

# Default mode network connectivity in children with a history of preschool onset depression

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**Background:** Atypical Default Mode Network (DMN) functional connectivity has been previously reported in depressed adults. However, there is relatively little data informing the developmental nature of this phenomenon. The current case-control study examined the DMN in a unique prospective sample of school-age children with a previous history of preschool depression. **Methods:** DMN functional connectivity was assessed using resting state functional connectivity magnetic resonance imaging data and the posterior cingulate (PCC) as a seed region of interest. Thirty-nine medication naïve school age children (21 with a history of preschool depression and 18 healthy peers) and their families who were ascertained as preschoolers and prospectively assessed over at least 4 annual waves as part of a federally funded study of preschool depression were included. **Results:** Decreased connectivity between the PCC and regions within the middle temporal gyrus (MTG), inferior parietal lobule, and cerebellum was found in children with known depression during the preschool period. Increased connectivity between the PCC and regions within the subgenual and anterior cingulate cortices and anterior MTG bilaterally was also found in these children. Additionally, a clinically relevant ‘brain-behavior’ relationship between atypical functional connectivity of the PCC and disruptions in emotion regulation was identified. **Conclusions:** To our knowledge, this is the first study to examine the DMN in children known to have experienced the onset of a clinically significant depressive syndrome during preschool. Results suggest that a history of preschool depression is associated with atypical DMN connectivity. However, longitudinal studies are needed to clarify whether the current findings of atypical DMN connectivity are a precursor or a consequence of preschool depression. **Keywords:** Depression, functional connectivity, preschool, default mode network.

## Introduction

Based on findings that depressive disorders are characterized by an increased negative self-focus (Koster, De Lissnyder, Derakshan, & De Raedt, 2011; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), a number of recent investigations examining major depressive disorder (MDD) have begun to explore brain regions and networks associated with self-related processing (Grimm et al., 2009; Johnson, Nolen-Hoeksema, Mitchell, & Levin, 2009; Lemogne et al., 2009; Sheline et al., 2009). The Default Mode Network (DMN) has been of primary interest given its suggested importance in self-referential processing and, more recently, emotion (Buckner, Andrews-Hanna, & Schacter, 2008; Wiebking et al., 2011). In general, findings from these studies have indicated that regions within the DMN demonstrate increased functional connectivity (i.e., highly similar patterns of fluctuation in the blood oxygen level dependent [BOLD] signal) with each other and/or fail to ‘deactivate’ in individuals

with MDD during activities requiring a shift to an external focus of attention (Berman et al., 2011; Greicius et al., 2007; Sheline et al., 2009; Zhou et al., 2010; Zhu et al., 2012). Altered connectivity within this network has also been related to variation in the phenomenology of depression, such as duration of depressive episode or ruminative thinking in adults (Berman et al., 2011; Greicius et al., 2007; Zhu et al., 2012).

While there are few published studies available examining the DMN in currently or previously depressed children and adolescents, those that are available suggest reduced connectivity between regions within ventral anterior portions of frontal cortex commonly associated with this network (e.g., subgenual anterior cingulate) and cortical regions potentially important for attending to- and adjusting one’s behavior to externally salient events (Cullen et al., 2009; Gaffrey et al., 2010). This is particularly evident in prior work from our group suggesting that reduced functional coupling between the subgenual cingulate and dorsomedial prefrontal cortex is associated with dysregulated behavioral expressions of sadness in school age children with a history of preschool depression (PO-MDD; Gaffrey et al., 2010). Nevertheless, to our knowledge there are no studies currently available informing the functional

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relationships of posterior regions within the DMN in currently or previously depressed children. The lack of data informing the developmental trajectory of these regions in depressed children represents a critical gap in our understanding of the role of the DMN in depression.

