Research paper

Differential neural responding to affective stimuli in 6- to 8-year old children at high familial risk for depression: Associations with behavioral reward seeking

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ABSTRACT
Objective: Children of depressed parents are at increased risk for psychopathology. One putative mechanism of risk appears to be altered processing of emotion-related stimuli. Although prior work has evaluated how adolescent offspring of depressed parents may show blunted reward processing compared to low-risk youth, there has been less attention to how young children with this familial history may differ from their peers during middle childhood, a period of critical socio-affective development.

Method: The current study evaluated 56 emotionally healthy 6- to 8-year old children who were deemed at high-risk (n = 25) or low-risk (n = 31) for depression based on maternal history of depression. Children completed a behavioral reward seeking task in the laboratory and an fMRI paradigm assessing neural response to happy faces, a social reward.

Results: Findings demonstrated that high-risk children showed blunted responding to happy faces in the dorsal striatum compared to low-risk children. Further, lower responding in the dorsal striatum and dorsolateral prefrontal cortex was related to lower behavioral reward seeking, but only in high-risk children.

Conclusion: Function within neural reward regions may be altered in high-risk offspring as young as 6- to 8-years of age. Further, neural reward responding may be linked to lower behavioral response to obtain reward in these high-risk offspring.

1. Introduction
Children of depressed parents are at increased risk for developing depression and other psychiatric illnesses relative to their peers (Goodman and Gotlib, 1999; Weissman et al., 2006). Although these elevated rates of psychiatric illness are well established, the mechanisms underlying this transmission of risk are less understood. Some evidence suggests that high-risk youth appear to possess neurophysiological differences in the way they process threat and that these differences emerge prior to the onset of psychiatric illness and predict the onset of symptoms (LeMoult et al., 2015; Waugh et al., 2012). Given that depression is a disorder of altered positive affect (Forbes and Dahl, 2005; 2012), with anhedonia and disrupted social behavior being particularly characteristic of depression, differences in how these youth neurally respond to positive emotion-eliciting events and stimuli may be especially important.

Positive affect has important functions including buffering against stress and facilitating recovery from illness (Fredrickson, 1998; 2001). Importantly, positive affect also promotes approach toward new and social experiences, even in the face of adversity (Fredrickson, 1998; 2001). Indeed, in early and middle childhood, positive affect may assist in building new friendships and in the pursuit of emotional and social learning (Izard, 2002). In that regard, altered responding in reward and positive affective circuitry may interfere with social approach and pursuit in new and challenging situations.

Neural regions implicated in reward and positive affective proces-
A growing body of work has demonstrated that adolescent offspring of depressed parents show altered neural responding to reward in multiple of the aforementioned neural regions (Gotlib et al., 2010; Luking et al., 2016; Monk et al., 2008; Oline et al., 2014; Sharp et al., 2014). Specifically, high-risk adolescents have been demonstrated to show blunted responding in the ventral and dorsal striatum and orbitofrontal cortex in response to anticipating or winning monetary reward or in response to positive stimuli, such as happy faces. These findings mirror similar neural reward patterns observed in clinically depressed adolescents and adults (Forbes et al., 2009; Ng et al., 2018; Zhang et al., 2013). Our prior work has also demonstrated that these reward-related alterations preceded increases in depressive symptoms across a 2-year period in community adolescents (Morgan et al., 2013a, 2013b), suggesting that these reward disruptions are important to the pathophysiology of depression.

