Neural Correlates of Self-Referential Processing in Children Vulnerable to Depression

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Abstract

Background

According to cognitive theories of depression, more negative and less positive self-schemas are thought to play a causal role in the disorder. Existing evidence speaks to the neural substrates of self-referential processes in both healthy and depressed individuals; however, little is known about how the brain relates to self-referent processing in the context of depression risk in youth. We therefore studied the neural substrates of self-referential processing in never-depressed preadolescent children at high and low risk for depression based on maternal depression history.

Method

Eighty-seven never-depressed 10-12-year-old children (29 with maternal depression) completed a self-referential encoding task during an fMRI scan session, in which they were presented a series of positive and negative trait adjectives and endorsed whether each word was self-

descriptive. Small volume correction (SVC) analyses were conducted within seven regions of interest important for self-referent and emotion-related processes.

Results

Analyses of SVC indicated that high-risk children showed greater activation in vlPFC and vmPFC during the positive-word condition than low-risk children. vlPFC activation was associated slower response time in endorsing positive words. vlPFC activation mediated the association between maternal depression and child depressive symptoms only when children had lower positive self-schemas, indicating that more positive self-schemas may protect at-risk children from developing depressive symptoms.

Conclusions

Cortical midline and prefrontal regions are important to self-, emotion-, and regulation-related processes. Heightened activation within these regions in never-depressed, high-risk youth indicates that these neurobiological substrates may mediate early vulnerability to depression in the context of cognitive processes relevant to self-concepts.

Introduction

Depression is projected to become the world's largest health challenge by 2030 (1). Adolescents are at high risk for depressive symptoms that can portend a lifelong struggle with the disorder (2, 3), highlighting the importance of understanding risk mechanisms for targeted prevention. Theories of cognitive vulnerability to depression are central models that guide efforts in understanding mechanism and developing treatment (REF). One established risk mechanism is cognitive vulnerability in the form of biased *self-referential processing* or *self-schemas* (4). Self-referential processing is conceptualized as a latent, trait-like cognitive construct that guides the processing of positive and negative descriptors of personal traits in self-reflection. Depressogenic self-referential biases (deeper processing of negative self-descriptors; superficial processing of positive self-descriptors) are thought to be early emerging, modestly stable, and predictive of depressive symptoms even during childhood (8-12).

Importantly, self-referential biases can be measured early in development, prior to onsets of depression, rendering them potential targets for early prevention (5-7). Effective prevention may benefit further from knowledge of the neural mechanisms involved in depressogenic self-referential biases. Indeed, neural manifestations of childhood risk may emerge earlier than behavioral markers (13), potentially showing greater sensitivity than behavioral measures in tapping individual variation in risk, or at least hold incremental predictive validity for risk beyond behavior. This highlights the importance of investigating the neural substrates of depressogenic self-referential processing in at-risk children, which will also contribute to the further refinement of cognitive theories of depression.

The self-referential encoding task (SRET; 14) is a standard paradigm assessing self-referential processing. Participants are shown a series of negative and positive traits and indicate

whether each word is self-referent ("Is this like you?"). Next, participants recall as many of the adjectives presented as possible, with the proportion of words of each valence (positive or negative) both endorsed *and* recalled indexing self-schemas. Faster response times (RTs) in endorsing (or denying) positive or negative words indicate the ease with which participants determine whether the adjective is self-descriptive. Clinically depressed adults (15-18) and youth (19-21) show more negative and less positive self-schemas than healthy controls and tend to be slower to endorse positive words and faster to endorse negative words (14, 16, 18-19). In typically developing children, self-referential processing shows modest yet significant stability as early as middle childhood (8, 10); depressogenic self-schemas are also concurrently and prospectively associated with depressive symptoms, especially for those with heightened depression risk (8-12, 21-24).

Despite a well-developed literature characterizing the neural substrates of normative self-referent processing, less is known about the neural processes associated with depressogenic self-referential biases. In non-depressed individuals, regardless of stimulus valence, self- versus other-referential processing activates brain regions including cortical midline structures (e.g., ventral medial prefrontal cortex (vmPFC), cingulate cortex (CC), precuneus) that are critical for self-referential processing (25), amygdala (salience processing and emotional arousal; 26), and hippocampus (self-related memories; 25). A smaller literature suggests that depression is associated with heightened activation in these regions during self-related processes. Currently depressed adults show heightened activation in anterior midline structures during negative self-referential processing (27). In adults with lifetime depression, those who recall more negative words show heightened amygdalar activation during negative self-referential encoding (28), and also show greater hippocampal activation when retrieving specific self-related memories (29).

