

## Neural Activity During Self-referential Processing in Children at Risk for 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, but little is known about how the brain relates to self-referential processing in the context of depression risk in children. 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.

**METHODS:** A total of 87 never-depressed 10–12-year-old children (29 with maternal depression) completed a self-referential encoding task during a functional magnetic resonance imaging 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 analyses were conducted within 7 regions of interest that are important for self-referential and emotion-related processes.

**RESULTS:** Analyses of small volume correction indicated that high-risk children showed greater activation in the ventrolateral prefrontal cortex and ventromedial prefrontal cortex during the positive-word self-referential encoding task condition than low-risk children. Ventrolateral prefrontal cortex 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 children indicates that these neurobiological substrates may mediate early vulnerability to depression in the context of cognitive processes relevant to self-concepts.

**Keywords:** Depression, fMRI, Maternal history, Preadolescence, Self-referential encoding task, vIPFC

<https://doi.org/10.1016/j.bpsc.2019.12.012>

Depression is the world's largest health challenge (1). Adolescents are at high risk for depressive symptoms that can portend lifelong struggles (2,3), highlighting the importance of understanding risk mechanisms of depression for targeted prevention. Regarding mechanisms of depression, cognitive theories play a central role in understanding vulnerability and treatment (4,5). Specifically, cognitive vulnerability in the form of biased self-referential processing or self-schemas (4,5) has received tremendous attention. 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. Self-referential processing emerges early and is at least moderately stable, even in childhood (6–11). Behavioral measures of self-referential bias (i.e., deeper processing of negative self-descriptors; superficial processing of positive self-descriptors) predict children's depressive symptoms (6–11) and appear to enhance risk for depression later in development.

The self-referential encoding task (SRET) (12), the standard paradigm for assessing self-referential processing, entails participants viewing a series of negative and positive traits and indicating whether each word is self-referential. Next, participants recall as many of the adjectives presented as possible, with the proportion of words (positive or negative) both endorsed and recalled indexing self-schemas. Faster response times (RTs) in endorsing or rejecting positive or negative words indicate the ease with which participants determine whether the adjective is self-descriptive. Compared with control subjects, clinically depressed adults (12–16) and youths (17–19) have relatively more negative and less positive SRET scores, and they endorse positive traits more slowly and negative traits more rapidly (12–17). Supporting their validity, SRET scores show significant stability as early as middle childhood in typically developing children (6,9,18,19); scores are also concurrently and prospectively associated with depressive symptoms (6–11,19–23).

Thus, the construct validity of measures of self-referential biases, including the SRET, is established even in childhood (6–11), and such biases can be assessed prior to depression onsets, rendering them potential targets for early prevention (24–26). However, prevention may be enhanced by understanding the neural mechanisms involved in children's depressogenic self-referential biases. Neural manifestations of childhood depression vulnerability may emerge earlier than behavioral markers (27) and may have greater sensitivity as indices of vulnerability relative to overt behavior, or at least hold incremental predictive validity for risk. Understanding the neural underpinnings of cognitive risk may inform brain-based preventions and interventions for depression, highlighting the importance of investigating the neural substrates of depressogenic self-referential processing in at-risk children.

However, despite a well-developed literature characterizing the neural substrates of normative self-referential processing, less is known about depressogenic self-referential biases. In nondepressed individuals, self-referential processing activates cortical midline structures, including the ventromedial prefrontal cortex (vmPFC), cingulate cortex (CC), and precuneus (28), and limbic regions, including the amygdala (29) and hippocampus (28). A smaller literature suggests that depression is associated with heightened activation in these regions during self-related processes. While work with youths is sparse, depressed adolescents show heightened activation in the posterior CC and precuneus during positive self-referential encoding (30). Currently depressed adults show heightened activation in anterior midline structures during negative self-referential processing (31); previously depressed adults show greater hippocampal activation when retrieving specific self-related memories (32), and heightened amygdalar activation during negative self-referential encoding (33). Interestingly, previously depressed adults with both heightened amygdalar activation and enhanced memory for negative words showed greater current depressive symptoms (33). Consistent with diathesis-stress theory (4,34,35), this indicates that depression is related to interplay between multiple vulnerabilities (e.g., altered neural activity and maladaptive cognitive patterns).