However, less work has evaluated how young, prepubertal children at high familial risk for depression may respond neurally to reward-related stimuli. Behavioral work has demonstrated that high-risk children as young as 3-months to 3-years old show lower positive emotion expression compared to their low-risk peers (Durbin et al., 2005; Field, 2010). Given that neurobehavioral work has found a link between neural responding in reward regions (e.g., ventral striatum) and positive affect expression in healthy adolescents (Forbes et al., 2010), high-risk children may likewise show diminished responding in neural reward regions and this diminished neural responding may be related to the lower behavioral responding previously observed in young children. Two recent studies have demonstrated that prepubertal offspring (ages 6–10) showed blunted striatal and prefrontal response to gain feedback relative to low risk peers (Luking et al., 2016; Wiggins et al., 2017). Likewise, blunted responsivity to reward has been demonstrated in prepubertal children either at high-risk for depression due to family history or increases in depressive symptoms in work using event related potentials (ERP) (Bress et al., 2012; Kujawa et al., 2019, 2014). However, more work is needed to confirm these aberrations and link them to behavioral differences in children of this age and younger.

More specifically, altered function in reward-related regions may already be present in children at familial risk for depression during early to middle childhood and these alterations may be directly related to disruptions in the pursuit of socially rewarding, goal-driven behavior during this developmental point at which social and play behavior is becoming more sophisticated and is important for normative social and emotional learning (Nelson et al., 2016). Understanding these neurobehavioral differences during early to middle childhood is key, as this is a period during which critical socio-affective foundations (e.g., regulating affect, creating social bonds) are built. Disruptions to these developmental processes could create susceptibility to depression during the vulnerable period of adolescence.

In the current study, we evaluated neural and behavioral reward-related differences in young 6- to 8-year-old emotionally healthy children who were designated to be at high- or low-risk for depression based on maternal history. We chose to evaluate children of this age as middle childhood is a period of vast socio-emotional learning, and changes during this period may be foundational for adolescent vulnerability in the coming years. Similar to prior work (e.g., Kerestes et al., 2016; Monk et al., 2008), we evaluated neural response to happy faces as a measure of social reward in children of this age. We hypothesized that high-risk children would show blunted responding in multiple reward regions (ventral and dorsal striatum, orbitofrontal cortex, prefrontal cortex) and lower behavioral reward seeking relative to low-risk children. We also hypothesized that neural and behavioral reward-related responding would be positively associated with one another.

2. Method

2.1. Participants and procedures

Participants were 56 typically developing 6- to 8-year old (M = 6.82 years, SD = .77 years) children with no lifetime history of psychiatric illness or other health problems. Participants were 55% female, and 77% White/Caucasian, 14% Black/African American, and 7% Multiracial. Participants were recruited from existing studies evaluating maternal depression as well as community advertisements. Children were excluded from the study if they met criteria for any Axis I psychiatric disorder (e.g., ADHD, anxiety, depression), developmental disability, or neurological disorder. Children were categorized as high-risk for depression (n = 25) if mothers met criteria for two or more lifetime episodes of Major Depressive Disorder or Dysthymia on the Structural Clinical Interview for DSM-IV Disorders (SCID-IV) (i.e., recurrent and/or chronic depression). Mothers were ineligible if they met lifetime criteria for a manic or hypomanic episode, psychotic symptoms, and/or Substance Dependence. In the high-risk group, seven mothers were currently depressed at the time of the study and 17 met lifetime criteria for an Anxiety Disorder (n = 9 Panic Disorder, n = 8 Social Phobia, n = 6 Post-Traumatic Stress Disorder, n = 4 Generalized Anxiety Disorder, n = 1 Obsessive Compulsive Disorder). Children were categorized as low-risk for depression (n = 31) if mothers had no lifetime history of any Axis I disorder.

Originally, 66 participants were enrolled in the study. An additional 4 participants did not complete the fMRI scan (n = 1 parent refusal, n = 2 child refusal, and n = 1 scanning contraindication). Of the 62 who completed the entire assessment including the fMRI, n = 6 had excessive movement (see fMRI preprocessing), n = 1 had low
behavioral responding in the scanner (<80% responding), and $n = 1$
was missing behavioral reward seeking data due to a computer error,
for a final sample of $n = 56$ (90% of scanned). Children with usable
data $(n = 56; 31$ low risk, $25$ high risk) did not differ from children
removed from the study on child age or mother age ($M$s = 6.80 years
and 6.70 years, respectively, $p = .70; Ms = 37.98$ years and $36.20$ years
respectively, $p = .36$), behavioral reward seeking ($M$s = 14.70 and
13.78 tokens won respectively, $p = .65$) or risk status ($\chi^2 = .80,$
$p = .50, 4$ low risk, $6$ high risk removed). However, more boys were
removed from the study due to unusable scan data than girls
($\chi^2 = 4.24, p = .04; 8$ boys vs $2$ girls). High risk and low risk children
did not differ on study demographic variables including child age, child
sex, child race, parent age, parent educational level, or single parent-
hood (see Table 1).