This suggests that in more complex models, depression is related to the combination of multiple risk markers, e.g., altered neural activity *and* maladaptive cognitive patterns. Finally, while work with youth is sparse, depressed adolescents show heightened activation in posterior CC and precuneus during positive self-referential encoding (30).

While an important first step, research on depressed individuals does not inform whether the observed neural patterns are precursors or consequences of the disorder. We aimed to address this gap by characterizing neural functioning associated with self-referential biases in never-depressed preadolescents with high depression risks based on maternal depression. Compared to later developmental periods, clinical depression is rare in late childhood and preadolescence, providing the opportunity to identify risks that are not yet confounded by clinical disorder. Based on past work (25-30), we expected high-risk youth to show heightened activation within *a priori* regions important for self-referential processing, including cortical midline structures including vmPFC, CC, and precuneus (25). We also predicted greater activation in amygdala and hippocampus, given their roles in emotion- and self-related processes (25-26, 28-29). We further included ventrolateral and dorsolateral PFC (vlPFC, dlPFC) as *a priori* ROIs, given their roles in downregulating amygdalar reactivity and maintaining regulatory control (31-33). Compared to adults, youth tend to have relatively more positive than negative self-views, such that lower positive self-schemas may be a stronger risk marker than negative schemas (8-12, 34). We therefore anticipated stronger associations during the positive self-referential condition.

In exploratory analyses, we tested whether the expected neural activity mediated associations between maternal depression and children's depressive symptoms. Based on the literature (28, 35-36), we speculated that this mediating process might be especially salient for youth with cognitive vulnerability. Maternal depression marks a host of environmental and

biological risks for offspring, including maladaptive neural functions; nevertheless, this risk is probabilistic such that not all children of depressed mothers become depressed. Thus, the pathways that link maternal depression to child outcomes (e.g., maladaptive neural functions) are potentially moderated by additional risks, such as children's cognitive vulnerability. Likewise, diathesis-stress theories purport that cognitive vulnerability is linked to depression via interactive processes with other risks (36). For instance, among adults with remitted depression, only those with both heightened amygdalar activation during negative self-referential processing (maladaptive neural function) *and* enhanced memory for negative words (cognitive vulnerability) had greater depressive symptoms (28). In line with both theoretical models and empirical literature, we posited that any neural activity mediating associations between maternal depression and children's symptoms would be stronger for children with lower positive or higher negative self-schemas.

Methods and Materials

Participants and Procedure

Children and mothers were recruited from an ongoing longitudinal study that began at child age 3. At baseline, children with major medical or psychological problems were excluded; their normative cognitive development was verified by the Peabody Picture Vocabulary Test (37). For this study, 229 families were contacted, 110 were enrolled, and 87 children (49 boys; M_{age}=11.09, SD=.66; 96.6% White) participated. Of these, 78 contributed usable fMRI data (one had braces[1]; one discontinued after the structural scan; seven had excessive head motion).

[1]Although children were screened for conditions that contradict scanning, information regarding orthotics was miscommunicated and one family was accidentally recruited.

Children's mothers were previously assessed for lifetime psychopathology using the Structured Clinical Interview for the DSM-IV-TR Axis I Disorders Non-Patient Edition (SCID; 38). We recruited a high-risk group of 29 children (17 boys) whose mothers had at least two major depressive episodes (MDE; N=26) or one MDE and a major anxiety disorder (N=3)[2], given that both mark risk for offspring depression (35, 40). A low-risk group of 58 children (32 boys) was recruited with no maternal history of depressive or anxious disorder[3]. All children were screened for past or current depressive disorder via the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (41), conducted with both the primary caregiver and the child. During a home visit ~4 weeks before the fMRI visit (M=3.7; SD=3.0), mothers completed the Child Behavior Checklist (CBCL; 42); here, the withdrawn-depressed subscale was used to measure maternally reported symptoms (Cronbach's α=.71). Children completed the Children's Depression Inventory (CDI; 43; Cronbach's α=.84) at this same home visit.