The developmental trajectory of the DMN remains understudied and poorly understood. However, there is evidence to suggest that the DMN develops from a set of sparse, regional connections early in development to a more distributed and cohesive interconnected network in adulthood (Fair et al., 2008, 2009; Supekar et al., 2010). More specifically, patterns of connectivity within the DMN demonstrate a developmental 'curve' where connections between anatomically close regions weaken and more distal connections gain in strength, eventuating in a distributed (i.e., across the brain) and cohesive interconnected DMN that stabilizes in adulthood (Dosenbach et al., 2010; Fair et al., 2009). This pattern has also been found to coincide with a developing 'community' of DMN regions that shifts from a largely anatomically based configuration to more functionally based grouping (Fair et al., 2009). In addition, previous work has also raised the intriguing possibility that functional relationships between anterior and posterior regions within the DMN undergo the most prolonged period of maturation. For example, two recent studies comparing children between 7–9 years of age with adults reported significantly stronger connectivity between posterior cingulate (PCC) and medial prefrontal cortices (Fair et al., 2008; Supekar et al., 2010).

Based on normative developmental data and findings of alterations of the DMN in adult MDD, one hypothesis is that the experience of clinically significant depressive symptomatology during early childhood may differentially influence the development of regions that integrate to form the DMN and, as a result, have negative and enduring consequences on the behavior and adaptive functioning this network eventually supports. As such, functional connectivity studies examining posterior regions of this network in early onset depression are critically important for a more fully informed understanding of the potential influence of this disorder on DMN formation and function.

The current study sought to extend our prior work (Gaffrey et al., 2010) by focusing on the PCC, a posterior cortical hub region (Fox et al., 2005) frequently implicated in neurobiological models of adult depression (e.g., Mayberg, 1997) and of particular interest developmentally due to its protracted period of functional maturation within the DMN as described above. A 'seed' based examination (Cordes et al., 2000) of the relationship of the PCC to other cortical and subcortical structures was used. The current analyses also further extends our previous work by including a larger sample of school age

children with a history of PO-MDD and by incorporating current diagnostic and behavioral data (not previously available) with prior assessments to guide study design and analysis. Taking guidance from previous adult literature, where patterns of increased connectivity between the PCC and medial prefrontal regions have been reported in MDD, we anticipated that the PCC in children with a previous history of PO-MDD would demonstrate a pattern of increased connectivity with other cortical midline regions believed to be highly involved in self-related processing (Berman et al., 2011; Northoff, 2007). As a complimentary hypothesis, we also anticipated the potential for reduced connectivity between the PCC and more lateral structures purported to support the transition from an internal to external focus of attention (Laird et al., 2009). That is, we anticipated that increased connectivity between the PCC and cortical midline regions would co-occur with decreased functional connectivity between the PCC and regions suggested to regulate these relationships. Additionally, similar to previous studies in adult MDD suggesting a relationship between disrupted DMN connectivity and rumination (Berman et al., 2011), we hypothesized that increased connectivity between the PCC and midline regions would be associated with greater difficulties in effectively regulating and coping with negative affect measured behaviorally.

## Method and materials

### *Participants*

The Preschool Depression Study (PDS) is an ongoing longitudinal investigation of 306 preschoolers and their families. Children 3–5.11 years of age and their families were recruited from pediatricians' offices, daycare centers, and preschools in the greater St. Louis area. A screening checklist was used to oversample preschoolers with depressive symptoms and identify a healthy control group. Following screening and subsequent study enrollment, each family was invited to participate in at least 4 annual comprehensive age appropriate mental health and developmental assessments (spanning 3 years for each subject). For complete recruitment and assessment details see supplemental information and Luby, Si, Belden, Tandon, & Spitznagel, 2009.

Using diagnostic information acquired during these assessments, a subset of 39 medication naïve children who completed their first scan in an ongoing longitudinal neuroimaging study of the PDS sample (see supplemental information for additional detail) were divided into groups based upon the presence or absence of PO-MDD before the age of 6 and, for those without a history of PO-MDD, the absence of any other psychiatric disorders at all assessment points (see Diagnostic Assessment below). This resulted in a group of 21 PO-MDD children (average age:  $9.5 \pm 1.1$  years) and 18 healthy controls (average age:  $9 \pm 1.1$  years). Histories of head trauma, neurological disorders, or significant developmental delay were exclusionary. Parental

written consent was obtained for all subjects and child assent was obtained when appropriate. The Institutional Review Board at Washington University approved all experimental procedures.