Children and mothers completed two laboratory visits for the study.
At the first visit, mothers and children completed clinical interviews to
assess psychiatric history, children completed a computerized reward
seeking task with an experimenter, and an experimenter took pictures of
mothers using standardized methods (i.e., lighting, backdrop, angle,
size). At the second visit, children completed an fMRI scan. The two
visits were on average 34.27 days apart (SD = 28.79 days,
range = 1–188 days). The University of Pittsburgh Institutional Review
Board approved all research procedures, and written informed consent
was obtained from each participant and his/her mother.

### 2.2. Measures

#### 2.2.1. Clinical interviews

Mothers completed the SCID-IV (First et al., 1995) with a bachelor’s
or master’s level interviewer trained to reliability by a licensed clinical
psychologist. Children and mothers were interviewed separately using
the Kiddie Schedule for Affective Disorders (KSADS) by the same
interviewer to assess child present and lifetime psychiatric history.
Summary scores on the KSADS were derived of a synthesis of parent
and child report. Discrepancies between child and parent report were
distinguished via further inquiry with the parent. Once again, none of
the children in either group met criteria for any Axis I disorder on the
KSADS. Sixteen percent of the SCID-IV clinical interviews and the
KSADS clinical interviews ($n = 12$) were double coded by a licensed
clinical psychologist and inter-rater reliability was high (97.7% diag-
nostic agreement for SCID-IV; 98.0% for KSADS).

#### 2.2.2. Progressive ratio schedule

Children completed a computerized progressive ratio schedule (see
Chelonis et al., 2011). In this task, children pressed a button to blow up
a virtual balloon. Children were informed that once the balloon was
blown all the way up, they would receive a token. Children were also
informed that they would be able to exchange their earned tokens at the
end of the task for a prize from a prize box (i.e., the more tokens won,
the better the prize). The task was set to a progressive ratio of 1:10—the
task required increasing levels of effort (i.e., 10 extra presses on each
trial relative to the previous trial) to blow up the balloon as the game
progressed. Children were able to stop playing the game whenever they
wanted (i.e., complete as many trials as they wanted for tokens) for up
to 30 min. In this regard, number of button presses reflected the number
of trials completed. The PR schedule is a widely used measure of reward
motivation that has been utilized in both human and animal studies.
The task can be used with various reinforcers including money, food, or
addictive drugs, is associated with other measures of reward sensitivity,
and has been shown to produce similar within-person breakpoints with
repeated assessment (Der-Avakian and Markou, 2012; Glover et al.,
2008; Miras et al., 2012). The task measured effort a child is willing to
exert to achieve a reward and served as a behavioral measure of reward
seeking. Similar to other studies (Bell and DeWall, 2019; Chelonis et al.,
2011), we used total number of button presses as our measure of be-
havioral reward seeking in analytical models.

#### 2.2.3. Child affective symptoms

Parents reported on child depressive and anxiety symptoms using the
Mood and Feelings Questionnaire (MFQ; Angold and Costello, 1987) and
the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997) respectively. The MFQ has 34 items and includes items such as “s/he felt miserable or unhappy”
and “s/he cried a lot”. Parents rated their children’s depressive symp-
toms within the past two weeks a 3-point Likert scale (0 = not true,
1 = sometimes, 2 = true). The SCARED has 41 items such as “my child
is nervous” and “my child is a worrier”. Parents rated their children’s
anxiety symptoms within the past week on a 3-point Likert scale (0 = not true/hardly ever true, 1 = somewhat true or sometimes true,
2 = very true or often true). Both the MFQ and the SCARED had good
internal consistency in our study ($\alpha = 0.73$ for MFQ and 0.86 for
SCARED).