Imaging data were collected at the UWO Robarts Research Institute on a Siemens Magnetom Prisma fit 3T scanner with a 32-channel head coil. As dysphoric mood is thought necessary to elicit depressogenic cognitive biases (44), children were first shown an age-appropriate, 3-minute sad video (from *The Neverending Story*) in the scanner (without being scanned). Children's mood ratings on a 5-point scale (1=very sad, 5=very happy) pre- and post-induction indicated that the induction was successful, M_{Pre}=3.72, SD_{Pre}=.75; M_{Post}=2.18,

[2]We excluded specific phobia and social anxiety limited to public speaking given that these are less heritable, less impairing, and potentially weaker markers of children's internalizing risk (38).

[3]Six mothers had single MDE with late onset (after child age 8). We consider this is less impairing and inheritable and included children of these mothers as low-risk.

SD_{Post}=.76; $t(83)$ =15.678, p<.001. High- and low-risk children did not differ in their response to mood induction, p=.88.

Children next completed a block design SRET (Figure 1) in the scanner. The task was adopted from the standard SRET commonly used in the developmental literature (8-12). It included a series of 12 positive (e.g., smart), 12 negative (e.g., lazy), and 4 neutral (e.g., tall) adjectives selected for Grade 3 reading level, with word frequency (i.e., how often the word appears in age-appropriate texts) matched across valences (45). Words were organized into 7 blocks of 4 words (1 neutral, 3 positive, and 3 negative blocks) with the task beginning and ending with the neutral block to address primacy and recency effects. Between the neutral blocks, alternating positive and negative blocks were presented both visually and aurally in fixed order. Each word was visually presented for 4s, followed by a 0.5s fixation, rendering each block 18s ((4s+0.5s)×4). Each block was followed by a 10s interval. For each word, children indicated whether the word was self-descriptive via button press (pointer finger=yes, middle finger=no). Next, scanning ended and children were asked to recall as many of the presented words as possible for up to two minutes.

Insert Figure 1

Calculation of SRET indices

Following standard scoring (8-12, 14), positive and negative words both endorsed and recalled were used to calculate a positive SRET score (# positive words endorsed and recalled/all words endorsed) and a negative SRET score (# negative words endorsed and recalled/all words endorsed) as primary indicators of self-schemas. As is typical for this age group (8-12), 64% of children did not endorse any negative words leading to a zero-inflated distribution of negative scores. Thus, non-parametric tests were used for this variable. Averaged RTs were calculated for

each of the four categories: positive endorsed, positive not endorsed, negative endorsed, and negative not endorsed (18-19, 22). Faster RTs to *positive endorsed* and *negative not endorsed* reflect decreased vulnerability; faster RTs to *positive not endorsed* and *negative endorsed* reflect increased vulnerability. One child had RTs>3SD above the overall mean and had the RTs for each category replaced by 2SD+Mean. Thirty-three children did not endorse any negative words and 24 children did not reject any positive words and therefore, had no RTs for these categories. While decreased sample sizes limited the power of statistical analysis involving these two variables, the absence of scores here was likely meaningful to children's self-views (e.g., endorsing no negative words reflects the perceived lack of negative traits and lower depression risk). However, given the reduced sample, we emphasize that these data should be considered exploratory. Seven other children's SRET data were missing due to a software error and subjected to multiple imputation for subsequent analysis[4] (R mice package, 46; 47).

fMRI acquisition and processing

High-resolution T1-weighted anatomical images were acquired using a magnetization-prepared rapid gradient-echo sequence (TR=2300 ms, TE=2.98ms, TI=900ms, flip angle=9°, 192 slices, FOV=256mm, voxel size=1mm^3). Functional T2*-weighted gradient echo images were acquired with 48 contiguous axial interleaved slices with a 0mm gap (TR=1000ms, TE=30ms, flip angle=45°, FOV=210mm, voxel size=3mm^3, matrix size=64^2).

fMRI data were preprocessed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK) and MATLAB 7.14.0 (Mathworks, Inc., Natick, MA). Functional images were

[4]These data were missing completely at random according to Little's Missing Completely At Random test (48), $\chi 2$=29.32, *df*=46, *p*=.97. Variables used in Little's test and multiple imputation included age, sex, risk group, positive and negative SRET scores, child-report and maternal-report symptoms, mood ratings before and after mood induction. We ran 50 imputations with 10 iterations each, and averaged data across the 50 imputed datasets for subsequent analysis.

realigned to the first image for motion correction and were corrected for slice timing. The mean realigned functional image was coregistered to each individual's T1 image and normalized to MNI space. The normalized images were then resampled to $2mm^3$ voxels and spatially smoothed with a 6mm Gaussian kernel. Of the 85 children who completed SRET, 7 were excluded (2 high-risk) due to head motions exceeding 3mm translation or 3-degree rotation.