In addition, studies of depressed individuals do not inform whether the observed neural patterns are precursors or consequences of the disorder. We therefore characterized neural functions underlying self-referential biases in never-depressed preadolescents at risk for depression based on maternal depression (36). Clinical depression is rare in late childhood and preadolescence, providing the opportunity to identify preexisting risk. Given past work (28–33), we expected that high-risk children would show heightened activation within a priori regions important for self-referential processing, including the cortical midline structures vmPFC, CC, and precuneus (28). We also anticipated greater activation in the amygdala and hippocampus, given their roles in emotion- and self-related processes (28,29,31–33). We included the ventrolateral (vlPFC) and dorsolateral PFC as additional a priori regions of interest (ROIs), given their roles in downregulating amygdalar reactivity and maintaining regulatory control (37–39). Given that children tend to show greater variability in positive self-schemas (6–11,40), we anticipated stronger effects for positive self-referential processing compared with negative processing.

In exploratory analyses, we tested whether expected neural activity in a priori ROIs mediated associations between maternal depression and children's symptoms. Based on the literature (33–35), this mediating process might be especially salient for children with cognitive vulnerability. Maternal depression marks a host of environmental and biological risks for offspring, including maladaptive neural functioning; nevertheless, this risk is probabilistic such that not all children of depressed mothers become depressed. Pathways linking maternal depression to child outcomes (e.g., maladaptive neural function) are potentially moderated by additional risks, such as children's cognitive vulnerability, as consistent with diathesis-stress theories in which cognitive vulnerability interacts with other risks to predict depression (4,34,35). For instance, among adults with remitted depression, only those with both heightened amygdalar activation during negative self-referential processing and enhanced memory for negative words had greater depressive symptoms (33). In line with this work and theory, we posited that any neural activity mediating associations between maternal depression and children's symptoms would be stronger for children with maladaptive self-schemas.

## METHODS AND MATERIALS

### Participants and Procedure

Participants were recruited from an ongoing longitudinal study that began when children were 3 years of age. At baseline, children with major medical or psychological problems were excluded; their normative cognitive development was verified with the Peabody Picture Vocabulary Test (41). For the present study, 229 families were contacted, 110 were enrolled, and 87 children (49 boys; age, mean  $\pm$  SD 11.09  $\pm$  0.66 years; 96.6% white) participated. Of these, 78 contributed usable functional magnetic resonance imaging (fMRI) data (of those that did not, 1 had braces, 1 refused, and 7 had excessive head motion).

Mothers were previously assessed for lifetime psychopathology with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Nonpatient Edition (42). We recruited a high-risk group of 29 children (17 boys) whose mothers had at least 2 major depressive episodes ( $n = 26$ ) or 1 major depressive episode and a major anxiety disorder ( $n = 3$ ),<sup>1</sup> given that both of those suggest risk for offspring depression (36,43). A low-risk group of 58 children (32 boys) was recruited with no maternal history of depressive or anxious disorder.<sup>2</sup> All children were screened for past or current depressive disorder with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (44) conducted with both the primary caregiver and the child. During a home visit  $\sim$  4 weeks before the fMRI visit (mean  $\pm$  SD 3.7  $\pm$  3.0 weeks), mothers completed the Child Behavior Checklist (45); the Withdrawn-Depressed subscale was used to index depressive

<sup>1</sup>We excluded specific phobia and social anxiety limited to public speaking, given that these are less heritable, less impairing, and weaker markers of children's depression risk (80).

<sup>2</sup>Six mothers had a single major depressive episode with late onset (after the child was 8 years of age). We consider this to be less impairing and heritable and included children of these mothers as being at low risk.