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>High Risk ($n = 25$)</th>
<th>Low Risk ($n = 31$)</th>
<th>F/t/p</th>
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<tbody>
<tr>
<td>Child age in years</td>
<td>6.72</td>
<td>6.87</td>
<td>$F = .52, p = .47$</td>
</tr>
<tr>
<td>Number of Females</td>
<td>15 (60%)</td>
<td>16 (52%)</td>
<td>$\chi^2 = .39, p = .60$</td>
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<tr>
<td>Number of Minority Race</td>
<td>4 (16%)</td>
<td>9 (29%)</td>
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<td>Number with Single Parent</td>
<td>4 (16%)</td>
<td>6 (19%)</td>
<td>$\chi^2 b = .11, p = .75$</td>
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<tr>
<td>Parent age in years</td>
<td>38.92</td>
<td>37.26</td>
<td>$F = 1.13, p = .29$</td>
</tr>
<tr>
<td>Number with Parent with High School education</td>
<td>4 (16%)</td>
<td>5 (16%)</td>
<td>$\chi^2 = .95, p = .31$</td>
</tr>
<tr>
<td>Child Tokens Won</td>
<td>13.96</td>
<td>15.29</td>
<td>$F = .90, p = .35$</td>
</tr>
<tr>
<td>Child Depressive Symptoms</td>
<td>40.48</td>
<td>38.58</td>
<td>$F = 5.25, p = .026$</td>
</tr>
<tr>
<td>Child Anxiety Symptoms</td>
<td>9.66</td>
<td>7.10</td>
<td>$F = 2.02, p = .161$</td>
</tr>
</tbody>
</table>
2.2.4. Faces task

In this 3.5 min task, adapted from Gaffrey et al. (2011), participants were presented with 5 blocks of unfamiliar adults displaying happy, sad, and neutral expressions and their own mother displaying happy expressions and neutral expressions. Thus, the 5 blocks were unfamiliar happy, unfamiliar sad, unfamiliar neutral, mother happy, and mother neutral blocks. Each block had 7 distinct images and each image was displayed for three seconds with an inter-trial interval of 1 s; thus each block lasted 28 s long. For both unfamiliar and mother blocks, images were not repeated. Children were asked to respond with a button press each time they saw a face in order to ensure task engagement. Blocks were separated by a 14 s inter-trial interval where children viewed a cross-hair (see Fig. 1). To prevent non-standardized carry-over effects, all children viewed blocks in the same order. This task measured implicit emotion processing and contrasts using sad, angry, and fearful faces have been demonstrated to reliably activate multiple regions implicated in emotion processing in prior work (Gaffrey et al., 2011, 2013). To evaluate neural response to happy faces as a measure of positive emotion processing and social reward processing, we evaluated neural response to happy faces > neutral faces using the images of unfamiliar adults (taken from the NimStim; Tottenham et al., 2009) in analyses as they are standardized and have been validated in prior work. Our second contrast of interest was mother happy faces > mother neutral faces, a measure of personally relevant social reward and affective processing.

2.2.5. Post-scan ratings

After completing the scan, children were shown the same faces as appeared in the Faces fMRI task in the scanner. Images were not displayed in the same blocks as in the Faces fMRI task (i.e., were mixed by valence and familiarity) but did appear in a standard order across participants. Children were asked to rate the facial expressions viewed during the scan on a 5-point Likert scale (1 = very sad, 2 = sad, 3 = neither happy nor sad, 4 = happy, 5 = very happy). Across the children in the study, children rated the mother happy faces as 4.78 out of 5, unfamiliar happy faces with an average score of 4.73 out of 5, mother neutral faces with an average score of 3.16 out of 5, unfamiliar neutral faces with an average score of 2.91 out of 5, and unfamiliar sad faces with an average score of 1.51 out of 5.