### Diagnostic assessment

Diagnostic assessments prior to age 8 were conducted using the Preschool Age Psychiatric Assessment (PAPA; Egger, Ascher, & Angold, 1999, 2003). PO-MDD was assessed using the PAPA and defined as meeting developmentally adjusted DSM-IV MDD criteria prior to 6 years of age (i.e., gateway and required number of symptoms remained unchanged but the 2-week duration criteria was set aside; Gaffrey, Belden, & Luby, 2011; Luby et al., 2002; Stalets & Luby, 2006). When children were 8 years of age and older, the Child and Adolescent Psychiatric Assessment (CAPA) was used to gather diagnostic information from both the primary caregiver and child during separate interviews (Angold & Costello, 2000), which were combined using the standard either/or rule for the endorsement of symptoms (Bird, Gould, & Staghezza, 1992) and used to generate DSM-IV (APA, 2000) diagnoses. A current school age diagnosis of MDD required meeting all DSM-IV criteria including duration and was based on information from the CAPA obtained closest to their MRI scan.

Comorbid disorders were also identified at each study wave. To account for comorbidity, we created a dichotomous variable indicating the presence or absence of internalizing (Generalized Anxiety Disorder, Separation Anxiety Disorder, and Post-traumatic Stress Disorder) and externalizing (Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, and Conduct Disorder) disorders at any available annual assessment wave. If a child currently or ever met for a disorder it was coded as 'present'. These variables were then used as covariates in the analyses detailed below. By definition, the healthy control group was defined by an absence of any psychiatric diagnosis at all annual assessments prior to their MRI scan. The majority of children underwent their MRI scan within 7–10 days of their annual assessment ( $N = 36$ ). Two children in the PO-MDD group and 1 healthy control did not. As a result, the portion of the CAPA addressing MDD was administered on the day of scan and used in the current study while all other diagnostic measures were taken from their proximal annual assessment point (1–2 months prior to scan).

### Wechsler abbreviated scale of intelligence

To obtain a brief measure of IQ, children were administered the two subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

### Child depression inventory

To measure current mood state and level of depressive symptomatology and impairment, each child completed the Child Depression Inventory-Child (CDI-C) version at the time of scan (Kovacs, 1985). *T*-scores derived from CDI-C total scores were used in the current study.

### Children's emotion management scale

Children completed the Children's Emotion Management Scale (CEMS) during their prescan assessment. The CEMS is a measure of sadness and anger management with reliability and validity previously established in normative samples (Zeman, Shipman, & Penza-Clyve, 2001). It provides three scales for measuring a child's ability to inhibit (Inhibition), regulate (Dysregulated Expression), and cope with (Regulation-Coping) experiences of sadness or anger. Higher scores on the Inhibition and Dysregulated Expression scales indicate poor emotion management while higher scores on the Regulation-Coping scale suggest the increased use of more effective emotion management strategies.

### Data acquisition and preprocessing

Imaging data were collected using a 3T TIM TRIO Siemens system (Siemens, Malverna, PA). Two functional runs of 164 TRs (~14 min total) were collected while children rested with their eyes closed. For two PO-MDD and three controls only one resting state functional run was available. Preprocessing and resting state functional connectivity (rs-fcMRI) analyses were carried out using in-house software available to the Washington University community as well as Matlab 7.8 (The MathWorks, Natick, MA) and were based on previously published techniques (Anticevic, Repovs, Shulman, & Barch, 2010; Fox et al., 2005). Average signal-to-noise ratios did not differ between groups ( $p > .05$ ). See supplemental information for details of imaging protocol, data preprocessing and scan quality comparison.

### Posterior cingulate region of interest identification

The seed region for the left PCC was taken from a previous study of the DMN in adults (Fox et al., 2005). Specifically, Talairach (Talairach & Tournoux, 1988) coordinates  $x = -2$ ,  $y = -36$ ,  $z = 37$  were used to create a 12 mm sphere centered in the posterior cingulate. This region has been used to examine the DMN in children and adolescents as well (Fair et al., 2010; Weng et al., 2010).