A first-level, fixed-effects analysis was run on each participant with 3 condition regressors (positive-word, negative-word, and neutral-word) and 6 motion regressors (3 translation, 3 rotation). Intervals between blocks were used as baseline. Regressors were convolved by the canonical hemodynamic response function. Each child's contrast images generated by first-level modelling were entered into a second-level, mixed-effects model, which was conducted for the positive (positive-word>baseline) and negative condition (negative-word>baseline) separately. For each condition, we started with a whole-brain voxel-wise two-way ANOVA to test main effects of risk group and SRET scores (positive or negative) with child age and sex as covariates. We also tested interactions between risk group and SRET scores to see whether high- and low-risk children differed in associations between cognitive vulnerability and neural activity. This term was non-significant (*p*s>.61) and dropped to conserve power.

To increase the sensitivity of analyses, we used small volume correction (SVC) to constrain analyses within seven *a priori* bilateral anatomical ROIs (Automated Anatomical Labeling, 49), including cortical midline (vmPFC, CC, precuneus) and fronto-limbic regions (amygdala, hippocampus, vlPFC, dlPFC). For positive-word condition, activation was thresholded at whole-brain level at uncorrected $p<.001$, followed by SVC within each *a priori* ROI. For negative-word condition, we used non-parametric test to account for the non-normal distribution of negative SRET scores, by running 5000 permutations within each *a priori* ROI

(Threshold Free Cluster Enhancement toolbox, 50). For both conditions, clusters that remained significant following a family-wise error correction ($p<.05$) were identified as significant; for each significant cluster, the percentage of signal change (%SC) was extracted for post-hoc analysis (SPSS 24.0.1, IBM, Armonk, NY).

Exploratory moderated mediation analysis

A moderated mediation model (PROCESS macro; 51) was conducted to explore whether associations between maternal risk and child symptoms were accounted for, or potentially mediated by, neural activity during SRET. Each model included maternal risk as the predictor, child symptoms as the outcome, and %SC of each significant cluster as the mediator. We included all clusters as mediators in parallel in one model to minimize comparisons. We further examined whether any associations between maternal risk and symptoms were stronger for children with less positive or more negative self-schemas by including positive or negative SRET scores as the moderator to test the moderated mediation effect.

Results

Descriptives and associations between behavioral variables

Descriptives and correlations for main variables are in Table 1. For multi-comparison correction, we applied the Benjamini-Hochberg procedure to each analysis with a False Discovery Rate (FDR) of 0.10 (52-53). Two-sample t-tests showed that high-risk children had greater symptoms than their low-risk peers, in both maternal report, $t(82)=3.44$, $d=0.82$, uncorrected $p=.00$, FDR-corrected $p=.04$, and child self-report, $t(84)=2.47$, $d=0.54$, uncorrected $p=.02$, FDR-corrected $p=.06$. No group differences were found on any behavioral indices of

SRET, uncorrected *ps*>.07, FDR-corrected *ps*>.13, nor were any sex differences significant (uncorrected *ps*>.17).

Overall, maternal- and child-reported symptoms were associated with lower positive and higher negative SRET scores; positive and negative SRET scores were negatively correlated with each other. Child-reported symptoms were associated with faster RTs in rejecting positive words and slower RTs in rejecting negative words, although none of these survived multi-comparison correction. Positive SRET scores were associated with slower RTs in rejecting positive and faster RTs in rejecting negative words; negative SRET scores were associated with faster RTs in rejecting positive and slower RTs in rejecting negative words.

fMRI results

Whole-brain, voxel-wise analysis did not produce significant results after multi-comparison correction (see Supplement for uncorrected results). However, SVC yielded significant group difference for the positive-word condition in two *a priori* ROIs, vlPFC and vmPFC. Plotting the extracted %SC indicated that high-risk children showed greater activation than low-risk children in these areas (Figure 2). No significant effect was found for the negative-word condition.