## Neural Bases of Depressogenic Self-schemas in Children



**Figure 1.** Abrridged illustration of the block-design self-referential encoding task.

symptoms (Cronbach's  $\alpha = .71$ ). Children completed the Children's Depression Inventory (46) (Cronbach's  $\alpha = .84$ ) at this same visit.

Imaging data were collected at the University of Western Ontario Robarts Research Institute with a Siemens Magnetom Prisma 3T scanner using a 32-channel head coil (Siemens, Erlangen, Germany). Because dysphoric mood is thought necessary to elicit depressogenic cognitive biases (47), 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) before and after induction indicated that the induction was successful: before, mean  $\pm$  SD  $3.72 \pm 0.75$ ; after,  $2.18 \pm 0.76$ ;  $t_{83} = 15.678$ ,  $p < .001$ . High- and low-risk children did not differ in responses to mood induction ( $p = .88$ ).

Children next completed a block-design SRET (Figure 1) in the fMRI scanner. The task was adopted from the standard SRET commonly used in the developmental literature (6–11,18–20). To enhance comprehension of word stimuli, words were at grade 3 reading level or lower with word frequency matched across valences (48). We selected 12 positive (e.g., smart), 12 negative (e.g., lazy), and 4 neutral (e.g., tall) self-descriptive traits. This number of words is comparable to those used in previous SRET studies with children (6,9,11).

Words were organized into 7 blocks of 4 words (1 neutral, 3 positive, 3 negative), with the task beginning and ending with the neutral block to address primacy/recency effects. Between neutral blocks, alternating positive and negative blocks were presented both visually and aurally in fixed order. Each word was visually presented for 4 seconds, followed by 0.5 seconds for fixation, rendering each block 18 seconds ([4 seconds + 0.5 seconds]  $\times$  4). Each block was followed by a 10-second 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 2 minutes.

### Calculation of SRET Indices

Following standard scoring (6–12), words both endorsed and recalled were used to calculate a positive SRET score (number of positive words endorsed and recalled/all words endorsed) and a negative SRET score (number of negative words endorsed and recalled/all words endorsed) as indices of self-schemas. As is typical for children (6–11), 64% of children did not endorse any negative words, leading to a zero-inflated negative score distribution. Therefore, nonparametric tests were used for this variable. Average RTs were calculated for each of the 4 categories: positive endorsed, positive rejected, negative endorsed, and negative rejected (16,17,21). Faster RTs to positive endorsed and negative rejected reflect decreased vulnerability; faster RTs to positive rejected and negative endorsed reflect increased vulnerability. One child

had RTs  $>3$  SD above the overall mean and had the RTs for each category replaced by 2 SD + mean. Thirty-three children did not endorse any negative words, and 24 children did not reject any positive words; therefore, they had no RTs for those categories. While decreased sample sizes limited the power of analyses including these 2 variables, endorsing no negative words is likely meaningful in that it reflects lower negative self-schemas and lower depression risk. However, given the reduced sample, we emphasize that these analyses require replication. Seven other children's SRET data were missing owing to a software error and subjected to multiple imputation for subsequent analysis (R MICE package) (49,50).<sup>3</sup>

### fMRI Acquisition and Processing

High-resolution T1-weighted anatomical images were acquired using a magnetization-prepared rapid gradient-echo sequence (repetition time = 2300 ms, echo time = 2.98 ms, inversion time = 900 ms, flip angle =  $9^\circ$ , 192 slices, field of view = 256 mm, voxel size =  $1 \text{ mm}^3$ ). Functional T2\*-weighted gradient echo images were acquired with 48 contiguous axial interleaved slices with a 0-mm gap (repetition time = 1000 ms, echo time = 30 ms, flip angle =  $45^\circ$ , field of view = 210 mm, voxel size =  $3 \text{ mm}^3$ , matrix size =  $64^2$ ).