### Seed-based whole-brain correlational analysis

To produce correlation maps for each child, we extracted the BOLD time course for the PCC and computed the correlation coefficient between its time course and all other voxels in the brain. Fisher's  $r$  to  $z$  transform was applied to each map and group comparisons were conducted with this transformed data using a random effects analysis approach. The necessary  $z$ -value/cluster size combination for a corrected false positive rate of .05 [ $z \geq 2.25 + \text{cluster size thresholding}$  (53 voxels)] was determined using Monte Carlo alpha simulations (McAvoy, Ollinger, & Buckner, 2001).

### Specificity to PO-MDD and brain-behavior relationships: data analytic plan

Following the whole-brain analysis, areas of between-group difference in connectivity were used to explore

brain-behavior relationships and the specificity of identified differences to a diagnosis of PO-MDD. Spheres 12 mm in diameter were placed on the center of mass coordinates for each cluster showing a group difference in connectivity (see Table 2) and the connectivity (i.e.,  $z$  transformed correlation coefficient) between each of these regions and the original PCC seed was obtained. To examine any potential influence of gender, age, comorbidity, IQ, or current depressive symptomatology on group differences, an analysis of covariance (ANCOVA) was conducted for each set of brain region relationships covarying separately for these sets of factors (a) gender and age, (b) comorbidity, (c) IQ, and (d) CDI-C total score using SPSS version 18 (Chicago, IL). Additionally, the relationship between individual differences in emotion regulation and expression, as measured by the CEMS, and functional connectivity of the PCC and areas of difference were evaluated using linear regression analyses. To correct for multiple comparisons, an adjusted  $p$ -value was generated based on the 3 CEMS subscales examined for each emotion as well as the number of regions differing between the groups in each hemisphere [Left ( $N = 4$ ):  $p < .004$ ; Right ( $N = 3$ ):  $p < .005$ ]; only associations between the two measures surviving their respective correction were explored as independent variables in the regression analyses. Age, gender, comorbid disorder(s), IQ, and CDI-C total scores were used as independent variables in the CEMS regressions as well.

## Results

### Demographics and diagnostic characteristics

The PO-MDD and healthy groups did not differ in age, gender, handedness, or CEMS subscale scores except for anger Regulation-Coping (see Table 1). CDI-C total score also did not differ between groups. Group differences were found for IQ, with healthy

control children having higher IQs than children in the PO-MDD group (see Table 1). Four children in the PO-MDD group met DSM-IV criteria for current MDD. See Table 1 for comorbidity data.

### Whole brain fMRI analysis

**Healthy controls.** Consistent with previous research (Supekar et al., 2010), the healthy control group exhibited a strong positive functional relationship between the PCC seed and a large cluster extending bilaterally from the paracentral lobule to the retrosplenial cortex. Additional, smaller clusters within the dorsal medial prefrontal cortex and cerebellum were noted as well (see Figure 1 and Supplemental Table S1).

### PO-MDD

Within the PO-MDD group, a strong positive functional relationship between the PCC and a large cluster extending bilaterally from the paracentral lobule to the retrosplenial cortex was observed. Notably, strong functional connections with dorso-medial prefrontal and rostral anterior cingulate regions were present as well (see Figure 1 and Supplemental Table S1).

### Differences between healthy and PO-MDD

Group differences in PCC connectivity were evident in both hemispheres. Specifically, the PO-MDD group demonstrated a pattern of significantly increased connectivity between PCC and clusters located in the anterior portions of the left and right middle temporal gyri, the caudate and subgenual

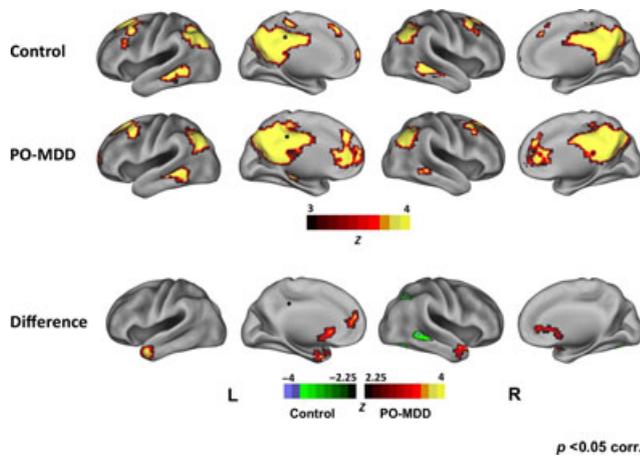
**Table 1** Characteristics of study groups