Insert Figure 2

Insert Table 1

Associations between maternal risk, child symptoms, neural activation, and SRET performance

As shown in Tables 1, maternally reported, but not child-reported, symptoms were associated with greater vlPFC activation during positive-word condition. Maternally reported

symptoms were correlated with vmPFC activation, although it did not survive multi-comparison correction. None of the behavioral SRET variables was correlated with neural activation of the two clusters.

As no significant fMRI results were found for the negative condition, one mediation model was conducted for the positive condition, with neural activation of the vlPFC and vmPFC clusters that distinguished high- versus low-risk children as mediators of the association between maternal risk and child symptoms. No significant effect was observed treating vmPFC as the mediator or treating child-reported symptoms (CDI) as the outcome[5]. However, vlPFC activation mediated the association between maternal risk and maternal reports of symptoms. As shown in Figure 3, path *a* from maternal risk to vlPFC activation was significant as expected; path *b* from vlPFC activation to maternally reported symptoms was significant; the direct effect of maternal risk on symptoms was non-significant. As predicted, we observed a significant moderated mediation effect: positive SRET scores moderated the indirect path (*ab*) from maternal risk to symptoms via vlPFC activation, *index*=-2.34, *SE*=1.31, *CI*=[-5.32, -.14]. To decompose the moderating effect, we further tested path *ab* at three levels of the moderator: mean positive SRET scores, mean+1SD, mean-1SD (54). The indirect effect was significant for children with positive SRET scores at mean and mean-1SD levels, but not mean+1SD (Figure 3). This suggests that maternal depression influences offspring symptoms via vlPFC activation during positive self-referential processing; however, this mediating effect was significant only for children with less positive, or more depressogenic, self-schemas.

[5] Using the child-report version of the CBCL withdrawn-depressed subscale (Youth Self Report) yielded similar findings to those based on CDI.

Insert Figure 3

Discussion

We investigated the neural correlates of self-referential processing in what is, to our knowledge, the first study of this kind in never-depressed children with depression risk. By conducting SVC within seven *a priori* ROIs, we found that high-risk children showed increased activation within vlPFC and vmPFC during positive self-referential processing than the low-risk group. In exploring the potential mechanisms that link maternal risk to child symptoms, we found that the vlPFC activation that differentiated high- and low-risk children mediated the association between maternal risk and children's symptoms, but only for children with lower positive self-schemas. While drawn from exploratory analyses and warranting replication, this latter finding suggests that vlPFC activity during positive self-referential processing is most predictive of depressive symptoms when children had greater cognitive vulnerability.

Among the significant clusters that characterized high-risk youth, vlPFC is commonly involved in affective processing and regulation (REF). It plays a role in inhibiting or copying with emotionally distracting information and downregulates amygdalar reactivity to emotionally distracting cues with the aim of maintaining task-relevant performance (32-33). Similar patterns of vlPFC activation is found in youth with trait-level anxiety during tasks requiring attention shift from task-irrelevant, threatening distractors (55-58). In our study, given high-risk children's tendency of having less positive self-schemas, they may experience conflict or negative affectivity in deciding whether to self-endorse a positive trait. It may also be more difficult or effortful for them to make positive self-judgements in general. The need to recruit regulatory resources to inhibit or downregulate these task-irrelevant, negative feelings may lead to increased vlPFC activation. Indeed, children with greater vlPFC activation might tend to respond

slowly when endorsing positive traits, although the correlation between these two constructs were trend-level in our data, pending further examination in future research. The heightened activation was observed in left, but not right, vlPFC. This may be associated with the lateralized functions of vlPFC upon the nature of stimuli, i.e., left vlPFC supports the control processes over verbal processing, while right vlPFC is more involved in processing non-verbal, visuospatial information (59). Overall, heightened vlPFC activation may reflect self-regulatory difficulties in high-risk children when processing self-related, affective stimuli, which might portend maladaptive emotion regulation that eventuates in depression.