The fMRI data were preprocessed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK) and MATLAB 7.14.0 (The Mathworks, Inc., Natick, MA). Functional images were realigned to the first image for motion correction and corrected for slice timing. Mean realigned functional image was coregistered to each individual's T1 image and normalized to Montreal Neurological Institute space. Normalized images were then resampled to  $2\text{-mm}^3$  voxels and spatially smoothed with a 6-mm Gaussian kernel. Of the 85 children who completed SRET, 7 were excluded (2 at high risk) owing to head motions exceeding 3 mm translation or  $3^\circ$  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.<sup>4</sup> Regressors were convolved by the canonical hemodynamic response function. Each child's contrast images generated by first-level modeling were entered into a second-level, mixed-effects model, which was conducted for the positive (positive

<sup>3</sup>Data were missing completely at random according to Little's test (81):  $\chi^2_{46} = 29.32$ ,  $p = .97$ . Variables used in Little's test and imputation included age, sex, risk group, positive and negative SRET scores, child-report and maternal-report symptoms, and 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.

<sup>4</sup>Raw fMRI activation during the positive (or negative) condition was standardized relative to the baseline to statistically control any group differences during baseline.

word > baseline) and negative (negative word > baseline) conditions separately. Following the literature (32), we included words both endorsed and rejected in each condition, because participants are engaged in self-referential processing even when they reject a word, i.e., they are considering and determining that a trait is not self-descriptive. Thus, fMRI activation underlying both endorsed and rejected words indexes the neural substrates of “broader” self-referential processing, while behavioral SRET scores (and RTs) more specifically reflect the “depth” of positive or negative self-referential processing. For each condition, we started with whole-brain voxel-wise 2-way analyses of variance 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 nonsignificant ( $p > .61$ ) and dropped to conserve power.

To increase sensitivity of analyses, we used small volume correction (SVC) to constrain analyses within 7 a priori bilateral anatomical ROIs as determined by automated anatomical labeling (51), including cortical midline (vmPFC, CC, and precuneus) and frontolimbic (amygdala, hippocampus, vIPFC, and dIPFC) regions. For the positive-word condition, activation was thresholded at uncorrected  $p < .001$  at the whole-brain level, followed by SVC within each a priori ROI. For the negative-word condition, we used nonparametric tests owing to the nonnormal distribution of negative SRET scores by running 5000 permutations within each a priori ROI using threshold-free cluster enhancement (52). For both conditions, we considered all clusters significant that remained so after a familywise error correction ( $p < .05$ ); for each significant cluster, percentage signal change was extracted for post hoc analysis (SPSS 24.0.1; IBM Corp., Armonk, NY).

### Exploratory Analysis

The PROCESS moderated mediation model (53) was conducted to explore whether associations between maternal risk and child symptoms were accounted for, or potentially mediated by, neural activity during the SRET. Each model included

maternal risk as the predictor, child symptoms as the outcome, and percentage signal change 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, probing any moderation effects further with Mplus (54).

## RESULTS

### Behavioral Variables

Descriptions and correlations for the main variables are presented in Table 1. For multicomparison correction, we applied the Benjamini-Hochberg procedure to each analysis with a false discovery rate of 0.10 (55,56). Two-sample  $t$  tests showed that high-risk children had greater symptoms than low-risk children based on maternal report ( $t_{82} = 3.44$ ,  $d = 0.82$ , false discovery rate–corrected  $p = .04$ ), but not child self-report (false discovery rate–corrected  $p > .05$ ). No group differences were found on any behavioral SRET indices (uncorrected  $p$  values  $> .07$ ), nor were any sex differences significant (uncorrected  $p$  values  $> .17$ ). As shown in Table 1, maternally reported symptoms correlated with lower positive SRET scores, 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 slower RTs in rejecting negative words. Positive SRET scores were associated with slower RTs in rejecting positive words.