2.3. fMRI acquisition and preprocessing

Each participant was scanned using a Siemens 3T TIM Trio scanner. Structural images were acquired using MPRAGE 192 axial slices, 1.0 mm thick (TR/TE = 2200/3.35 ms, FOV = 256 mm, matrix 256 × 240, flip angle = 9°). BOLD functional images for the Faces task were acquired in a single run, with a gradient echo planar imaging sequence and covered 39 axial slices, 3.1 mm thick, beginning at the cerebral vertex and encompassing the entire cerebrum and the majority of the cerebellum (TR/TE = 2010/28 ms, FOV = 205 mm, matrix = 64 × 64, flip angle = 90°). All scanning parameters were selected to optimize the quality of the BOLD signal while maintaining a sufficient number of slices to acquire whole-brain data. Before the collection of fMRI data for each participant, we acquired and inspected a reference EPI scan to confirm the absence of artifacts and good signal across the entire volume of acquisition.

Preprocessing and analysis of fMRI data were completed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Structural images of each
participant were segmented to focus on gray matter. For each functional scan, data were realigned to the first volume to correct for head motion and unwarped to correct for static inhomogeneity interactions. Realigned and unwarped images were then coregistered with the participant's anatomical image. The anatomical image was then spatially normalized into standard stereostatic space (Montreal Neurological Institute template) using a 12-parameter affine model and smoothed with a 6-mm full-width at half-maximum Gaussian filter based on conventional recommendations (e.g., see Huettel et al., 2004). Voxels were resampled during preprocessing to 2 mm³. Preprocessed data were conventional recommendations (e.g., see Huettel et al., 2004). Voxels with a 6-mm full-width at half-maximum Gaussian filter based on Institute template) using a 12-parameter affine model and smoothed normalized into standard stereostatic space (Montreal Neurological Institute). The anatomical image was then spatially normalized into standard stereostatic space (Montreal Neurological Institute). Further quality control measures revealed that of the 56 participants who met these criteria, 46 had maximum movement less than 2 mm in each plane for analyzed contrasts (82% of participants). Of the remaining 10 participants included in analyses, 6 participants had <10% volumes with movement above 2 mm. in any plane. Motion parameters from the realignment phase were entered as covariates in first level models, along with estimates of cerebrospinal fluid and white matter, to control for participant movement and non-task related brain activity. This process ensured a balance of retaining as many participants as feasible while still appropriately handling motion in a young child sample. Second level random effects models that account for participant-to-participant variability were then conducted to determine task-specific regional responses.

2.4. Data analytic strategy

Regression models that included child age, child sex, child risk status, number of tokens received in the PR schedule, and the multiplicative interaction of risk status and tokens (in order to evaluate how the brain-behavior associated varied by risk status) were conducted in SPM8. Whole brain analyses were used to probe significant clusters of interest at a cluster forming threshold of p < .001 and corrected for multiple comparisons using family wise error of p < .05. We used conjunction analyses for simple slope analyses to probe interactions (Nichols et al., 2005). We then extracted values from significant clusters and evaluated associations between risk and reward-related brain regions and child’s own depressive and anxiety symptoms.

3. Results

3.1. Descriptives

There were no significant risk group differences in child age or sex (ps = .47–.81). Neither child age nor sex were associated with behavioral reward seeking (ps = .13–.65). There was also no significant effect of risk status on behavioral reward seeking (i.e., number of tokens received in the PR Schedule; Mlowrisk = 15.29 tokens, Mhighrisk = 13.96 tokens) (p = .35). High risk children had higher parent ratings of child depressive symptoms but not anxiety symptoms relative to low risk children (MFQ-P: Mhighrisk = 40.48; Mlowrisk = 38.58, p = .026; SCARED: Mhighrisk = 9.66; Mlowrisk = 7.10, p = .161). Child depressive symptoms and anxiety symptoms were positively correlated (r = .34, p = .011). Child depressive symptoms were also significantly correlated with child behavioral reward seeking, such that higher levels of depressive symptoms were associated with less behavioral reward seeking (r = −.33, p = .014) (see Table 2).