The heightened vlPFC activation is also consistent with recent cognitive neurobiological models (60) positing that the development of depressogenic cognitive biases are perpetuated by hyperactive patterns along a pathway starting from the lower-order subcortical regions (e.g., amygdala) up to higher-order cortical areas (e.g., PFC). Hyperactivation of these regions is associated with elevated, perceived self-related salience of stimuli and attenuated cognitive control, which eventually reinforce depressogenic self-schemas and depressive symptoms. Similarly, a recent review (61) concluded that elevated neural activity in the extended medial network, (e.g., CC, mPFC, and amygdala) was implicated in depressed youth during self-related processes. While this literature was based on clinical depression, finding similar patterns in high-risk children suggests that the heightened activation of at least part of the neural pathway may serve as a neurobiological marker of depression risk.

High-risk children also showed higher vmPFC activation during positive self-referential processing. As part of the cortical midline structures, vmPFC is directly engaged in self-related processes, including representing and evaluating self-related stimuli and making self-judgements (25, 61-66). Increased vmPFC activation is considered a neural indicator of excessive self-focus,

which is also associated with other aspects of cognitive risk for depression (e.g., rumination; 27, 67). For example, clinically depressed adults show heightened vmPFC activation when attributing negative traits to themselves (68). We did not find high- vs. low-risk difference in the negative condition, suggesting that negative self-schemas may be more relevant for clinical depression or later developmental stages. However, our observation of heightened vmPFC activation of high-risk children in the positive condition implies that heightened self-focus, even when processing positive stimuli, may be an early marker of risk (69), possibly because at-risk youth are processing a perceived absence of positive self-traits.

In moderated mediation analysis, we found that vlPFC activation mediated the association between maternal risk and child symptoms, but only for children with lower positive self-schemas. The direct effect of maternal risk on symptoms was no longer significant when vlPFC activation (as the mediator) and positive SRET scores (as the moderator) were included in the model, indicating that the regulatory function of vlPFC, moderated by positive self-schemas, may be a potential mechanism by which maternal depression confers risk for offspring. This observed pattern is consistent with both theories (e.g., the diathesis-stress model) and evidence regarding how multiple vulnerabilities are related to depression (28, 36); however, we acknowledge that these analyses were exploratory, warranting replication using longitudinal designs.

The moderated mediation effect was found for maternally reported, but not for child-reported, symptoms. Given that the two measures differ in content and were only moderately correlated with each other, as is typical (70), this was unsurprising. The maternal report (CBCL) covers a broader range of depression-related problems, including both symptoms and more observable aspects of child behaviors such as withdrawal, low activity, and decreased positive

expressions. The child self-report measure (CDI), however, focuses more exclusively on depressive “feelings.” It is possible that the observed neural activation patterns are associated more closely with behaviors tapped by maternal report that are not included in child-report, or aspects of youth depression that require greater insight or self-awareness than youth of this age possess. While depressed mothers may tend to endorse more depressive symptoms for offspring, it is unclear how such reporting biases would be systematically related to children’s neural activation. Analyses not reported here using the youth-report version of CBCL withdrawn-depressed subscale yielded similar findings to those based on CDI.

In the negative condition, we did not observe group difference in SRET or fMRI measures. Given that negative SRET was relatively weakly, albeit meaningfully, associated with children’s depressive symptoms, it may be that such processing is a less powerful marker of risk at this stage of development. During late childhood and preadolescence, youth are known to have more positive and less negative self-views than later in development (34), suggesting that positive self-schemas may play a more prominent role in the development of depression earlier in development. Future work with older, at-risk samples may speak to whether negative self-schemas become more important with age.

Limitations of this study include the modest number of trials in SRET, limited by the vocabulary of children at this age. Some of the SRET behavioral data were limited in psychometric properties and/or sample size (e.g., the negative RTs), and should be regarded as exploratory and interpreted with caution. The block design of the fMRI task prevented us from isolating the neural underpinnings of words endorsed versus those declined. The cross-sectional design cannot establish directional relations between neural markers of risks and depressive outcomes, or to what extent these neural markers are a precursor, concomitant, or product of self-

referential risks. It would be challenging and expensive to collect longitudinal imaging and behavioral data to permit more conclusive tests of mechanisms in younger children. Thus, our mediation model speaks more clearly to theoretical/conceptual processes rather than specific causal mechanisms. We aim to continue exploring these issues by following this cohort into adolescence, a period marked by a sharp increase in onsets of clinical depression. The development of youth cognition and vocabulary will enable us to conduct increasingly refined assessments of self-schemas (e.g., distinguishing endorsed vs. rejected) and their corresponding neural processes.