### fMRI Results

Whole-brain voxelwise analysis did not produce significant results after multicomparison correction (Supplemental Tables S1–S4). However, SVC yielded significant group difference for the positive-word condition in 2 a priori ROIs: the vIPFC and the vmPFC. Plotting the extracted percentage signal change indicated that high-risk children showed greater activation than

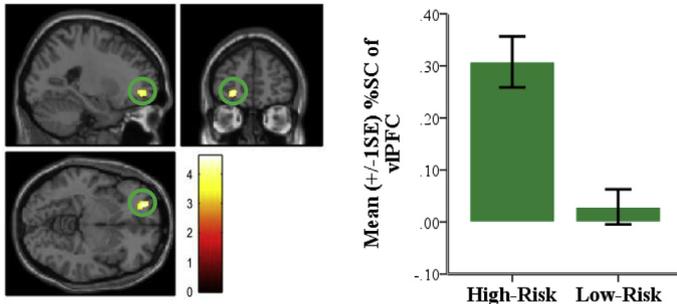
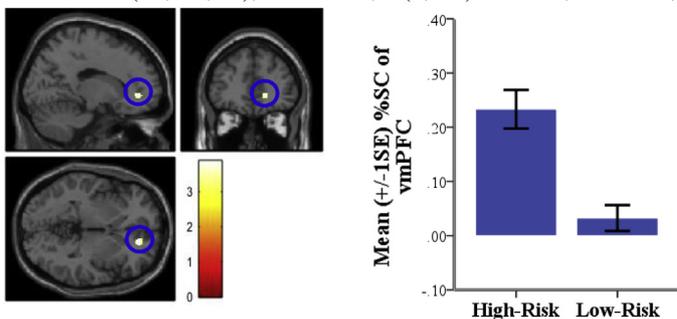
**Table 1. Descriptions of the Main Variables and Bivariate Correlations Between Them Across the Two Groups**

Variable No.	Description	Result, Mean ± SD	Correlation									
			1	2	3	4	5	6	7	8	9	
1	Maternally reported depression (CBCL)	1.30 ± 1.78										
2	Child-reported depression (CDI)	5.02 ± 5.30	.45 <sup>a</sup>									
3	Positive SRET score	0.31 ± 0.15	-.48 <sup>a</sup>	-.50 <sup>a</sup>								
4	Negative SRET score	0.04 ± 0.06	.19 <sup>b</sup>	.31 <sup>a,b</sup>	-.30 <sup>a,b</sup>							
5	RT: positive endorsed, ms	1371.79 ± 291.61	.20	.03	-.09	-.18 <sup>b</sup>						
6	RT: positive rejected, ms	1954.55 ± 703.88	-.08	-.26	.31 <sup>a</sup>	-.26 <sup>b</sup>	.36 <sup>a</sup>					
7	RT: negative endorsed, ms	1692.33 ± 453.06	-.13	-.16	.14	.02 <sup>b</sup>	.49 <sup>a</sup>	.47 <sup>a</sup>				
8	RT: negative rejected, ms	1323.93 ± 282.97	.12	.26 <sup>a</sup>	-.19	.24 <sup>b</sup>	.53 <sup>a</sup>	.25	.35 <sup>a</sup>			
9	%SC: vIPFC	0.13 ± 0.28	.26 <sup>a</sup>	.02	.02	.09 <sup>b</sup>	.23	.01	-.04	.06		
10	%SC: vmPFC	0.10 ± 0.20	.24	-.04	.05	.11 <sup>b</sup>	.03	.00	-.11	-.06	.75 <sup>a</sup>	

CBCL, Child Behavior Checklist; CDI, Children’s Depression Inventory; RT, response time; %SC, percentage signal change; SRET, self-referential encoding task; vIPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

<sup>a</sup>False discovery rate–corrected  $p < .10$ .

<sup>b</sup>Nonparametric correlations for nonnormally distributed variables (negative SRET score).

**A** vIPFC (-26, 50, -6), 58 voxels,  $F(1, 73) = 21.49$ ,  $Z = 4.17$ ,  $p\text{-FWE} = .027$ **B** vmPFC (14, 44, -2), 16 voxels,  $F(1, 73) = 16.90$ ,  $Z = 3.71$ ,  $p\text{-FWE} = .031$ 

**Figure 2.** High- and low-risk children differed in neural activation (indexed by percentage signal change [%SC]) in **(A)** left ventrolateral prefrontal cortex (vIPFC) and **(B)** right ventromedial prefrontal cortex (vmPFC) regions during the positive-word condition. FWE, familywise error corrected.

low-risk children in these areas (Figure 2). No significant effect was found for the negative-word condition.

