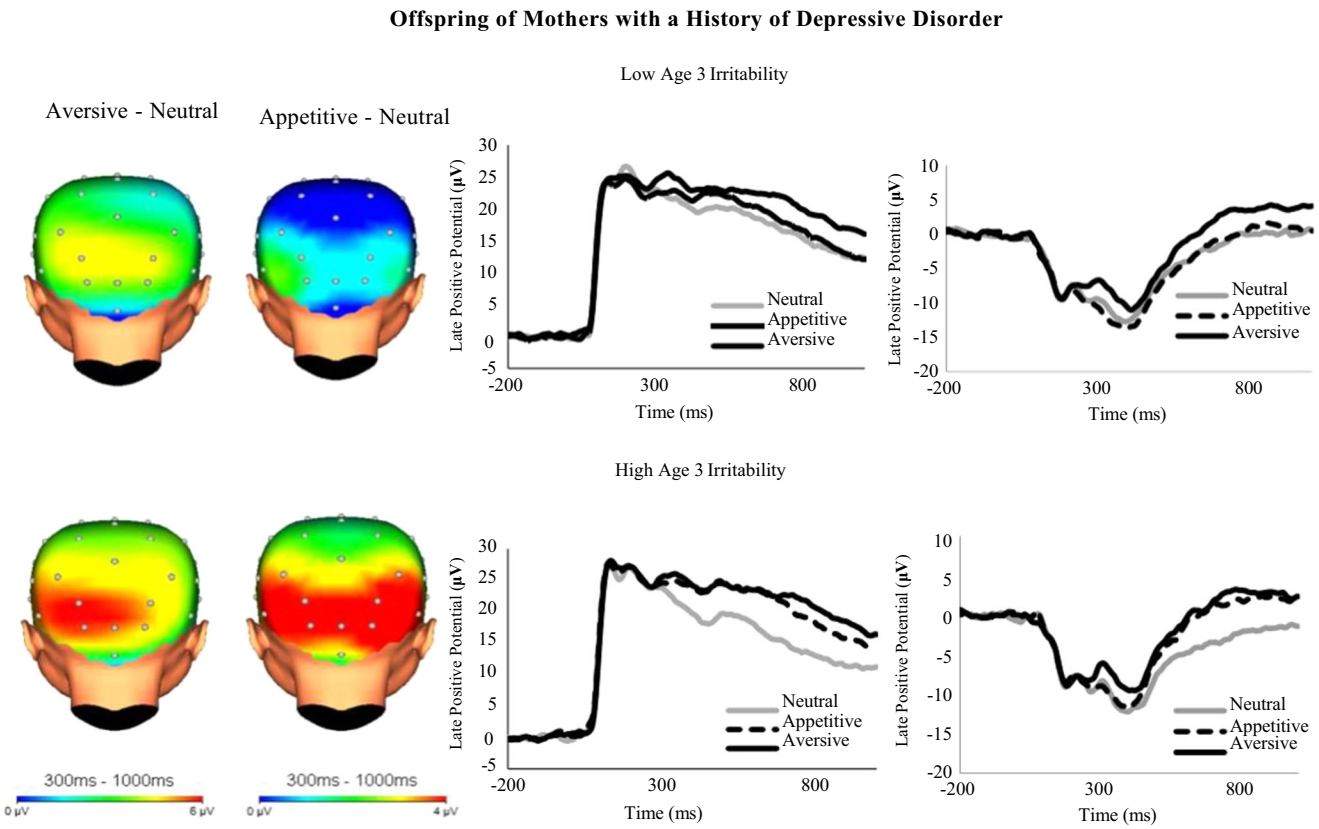

Fig. 1 ERPs at occipital (*left*) and parietal (*right*) sites following neutral, appetitive, and aversive stimuli (*right*) and the scalp distribution (*left*) depicting the aversive-neutral and appetitive-neutral difference 300-1000 ms after picture onset in offspring of mothers with a lifetime history of depression with high (*top*) and low (*bottom*) levels of early irritability based on a median split

history of depression show aberrant patterns of emotion processing (Gotlib et al. 2014). However, to our knowledge, the present findings are the first to suggest that children's persistent irritability influences the nature of these emotion-processing abnormalities. Among offspring of depressed mothers, children with high levels of early irritability exhibited heightened neural reactivity to both appetitive and aversive vs. neutral emotional images, whereas children with low levels of early irritability were characterized by reduced neural reactivity to both appetitive and aversive vs. neutrally valenced emotional information. These different patterns of emotion processing associated with maternal depression raise the possibility that there may be at least two subgroups of high-risk youth, one of which is relatively more disengaged from, and another that is relatively more sensitive to, the environment. There is an accumulating body of evidence suggesting that both of these patterns of emotion processing are evident in depressed adults and the offspring of depressed mothers (e.g. Bylsma et al. 2008; Gibb et al. 2009; Joormann et al. 2007; Monk et al. 2008). However, the present findings suggest that seemingly conflicting results in the literature may actually reflect meaningful heterogeneity, and that the presence or absence of early persistent irritability may be an indicator of distinct patterns of emotional reactivity.