3.2. Neural response to standardized happy faces

There was a significant main effect of tokens on neural response to happy faces in the dorsal striatum, posterior cingulate, inferior parietal lobe, and dorsolateral prefrontal cortex, such that greater behavioral reward seeking was associated with greater responding in those regions (see Table 3).

This regression model also revealed a significant main effect of risk status on neural response to happy faces in the dorsal striatum, such that children at high risk for depression showed lower response in the dorsal striatum to happy faces relative to low risk children (see Fig. 2; 220 voxels, t = 5.39, [−16, 2, 12], pFWE = .031).

There was also a significant interactive effect of risk status by number of tokens on neural response to happy faces in both the dorsal striatum (297 voxels, t = 4.68, [−16, 2, 12], pFWE = .013) and in the dlPFC/BA 9 (315 voxels, t = 5.62, [−40, 22, 34], pFWE = .016; see Fig. 3). Simple slope analyses conducted by group revealed that the association between behavioral reward seeking and neural response to social reward in the dorsal striatum and dorsolateral prefrontal cortex was significant only for children at high risk for depression (276 voxels, t = 6.26, [−14, 2, 10], pFWE = .002; 144 voxels, t = 5.56, [−40, 22, 34] pFWE = .019).¹

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tr>
<td>1. Child age in years</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>2. Child Behavioral Reward Seeking</td>
<td>.12</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>3. Child Depressive Symptoms</td>
<td>−.32*</td>
<td>−.33*</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>4. Child Anxiety Symptoms</td>
<td>−.15</td>
<td>−.20</td>
<td>.34*</td>
<td>−</td>
</tr>
</tbody>
</table>

Note. ¹ p < .05.

Fig. 2. Altered dorsal striatal response in 6- to 8-year old children at high familial risk for depression.
(a) Dorsal Striatum (caudate and putamen), 297 voxels, [-16, 2, 12], t=4.68, pFWE=.013

(b) Left dorsolateral prefrontal cortex, 315 voxels, [-40, 22, 34], t=5.62, pFWE=.016

Fig. 3. Lower response in the dorsal striatum (a) and dorsolateral prefrontal cortex (b) to happy faces is related to lower behavioral reward seeking, but only in high-risk children.

(b) Left dorsolateral prefrontal cortex, 315 voxels, [-40, 22, 34], t = 5.62, pFWE = .016.
3.3. Neural response to mother happy faces

There was no association between risk status or behavioral reward seeking and neural response to mother happy faces relative to mother neutral faces. Risk status also did not moderate the association between behavioral reward seeking and neural response to mother happy faces.

3.4. Associations with child depressive and anxiety symptoms

There were no significant associations between task-related activation in the dorsal striatum or dorsolateral prefrontal cortex and child depressive or anxiety symptoms.2

4. Discussion

Our study provided evidence that children as young as 6- to 8-years old at high familial risk for depression show blunted responding to happy faces in the striatum and the dorsolateral prefrontal cortex relative to low-risk children, but this finding was qualified by an interactive effect with child behavioral reward seeking. Our study revealed a unique effect in that lower responding in these regions was associated with less behavioral reward seeking in a task designed to measure effort to pursue reward, but only in high-risk children. Our findings add to the growing body of literature demonstrating that clinically healthy offspring of depressed parents show neurobiological aberrations and illustrate that (1) these neural aberrations are present as early as 6- to 8-years of age and (2) that they relate to differences in behavioral effort to receive reward.