### Associations Between Maternal Risk, Child Symptoms, Neural Activation, and SRET Performance

As shown in Table 1, maternally reported, but not child-reported, symptoms were associated with greater vIPFC activation during the positive-word condition. None of the behavioral SRET indices was correlated with neural activation of the 2 clusters.

Because no significant fMRI results were found for the negative condition, a mediation model was run for the positive condition, with neural activation of the vIPFC and vmPFC clusters that distinguished high- versus low-risk children as a mediator of the association between maternal risk and child symptoms. No significant effect was observed when treating vmPFC as the mediator or treating child-reported symptoms (Children's Depression Inventory) as the outcome.<sup>5</sup> However, vIPFC activation mediated the association between maternal risk and maternal reports of symptoms. As shown in Figure 3A, simple paths *a* (maternal risk to vIPFC activation) and *b* (vIPFC activation to symptoms) were significant, but the direct path *c'* (maternal risk to symptoms) was nonsignificant. As predicted, positive SRET scores moderated the indirect path (*ab*) from maternal risk to symptoms via vIPFC activation: index =  $-2.34$ ,

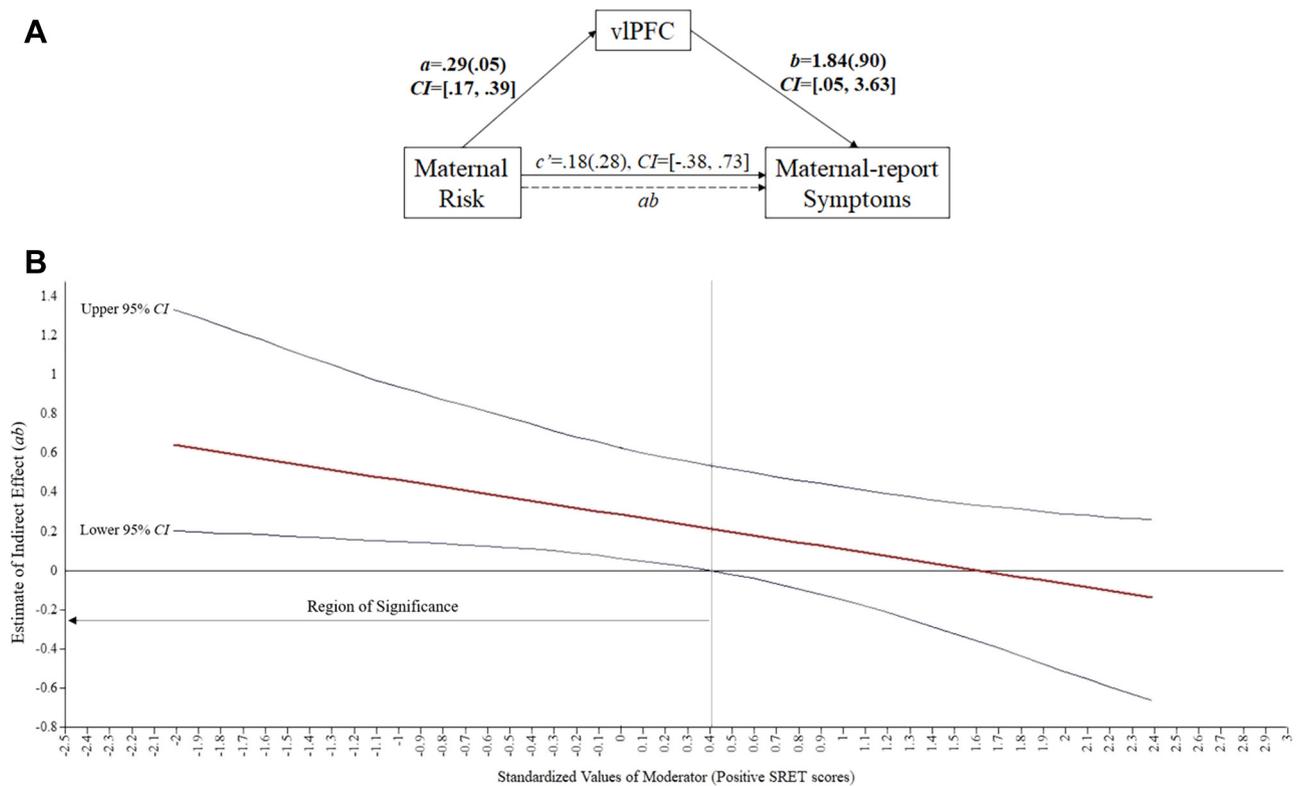
standard error = 1.31, confidence interval =  $-5.32$  to  $-0.14$ . We further probed this moderation using the Johnson-Neyman approach (57) in Mplus. The indirect effect was significant for children with relatively lower positive SRET scores (lower than the standardized score of 0.42) (Figure 3B). Maternal depression was related to child symptoms via vIPFC activation during positive self-judgment; however, this mediating effect was significant only for children lacking high positive self-schemas.