Characteristic	PO-MDD ( $N = 21$ )	Healthy ( $N = 18$ )	$t/x^2$ value	$p$ -value
Age (years)	9.5 ( $\pm 1.1$ )	9 ( $\pm 1.1$ )	-1.3	0.19
Gender	12F/9M	9F/9M	0.06	0.79
Handedness	20R/1A	15R/2L/1A	1.3	0.52
IQ (Standard Score)	104 ( $\pm 17$ )	115 ( $\pm 15$ )	-2.1	.045
Comorbidity				
None	6	18		
Internalizing	0	NA		
Externalizing	3	NA		
Int. and Ext.	12	NA		
Child Depression Inventory-Child <sup>a</sup>				
Total T-score	45.2 (9.5)	40.7 (5)	-1.6	0.12
Children's Emotion Management Scale <sup>b</sup>				
Anger				
Inhibition	7.4 (2.1)	7.3 (2.2)	0.79	0.43
Regulation-Coping	8.1 (1.8)	10.1 (2.1)	3.03	0.005
Dysregulation	4.8 (1.5)	4.2 (1.3)	-1.2	0.23
Sadness				
Inhibition	7.4 (1.8)	7.3 (2.2)	-0.267	0.79
Regulation-Coping	10.8 (1.8)	11.4 (1.4)	1.22	0.23
Dysregulation	5.5 (1.6)	4.8 (1.9)	-1.2	0.23

A, ambidextrous; F, female; L, left; M, male; NA, not applicable; R, right.

<sup>a</sup>Unavailable for three healthy controls and 1 PO-MDD child.

<sup>b</sup>Unavailable for one control child.



**Figure 1** Whole brain resting state functional connectivity maps for Controls, children with a history of preschool depression (PO-MDD), and group differences (Difference). Group maps were generated using a seed region in the posterior cingulate (PCC; -2, -36, -37; black dot in image). For group differences, warm colors indicate areas of greater connectivity with the PCC seed region in the PO-MDD group while cool colors indicate areas of greater connectivity with the PCC seed region in the control group. Functional images displayed on an inflated cortical surface representation using Caret (Van Essen et al., 2001). Note: L, Left; R, Right

cingulate bilaterally, as well as the left perigenual anterior cingulate cortex. Conversely, children without a history of PO-MDD demonstrated significantly stronger functional relationships between the PCC and clusters within the right cerebellum, right middle temporal gyrus, and right inferior parietal lobe (see Table 2 and Figure 1). When separate ANCOVAs were conducted to examine the robustness of identified PCC functional connectivity differences (see Methods above), the only affected relationships included the PCC-caudate/subgenual cingulate cluster which was no longer significantly different when age and gender, comorbidity, or CDI-C scores were covaried and the PCC-right inferior middle temporal gyrus cluster which was no longer significantly different when comorbidity was accounted for (all  $p > .05$ ). ANCOVAs excluding the

four PO-MDD children meeting for current MDD were run in an identical fashion. Again, all clusters remained significantly different between groups except for the caudate/subgenual cingulate cluster when comorbidity or current CDI-C scores were covaried.

**Brain-behavior relationships**

Examination of brain-behavior relationships revealed that the strength of the functional connection between PCC cortex and perigenual anterior cingulate cortex (see Table 2 and Figure 2), was negatively related to current level of emotion regulation and coping (i.e., decreased connectivity/increased regulation and coping) as reported on the CEMS for both sadness [Pearson  $r = -0.535$ ,  $p = .001$  (two-tailed)] and anger [Pearson  $r = -0.512$ ,  $p = .001$  (two-tailed)]. This connectivity relationship continued to account for a significant proportion of variance in regulation/coping scores even after current age, gender, comorbidity, CDI-C total scores and IQ were included in the model for both sadness ( $B = -.544$ ,  $p = .007$ ;  $R^2 = .429$ ) and anger ( $B = -.540$ ,  $p = .01$ ;  $R^2 = .347$ ). Further examination of the individual groups revealed that this pattern held for both sadness [ $r = -0.462$ ,  $p = .035$  (two-tailed)] and anger [ $r = -0.568$ ,  $p = .007$  (two-tailed)] in the PO-MDD group, but was only significant for sadness [ $r = -0.643$ ,  $p = .005$  (two-tailed)] in the control group, though still in the anticipated direction for anger [ $r = -0.263$ ,  $p = 0.308$  (two-tailed)]. These findings remained unchanged when the four children in the PO-MDD group with a current diagnosis of MDD were removed. IQ did not correlate with functional connectivity scores for any of the identified regions (all  $p > 0.3$ ).