In conclusion, we provide novel evidence on the neural correlates of self-referential processing in preadolescents with maternal risk for depression. High-risk children showed heightened activation during positive self-referential processing within vlPFC and vmPFC regions. The activity of vlPFC, a critical region for affective regulatory functions, might mediate the association between maternal risk and child symptoms for children with diminished positive self-schemas. While we cannot establish a causal role of vlPFC in the development of depression, it is consistent with the notion that neurobiological substrates important to self-regulation may mediate the pathway from maternal depression to offspring outcomes. Drawing on preventative programs on attentional risk for youth anxiety (71), future work aimed at altering depressogenic self-schemas and testing whether such manipulation causes shifts in relevant neural activity can more conclusively establish causal pathways between cognitive risk, brain activity, and youth outcomes. Evidence as such will not only inform the development of early prevention tools, but also contribute to refinements of etiological theories of depression.

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Tables

Table 1. Descriptives of, and bivariate correlations between, main variables across the two groups. The Benjamini-Hochberg procedure with an FDR of 0.1 was applied for multi-comparison correction.

	Mean (SD)	1	2	3	4	*5*	*6*	*7*	8	9	10	11	12	13	14
1 Age	11.09 (0.66)														
2 Maternal-report depression (CBCL)	1.3 (1.78)	-0.19													
3 Self-report depression (CDI)	5.02 (5.3)	-0.19	.45**												
4 Positive SRET score	0.31 (0.15)	0.15	-.48**	-.50**											
5 Negative SRET score	0.04 (0.06)	*-0.15*	*0.19*	*.31***	*-.30***										
6 Positve # endorsed	10.31 (1.69)	*0.15*	*-.23**	*-.37***	*0.11*	*-0.11*									
7 Negative # endorsed	1.18 (1.41)	*-.22**	*0.15*	*.40***	*-.38***	*.69***	*-0.20*								
8 Positve # recalled	3.93 (1.89)	0.21	-.36**	-.41**	.88**	*-0.17*	*0.07*	*-0.18*							
9 Negative # recalled	4.23 (2.09)	0.02	-0.13	0.02	0.08	*0.12*	*0.05*	*0.06*	.24*						
10 RT positive endorsed (ms)	1371.79 (291.61)	-0.09	0.20	0.03	-0.09	*-0.18*	*-.24**	*-.27**	-.25*	0.05					
11 RT positive not endorsed (ms)	1954.55 (703.88)	-0.07	-0.08	-0.26	.31*	*-0.26*	*0.07*	*-.29**	0.14	0.04	.36**				
12 RT negative endorsed (ms)	1692.33 (453.06)	-0.14	-0.13	-0.16	0.14	*0.02*	*0.19*	*0.05*	0.13	0.09	.49**	.47**			
13 RT negative not endorsed (ms)	1323.93 (282.97)	-0.23*	0.12	.26*	-0.19	*.24**	*-.25**	*0.20*	-0.21	0.17	.53**	0.25	.35*		
14 %SC vlPFC	0.13 (0.28)	-0.06	.26*	0.02	0.02	*0.09*	*-0.12*	*-0.03*	-0.08	-0.18	0.23	0.01	-0.04	0.06	
15 %SC vmPFC	0.1 (0.2)	-0.07	.24*	-0.04	0.05	*0.11*	*-0.16*	*0.00*	-0.07	-0.18	0.03	0.00	-0.11	-0.06	.75**

Italicized: non-parametric correlations for non-normally distributed variables (5, 6, 7);
* uncorrected $p<.05$; ** uncorrected $p<.01$; grey shade FDR-corrected $p<.1$.
CBCL: Child Behavior Checklist; CDI: Child Depression Inventory; SRET: Self-Referential Encoding Task; RT: response time; %SC: percent signal change.

Figure legends

Figure 1. Abridged illustration of the block design SRET.

Figure 2. High- and low-risk children differed in neural activation (indexed by %SC values) in (A) left vlPFC and (B) right vmPFC regions during the positive-word condition.