The dorsal striatum is thought to be involved in decision-making, including action-selection and initiation. Further, the caudate nucleus, particularly the left caudate nucleus, has been shown to respond to both social and monetary reward (Izuma et al., 2008). In the context of positive affect, the dorsolateral prefrontal cortex, among other functions, is implicated in promotion of motivated behavior and appraisal of unexpected, positive stimuli (Ballard et al., 2011). Together, both regions may be involved in pursuit of positive experiences, such as effort to pursue reward. For children with a familial history of depression, lower activity within these regions may be paired with lower approach and effort in situations that typically evoke positive emotions (e.g., playing with friends or engaging in a game). This pattern may be part of an early emerging endophenotype for depression (Hasler et al., 2004) that may place them at greater risk for the onset of depression, a disorder of disrupted positive affect and motivation, later in development.

Prior work had established that neural reward-related disruptions are present in adolescent offspring of depressed parents (Gotlib et al., 2010; Monk et al., 2008; Olino et al., 2014; Sharp et al., 2014). Newly emerging evidence of neurobehavioral reward-related differences during middle childhood is troubling, as this is a developmental period in which vast emotional growth is occurring in the context of positive experiences. In particular, play behavior and its pursuit fosters intellectual, academic, and emotional learning and may serve as a building block through which younger children learn to regulate their emotions and get along with peers (Ginsburg, 2007; Nelson et al., 2016; Rubin and Coplan, 1998). Further, the formation of regulated affect and positive social bonds will be key during the relatively rocky period of adolescence when new stressors emerge, momentary mood becomes less positive in tone (Larson et al., 2002), and vulnerability for depression and other disorders increases (Morgan et al., 2013a, 2013b).

In the current study, neural response in the dorsal striatum and dorsolateral prefrontal cortex were not associated with child depressive or anxiety symptoms. This may have been because children in the study were required to be free of Axis I psychiatric disorders. Further, findings remained significant with inclusion of child depressive and anxiety symptom level in our models. Thus, our findings provide critical evidence that these neural alterations in response to affective stimuli and social reward appear to emerge before the onset of psychiatric illness and are not explained by pre-existing sub-threshold symptomatology. Future work should evaluate how these neurobehavioral reward-related alterations during middle childhood predict adolescent reward-related behavior and onset of psychiatric illness.

We did not find that activity in other key reward regions, such as the ventral striatum or orbitofrontal cortex, differed by risk group or was differentially associated with behavioral reward seeking. This is surprising given prior findings demonstrating their importance in high-risk adolescent offspring and in depressed adolescents and adults. This may suggest that these regions may be more relevant to normative changes that occur during adolescence, rapid neural changes that are related to social re-orientation (Nelson et al., 2016). However, other recent work using monetary-like rewards (i.e., candy) demonstrated altered responding in the ventral striatum in high-risk young offspring (see Luking et al., 2016). Thus, it may be that these alterations are only apparent in response to “wanting” or anticipatory stimuli (which our paradigm of happy faces did not include), given the ventral striatum’s putative role in anticipatory aspects of reward processing (Haber and Knutson, 2010). Longitudinal research that follows high-risk offspring from early and middle childhood through adolescence and that includes both monetary and social reward paradigms and assessment of both reward anticipation and outcome will be important to elucidate this possibility. Future work should also consider evaluating group differences in circuit-level function (e.g., functional connectivity) to further test how diverse reward-related regions may act in tandem to promote reward-related behavior and how this may differ depending on risk status.