These results also fit with an accumulating body of evidence that disrupted emotion processing comprises a liability spectrum that cuts across traditional diagnostic boundaries (Kret & Kret and Ploeger 2015). The pattern of relative emotional disengagement among offspring of mothers with a history of depression, which was evident in those with low irritability, may indicate withdrawal from and consequently poorer adjustment to one's environment. Indeed, such patterns have been associated with deficits in emotional awareness, social attachment, empathy, and interpersonal relating (Bird and Viding 2014). The pattern of relative emotional hypersensitivity that was evident in children of mothers with a history of depression and early persistent irritability, on the other hand, may indicate a vulnerability linked to increased sensitivity to the environment. Increased reactivity to aversive information may be a causal mechanism underlying persistent fear and dysphoria (e.g. Bar-Haim et al. 2007; Kilford et al. 2015). Increased reactivity to appetitive stimuli, on the other hand, may indicate a specific vulnerability to feelings of frustration and anger when appetitive goals are blocked (Hankin et al. 2012), which, in some cases, may manifest in externalizing behavior (Yoon and Knight 2015).

Interestingly, early persistent irritability only showed meaningful associations with later neural reactivity to appetitive and aversive stimuli in offspring of mothers with a history of depression; irritability in offspring of mothers with no history of depression was unrelated to the ΔLPP to appetitive or aversive emotional images. Although irritability is commonly conceptualized as a dimension that cuts across disorders, it may itself be a heterogeneous construct. That is, the irritability in children at high risk for depression may be etiologically and pathophysiologically distinct from some of the other forms of irritability in other types of youth psychopathology. Twin studies indicate that shared genetic effects influence the overlap between irritability and depression, whereas non-shared influences are largely due to environmental factors (Stringaris et al. 2012). This raises the possibility that irritable offspring of depressed mothers may be distinguished by a specific heritable component that is not present in offspring of non-depressed mothers. It is unclear, however, what processes mediated the relationship between early persistent irritability and the ΔLPP to appetitive or aversive emotional images six years later. One possibility is that mothers with a history of depression may be more likely to engage in parenting practices that may maintain or exacerbate the emotional reactivity characteristic of early irritability throughout development. That is, highly irritable children of depressed mothers may fail to receive parenting that bolsters the development of the self- regulatory skills that can buffer against a propensity for heightened emotional reactivity (Whelan et al. 2015). Alternatively, given evidence that symptoms of irritability show moderate stability (Leibenluft et al., 2006), it is also plausible that irritability's association with the ΔLPP may be the result of its current rather than early manifestations. Future research is needed to examine these possibilities.

It is important to note that there was significantly more variation in irritability among offspring of mothers with a history of depression compared to offspring of mothers with no history of depression to detect associations between irritability and the ΔLPP to aversive and appetitive stimuli. However, given that there was a comparable range in irritability scores and the association between irritability and the ΔLPP were in opposite directions in the two groups, even though it was only significant among offspring of depressed mothers, it is unlikely that both groups of offspring show the same pattern of associations between irritability and the ΔLPP to appetitive and aversive stimuli.

There were no associations between current child depression, anxiety, and DBD symptoms and the ΔLPP. This is not particularly surprising given the limited range of depression symptoms in the current sample, and the enormous heterogeneity comprising both anxiety and DBD. Examining specific phenotypes such as irritability to identify more homogenous subgroups of individuals may be a more promising approach to identifying transdiagnostic neural mechanisms associated with psychopathology.

Despite its strengths, such as the large sample size and multi-method prospective design, this study has a number of

limitations. First, as there is no validated measure for persistent irritability in preschoolers, we derived our own measure using items from a well-validated diagnostic interview (Egger et al. 2006) and guided by the content of a well-validated scale for irritability in older children (Stringaris et al. 2012). However, our measure has shown good concurrent and predictive validity in previous reports (Dougherty et al. 2013, 2015). Second, we did not examine the ΔLPP to emotional images in early childhood or current manifestations of persistent irritability; thus we are unable to determine whether emotion-processing abnormalities precede, or are a correlate or consequence of early persistent irritability. Third, we cannot address the process of how early irritability influences later emotion processing. Fourth, the percentage of explained variance of the regression models is relatively small. However, this may be attributed to the substantial difference in methods, as small associations are commonly found between neurophysiological and parent-report measures (Patrick et al. 2013) as well as the lengthy interval between the clinical and electrophysiological assessments. Fifth, we cannot determine whether irritable and non-irritable offspring of mothers with a lifetime history of maternal depression show abnormal patterns of emotional engagement or disengagement in an absolute sense. Lastly, it is unclear whether the patterns of emotion-processing disruptions found in offspring of depressed mothers mediate the developmental pathway to later psychopathology or whether they are simply correlates of a maternal history of depression. However, they are unlikely to be correlates of current maternal depression, as only a handful of mothers were in a current depressive episode. To address these questions, we are continuing to follow these children and will examine the potential mediating role of the ΔLPP to aversive and appetitive stimuli on risk for developing psychopathology.

Conclusions

The present study was the first to examine whether early child persistent irritability moderates the relationship between maternal history of depression and neural reactivity to appetitive and aversive emotional stimuli. Results indicate that irritability influences the pattern of emotion-processing abnormalities in offspring of depressed mothers, such that offspring with high levels of early irritability showed enhanced ΔLPPs, whereas offspring with low levels of early irritability showed reduced ΔLPPs to *both* appetitive and aversive emotional stimuli. These findings suggest that early childhood irritability may be an important offspring characteristic to consider when examining child emotion processing biases and their role in the intergenerational transmission and development of depression.

Compliance with Ethical Standards

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Conflicts of Interest None.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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