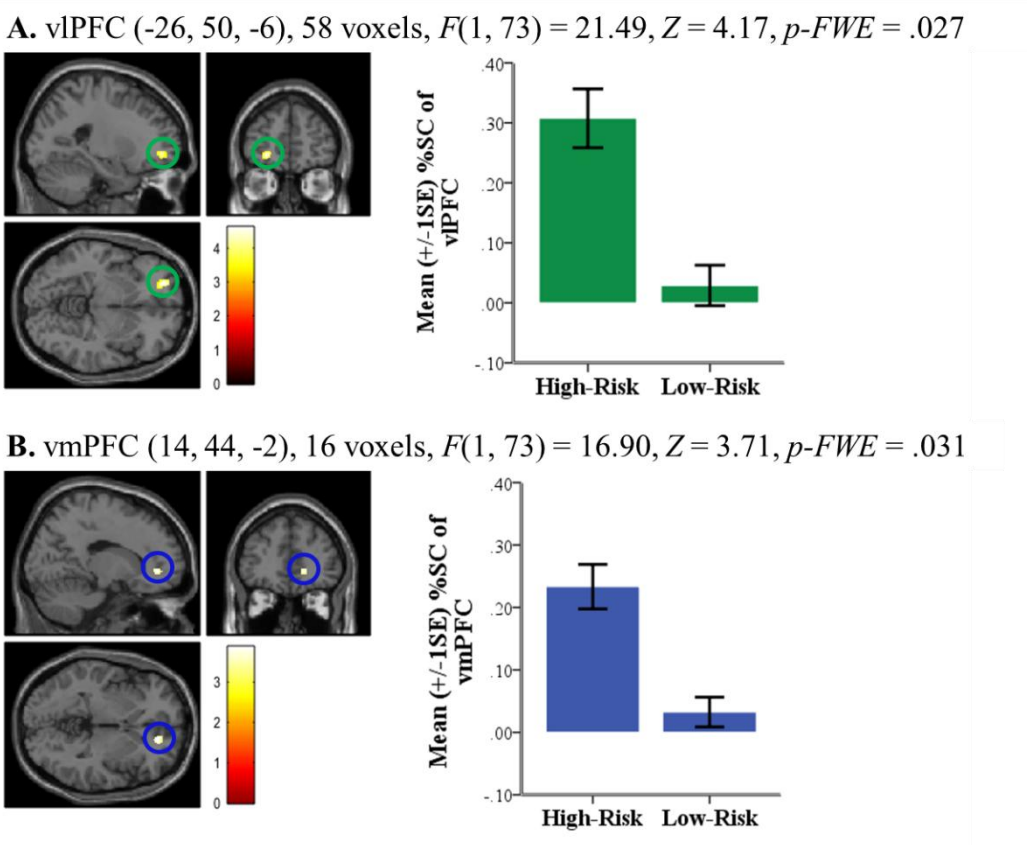
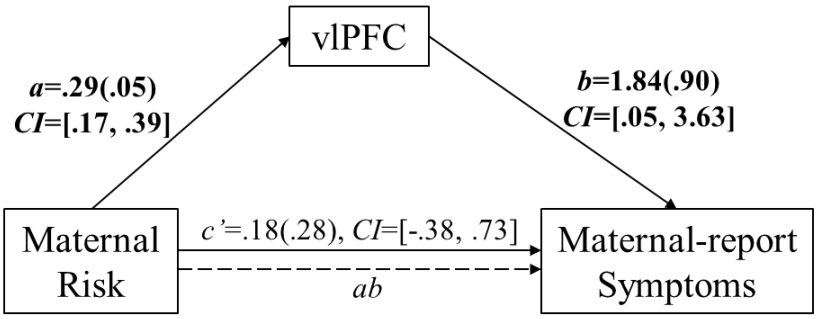


Figure 3. Moderated mediation model testing the indirect effect of maternal depression on child symptoms via vlPFC activation during positive self-referential processing, with positive SRET scores as the moderator. Significant effects are in bold.



Mean-1SD Positive SRET: ***ab*=.87(.38), *CI*=[.23, 1.17]**
Mean Positive SRET: ***ab*=.52(.26), *CI*=[.04, 1.07]**
Mean+1SD Positive SRET: *ab*=.16(.28), *CI*=[-.42, .70]