We also did not find that high risk and low risk children responded differently to personally relevant happy faces (i.e., mother faces) nor was neural response to personally relevant happy faces differentially associated with behavioral reward seeking based on risk status in our sample. This may suggest that, at ages 6–8 years, neural differences in affective stimuli and reward-related stimuli may be present only for generalized stimuli, but not for stimuli that is family-related. Another possibility is that findings may have been more pronounced and evident for the unfamiliar faces because of their standardization and prior

<table>
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<th>Variable Region</th>
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<th>t, p (peak-level)</th>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sex</td>
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<td>–</td>
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<td>Behavioral Reward Seeking</td>
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<td>–</td>
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<tr>
<td>Dorsal Striatum</td>
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<td>−14, 2, 10</td>
<td>t = 6.26 (pFW = .002)</td>
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<td>3658</td>
<td>−22, −58, 28</td>
<td>t = 6.03 (pFW = .004)</td>
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<td>Inferior Parietal</td>
<td>387</td>
<td>28, 52, 44</td>
<td>t = 5.91 (pFW = .007)</td>
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<tr>
<td>Dorsolateral Prefrontal Cortex</td>
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<td>−40, 22, 34</td>
<td>t = 5.56 (pFW = .019)</td>
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<tr>
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<td>–</td>
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<td>Dorsal Striatum</td>
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</tr>
<tr>
<td>Dorsolateral Prefrontal Cortex</td>
<td>219</td>
<td>−40, 20, 36</td>
<td>t = 5.09 (pFW = .074)</td>
</tr>
<tr>
<td>Behavioral Reward Seeking x Risk Status</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dorsal Striatum</td>
<td>297</td>
<td>−16, 2, 12</td>
<td>t = 4.68 (pFW = .013)</td>
</tr>
<tr>
<td>Dorsolateral Prefrontal Cortex</td>
<td>315</td>
<td>−40, 20, 36</td>
<td>t = 5.62 (pFW = .016)</td>
</tr>
</tbody>
</table>
support of their valence (Tottenham et al., 2009). The use of images of children's mothers required a tradeoff of personal relevance and standardization, which may have limited their utility.

Other limitations to our study include the use of an emotional faces task as a social reward paradigm rather than a traditional monetary reward paradigm. Although prior work has demonstrated that happy faces elicit activation in primary reward regions (e.g., Kerestes et al., 2016; Monk et al., 2008), our findings may have differed with use of a more traditional incentive-based reward task (e.g., monetary incentive delay task, Wiggins et al., 2017). We chose to focus on happy faces due to our interest in altered responding in positive affective and rewarding stimuli in children at risk for depression. Future work should evaluate how risk status is related to neural responding to sad faces. Our task was also 3.5 min long and included only one run due to need for brevity due to developmental needs of 6- to 8-year old children. Task length may have limited our ability to detect reward-related effects in our sample. All participants viewed the blocks in the same order (unfamiliar happy, sad, neutral then mother happy and neutral) which may have introduced confounds such as subject fatigue and scanner drift.

Our findings build on newly emerging research evaluating reward-related brain function in young children with use of a social reward paradigm. Specifically, our study is unique in (1) evaluation of neural response to social reward stimuli in a very young sample of 6- to 8-year old children, (2) in linking these brain findings to behavioral responding to reward and (3) in use of a sample with a maternal history of recurrent or chronic depression.

Altogether, our findings provide further evidence that function within neural reward regions may be altered in high-risk offspring as young as 6- to 8-years of age, even in the absence of differences in reward-motivated behavior. Furthermore, the level of neural alteration in reward responding may be linked to lower behavioral response to obtain reward in these high-risk offspring. For young children without this familial risk, response in this circuitry does not appear to be related to their effort to seek out rewards. It should be noted that the opposite effect also appears to be true based on our findings: greater neural response to reward in high-risk children is associated with more effort to obtain rewards. In line with a differential susceptibility framework (Belsky et al., 2007), our findings also suggest that stronger response in these reward regions may also uniquely promote pursuit of reward in difficult circumstances for young children with a genetic predisposition for depression. Combined with prior findings that children exposed to depressed parents may be more susceptible to environmental influences (e.g., maternal warmth; Morgan et al., 2014), our findings may provide a hopeful goal—to strengthen neural responding in reward and emotion regulatory regions early in development, perhaps via positive affective support.

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CRediT authorship contribution statement

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Conflict of interest
We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.06.058.

References

Sinauer Associates, Sunderland, MA.