**Discussion**

In the current study we found alterations in connectivity between the PCC and core DMN regions in

**Table 2** Regions significantly different between groups

Region	Hemisphere	BA <sup>d</sup>	x y z			Cluster (voxels)
			Healthy > PO-MDD			
Middle temporal gyrus	R	21	61	-43	-4	111
Inferior parietal lobule	R	40	39	-58	48	137
Cerebellum	R		40	-66	-18	98
			PO-MDD > Healthy			
Middle temporal gyrus <sup>a</sup>	R	21	46	3	-18	130
Caudate/subgenual cingulate <sup>b</sup>	R	24	0	14	-2	163
Middle temporal gyrus	L	21	-37	4	-29	198
Anterior cingulate cortex <sup>c</sup>	L	32	-8	41	14	60

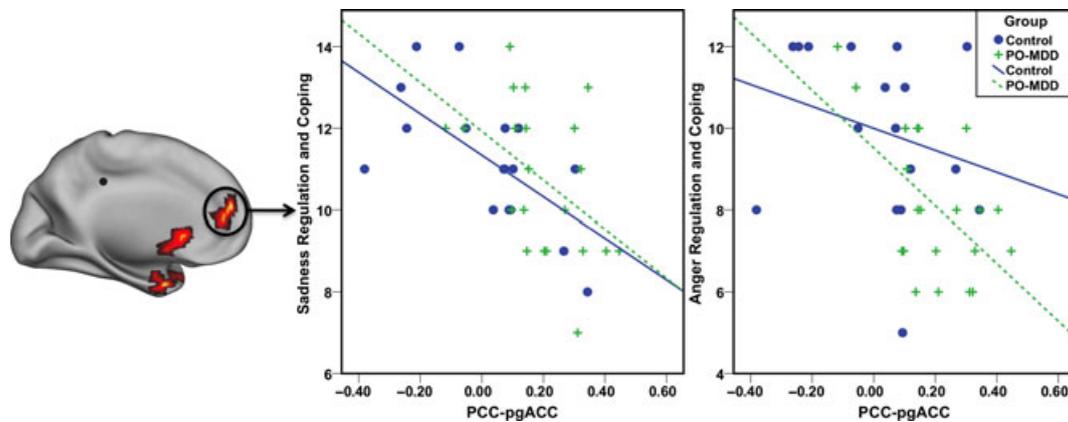
L, left; PO-MDD, preschool depression; R, right.

<sup>a</sup>No longer significant after covarying for comorbidity (see text).

<sup>b</sup>No longer significant after covarying for age and gender, comorbidity, or current depressive affect and impairment (see text).

<sup>c</sup>Connectivity with posterior cingulate seed significantly related to emotion regulation and coping behavior (see text and Figure 2).

<sup>d</sup>Braodmann area.



**Figure 2** Reduced functional connectivity between the posterior cingulate (PCC, black dot in image) and perigenual anterior cingulate cortex (pgACC; circled in figure) is associated with more effective use of sadness and anger regulation coping strategies. Regulation-Coping scores derived from the CEMSS. Greater scores indicate more effective use of regulation and coping strategies. Relationships are significant at the whole group level ( $p = .001$ ) and at the subgroup level for sadness and anger Regulation-Coping in children with a history of preschool depression (PO-MDD) and sadness Regulation-Coping in healthy controls (all  $p < .05$ )