### 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 7 a priori ROIs, we found that high-risk children showed increased activation within the vIPFC and vmPFC during positive self-referential processing compared with low-risk children. In exploring the potential mechanisms that link maternal risk to child symptoms, we found that the vIPFC activation that differentiated high- and low-risk children mediated the association between maternal risk and children's symptoms, but only for children with relatively lower positive self-schemas. While these exploratory analyses require replication, this latter finding suggests that vIPFC activity during positive self-referential processing is most predictive of depressive symptoms when children have greater cognitive vulnerability.

The vIPFC is consistently involved in affective processing and regulation (58–61), serving to downregulate amygdalar reactivity to emotionally distracting cues to maintain performance on the main task (37,38,60,61). vIPFC activation similar

<sup>5</sup>Using the child-report version of the Child Behavior Checklist Withdrawn-Depressed subscale (Youth Self-Report) yielded findings similar to those using the Children's Depression Inventory.



**Figure 3.** (A) Moderated mediation model testing the indirect effect of maternal depression on child symptoms via ventrolateral prefrontal cortex (vIPFC) activation during positive self-referential processing, with positive self-referential encoding task (SRET) scores as the mediator. (B) Region of significance for the moderated effect of positive SRET scores. CI, confidence interval.

to that in our high-risk children has been reported in anxious adolescents during tasks requiring attention shifting from irrelevant threat distractors (62–65). Given high-risk children’s tendency to have less positive self-schemas, they may experience conflict or negative affectivity when deciding whether to self-endorse a positive trait, or it may generally be more challenging for them to make positive self-judgments. The need to recruit resources to inhibit distracting feelings or downregulate task-irrelevant cognition and affect may account for the increased vIPFC activation. Heightened activation was observed in the left but not the right vIPFC, possibly due to the lateralized function of vIPFC, depending on the nature of stimuli—that is, the left vIPFC supports control processes over verbal processing while the right vIPFC is more involved in processing nonverbal visuospatial information (66). Overall, heightened vIPFC activation may reflect self-regulatory difficulties or compensatory processes in high-risk children when making positive self-judgments, which might portend maladaptive emotion regulation that eventuates in depression.

The observed heightened vIPFC activation is also consistent with recent cognitive neurobiological models (67,68) positing that depressogenic cognitive biases are subserved by hyperactivation of areas along a pathway from lower-order subcortical regions (e.g., amygdala) to higher-order cortical areas (e.g., PFC), which leads to elevated, perceived self-related salience of stimuli and attenuated cognitive control that strengthens depressogenic cognitive styles and,

ultimately, depressive symptoms. Our finding of similar patterns in high-risk children suggests that the heightened activation may be at least partially related to preexisting risk for the disorder.