children with known PO-MDD, the majority of whom were not currently depressed. As hypothesized, greater functional connectivity was found between the PCC and cortical midline regions in children who had PO-MDD as compared to healthy controls, as was reduced connectivity between PCC and lateral cortical regions. Importantly, these differences remained significant after accounting for the potential influences of age and gender, IQ, comorbidity, and CDI-C total score at the time of scan. Thus, the current findings replicate previous research in depressed adults demonstrating increased connectivity between PCC and medial prefrontal regions (Berman, et al., 2011; Sheline et al., 2009; Zhu et al., 2012) and the association of connectivity differences with clinically relevant behavior (Berman, et al., 2011; Zhu et al., 2012). We interpret these findings as suggesting a critical role for the DMN in depression and its associated phenomenon, as well as a unique extension of these findings into subjects with the earliest known onset of this disorder during the preschool period of development (Berman, et al., 2011; Greicius et al., 2007; Sheline et al., 2009).

As with previous studies of the DMN in adults with MDD (Berman, et al., 2011; Greicius et al., 2007), the etiology of increased connectivity between the PCC and other regions identified within our PO-MDD group remains to be determined. While the findings could be viewed as reflecting an 'overactive' contribution from each brain region within the DMN, or a failure by one or all regions to selectively limit information flowing into this network, future research incorporating neural network modeling and directional measures of connectivity (i.e., effective connectivity) will be necessary to further explore and answer these questions.

Replicating previous research in typically developing school age children (Supekar et al., 2010), our healthy control group exhibited functional relationships between the PCC seed and other posterior (e.g.,

lateral parietal) and anterior (e.g., medial prefrontal cortex) regions composing the DMN. Although speculative, but with some basis in the few available imaging studies suggesting a developmental shift from locally integrated to distally segregated connections within the DMN (Fair et al., 2008; Supekar, Musen, & Menon, 2009), our findings may also partially reflect a pattern of 'precocious' DMN development in our PO-MDD group. That is, the connectivity between anterior and posterior midline regions of the DMN in children with a history of preschool depression may develop and become more fully integrated at an accelerated rate, which could contribute to, or be a result of, increased self-focus and potential difficulties regulating the DMN. It is premature to speculate further given the limited body of research addressing the nature of functional relationships within the DMN at school age or across development more generally. However, studies investigating the 'age appropriateness' of network connectivity in other disorders (see Church et al., 2009; Fair et al., 2010) have proven informative and now may also prove useful for the study of depression.

Consistent with a recent study of the DMN in first-episode depressed adults (Zhu et al., 2012), the pattern of posterior DMN regions identified as having decreased connectivity with the PCC in our PO-MDD group is also noteworthy. Based on recent reports examining the functional heterogeneity of regions within the DMN (Laird et al., 2009), our findings suggest that cortical areas (e.g., parietal lobule) potentially involved in facilitating the down regulation or disengagement of the DMN are less well integrated in children with a history of PO-MDD. This finding is intriguing in that it suggests that potential abnormalities in functional relationships are not only present within the DMN but also between the DMN and other disorder relevant neural systems (e.g., task control). However, whether the

current findings represent a failure of regions or networks involved in the processing of externally relevant stimuli to adequately signal the need to shift or maintain an external focus of attention, or the inability of these areas to respond and further facilitate this shift (or some combination thereof), remains unclear. Future research using methods to directly assess the relationship between multiple brain regions and networks (e.g., graph theory) will be necessary to more fully address this question.

Importantly, connectivity between the PCC and perigenual anterior cingulate cortex was related to emotion regulation and coping behavior reported outside of the scanner. These results are consistent with research supporting a critical role for medial cortical regions such as the perigenual anterior cingulate cortex and PCC in self-referential processing (Northoff et al., 2006), and a noted relationship between connectivity within these areas and measures of rumination (Berman, et al., 2011). As such, these findings raise the intriguing possibility that the interaction between cortical midline structures may be of additional importance for understanding the brain basis of increased self-focus in depression and its relationship to difficulties with engaging in proactive emotion regulation strategies (e.g., distraction). Interestingly, follow-up analyses in our study accounting for other potentially confounding variables (e.g., depressive affect) and states (i.e., current depression) suggest that this relationship cannot be explained simply as a 'state' related phenomenon. However, whether this represents a 'scar' upon the developing brain from the effects of depression very early in life, or a trait that could be detected even prior to the onset of symptoms in high-risk groups, remains an open question requiring longitudinal studies of at-risk samples. In either case, findings such as these are informative to new initiatives designed to understand the pathophysiology of mental disorders in the context of alterations of neural circuits, as has been elaborated in the NIMH Research Domain Criteria (RDoC) project (Insel et al., 2010).

The current findings also build upon and extend our previous investigation of subgenual cingulate functional connectivity in PO-MDD (Gaffrey et al., 2010) in two unique ways. Firstly, the current study includes larger samples in both groups and, most importantly, makes use of current diagnostic information that was not available for our previous work. As such it ensures that our healthy control group was absent of any psychiatric or neurological concerns from preschool onward, a notable difference from other studies where healthy comparison groups are typically defined based on a single assessment. Additionally, the availability of current MDD diagnostic status in our PO-MDD group allowed for a more thorough examination of potential MDD state related effects as well as a fuller interpretive context for considering study findings. Secondly, the current

study extends our previous subgenual anterior cingulate findings by examining the functional connectivity of the posterior cingulate, a posterior region in the DMN. Our previous findings suggested that *reduced* connectivity between the subgenual anterior cingulate and dorsomedial prefrontal regions was related to *increased* dysregulated emotional behavior. In contrast, the current study found an inverse relationship between *increased* posterior cingulate/perigenual cingulate connectivity and *decreased* use of proactive emotion regulation strategies. As such, the anterior and posterior regions of the DMN may be differentially involved in distinct aspects of emotional behavior and, potentially, uniquely affected by a very early occurrence of depressive symptomatology during development. Continued study of these functional brain relationships across development using a longitudinal approach appears warranted and important for fully capturing the influence of developmental phenomena on DMN development.

There are several limitations of the current study. One factor potentially limiting the generalizability of our findings was the use of a healthy control group known to have no psychiatric diagnoses from a very early age. Taken together with the finding of higher IQ in our control group, it is difficult to assess the degree to which these factors may have contributed to the identified group differences in connectivity. The seed-based method we used does have certain constraints upon its interpretation (Power, Fair, Schlaggar, & Petersen, 2010). While this method is able to identify significant patterns of temporal coherence between regions, it does not allow for any conclusions about directionality or causality of these relationships to be made. In addition, it is limited to the examination of the relationship between the *a priori* selected seed region of interest and other voxels within the brain exhibiting highly similar (or dissimilar) patterns of BOLD fluctuation. As such, differences in connectivity between groups can only be interpreted at this level (i.e., blood flow as measured by the BOLD signal). With the increasing application of more complex analytical methods such as graph theory (Bullmore & Sporns, 2009) to the study of brain networks, future research promises to overcome these limitations and shed more light on the dynamic activity of neural networks in this early childhood disorder.

In conclusion, this is the first study to our knowledge to examine the functional connectivity of the PCC in children known to have experienced depression during preschool. The findings are largely consistent with previous MDD research in adults, but extend prior work by suggesting that a history of depression prior to age 6 is associated with atypical connectivity of the PCC and other regions within the DMN. The current study also provides evidence for a clinically relevant relationship between disruptions in PCC connectivity and emotion regulation behavior. Future longitudinal studies are needed to replicate the current findings of atypical PCC connectivity

in children with a history of PO-MDD and to further clarify their potential usefulness for identifying and treating this disorder.

## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1** Regions significantly correlated with the posterior cingulate seed region in each group

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## Key points

- Atypical patterns of functional connectivity within the default mode network (DMN) have been previously demonstrated in depressed adults.
- A very early history of depression may be associated with similar disruptions of functional connectivity within the DMN.
- Similar to previous findings in depressed adults, we demonstrated that school age children with a known history of preschool depression exhibit patterns of disrupted functional connectivity within the DMN.
- Importantly, these disruptions were also significantly related to emotion regulation and coping skills.
- Our findings extend previous research in depression by suggesting that DMN disruptions can be detected as early as school age in children with a history of preschool depression.

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