We found that vIPFC 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 vIPFC activation (as the mediator) and positive SRET scores (as the moderator) were included in the model, suggesting that the regulatory function of vIPFC, moderated by positive self-schemas, may be a potential mechanism by which maternal depression confers risk for offspring. This observation is consistent with diathesis-stress models of depression (33–35); however, we acknowledge that these analyses were exploratory, warranting replication using longitudinal designs.

The moderated mediation effect was found for maternally reported, but not child-reported, symptoms. This was unsurprising, given that the two measures differ in content and were only moderately correlated with each other, as is typical (69). The maternal report (Child Behavior Checklist) 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 (Children’s Depression Inventory), 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 with aspects of child depression that require greater insight than children of this age possess. While depressed mothers may tend to endorse more depressive symptoms for their offspring, it is unclear how such reporting biases would be systematically related to children's neural activation.

In addition to our main findings in the vIPFC, we also found that high-risk children showed higher vmPFC activation during positive self-referential processing. As part of the cortical midline structures, the vmPFC is directly engaged in self-related processes, including representing and evaluating self-related stimuli and making self-judgments (28,70–74). 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) (30,75). For example, clinically depressed adults show heightened vmPFC activation when attributing negative traits to themselves (76). While we did not find high- versus low-risk differences in the negative condition, 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 (77), possibly because at-risk children are processing a perceived absence of positive self-traits.

In the negative condition, we did not observe group difference in behavioral SRET or fMRI measures. Given that negative SRET scores were 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 developmental stage. During late childhood and preadolescence, youths are known to have more positive and less negative self-views than later in development (39,78), 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.

Our study had several important limitations. First, the young age of children precluded an extensive MRI session or the use of extensive trait stimuli (although the number used was comparable to other studies using the SRET with children of similar ages). To keep the MRI session short, we did not include a nonreferential condition as a control. Some of the behavioral SRET indices were limited in psychometric properties and/or sample size (e.g., negative-word RTs) and should be regarded as exploratory and interpreted with caution. The block design of the fMRI task prevented us from isolating neural underpinnings of words being endorsed versus rejected. The cross-sectional design cannot establish directional relations between neural markers of risks and depressive outcomes, or to what extent these neural markers are precursors or concomitants of self-referential biases. It would be challenging and expensive to collect longitudinal imaging and behavioral SRET data to permit more conclusive tests of mechanisms in younger children. Therefore, our mediation model speaks more clearly to theoretical/conceptual processes rather than specific causal mechanisms. However, we plan to further explore these considerations by following this cohort into adolescence, a period marked by a sharp increase in clinical depression. The increased vocabulary (i.e., greater availability of word stimuli) and tolerance of time in the scanner

will enable us to improve our assessments of self-schemas and their neural substrates (e.g., distinguishing endorsed vs. rejected words via event-related design, and including a non-referential condition). We will also examine the development of negative self-schemas, which are expected to become more relevant to depression as children age.

In conclusion, we provide new information on the neural substrates of self-referential processing in preadolescents at risk for depression, who showed heightened activation during positive self-referential processing within the vIPFC and vmPFC. The vIPFC activity mediated the association between maternal risk and child symptoms for those with lower positive self-schemas. Drawing on existing preventions for youth anxiety (79), future work aimed at altering depressogenic self-schemas and testing whether such manipulation causes shifts in relevant neural activity may conclusively establish causal pathways between cognitive risk, brain activity, and outcomes and contribute to further refinements of cognitive theories of depression.

## ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Canadian Institutes of Health Research (Grant No. CIHR MOP86458 [to EPH]). Neuroimaging costs were subsidized by a Canada First Research Excellence Fund grant to BrainsCAN. Computing infrastructure support was provided by an Nvidia Corporation grant (to MFJ).

We thank the families who participated in our studies, as well as the many individuals who contributed to data collection.

The authors report no biomedical financial interests or potential conflicts of interest.

## ARTICLE INFORMATION

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Received Mar 28, 2019; revised Dec 10, 2019; accepted Dec 16, 2019.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.bpsc.2019.12.012>.

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